ISBN: 978-969-2201-20-9

Unique Scientific Publishers
Journals Books Magazines

Complementary and Alternative Medicine: Nanotechnology-II

Editor

Rais Ahmed, Ahrar Khan
Rao Zahid Abbas
Shahid Hussain Farooqi
and Rida Asrar

Complementary and Alternative Medicine: Nanotechnology–II

Complementary and Alternative Medicine: Nanotechnology–II

Editors

Rais Ahmed

Ahrar Khan

Rao Zahid Abbas

Shahid Hussain Farooqi

Rida Asrar

Unique Scientific Publishers ®

House No. 1122, St No. 11, Liaquat Abad-II, Faisalabad, Pakistan.

Complementary and Alternative Medicine : Nanotechnology–II

ISBN: 978-969-2201-20-9

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment, and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of the patient, to make diagnosis, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the authors assume any liability for any injury and/or damage to humans and animals or property arising out of or related to any use of the material contained in this book.

The Publisher

Book Specifications:

Total Chapters: 47

Total Pages: 420

Page Size: A4 (210mm × 297mm)

Book Weblink: https://uniquescientificpublishers.com/nanotechnology-ii/

Publisher: Unique Scientific Publishers (https://uniquescientificpublishers.com)

Editor: Rais Ahmed, Ahrar Khan, Rao Zahid Abbas, Shahid Hussain Farooqi, Rida Asrar

Senior Designer : Muhammad Zafar Iqbal

Published: September 18, 2024

Printed in Pakistan

PREFACE

As nanotechnology continues to revolutionize various fields, its applications in medicine and veterinary science are particularly transformative. *Complementary and Alternative Medicine: Nanotechnology-II* offers a comprehensive look into how nanotechnology is reshaping healthcare, with a focus on its roles in precise drug delivery, disease prevention, immune modulation, and sustainable veterinary practices. Through advanced techniques and formulations, this book explores the versatility of nanoparticles in areas where traditional treatments often face limitations. Central to this volume is the examination of nanoparticles in targeted drug delivery, which enables highly precise therapeutic interventions, particularly in conditions like cancer and inflammatory diseases. The book delves into how innovations in polymeric nanoparticles and biomimetic designs are advancing the safety and efficacy of drug delivery, especially in complex treatments for renal cancer, diabetes, and beyond. The work also investigates how nanotechnology supports both human and veterinary medicine by allowing treatments that reduce side effects while enhancing effectiveness. The book further explores how nanotechnology addresses the challenge of antimicrobial resistance and infectious disease control, both in animal and human health. Solutions such as silver nanoparticles for poultry health, novel approaches to treat mastitis, and advanced formulations to manage avian influenza underscore the promising role of nanotechnology in combating resistant pathogens. Additionally, green nanoparticle solutions demonstrate the eco-friendly potential of nanotechnology in sustainable veterinary practices, and nanoparticle-based immune enhancers show new possibilities for boosting immunity against infections. In agricultural applications, nanotechnology has opened new paths for managing livestock health and enhancing productivity. This volume includes discussions on nanoparticles as alternatives to traditional antimicrobials, nano-based dewormers for animal health, and nano-vaccines, such as those aimed at controlling diseases like lumpy skin disease. With applications spanning ectoparasite control in companion animals to nanoparticle biofertilizers for optimized animal performance, this book showcases the broad scope of nanotechnology in elevating animal health and productivity in a sustainable manner. Diagnostics and preventative measures also benefit from nanotechnology, and this book highlights the potential of innovations like nano-biosensors for detecting contaminants in food, hydrogel-based nanoparticles that aid in wound healing, and novel approaches for identifying agricultural toxins. By improving diagnostic accuracy and promoting food safety, these advancements represent the essential role of nanotechnology in enhancing public health protections. The book further details key aspects of nanoparticle synthesis, characterization, and pharmacokinetics, including how mathematical modeling informs drug delivery systems. By examining methods of nanoparticle creation and exploring the science behind bio-inspired approaches, this volume emphasizes the interdisciplinary nature required to maximize nanotechnology's full potential in healthcare applications. *Complementary and Alternative Medicine: Nanotechnology-II* is an essential resource for researchers, students, and professionals seeking to understand the wide-ranging implications of nanotechnology in modern medicine. This work underscores the cutting-edge capabilities of nanotechnology as it bridges traditional and contemporary treatment methods, offering a glimpse into a future where advanced, targeted therapies transform healthcare practices in both human and veterinary fields.

Editor

Contents

Title	Pages
The role of Nanoparticles in Vaccine Development Javeria Arshad, Savaira Tariq, Khadija Babar, Maha Khalid, Syed Sharf ud Din, Munazza Habib, Gulab Ali, Mohsan raza, Wajeeha Sultan and Aimen Khalid	1
Nanoparticle Formulation in Nasal Drug Delivery Javeria Arshad, Ijaz Ali, Javeria Javed, Muhammad Najeeb Ullah, Hammad Afzal, Muhammad Ahsan Samran and Muhammad Talha	10
Application of Nanotechnology in Combating Bovine Mastitis Mona Mohamed Hassan Soliman, Nagwa Sayed Ata, Amany Ahmed Arafa and Mai Mohamed Kandil	19
Use of Nanoparticles for drug delivery in cancer treatment Sofia Qasim, Ahmed Faraz, Madeeha Arshad, Muhammad Muazim Sharif, Adil Jamal, Muhammad Madni, Kashif Hussain Mangi, Ifrah Tahir, David Atuahene and Adil Munir	27
Role of Nanoparticles in the Treatment of Renal Cancer Hassaan Bin Sajid, Amisha Naz, Laiba Naeem, Bint-e-Zahra, Muhammad Zeeshan Haider, Safoora Murad, Hafiz Aamir Ali Kharl, Muhammad Usama Javed, Muhammad Ijaz Saleem, Arslan Muhammad Ali Khan	34
Evaluation of Anti-Bacterial Efficacy of Nanoparticals Against Major Mastitis Associated Pathogens Bilal Ahmed, Kainat, Abdul Baseer, Abdul Jabbar, Asif Ali, Muhammad Mohsin Jamil, Maaz Anjum, Sami Ullah Khan, Muhammad Ashraf, Mansoor-Ul-Haq and Ghulam Muhammad	40
Use of Nanotechnology to Treat Avian Influenza Muhammad Ifham Naeem, Farooq Hussain, Elif Sibel Aslan, Javeria Nousheen, Qamar un Nisa, Mobeen Sarwar, Minahal Fatima, Afifa Khanim, Waqar Younis and Ghulam Murtaza	47
Use of Nanotechnology to Treat Infectious Bronchitis in Poultry Muhammad Ifham Naeem, Farooq Hussain, Hina Faiqa, Sadia Asghar, Qamar un Nisa, Muhammad Umair Saleem, Minahal Fatima, Kinza Fatima, Noman Yousaf and Waqar Younis	55
Use of Nanoparticles in Elimination of Ectoparasites in Companion Animals Mehroz Latif, Muhammad Numair Ahmad, Muhammad Saad Arshad and Muhammad Ahmad Sannan	61
Green Nanoparticles; Sustainable Approaches and Applications in Veterinary Medicine Ume Habiba Firdous, Sehrish Kiran, Muhammad Umair Waqas, Abdullah Saghir Ahmad, Saleena Ahmad, Atif Rehman, Amina Iqbal, Idrees Raza, Muhammad Hamza Muneer and Ali Haider	68
Nanoparticles in Targeted Drug Delivery and Therapeutics	79

Amina Iqbal, Ume Habiba Firdous, Kashif Hussain, Abdullah Saghir Ahmad, Sehrish Kiran, Salena Ahmad, Muhammad Usman, Idrees Raza, Rana Muhammad Shahbakht, Muhammad Umair Waqas and Ali Haider	
Nanomaterials Characterization Hira Qamar, Amina Iqbal, Abdullah Saghir Ahmad, Sehrish Kiran, Salena Ahmad, Muhammad Usman, Muhammad Hamza Muneer, Kashif Hussain, Rana Muhammad Shahbakht, Atif Rehman and Ali Haider	94
Revolutionizing Nanoparticles in Veterinary Care: Classifications and Benefits Muhammad Uzair, Muhammad Ali, Muhammad Ahsan Sheraz, Rida Nawaz, Shabab Ahmad, Areesha Arkan, Khushbo Prince, Ali Abdullah, Muhammad Ali Assad, Habiba Shabbir and Momna Mehmood	107
Poly Lactic-co-Glycolic Acid Nanoparticles for Drug Delivery Sidra Altaf and Tasawar Iqbal	119
Role of Nanoparticles for the Control of Haemonchosis Faiq Ahmad	128
Role of Silver Nanoparticles in Poultry Health Syed Muhammad Faizan, Zain ul Abadeen and Muhammad Asif Javed	140
Overview of Nanoparticles and their Role in Management of Parasitic Diseases Abu Baker Yameen, Hafiz Aamir Ali Kharal, Kashif Isamail and Kashif Iqbal	146
Nanomedicines Utilizing Trace Elements as Targeted Intervention to Revolutionize Diabetes Treatment Muhammad Sajid, Ghulam Murtaza, Muhammad Azam, Wazir Muhammad Ikhlaq, Sajawal Ali, Abdul Mateen, Hussain Abbas, Faiza Bibi, Sara Khan and Shahna Jabeen	155
Nano-biotics: An Advanced Approach to Control Biofilm of Antibiotic Resistant ESKAPE Pathogens Kaleem Ullah, Rimsha Kanwal, Izza, Rabia Kanwar, Muhammad Usman Qaiser, Hadia Bilal, Abid Ahmad, Mushtaq Ahmad, Usama Saleem and Sajjad Ahmad	163
Low Molecular Weight Hyaluronic Acid FeO Nanoparticles: Biological Assessment of Their Ability to Target Breast Cancer Cells Zainab Shahid, Zaib un Nisa, Muhammad Zafran, Tanziha Zualfiqar, Orba Maan, Muqadas Fatima, Baby Hooria Azam, Aneela Nazir, Noor ul Huda and Dilshad Fatima	172
Overview of Nanoparticles and their Biomedical Applications Moazama Batool, Qurat ul Ain, Sheeza Bano, Mamoona Mahmood, Hafsa Sultan and Fatima Talib	180
Trends in Application of Nanotechnology for Poultry Production Iqra Zaheer, Muhammad Arslan, Tahreem Asad, Uzair Safdar, Umar Iqbal, Abdul Qudoos, Saad Ahmad Khan, Rana Kamal Elahi, Sana Ali and Mahreen Fatima	189

Exploring the Potential of Plant Extract, Green Nanoparticles, and Oil Formulation for the Control of Disease Caused by Cestodes: Trends and Challenges Farhana Yousaf, Saba Kousar, Kainat Farooq Khokhar, Maher Nigar, Mahnoor Aslam, Madiha Fatima,, Madiha Rasool,, Amina Riaz, Hira Muqaddas and Naunain Mehmood	198
Nanotechnology in Parasite Control: New Therapeutic Horizons Maryam Bashir, Naseer Khan, Nimra Mushtaq, Muhammad Kasib Khan, Kashif Hussain, Maryam Arshad, Fouzia Tabassum, Mah Noor, Ali Haider, Muhammad Umair Waqas, Rana Muhammad Shahbakht and Asghar Abbas	208
Characterization Techniques of Nanoparticles Javeria Arshad	218
Use of Nanoparticles against Salmonellosis in Poultry Muhammad Abu Bakar, Muhammad Fahad, Muhammad Saad Arshad, Ali Hussain, Abdul Ali, Furqan Ali, Ahmed Suleman, Zaighum Ali, Syed Abdullah Bukhari and Aftab Shahzad	227
Nanoparticle-Mediated Antimicrobial Armory: Employing Nanotechnology for Precision Control of Bacterial and Viral Infections Muhammad Usama Javed, Tahreem Fatima, Muhammad Haseeb Amir, Muhammad Tayyab Naveed, Nida Liaqat, Muhammad Abdullah, Muhammad Abubakar Amin, Tayyab ur Rehman, Fasih Yousaf and Muhammad Zeeshan Hadier Javed	233
Role of Nanoparticles in Biofertilizers Javeria Arshad	243
Synthesis Techniques and Applications of Diverse Nanoparticles Muhammad Adil, Farrah Deeba, Bushra Mumtaz, Marwa Abbas, Sayeda Nimra Jabeen, Hassan Raza, Rabia Ali, Saba Imtiaz, Saifuddin and Maham Naseer	254
Effectiveness of intra articular steroid injection in osteoarthritic patients Abdur Rehman, Maida Ilyas, Hamid Mushtaq, Hamza Zahid, Faiza zubair, Naila Riaz, Muhammad Danial Musa and Tasawar Iqbal	261
Hydrogel Based Nanoparticles for Enhanced Wound Healing Awn Abbas, Sadia, Sameera Naseer, Dongbo Li, Chao Li, Nanxin Li, Yifan Zhang, Lian Chen, Shaungcai Qi and Hualin Fu	269
Nanoparticles: An Alternative Strategy against Antibiotic-Resistant Mastitogens Asma Ayoob, Ammara Khaliq, Sundas Mehboob, Ahmad Murtaza, Muhammad Aafaq Khan, Muhammad Ibraheem Ijaz and Muhammad Arif Zafar	276
Nanotechnological Approaches to Immune Enhancement: A Novel Strategy Saima Somal, Shujaat Hussain, Muhammad Kamran Rafique, Zeeshan Nawaz, Imtiaz Hussain, Lieza Iftikhar, Hammad Ahmed Hashmi, Muhammad Arif Zafar and Muhammad Zishan Ahmad	284
Nano-Particles: The New Frontiers in Drug Delivery Systems	292

Farah Ijaz, Abdul Mateen, Muhammad Farhan Rahim, Sayyed Aun Muhammad, Muhammad Abid Hayat Adnan Hassan Tahir, Shokat Ali and Abdul Rauf	
Harnessing Nanomedicine for Targeted Sepsis Therapy Zaman Javed, Muhammad Sabir Farooq, Muhammad Saqlain, Kashif Javed, Riaz Hussain Pasha, Mujeeb ur Rehman Sohoo, Muhammad Zishan Ahmad, Muhammad Farhan Rahim, Adnan Hassan Tahir and Muhammad Arif Zafar	302
Nanoanthelmintics: A way forward towards anthelmintic resistance Hira Altaf, Sadia Nageen, Sidra Ayub, Faisal Hafeez, Naveed Ahmad, Muhammad Kasib Khan, Muhammad Imran, Haider Abbas and Muhammad Imran	310
Potential Application of Nanoparticles In Human Medicine Fatima Azam, Shaiza Muqadus, Rimsha Jamil, Sadia Yousuf, Zia ud Din Sindhu, Muhammad Kasib Khan, Muhammad Imran and Shah Nawaz	322
Role of Platelet Membrane Coated Nanoparticles to Treat Rheumatoid Arthritis Tasawar Iqbal, Mahvish Fatima and Sidra Altaf	331
Therapeutic Effect of Nanoparticles as Anti-inflammatory, Antibacterial and Anti-parasitic Muhammad Asif, Ayesha Safdar Ch, Ubaidullah, Zia-Ullah, Naveed Hussain, Muhammad Hassan Saleem, Muhammad Azhar, Zeeshan Ahmad Bhutta, Sana Sagheer, Muhammad Fakhar-e-Alam Kulyar, Shah Nawaz, Rida Fatima Hussain, Muhammad Awais, Muhammad Tauseef Ahmad, Inam ul Hassan, Aisha Arhad and Syeda Faiza Muzammal	339
Utilizing Nano Vaccines for Enhanced Immunization against Lumpy Skin Disease Shafiq ur Rehman, Farrah Deeba, Ehtasham ul Haq, Muhammad Adil, Hafiza Rikza Tanveer, Sheraz Ahmad, Ali Haider, Muhammad Ramzan, Nayyar Abbas, Haseeb Jamal and Muhammad Tayyab	350
Effectiveness of Nanoparticles to Control Ticks and Tick-borne Diseases Sajida Bibi, Sidra Abbas, Muhammad Arfan Zaman, Roquyya Gul, Aima Iram Batool, Dwight Bowman, Timothy Wu, Muhammad Zulqarnain, Iqra Khalil, Muhammad Zahid Sarfaraz and Tashifa Naheed	356
Mathematical Pharmacokinetics and Drug Delivery Muhammad Saleem, Rabia Munir, Tooba Aslam, Sidra Altaf and Amna Aziz	364
Novel Nano-biosensors for the Detection of Organophosphate Residues in Food Commodities Sidra Altaf, Kinza Javed Iqbal, Muqaddas Saqib and Ume Salma	374
Pharmacological Importance of Ketamine Loaded Nanoparticles Asmara, Laiba Fatima, Vishah Fatima, Maham Ahmed Butt, Anam Ghos, Muhammad Saleem, Muzammil Zaman Khan, Saad Hassan Qadir and Muhammad Sikander Afzaal	383
Pharmacological Importance of Biomimetic Polymeric Nanoparticles	391

Sidra Altaf	
Antimalarial Activity of Metallic Nanoparticles Huma Fatima, Nargis Shaheen, Sumbal Haleem, Asma Ashraf, Attiya Iqbal and Shawana Qayyum	403
Application of Nanoparticles and Nanomaterials in Animal Health and Performance Aneela Amin, Sadaf Faiz, Muhammad Asmat Ullah Saleem, Muhammad Usman, Muhammad Abdullah Arshad, Muhammad Asad Ali, Muhammad Bilal, Ali Haider and Aisha Khatoon	413

Chapter 01

The role of Nanoparticles in Vaccine Development

Javeria Arshad[1*], Savaira Tariq[2], Khadija Babar[2], Maha Khalid[3], Syed Sharf ud Din[3], Munazza Habib[3], Gulab Ali[2], Mohsan raza[4], Wajeeha Sultan[5] and Aimen Khalid[6]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
[2]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
[3]Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore-54000, Punjab, Pakistan
[4]Department of Pharmacy, University of Agriculture Faisalabad-38000, Punjab, Pakistan
[5]Department of Pharmacy, Faculty of Pharmaceutical sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
[6]Department of Microbiology, Faculty of Biological Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
*Corresponding author: pharmacistj.arshad@yahoo.com

ABSTRACT

Conventional vaccines come with low immunogenicity, an increased potential for toxicity, and a need for multiple administration. To overcome these problems associated with conventional vaccines, researchers have sought to incorporate nanotechnology in the science of vaccine development. Nanoparticles have addressed major issues concerned with the traditional and subunit vaccines. The advancements have increased the vaccine efficacy and effectiveness. Types of nanoparticles include Solid-Lipid Nanoparticles, Polymeric Nanoparticles, Liposomes, Virus-Like Particles. Nanoparticles have emerged as a promising platform for enhancing the immune response, either through innate immune potentiation or through improved delivery of antigens or other immune stimulants. This can be accomplished through the use of virus-mimetic nanostructures, which are designed to mimic viral assembly and elicit a strong immune response in the body. Nanoparticles can encapsulate antigenic material, protecting it from degradation and improving its stability during storage and transportation. This is particularly important for vaccines that require refrigeration, as nanoparticles can extend their shelf life and reduce the need for cold chain storage. Furthermore, obstacles are being removed by advances in intracellular delivery, which makes it easier for immune cells to absorb antigens and mount a strong defence. Stability is still a crucial component, and research is being done to create vaccines that can be stored at ambient temperature without the need for the laborious cold chain. Personalized vaccines, a novel frontier, leverage nanoparticle technology to tailor immunization to individual immune profiles. This not only maximizes efficacy but also minimizes adverse reactions, offering a paradigm shift in vaccination strategies. Thus through innovation, collaboration, and ethical practice, they hold the potential to revolutionize immunization worldwide.

KEYWORDS
Conventional Vaccines, Nanotechnology, Nanoparticles, Immunogenicity, Personalized Vaccines.

Received: 15-May-2024
Revised: 13-July-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Arshad J, Tariq S, Babar K, Khalid M, Din SSU, Habib M, Ali G, Raza M, Sultan W and Khalid A, 2024. The role of nanoparticles in vaccine development. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 1-9. https://doi.org/10.47278/book.CAM/2024.216

INTRODUCTION

Conventional vaccines proved to be a great success in the field of disease prevention and alleviating human health. But these conventional vaccines are short of many good things and raise concerns. Conventional vaccines come with low immunogenicity, an increased potential for toxicity, and a need for multiple administration. To overcome these problems associated with conventional vaccines, researchers have sought to incorporate nanotechnology in the science of vaccine development (Kheirollahpour et al., 2020). Previously, under nanotechnology, nanoparticles have already been used to deliver drugs such as cytotoxic drugs or immune-suppressive drugs (in case of transplantation). Nanoparticles can ensure a target-specific and controlled delivery of medications. Nanoparticles not only provide a site-specific delivery of medications but also protect the drug from degradation (Diaz-Arévalo and Zeng, 2020). Nanoparticles come with some diverse compositions, these versatile compositions help researchers to develop novel and innovative strategies and platforms for vaccine development. Nanoparticles ensure high effectiveness of vaccines (Lung et al., 2020a). Owning to the unique structure of nanoparticles, they can be used as adjuvants in vaccines. Their structure help to accommodate various

loading antigens. It also prevents degradation and prolongs in-vivo antigen exposure. Size of nanoparticles help to induce specific immune response and action at a particular target site. Furthermore, the response or impact of nanoparticles to the immune system can be modulated, if their physical and chemical properties are properly controlled and modified as per the desired action (Mao et al., 2021). As mentioned earlier, nanoparticles are capable of inducing site specific responses and vaccines require a site specific response to overcome concerns related to their effectiveness. Therefore, nanoparticles are what we need to improve the safety and effectiveness of vaccines. Nanoparticles provide benefit in two ways; they act as delivery systems and also as adjuvants. Their use as adjuvants or carriers enhance stability of antigens, decrease the rate of degradation, improve immunogenicity and therapeutic effectiveness, and enhance membrane permeability (Bezbaruah et al., 2022a). As discussed, nanoparticles have potential to be used as immune-stimulating adjuvants in vaccines, therefore they are referred to as nano-adjuvants. They work by encapsulating or absorbing an antigen or DNA in the formulation, and thus increasing stability, immunogenicity, and cellular uptake (Garg and Dewangan, 2020).

In this advancing world, new therapeutics are rapidly introduced by the researchers. Messenger RNA (mRNA) is also a novel therapeutic marking its importance in disease treatment and prevention. mRNA and DNA vaccines also present their therapeutic importance in the vaccination system taking it to new heights. They are cheap, quickly adaptable to changing pathogenic strains, and are cheap to manufacture. These nucleic acid therapeutics require stable and effective in-vivo delivery systems that protect against in-vivo degradation and enable cellular uptake and release. Therefore, instead of using viral vectors for nucleic acid delivery, non-viral vectors especially nanoparticles are rapidly used in the vaccine development. Nanoparticles provide effective targeted therapies with needed pharmacokinetics, bioavailability, efficacy, and bio-distribution. One such nanoparticle (Lipid nanoparticle-loaded mRNA vaccine) has been in clinics against COVID-19 and validates the importance of the use of nanoparticles in the vaccines (Ho et al., 2021; Hou et al., 2021).

Types of Nanoparticles used in Vaccines

In immunization, nanoparticles have made their mark as shown in Fig. 1. Nanoparticles have addressed major issues concerned with the traditional and subunit vaccines as in Table 1. The advancements have increased the vaccine efficacy and effectiveness (Vasudevan et al., 2024).

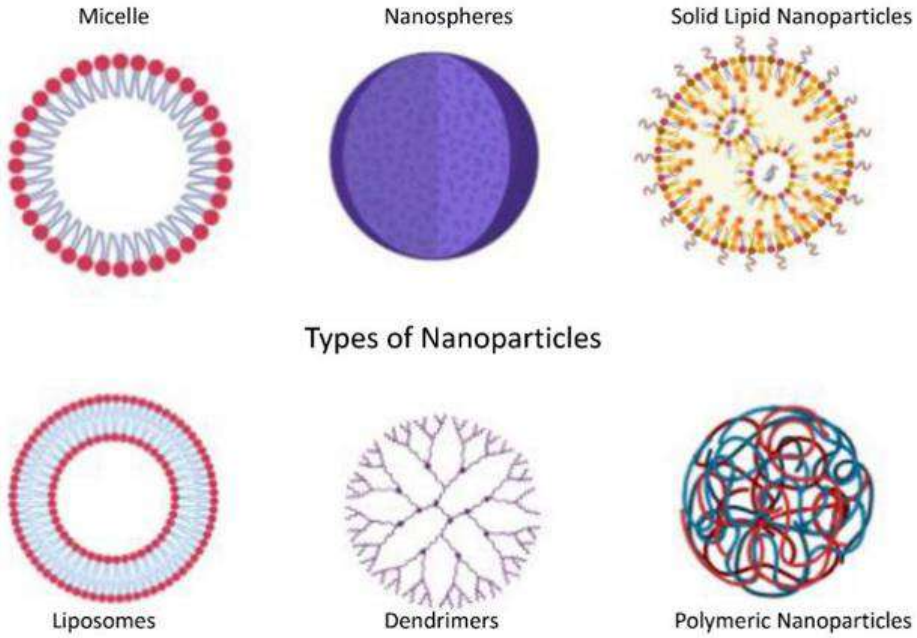


Fig. 1: Types of Nanoparticles.

Enhanced Immune Response with Nanoparticles

Nanoparticles have emerged as a promising platform for enhancing the immune response, either through innate immune potentiation or through improved delivery of antigens or other immune stimulants. This can be accomplished through the use of virus-mimetic nanostructures, which are designed to mimic viral assembly and elicit a strong immune response in the body (Bros et al., 2018). To increase immunogenicity, these nanostructures can be decorated with proteins or recombinant antigens. Nanoparticles' immunogenicity can also be affected by their size and surface charge; smaller particles and those with a positive surface charge are generally more immunogenic. Nanoparticles can be engineered to boost immune responses in the treatment of inflammatory and autoimmune disease (Gause et al., 2017). Nanoparticles have the potential to change the treatment paradigm for these diseases by interacting with various cellular and molecular

components of the immune system. Several strategies have been used to optimize vaccine immunogenicity and generate a strong B-cell response. Nanoparticles have been shown to improve the antigenicity of conjugated antigens, and this effect is dependent on particle size and surface charge. Particle size has been identified as a significant factor in determining whether antigens loaded into nanoparticles elicit type I or type II immune responses, thereby influencing the type of immune response (Glass et al., 2016). A leading hypothesis for why nanotechnology-driven compositions are effective in vaccine development is that non-soluble antigens release slowly, forming a depot at the injection site and providing protection in the destabilizing in vivo environment. The antigenicity of the nanoparticles themselves is less well understood. Two studies found that when C60 fullerene derivatives conjugated to a BSA were used for immunization, particle-specific antibodies were produced, implying that some water-soluble nanoparticles might act as haptens, i.e., they are not antigenic unless they bind to a protein carrier (Moni et al., 2023).

Table 1: Types of Nano-Particles with Theirs Specifications

Serial Number	Type of Nanoparticle	Explanation	Fabrication Technique	Characterization	References
1	Solid-Lipid Nanoparticles.	Lipid nanocarriers having a solid core. They are capable of holding both hydrophilic and hydrophobic drugs	1. Ultrasonication 2. Solvent emulsification evaporation 3. Solvent emulsification diffusion 4. Supercritical fluid extraction 5. High pressure homogenization 6. Hot homogenization 7. Cold homogenization	1. Particle size, charge analysis, polydispersity index (Photon Correlation Spectroscopy (PCS). Dynamic Light Scattering (DLS)) 2. Crystallinity (Differential Scanning Calorimetry) 3. Size, surface topography, stability (Scanning Electron Microscopy (SEM)) 4. Zeta potential (Phase Analysis Light Scattering (PALS))	(Duan et al., 2020; Paliwal et al., 2020; Fan et al., 2021; Khairnar et al., 2022)
2.	Polymeric Nanoparticles	They have substances entrapped or adsorbed into the polymeric core.	1. Solvent Evaporation 2. Emulsification/Diffusion 3. Emulsification/Reverse salting-out 4. Nanoprecipitation 5. Supercritical fluid technology 6. Membrane reactor method 7. Sono-precipitation	1. Particle size (laser Scattering (LS), Field Flow Fractionation (FFF), Electron Microscopy (EM)) 2. Size, polydispersity, zeta potential (Dynamic Light Scattering (DLS))	(Zielińska et al., 2020; Gagliardi et al., 2021; Castro et al., 2022; Sakhi et al., 2022)
3.	Liposomes	Spherical-lipid vesicles composed of one or more lipid bilayer structures. They are the most widely considered nanocarriers for the targeted drug delivery.	1. Thin film hydration method/ Bangham's method 2. Reverse-phase evaporation method 3. Solvent injection method 4. Detergent removal method 5. Heating method 6. Supercritical fluidic method 7. Packed-bed assisted hydration method 8. Curvature tuning method	1. Size (Dynamic Light Scattering (DLS)) 2. Shape (Optical Microscopy (OM), Electron Microscopy (EM), Scanning Electron Microscopy (SEM)) 3. Polydispersity Index and zeta potential (Dynamic Light Scattering (DLS))	(Has and Sunthar, 2020; Miere et al., 2020; Walunj et al., 2020; Nsairat et al., 2022)
4.	Virus-Like Particles	Multimeric structures having one or more non-genetic material viral structural proteins. They are formed by the self-assembly of viral structural proteins either in vivo or in vitro.	1. Use of yeasts to express virus-like particles 2. Cell-free protein synthesis	1. Electron Microscopy (EM) 2. Transmission Electron Microscopy (TEM)-negative staining 3. Super-resolution Florescence Microscopy (SRFM) 4. Nanoparticle Tracking Analysis (NTA) and Flow virometry	(Dondapati et al., 2020; González-Domínguez et al., 2020; Qian et al., 2020; Srivastava et al., 2023)

Immunological Mechanism of Nanoparticle Vaccines

Nanoparticle vaccines are a diverse category of vaccines used to prevent or treat a variety of diseases. Vaccines are

administered intramuscularly, and nanoparticles are coated with interstitial fluid proteins (Tursi et al., 2023). The composition and mass of this corona are influenced by the nanoparticle's physiochemical properties, such as size and surface chemistry, which may result in enhanced or diminished cellular interactions and immune system recognition (Wilson et al., 2017). Proteolytic analyses of coronas formed on nanoparticles after administration by injection or serum incubation consistently identify opsonins such as fibrinogen, complement, and immunoglobulin proteins. Nanoparticles quickly become coated in soluble factors such as complement and immunoglobulins (Zhang et al., 2021). This marks nanoparticles for comprehension and uptake by local innate immune cells like neutrophils, monocytes, macrophages, and dendritic cells, which are a subset of antigen presenting cells (Kapczynski et al.). Pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs), found on the cell surface, inside of the endosome, or in the APC's cytoplasm, can enhance this uptake. These PRRs recognize molecular patterns linked to pathogens (PAMPs) on nanoparticles (Zhao et al., 2023). The motions of particle trafficking to the lymph node (LN) are largely determined by nanoparticle size. Smaller particles can freely drain into the LN, whereas larger particles require cellular transport from APCs. In addition to improved LN drainage, nanoparticles are retained in the LN for longer than readily soluble antigens, providing more opportunities for interactions with immune cells (Zhao et al., 2018). A recurrent display of the most effectively spaced antigen on the nanoparticle surface promotes B cell receptor (BCR) crosslinking, which leads to B cell activation. T cell activation is also increased after nanoparticle vaccine administration. A portion of activated CD4+ T cells differentiate into T follicular helper (TFH) cells and migrate to the B cell follicle. In this case, TFH cells drive sustained germinal center reactions, resulting in the filtering of B cell clones with high antigen affinity into persistent memory B cells and/or plasma cells that produce antibodies (Diaz-Arévalo and Zeng, 2020).

Nanoparticles for Targeted Vaccines Delivery

Using nanotechnology to transform vaccine development, the field of nanovaccinology has grown quickly in the last few years. Because of their special qualities and abilities, nanoparticles have become important players in boosting immune responses. The capacity of nanoparticle-based vaccines to function as adjuvants that is to both act as antigens and increase the antigenicity of conjugated or adsorbed antigens is a key benefit. This dual function strengthens both the innate and adaptive immune responses, resulting in longer-lasting and more powerful immunity (Vu et al., 2021). When compared to traditional vaccination delivery methods, nanoparticles have a number of advantages. They make it possible for antigens to be delivered locally and specifically; they enhance the presentation and processing of antigens; they sustain and raise antigen concentrations at mucosal surfaces; they improve bioavailability; and they can either stimulate or suppress the immune response (Fan and Moon, 2015). In addition, nanoparticles have the ability to effectively target immune cells, cross physiological barriers, and regulate the kinetics of antigens, which makes them excellent choices for boosting vaccine efficacy. Antigen size plays a crucial role in the uptake by antigen-presenting cells (APCsLarger antigens have a greater ability to interact with APCs because of their varied surface characteristics, including charge, hydrophobicity, and receptor interaction potential. Examples of these include nano- or microparticles and whole-pathogen vaccines. Small protein antigens, on the other hand, are less effectively absorbed and presented by APCs, underscoring the significance of antigen size in the stimulation of the immune response (Trabbic et al., 2021). The antigens are exposed to the stomach's acidic environment and are broken down by enzymes in the gastrointestinal tract when immunized orally. The mucosa of the upper airways, saliva, and nasal secretions all experience an increase in antibody responses as a result of nasal immunization.

Nanoparticles Encapsulated Vaccine Antigen

Nanoparticles can encapsulate antigenic material, protecting it from degradation and improving its stability during storage and transportation. This is particularly important for vaccines that require refrigeration, as nanoparticles can extend their shelf life and reduce the need for cold chain storage (Fan and Moon, 2015).

Nanoparticles can also improve antigen presentation to the immune system, leading to enhanced immune responses. This is achieved by protecting antigens from degradation, enabling prolonged release, and modulating immune responses by entering antigen-presenting cells through various pathways (Fan and Moon, 2015). Nanoparticles can also be designed to target specific cells or tissues, such as mucosal surfaces or lymph nodes, further enhancing their ability to stimulate an immune response.

Different types of nanoparticles have been explored as effective delivery systems for vaccine antigens, including virus-like particles, liposomes, ISCOMs, and polymeric nanoparticles. Virus-like particles, for example, are non-infectious particles that mimic the structure of viruses but lack the viral genome (Fan and Moon, 2015). They can be used to deliver antigens from various pathogens, such as H1N1 influenza virus, hepatitis B surface antigen, and HPV. Liposomes, on the other hand, are spherical vesicles made of lipid bilayers that can encapsulate hydrophilic antigens. They have been used to deliver antigens from various pathogens, such as Leishmania infantum, Streptococcus equi, and M. tuberculosis.

ISCOMs are cage-like structures made of saponins, cholesterol, and phospholipids that can encapsulate antigens and adjuvants. They have been used to deliver antigens from various pathogens, such as influenza, HIV, and HCV (Zhao et al., 2014). Polymeric nanoparticles, such as PLGA-encapsulated SIV vaccine, have also been explored for vaccine delivery. They can protect antigens from degradation, enable prolonged release, and shape the immune response.

Recent advancements in chemical and biological engineering have allowed precise regulation of nanoparticle characteristics, leading to enhanced antigen presentation and robust immune responses in nanovaccines (Zhang et al., 2023). Self-healing encapsulation technology, for example, has been used to improve the stability and release kinetics of nanoparticle-based vaccines. Polymeric nanoparticles have been used to deliver DNA vaccines, and nanoparticles have been used to co-deliver multiple antigens or adjuvanting molecules.

Regulatory Considerations for Nanoparticle Vaccines

Nanoparticle vaccination regulations require careful assessment at different phases of research and implementation. Comprehensive preclinical studies are used to examine safety, and they look into the possible toxic effects, immunity, and distribution of particle materials (Banoun, 2023). Before moving on to clinical trials, these investigations give regulatory body's vital information about the risk profile of vaccines made with nanoparticles. Nanoparticle vaccines undergo extensive efficacy assessments in clinical trials (Bezbaruah et al., 2022b). Research designs are carefully thought out in order to assess how well nanoparticle formulations defend against traditional vaccines and how well they elicit immunogenic responses. Trial protocols incorporate markers and surrogate endpoints to expedite vaccine development schedules and enable efficacy assessments (Knezevic et al., 2021; Ali et al., 2023; Lu et al., 2023).

A key factor in guaranteeing the reliability and Caliber of vaccines containing nanoparticles is the application of manufacturing standards. Strict regulations control production sites, tools, and procedures to reduce unpredictability and preserve product integrity (De Jong et al., 2022). To guarantee uniformity and stability from batch to batch, nanoparticle characterization—including dimensions, form, and surface characteristics—is crucial. For continuous evaluation of the overtime safety and efficacy of nanoparticle vaccinations in real-world environments, post-marketing surveillance is essential (Lung et al., 2020b). Utilizing surveillance systems makes it possible to promptly intervene and manage risks by identifying and assessing unfavorable occurrences that occur after vaccination. Regulatory bodies, medical professionals, and vaccine producers working together to guarantee ongoing surveillance and assessment of vaccination safety profiles as shown in Figure 2 (Liu et al., 2020; Lung et al., 2020b; Naik and Peden, 2020; Ali et al., 2023).

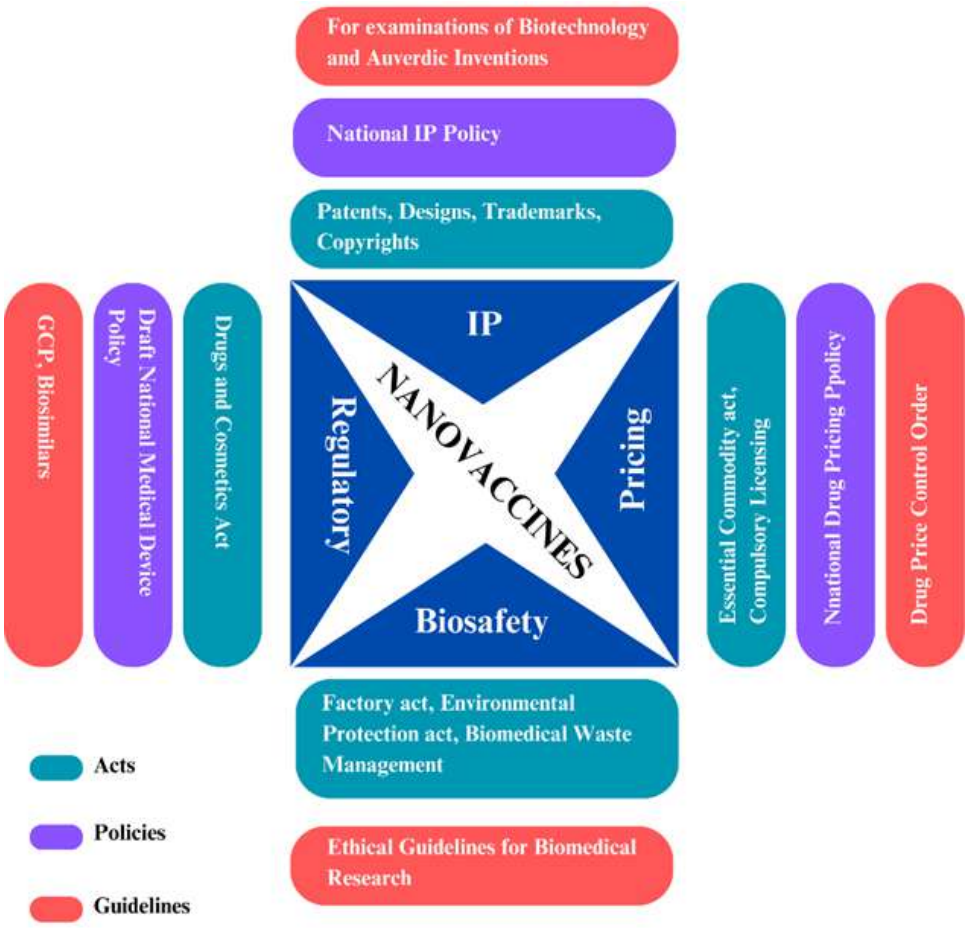


Fig. 2: Regulatory Considerations of Nano Vaccines.

Future Perspectives and Emerging Trends in Nanoparticle Vaccines

Nanoparticle vaccines have great potential in the field of vaccine development. Precision medicine techniques, which

allow vaccinations to be customized to a person's immunological profile and genetic composition, are being made possible by developments in vaccine design (Parupudi et al., 2022). Multivalent nanoparticle vaccines represent a significant advancement in the fight against complicated illnesses since they may target numerous pathogens or strains at once. With nanoparticles designed to target certain organs or tissues, tailored delivery systems are transforming the way vaccines are administered, increasing effectiveness while reducing adverse effects (Prasanna et al., 2021). Furthermore, obstacles are being removed by advances in intracellular delivery, which makes it easier for immune cells to absorb antigens and mount a strong defence. Stability is still a crucial component, and research is being done to create vaccines that can be stored at ambient temperature without the need for the laborious cold chain (D'Amico et al., 2021; Pippa et al., 2021).

Ethical and Societal Implications of Nanoparticle Vaccine Technology

A key component of moral behaviour in the field of nanoparticle vaccination research is informed permission. Because these technologies are complex, it is important to be extra careful to make sure clinical trial participants understand the advantages and disadvantages of new nanoparticle formulations (Chauhan et al., 2021). The need for fair access is even more urgent because vaccine nationalism is a major threat in today's world. Fairness and justice are major concerns that call for coordinated efforts to make sure that the benefits of scientific advancement are distributed fairly throughout communities and nations. With nanoparticle vaccinations, safety and risk evaluation present significant difficulties because of the possibility of unanticipated outcomes. The need to protect public health necessitates a close examination of the long-term impacts that nanomaterials have on people and ecosystems (Nath et al., 2021). Furthermore, the possibility of augmentation looms large, provoking moral discussions about the appropriate limits of scientific interference with human biology (Babatunde et al., 2019; Nath et al., 2021; Van de Voorde and Vlerick, 2021).

The adoption trajectory of nanoparticle vaccines is significantly influenced by public perception. It is critical to address issues with safety, effectiveness, and confidence in scientific institutions in order to promote broader use of these revolutionary technologies. Moreover, the incorporation of vaccines containing nanoparticles into healthcare systems requires a reevaluation of infrastructure and resource allocation in order to account for their distinct features (Van de Voorde and Vlerick, 2021). As policymakers grapple with issues of accessibility and affordability in the midst of rising healthcare expenditures, economic factors play a significant role. As vaccination technology utilizing nanoparticles advances, environmental sustainability becomes an increasingly important problem (Nath et al., 2021). The creation and elimination of nanomaterials give rise to complex inquiries about their environmental impact and enduring effects on the environment.

Future Directions in Nanoparticles Vaccine Research

Nanoparticle vaccines offer a game-changing approach to immunization, boasting enhanced efficacy and versatility. With their tiny structures, spanning lipid-based to viral-like particles, they hold immense promise in tackling a broad spectrum of pathogens (Tay et al., 2021).Efforts in nanoparticle vaccine research are particularly crucial in the face of emerging infectious diseases. By targeting specific pathogens, these vaccines can swiftly adapt to evolving threats, bolstering our defenses (Hu et al., 2023).Critical to their success is overcoming production and distribution challenges. Innovations in formulation and manufacturing are underway, aiming to ensure stability, scalability, and cost-effectiveness, essential for global deployment (Liu et al., 2019; Schuemann et al., 2020).

Personalized vaccines, a novel frontier, leverage nanoparticle technology to tailor immunization to individual immune profiles. This not only maximizes efficacy but also minimizes adverse reactions, offering a paradigm shift in vaccination strategies (Jain et al., 2021).Next-generation delivery systems, such as microneedle patches and inhalable nanoparticles, promise improved vaccine uptake and effectiveness, enhancing patient compliance. Nanoparticle-based adjuvants play a pivotal role in boosting vaccine efficacy by fine-tuning immune responses (Schuemann et al., 2020). Their targeted action ensures optimal vaccine outcomes. The fusion of nanotechnology and artificial intelligence accelerates vaccine development, streamlining processes from antigen prediction to immune response modelling (Liu et al., 2019).Yet, regulatory and ethical considerations must be carefully navigated. Establishing robust pathways and addressing ethical implications are vital for ensuring safety, efficacy, and public trust in nanoparticle vaccines. In conclusion, nanoparticle vaccines represent a transformative approach to global health challenges. Through innovation, collaboration, and ethical practice, they hold the potential to revolutionize immunization worldwide (Jain et al., 2021; Tay et al., 2021; Hu et al., 2023).

Conclusion

For a number of reasons, nanotechnology presents a huge possibility to enhance various diseases prevention and treatment. Firstly, complex antiviral and antibacterial designs can be realized by flexibly functionalizing nanomaterials with numerous compounds. Second, due to their diverse antiviral and antimicrobial properties, nanomaterials prevent infection in a number of ways. Third, because they share similar underlying processes, nanoparticles exhibit broad-spectrum effects. One effective measure to guard against microbial infection is vaccination. Compared to conventional vaccines, nano-based vaccines offer numerous clinical benefits, such as the capacity to deliver high antigen concentrations to B cells and elicit robust immune responses. The application of nanotechnology to vaccinations against bacteria and viruses, including

coronaviruses, HIV, and FMDV, is progressing, indicating that this method is promise for vaccine development, even though many nano-based vaccines are still in the pre-clinical phases. It is also necessary to conduct more research on the distribution, buildup, and removal of nanomaterials from the human body.

REFERENCES

Ali, F., Neha, K., Parveen, S. and Technology, (2023). Current regulatory landscape of nanomaterials and nanomedicines: *A Global Perspective*, *80*, 104118.

Babatunde, D. E., Denwigwe, I. H., Babatunde, O. M., Gbadamosi, S. L., Babalola, I. P., and Agboola, O. J. I. A. (2019). *Environmental and Societal Impact of Nanotechnology*, *8*, 4640-4667.

Banoun, H. (2023). mRNA: vaccine or gene therapy? The safety regulatory issues. *24*(13), 10514.

Bezbaruah, R., Chavda, V. P., Nongrang, L., Alom, S., Deka, K., Kalita, T., and Vora, L. (2022a). Nanoparticle-based delivery systems for vaccines. *Vaccines*, *10*(11), 1946.

Bezbaruah, R., Chavda, V. P., Nongrang, L., Alom, S., Deka, K., Kalita, T., an Vora, L. J. V. (2022b). Nanoparticle-based delivery systems for vaccines. *10*(11), 1946.

Bros, M., Nuhn, L., Simon, J., Moll, L., Mailänder, V., Landfester, K., and Grabbe, S. (2018). The protein corona as a confounding variable of nanoparticle-mediated targeted vaccine delivery. *Frontiers in Immunology*, *9*, 1760.

Castro, K. C. D., Costa, J. M., and Campos, M. G. N. (2022). Drug-loaded polymeric nanoparticles: a review. *International Journal of Polymeric Materials and Polymeric Biomaterials*, *71*(1), 1-13.

Chauhan, I., Verma, M., Yasir, M., and Safety, (2021). Nanoethics and Nanotechnology, 349-372.

D'Amico, C., Fontana, F., Cheng, R., Santos, H. A. J. D. D., and Research, T. (2021). Development of vaccine formulations: *Past, Present and Future*, *11*, 353-372.

De Jong, W. H., Geertsma, R. E., Borchard, G. J. D. D., and Research, T. (2022). Regulatory safety evaluation of nanomedical products: key issues to refine. *12*(9), 2042-2047.

Diaz-Arévalo, D., and Zeng, M. (2020). Nanoparticle-based vaccines: opportunities and limitations. In *Nanopharmaceuticals* (pp. 135-150). Elsevier.

Dondapati, S. K., Stech, M., Zemella, A., and Kubick, S. (2020). Cell-free protein synthesis: A promising option for future drug development. *BioDrugs*, *34*(3), 327-348.

Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., Sharma, P., and Vekariya, R. L. (2020). A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC Advances*, *10*(45), 26777-26791.

Fan, Y., Marioli, M., and Zhang, K. (2021). Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. *Journal of Pharmaceutical and Biomedical Analysis*, *192*, 113642.

Fan, Y., and Moon, J. J. (2015). Nanoparticle drug delivery systems designed to improve cancer vaccines and immunotherapy. *Vaccines*, *3*(3), 662-685.

Gagliardi, A., Giuliano, E., Venkateswararao, E., Fresta, M., Bulotta, S., Awasthi, V., and Cosco, D. (2021). Biodegradable polymeric nanoparticles for drug delivery to solid tumors. *Frontiers in Pharmacology*, *12*, 601626.

Garg, A., and Dewangan, H. K. (2020). Nanoparticles as adjuvants in vaccine delivery. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *37*(2).

Gause, K. T., Wheatley, A. K., Cui, J., Yan, Y., Kent, S. J., and Caruso, F. (2017). Immunological principles guiding the rational design of particles for vaccine delivery. *ACS Nano*, *11*(1), 54-68.

Glass, J. J., Yuen, D., Rae, J., Johnston, A. P., Parton, R. G., Kent, S. J., and De Rose, R. (2016). Human immune cell targeting of protein nanoparticles–caveospheres. *Nanoscale*, *8*(15), 8255-8265.

González-Domínguez, I., Puente-Massaguer, E., Cervera, L., and Gòdia, F. (2020). Quality assessment of virus-like particles at single particle level: a comparative study. *Viruses*, *12*(2), 223.

Has, C., and Sunthar, P. (2020). A comprehensive review on recent preparation techniques of liposomes. *Journal of Liposome Research*, *30*(4), 336-365.

Ho, W., Gao, M., Li, F., Li, Z., Zhang, X. Q., and Xu, X. (2021). Next-generation vaccines: nanoparticle-mediated DNA and mRNA delivery. *Advanced Healthcare Materials*, *10*(8), 2001812.

Hou, X., Zaks, T., Langer, R., and Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials*, *6*(12), 1078-1094.

Hu, L., Lao, G., Liu, R., Feng, J., Long, F., and Peng, T. J. A. R. (2023). The race toward a universal influenza vaccine: Front runners and the future directions. *210*, 105505.

Jain, S., Venkataraman, A., Wechsler, M. E., and Peppas, N. (2021). Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. *179*, 114000.

Kapczynski, D. R., Tumpey, T. M., Hidajat, R., Zsak, A., Chrzastek, K., Tretyakova, I., and Pushko, P. (2016). Vaccination with virus-like particles containing H5 antigens from three H5N1 clades protects chickens from H5N1 and H5N8 influenza viruses. *Vaccine*, *34*(13), 1575-1581. https://doi.org/https://doi.org/10.1016/j.vaccine.2016.02.011

Khairnar, S. V., Pagare, P., Thakre, A., Nambiar, A. R., Junnuthula, V., Abraham, M. C., and Dyawanapelly, S. (2022). Review on the scale-up methods for the preparation of solid lipid nanoparticles. *Pharmaceutics*, *14*(9), 1886.

Kheirollahpour, M., Mehrabi, M., Dounighi, N. M., Mohammadi, M., and Masoudi, A. (2020). Nanoparticles and vaccine development. *Pharmaceutical Nanotechnology*, *8*(1), 6-21.

Knezevic, I., Liu, M. A., Peden, K., Zhou, T., and Kang, H.-N. J. V. (2021). Development of mRNA vaccines: scientific and regulatory issues. *9*(2), 81.

Liu, J., Miao, L., Sui, J., Hao, Y., and Huang, G. (2020). Nanoparticle cancer vaccines: Design considerations and recent advances. *15*(5), 576-590.

Liu, J., Zhang, R., and Xu, Z. P. J. S. (2019). Nanoparticle-based nanomedicines to promote cancer immunotherapy: recent advances and future directions. *15*(32), 1900262.

Lu, J., Wei, W., and He, W. J. B. (2023). Regulatory perspective for quality evaluation of lipid nanoparticle-based mRNA vaccines in China. *84*, 101700.

Lung, P., Yang, J., and Li, Q. (2020a). Nanoparticle formulated vaccines: opportunities and challenges. *Nanoscale*, *12*(10), 5746-5763.

Lung, P., Yang, J., and Li, Q. J. N. (2020b). Nanoparticle formulated vaccines: opportunities and challenges. *12*(10), 5746-5763.

Mao, L., Chen, Z., Wang, Y., and Chen, C. (2021). Design and application of nanoparticles as vaccine adjuvants against human corona virus infection. *Journal of Inorganic Biochemistry*, *219*, 111454.

Miere, F., Fritea, L., Cavalu, S., and Vicaș, S. I. (2020). Formulation, Characterization, and Advantages of Using Liposomes in Multiple Therapies. *Pharmacophore*, *11*(3-2020), 1-12.

Moni, S. S., Abdelwahab, S. I., Jabeen, A., Elmobark, M. E., Aqaili, D., Ghoal, G., and Alnajai, M. M. A. (2023). Advancements in Vaccine Adjuvants: The Journey from Alum to Nano Formulations. *Vaccines*, *11*(11), 1704.

Naik, R., and Peden, K. (2020). Regulatory considerations on the development of mRNA vaccines. In *mRNA Vaccines* (pp. 187-205). Springer.

Nath, H., Subhranshu, S., and Manohara, S. (2021). Current guidelines and regulatory challenges, insight into the legal, societal, and ethical issues of nanomaterials. In *Nanotoxicology* (pp. 445-463). CRC Press.

Nsairat, H., Khater, D., Sayed, U., Odeh, F., Al Bawab, A., and Alshaer, W. (2022). Liposomes: Structure, composition, types, and clinical applications. *Heliyon*, *8*(5).

Paliwal, R., Paliwal, S. R., Kenwat, R., Kurmi, B. D., and Sahu, M. K. (2020). Solid lipid nanoparticles: A review on recent perspectives and patents. *Expert Opinion on Therapeutic Patents*, *30*(3), 179-194.

Parupudi, A., Mulagapati, S. H. R., and Subramony, J. (2022). Nanoparticle technologies: Recent state of the art and emerging opportunities. 3-46.

Pippa, N., Gazouli, M., and Pispas, S. J. V. (2021). Recent advances and future perspectives in polymer-based nanovaccines. *9*(6), 558.

Prasanna, P., Kumar, P., Kumar, S., Rajana, V. K., Kant, V., Prasad, S. R., and Pharmacotherapy. (2021). Current status of nanoscale drug delivery and the future of nano-vaccine development for leishmaniasis–a review. *141*, 111920.

Qian, C., Liu, X., Xu, Q., Wang, Z., Chen, J., Li, T., and Li, S. (2020). Recent progress on the versatility of virus-like particles. *Vaccines*, *8*(1), 139.

Sakhi, M., Khan, A., Iqbal, Z., Khan, I., Raza, A., Ullah, A., and Khan, S. A. (2022). Design and characterization of paclitaxel-loaded polymeric nanoparticles decorated with trastuzumab for the effective treatment of breast cancer. *Frontiers in Pharmacology*, *13*, 855294.

Schuemann, J., Bagley, A. F., Berbeco, R., Bromma, K., Butterworth, K. T., Byrne, H. L., and Biology, (2020). Roadmap for metal nanoparticles in radiation therapy: Current status, translational challenges, and future directions. *65*(21), 21RM02.

Srivastava, V., Nand, K. N., Ahmad, A., and Kumar, R. (2023). Yeast-based virus-like particles as an emerging platform for vaccine development and delivery. *Vaccines*, *11*(2), 479.

Tay, B. Q., Wright, Q., Ladwa, R., Perry, C., Leggatt, G., Simpson, F., and Cruz, J. L. J. V. (2021). Evolution of cancer vaccines—Challenges, achievements, and future directions. *9*(5), 535.

Trabbic, K. R., Kleski, K. A., and Barchi Jr, J. J. (2021). Stable gold-nanoparticle-based vaccine for the targeted delivery of tumor-associated glycopeptide antigens. *ACS Biology and Medicine Chemistry Au*, *1*(1), 31-43.

Tursi, N. J., Xu, Z., Kulp, D. W., and Weiner, D. B. (2023). Gene-encoded nanoparticle vaccine platforms for in vivo assembly of multimeric antigen to promote adaptive immunity. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *15*(4), e1880.

Van de Voorde, M., and Vlerick, M. (2021). 3 Nanotechnology: Societal impact and ethical considerations. 43.

Vasudevan, S. S., Kandrikar, T. Y., Sayyed, A. A., Sarker, P., Nasir, N. S., Venugopalan, S., and Gondaliya, P. (2024). Nanoparticle-based vaccines and future vaccine technologies. In *Advanced Vaccination Technologies for Infectious and Chronic Diseases* (pp. 477-495). Elsevier.

Vu, M. N., Kelly, H. G., Kent, S. J., and Wheatley, A. K. (2021). Current and future nanoparticle vaccines for COVID-19. *EBioMedicine*, *74*.

Walunj, M., Doppalapudi, S., Bulbake, U., and Khan, W. (2020). Preparation, characterization, and in vivo evaluation of cyclosporine cationic liposomes for the treatment of psoriasis. *Journal of Liposome Research*, *30*(1), 68-79.

Wilson, K., Xiang, S., and Plebanski, M. (2017). Inflammatory/noninflammatory adjuvants and nanotechnology—The secret to vaccine design. In *Micro and nanotechnology in vaccine development* (pp. 99-125). Elsevier.

Zhang, J., Shang, J., Tang, X., and Xu, X. (2023). TfR Aptamer-Functionalized MSNs for Enhancing Targeted Cellular Uptake and Therapy of Cancer Cells. *ACS Omega*, *8*(51), 48975-48983.

Zhang, X., Zhang, Z., Xia, N., and Zhao, Q. (2021). Carbohydrate-containing nanoparticles as vaccine adjuvants. *Expert Review of Vaccines*, *20*(7), 797-810.

Zhao, L., Seth, A., Wibowo, N., Zhao, C.-X., Mitter, N., Yu, C., and Middelberg, A. P. (2014). Nanoparticle vaccines. *Vaccine*, *32*(3), 327-337. https://doi.org/10.1016/j.vaccine.2013.11.069

Zhao, T., Cai, Y., Jiang, Y., He, X., Wei, Y., Yu, Y., and Tian, X. (2023). Vaccine adjuvants: Mechanisms and platforms. *Signal Transduction and Targeted Therapy*, *8*(1), 283.

Zhao, Z., Harris, B., Hu, Y., Harmon, T., Pentel, P. R., Ehrich, M., and Zhang, C. (2018). Rational incorporation of molecular adjuvants into a hybrid nanoparticle-based nicotine vaccine for immunotherapy against nicotine addiction. *Biomaterials*, *155*, 165-175.

Zielińska, A., Carreiró, F., Oliveira, A. M., Neves, A., Pires, B., Venkatesh, D. N., and Silva, A. M. (2020). Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology. *Molecules*, *25*(16), 3731.

Chapter 02

Nanoparticle Formulation in Nasal Drug Delivery

Javeria Arshad[1]*, Ijaz Ali[2], Javeria Javed[3], Muhammad Najeeb Ullah[2], Hammad Afzal[3], Muhammad Ahsan Samran[3] and Muhammad Talha[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
[2]Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad-38000, Punjab, Pakistan
[3]Department of Pharmacy, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Punjab, Pakistan
*Corresponding author: Pharmacistj.arshad@yahoo.com

ABSTRACT

Nasal drug delivery has emerged as an effective strategy for administering therapeutic drugs, with various benefits over traditional oral and parenteral methods. This chapter gives a detailed overview of nanoparticle formulation options for nasal drug delivery systems, with an emphasis on improving delivery and therapeutic effectiveness. The chapter provides a comprehensive discussion of nasal architecture and the physiological factors that influence nasal medication absorption, such as paracellular and transcellular transport. It then delves into nanoparticle selection and manufacturing techniques, focusing on polymer media, affinity chromatography, and sustainability metrics for particle selection, as well as nanoimprint lithography, milling, homogenization, and membrane contactor techniques for nanoparticle production. The chapter also looks at new developments in nanoparticle research, such as nose-to-brain medication administration, individualized dosage techniques, and the creation of novel delivery systems. Furthermore, the chapter discusses prospective developments in nasal drug administration, including liquid and powder formulations, emergency medicine delivery, and customized patient-specific formulations. Overall, this chapter provides a complete and current review of nanoparticle composition in nasal drug delivery systems, making it a useful resource for researchers, pharmaceutical scientists, and healthcare professionals wanting to harness this potential delivery method.

KEYWORDS
Nanoparticles, Drug delivery, Nasal administration, Therapeutics, Nano-formulation, Drug development

Received: 07-May-2024
Revised: 09-Jul-2024
Accepted: 04-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Arshad J, Ali I, Javed J, Ullah MN, Afzal H, Samran MA and Talha M, 2024. Nanoparticle formulation in nasal drug delivery. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 10-18. https://doi.org/10.47278/book.CAM/2024.217

INTRODUCTION

Nasal administration, commonly referred to as snorting, is a method of administering medications that involves inhaling them through the nose. It can be either topical or systemic administration, since the medications administered locally might have solely local or systemic effects, such as ibuprofen or Tylenol for headaches and severe toothaches. Systemically active pharmaceuticals accessible as nasal sprays include migraine meds, overdose and seizure rescue medications, nicotine replacement, and hormone therapy.

Nasal mucosa may be a more effective route for medication absorption than the gastrointestinal system due to its greater permeability and neutral pH. Nasal mucus causes less dilution than stomach contents. Nasal therapy, commonly known as "NASAYA KARMA," is a recognized treatment in Ayurvedic Indian medicine (Chien and Chang, 1987; Jadhav et al., 2007; Krishnamoorthy and Mitra, 1998).

Nasal delivery is a promising technique for the following reasons: it allows for lower doses, quicker attainment of therapeutic blood levels, quicker onset of pharmacological activity, and drug delivery directly to the brain via the olfactory nerve. The nose's large surface area for drug absorption is due to the numerous microvilli covering its epithelial surface. The subepithelial layer is highly vascularized. However, the nose's major function is olfaction, which warms and humidifies inspired air while filtering airborne particulates.

Drugs absorbed from the nasal cavity must pass through the mucus layer, which is the initial stage of absorption. Small, uncharged medications can easily flow through this barrier, but larger, charged substances are more difficult to cross. Mucin, the main protein in mucus, binds to solutes and inhibits their diffusion. Environmental factors such as pH and temperature can cause structural changes in the mucus layer (Illum, 1987). Several absorption processes have been developed, however, only two are widely employed, including:

First Mechanism

The process includes slow and passive aquatic transfer, often known as the paracellular pathway. Intranasal absorption exhibits an inverse log association with the molecular weight of water-soluble molecules. Drugs with a molecular weight of above 1000 Daltons have low bioavailability (Aurora, 2002).

Second Mechanism

This method of transfer, also known as the transcellular process, uses a lipoidal pathway. It transports lipophilic medicines at varying rates according on their properties. Drugs can permeate cell membranes via carrier-mediated transport or tight junction opening (Aurora, 2002).

The nasal cavity is lined by a thin mucosa that is highly vascularized (Proctor and Andersen, 1982). As a result, a medication molecule can be swiftly transported across a single epithelial cell layer and into the systemic bloodstream without first passing via the liver and the intestine. For smaller pharmacological molecules, the effect is usually achieved in 5 minutes or less (Ghori et al., 2015). If a rapid effect is required or if the medication is significantly destroyed in the intestines or liver (Fransén, 2008) medicines that are poorly absorbed orally can also be administered this way.

Large-molecule drugs can also be delivered directly to the brain via the intranasal route, which follows the olfactory and trigeminal nerves, allowing for widespread central distribution throughout the central nervous system with minimal exposure to blood (Jansson, 2004; Thorne et al., 2004; Thorne et al., 1995). This form of brain delivery was functionally shown in humans in 2006, employing insulin, a big peptide hormone that works as a nerve growth factor in the brain (Reger et al., 2006).

Olfactory Transfer

The adult human nasal cavity has around 20 mL capacity (Baig and Khan, 2014). The olfactory epithelium is located in the upper posterior region and spans roughly 10 cm2 of the human nasal cavity. The olfactory epithelium's nerve cells extend into the brain's olfactory bulb, establishing a direct connection between the brain and the outside world.

However, if drugs can pass through the olfactory nerve cells, they may bypass the BBB and reach the brain directly (Costantino et al., 2007). Drugs are believed to enter the brain through olfactory nerve cells or the cerebrospinal fluid, either slowly or quickly (Illum, 2004; Mathison et al., 1998). Olfactory transfer might theoretically be utilized to administer medications with a central nervous system impact, such as those used to treat Parkinson's or Alzheimer's disease.

Nanoparticles in Drug Delivery

According to the National Nanotechnology Initiative (Kromhout et al.), nanoparticles are tiny structures, usually between 1 and 100 nanometers in size.

These super small particles, called nanocarriers (liposomes, dendrimers), have special properties that make it easier for cells to take them in. That's why they're used as delivery tools for bioactive compounds (Wilczewska et al., 2012).

The purpose of nanoparticle encapsulating drugs is to enhance their targeted delivery to specific cells, minimize toxicity to non-target organs, and ultimately elevate the therapeutic index. This involves developing nanoparticles that are persistent and specific to their intended targets, thus optimizing the effectiveness of drug treatment while minimizing adverse effects on other organ systems (De Jong and Borm, 2008).

Characteristics of Nanoparticles

Nanoparticles have two major types characteristics

- Physical characteristics
- Chemical characteristics

Physical Characteristics

Nanoparticles have various physical characteristics like, optical, mechanical and electrical characteristics (Singh et al., 2020).

Additionally, properties like hydrophilicity, hydrophobicity, suspension and settling contribute to their application in everyday items (Khan and Hossain, 2022).

Optical Characteristics

The optical characteristics of nanoparticles are quite fascinating. These include properties like hue, light infiltration, reflection and UV sorption. These properties are size-dependent that are exclusive to nanoparticles not observed in bulk materials. Nanoparticles have a intense UV-visible extinction peak, which adds to their unique optical characteristics (Peng et al., 2016).

Mechanical Characteristics

The mechanical characteristics of nanoparticles are as these encompass characteristics like elasticity, tensile strength, hardness, and flexibility (Guo et al., 2013).

Magnetic and Electrical Characteristics

The magnetic and electrical characteristics of nanoparticles are characterized by their conductivity, semi-conductivity, and resistivity (Nongjai et al., 2012).

Chemical Characteristics

The chemical attributes of nanoparticles are crucial in deciding their applications. Nanoparticles are characterized by a pronounced UV-visible extinction band, which enhances their special optical features. The unique properties of nanoparticles, including antibacterial, disinfectant, and toxic characteristics enable their use in various biological and environmental applications (Khan et al., 2019).

The chemical characteristics of nanomaterials are affected by their size, and these characteristics change as the size varies. Smaller nanomaterials have a higher number of atoms on their surface than those in bulk materials, which leads to increased reactivity. Here are a few key points about these chemical characteristics:

- The abundance of surface atoms in nanomaterials significantly impacts their behavior. With up to half of the atoms located on the surface, nanomaterials exhibit enhanced properties like electrical transport compared to bulk materials.
- The large number of surface atoms also results in higher average energy in nanomaterials. This leads to increased catalytic activity, making nanomaterials more chemically active per exposed surface atom. In contrast, in bulk materials there is decrease in catalytic activity.
- Nanomaterial surfaces can attract impurities, and the collisions across nanoparticles and these impurities based on the nanomaterial's structure and the type of chemical bonding involved (Fubini et al., 2010).

Advantages of Nanoparticles

The advantages of nanoparticles over other drug delivery systems are:

- One of the benefits of utilizing nanoparticles as a drug delivery system is the capability to control and sustain the release of the drug during transportation and at the targeted site. This controlled release helps to alter the distribution of the drug within the body organs and subsequently enhances the clearance of the drug (Singh et al., 2011).
- Nanoparticles allow for the incorporation of the drug into the system without undergoing any chemical reactions (Lata et al., 2017).
- The characteristics of controlled release and drug degradation can be easily adjusted and modified to meet specific requirement (Saad et al., 2012).
- Efficient drug utilization is ensured, leading to an enhanced bioavailability of the drug at targeted sites (Brewer et al., 2011).
- Patient convenience and compliance are enhanced while simultaneously improving the therapeutic efficacy of the drug compared to conventional systems (Brewer et al., 2011).
- Nano particles can be easily prepared (Shinde et al., 2012).
- Chances of toxicity are less (Goldberg et al., 2011).
- Doses of drug are smaller (Zhao et al., 2010).
- Nanoparticles exhibit remarkable reactivity, characterized by distinctive physicochemical attributes, including a compact and manageable size, coupled with a substantial surface-to-mass ratio (Singh et al., 2011).
- They are also recognized as suitable options for transporting vaccines, contraceptives, and specific antibiotics to targeted areas (De Oliveira et al., 2014).

Nasal Drug Delivery Challenges

Mucociliary Clearance

The mucus layer covering the nasal epithelium is moved towards the nasopharynx by means of ciliary beating, which is how the nasal mucociliary clearing system works. Its main goal is to protect the respiratory system from potential injury from chemicals breathed. Through the coordinated activity of ciliated cells, the mucociliary clearance system of the nasal cavity effectively captures and transfers inhaled particles. These cells have many cilia, which are motile projections that are around 0.3 μm wide and 5 μm long. The mucus layer is propelled by the cilia, which beat at a frequency of around 1000 beats per minute, or 12–15 Hz. The cilia are divided into three layers: an upper gel layer, a more watery periciliary liquid layer, and a surfactant layer positioned in between. Effective clearance of trapped particles is ensured by the structural contact between the cilia and nasal mucus, which transports particles to the throat at a pace of 8–10 mm/h (Marttin et al., 1998). The physical properties of mucus and the healthy operation of cilia are prerequisites for effective mucociliary clearance. These factors can be impacted by drugs that alter ciliary beat frequency (CBF). Thus, using a photoelectronic approach, researchers examined the effect of preservatives on ciliary beat frequency (Gizurarson, 2015). Many approaches have been developed to overcome the challenges posed by mucociliary clearance in nasal medication administration. These include the creation of mucoadhesive drug delivery systems with the goal of prolonging the duration of medication residence in the nasal cavity. Additionally, the use of liposomes or nanoparticles protects medications against mucociliary clearance. Moreover, permeation enhancer integration improves medication absorption via the nasal epithelium. Furthermore, advancements in the design and administration of nasal medication delivery devices strive to enhance drug deposition and dispersion within the nasal cavity, hence maximizing therapeutic results (Batts et al., 1990). Researchers

have developed a number of techniques to get around the problems caused by mucociliary clearance in nasal medication administration. Developing mucoadhesive medication delivery devices that stick to the nasal mucosa is one useful strategy. These formulations stay on the nasal epithelium longer, increasing the amount of time medications stay in the nasal cavity and improving drug absorption (Illum, 2012). Apart from mucoadhesive systems, the use of liposomes or nanoparticles is another effective tactic. These nanocarriers have the ability to encapsulate medications, protecting them from the mucociliary system's quick clearance. Nanoparticles and liposomes increase medication stability and bioavailability and prevent drug breakdown and clearance, which increases therapeutic efficacy (Illum, 2012). Additionally, it has demonstrated a great deal of promise to overcome mucosal barriers in nasal medication formulations by including permeation enhancers. medicines are better transported into the systemic circulation when permeability enhancers help absorb medicines via the nasal epithelium. This strategy has been very successful in increasing the bioavailability of poorly soluble medications, resulting in improved therapeutic effects (Vllasaliu et al., 2014). The development of nasal medication delivery devices and their administration methods has also made a substantial contribution to the resolution of mucociliary clearance issues. For example, nasal sprays and nasal inserts have been created to maximize medication dispersion and deposition inside the nasal cavity. By guaranteeing accurate dosage and boosting patient compliance, these cutting-edge delivery methods seek to increase the efficacy of medication delivery (Merkus et al., 2006).

Nasal Permeability

The ability of a medication to pass through the nasal mucosa and into the bloodstream is known as nasal permeability. The nasal mucosa is a complex barrier that regulates molecular transport. It is made up of mucus layers, tight junctions, and epithelial cells. Numerous variables, including the integrity of the nasal epithelium, the presence of efflux transporters, and the physicochemical properties of medicines (such as molecular weight and lipophilicity), affect nasal permeability. All of these variables work together to determine how well drugs are absorbed through the nasal route (Merkus et al., 2006). The ability of a medication to pass through the nasal mucosa and into the bloodstream is known as nasal permeability. The nasal mucosa is a complex barrier that regulates molecular transport. It is made up of mucus layers, tight junctions, and epithelial cells. Numerous variables, including the integrity of the nasal epithelium, the presence of efflux transporters, and the physicochemical properties of medicines (such as molecular weight and lipophilicity), affect nasal permeability. All of these variables work together to determine how well drugs are absorbed through the nasal route (Illum, 2012). The limitations imposed by restricted nasal permeability provide challenges for nasal medication administration, necessitating creative approaches to enhance drug absorption. Surfactants and cyclodextrins are two examples of permeability enhancers that have become effective treatments because they temporarily damage the nasal epithelium, allowing medications to pass through more easily (Costantino et al., 2007). Prodrug techniques include chemically modifying medications to increase their lipophilicity or to target specific transport systems, which improves nasal permeability (Dhuria et al., 2010). Various approaches have been developed to tackle the challenges associated with limited nasal permeability. One such these is the use of permeation enhancers, which allow drugs to be absorbed more easily by momentarily disrupting the nasal epithelium's integrity. Surfactants, bile salts, and cyclodextrins are a few examples of these enhancers that have been investigated for their effectiveness in nasal medication delivery (Lee et al., 2000). Another strategy is to use prodrug strategies, in which the initial medication is chemically altered to increase its lipophilicity or to target specific transport systems in the nasal mucosa. Prodrugs can increase a drug's permeability and avoid efflux transporters, which improves the absorption of the medication (Illum, 2012). Furthermore, the development of innovative medication delivery technologies, such as liposomes, micelles, and nanoparticles, offers a possible remedy for increasing nasal permeability. These cutting-edge delivery methods have the power to increase a drug's stability and solubility, which will increase its absorption. Moreover, they facilitate the prolonged release of medications, lengthening the duration of their retention in the nasal cavity (Salamat-Miller et al., 2005).

Nanoparticle Formulation

Selection of Nanoparticle Materials

The selection of nanoparticles according to their properties is crucial for creating accurate and complex nanodevices that can be used for quantum sensing, photon generation, and quantum information processing. Nanoparticles are selected based on their quantum mechanical properties, by polymer media, affinity chromatography, and sustainability matrices (Fujiwara et al., 2021)

Polymer Method

By utilizing polymers as a medium, researchers can manipulate nanoparticles' shape, size, and surface characteristics, enabling customized designs for particular applications. When nanoparticles are soluble in the polymer medium their size becomes critical if the nanoparticles are sufficiently small, they disperse freely within the polymer brush film. If nanoparticles are large these nanoparticles disperse to the bottom which varies inversely to their volume. For instance, if nanoparticles are insoluble in the polymer, a different behavior emerges. The brush stabilizes the dispersion of the nonwetting particle at the surface of the film. The brush then selects the final morphology of the nanoparticle aggregates (Kim and O'Shaughnessy, 2002).

Affinity Chromatography

The solution lies in affinity chromatography. The nanoparticle sample is applied to a column containing a complementary binding substance. Under conditions favoring specific binding, the target nanoparticles attach to the ligand (binding substance). Unbound material is washed out of the column. Finally, the bound target nanoparticles are recovered by changing conditions to favor elution. One of the main challenges associated with this technology is forming a wide range of binding sites with varying affinities (Guerreiro et al., 2009).

Quantum Mechanical Properties

Nanoparticles like nanocrystals, nanoparticles of carbon and metals have great importance because of their quantum mechanical properties semiconductor quantum dots and diamond nanoparticles have distinct optoelectronic properties because of the quantum confinement and quantum resonances they exhibit. These properties affect the optical forces that act on the nanoparticles, including the gradient force, dissipative scattering force, and quantum resonant absorption force (Fujiwara et al., 2021).

By Sustainability Metrics

Metrics of unattainability play a crucial role in assessing various aspects such as the utilization of resources, consumption of energy, production of waste, and the possible impacts on health and the ecosystem (Naidu et al., 2008).

Manufacturing Techniques

A two-step process is followed by many methods for manufacturing nanoparticles. The first step involves the preparation of an emulsifying system and the second step is accomplished by the formation of the nanoparticles. In the second step, nanoparticles are formed by the polymerization of monomers or gelation/precipitation of the polymers. It's during this second step that the nanoparticles take shape (Vauthier and Bouchemal, 2009). Nanofabrication is the technique to manufacture nanoparticles. The nanoimprint lithography (NIL) is the well-developed of the alternative nanofabrication techniques. NIL is a cool fabrication technique that's malleable, low-cost, and compatible. It has some superiority over traditional nanofabrication methods, and there are different variations of NIL. One of these differences is called step and flash imprinting lithography (SFIL), where instead of applying pressure, a process is used called UV polymer curing process (Baron et al., 2007). The other methods for nanoparticle manufacturing are milling and homogenization. Wet milling is a important technique for producing nanoparticles in which the concentrated drug is dispersed along with the milling balls in an aqueous or non-aqueous medium. This process, also known as media milling, is more effective than dry milling. The procedure of wet milling method is shown in Fig. 1.

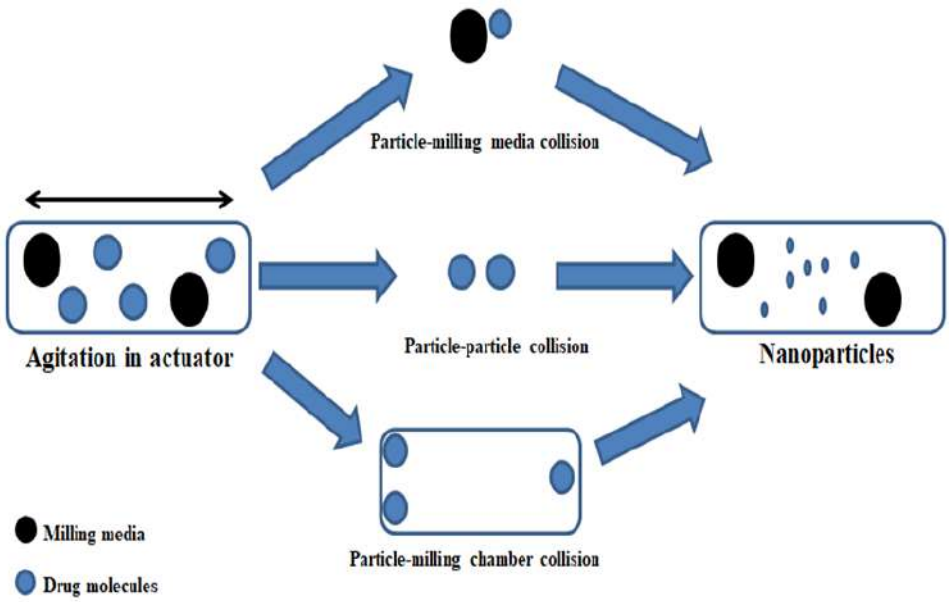


Fig. 1: Wet milling method.

The method for creating nanoparticles High-pressure homogenization. It includes subjecting the material to high pressure, which leads to reduction of particle size. This technique is particularly beneficial for achieving uniform particle sizes and enhancing bioavailability. Ultrasonic homogenization breaks down larger particles into smaller ones by ultrasonic waves. It's effective for creating stable nanoparticle suspensions (Table 1). The ultrasonic energy disorder agglomerates and promotes uniform dispersion (LLER et al., 2006). Another technique is the membrane contactor technique. In this method, a polymer solution is spread onto a stretched membrane, and as the solvent evaporates, the polymer forms a thin

film on the membrane. The film then undergoes contraction, directing towards the formation of nanoparticles (Vauthier and Bouchemal, 2009).

Table 1: Formulation used for nanoparticle preparations by the membrane contactor technique (Vauthier and Bouchemal, 2009)

Methods	Organic phase	Aqueous phase	Type of nanoparticles
Nanoprecipitation	Acetone (0.6 L) PCL (15 g)	Water (1.2 L) Tween® 20 (2.04 g)	Nanospheres
	Acetone (0.6 L) PCL (2.4-3 g) Labrafac® hydro (9.6-12 mL)	Water (1.2 L) Tween® 80 (2.8-4.8 g)	Nano capsules
	Water pH>5.2 Eudragit® L100	Water pH<2 PVA	Nanospheres
	Water pH<5.2 Eudragit® E100	Water pH>11 PVA	Nanospheres
Interfacial polycondensation combined with spontaneous emulsification	Acetone (0.6 L) Span® 80 (1.2 g) Oil: hexyl laurate (6 g) Lipophilic monomer (3.3 g)	Water (1.2 L) Tween® 20 (2.04 g) Hydrophilic monomer (19.65 g)	Nano capsules

Modification of Surface for Enhanced Delivery

Modification of the nanoparticles' surface is a critical strategy to enhance their performance in drug delivery systems. The physicochemical characteristics like surface composition and superficial charge of nanoparticles significantly affect their uptake efficiency and biocompatibility. By modifying the NP surface, we can improve their biocompatibility and cellular uptake. The polymer coating enhances the stability and reduces toxicity. The coating with polyethylene glycol (Stuen et al.) increases circulation time and reduces immune response (Natarajan and Selvaraj, 2014). Surface modification is a basic process for improving the transportation of nanoparticles and effectively inhibiting imprecise interactions with biological molecules, thus preventing early clearance. An example of this idea is using compatible-with-life materials to enclose tiny particles, creating a shield against the body's defense system. By changing the surface, nanoparticles can be accurately guided to specific cells or tissues by attaching ligands like antibodies or peptides to their surface. These ligands can bind to receptors on the target cells, thereby enhancing the efficiency of drug delivery while reducing adverse effects associated with systemic administration. This targeted approach aims to maximize efficacy and minimize unwanted impacts (Abdelkawi et al., 2023).

Future Perspectives

Emerging Trends in Nanoparticle Research

The next years will see a range of new products in the market. An underexplored research topic is the administering medication via the nasal passage allows for direct delivery to the central nervous system by way of the olfactory or trigeminal nerves located in the nasal cavity, circumventing the blood-brain barrier. The number of drugs that reach the CNS via the nasal route is usually very low, with less than 1% of the dose applied in the nasal cavity. The primary obstacle in administering treatments from the nose to the brain is effectively reaching the olfactory area within the nasal passages, which is difficult to access, and improving the movement of peptides and proteins through the olfactory membrane. There is a need for a nasal apparatus that can precisely target the olfactory area and a delivery mechanism that includes both a nasal absorption enhancer and a bio-adhesive substance to boost the transport of drugs into the central nervous system. Recently, some studies have reported new methods to enhance the brain 'bioavailability' of drugs by using innovative delivery approaches and absorption enhancers (Illum, 2012). Intranasal drug delivery is a rapidly growing research area that can be combined with therapeutic drugs to treat different diseases of the respiratory system, nasal cavity, and brain. Literature research in this field preceded patent applications, which started around 1974. Nasal devices and mechanisms were important patent clusters. The active ingredient analysis revealed that the FDA approved more nasal drugs after 1982, mainly small-molecule drugs. However, there are still many challenges in basic research that need further attention. One major problem is the changeability in drug absorption among individuals due to the compounded and variable nasal cavity (Lalan et al., 2019). Further investigation is essential to understand the processes of absorption and clearance included in nasal medication delivery to the brain, especially for pharmaceuticals that follow the intranasal route to the brain. Another challenge is the limited drug-loading volume of nasal DDS due to the small surface area of the nasal cavity for absorption. Ingenious delivery methods, including nanoparticles, liposomes, and micro-emulsions, are presently in development to improve the solubility and permeability of drugs. Safety and bearability of nasal DDS are important considerations, given the sensitivity of the nasal cavity. Some materials related to DDS may interact with normal clearance or result in unwanted immunogenicity that requires careful evaluation for long-duration safety. The development of safe and well-accepted nasal DDS is important for clinical application. In clinical practice, it is important to address the problems associated with enhancing the production of drug delivery systems (DDS) while maintaining uniform standards.

Ultimately, the progress of intranasal devices that are both easy to use and dependable is important for the effective administration of drug delivery systems (DDS) and to ensure high levels of patient compliance (Xu et al., 2024). Nanomedicine will benefit from the future development and enhancement of functionalized polymeric nanoparticles, which can help cure serious diseases like cancer with fewer adverse effects. Ongoing research on functionalized nanoparticles will increase the methods of disease diagnosis, treatment, and prevention. Research should objective to devise a simple, efficient, and direct production and scaling-up technique for nanoparticles. Regulatory guidelines should be established to ensure the safety of nanoparticles for humans and the environment (Sur et al., 2019). Nanoparticles hold significant potential for advancing various biomedical fields, notably in diagnosing diseases, enabling early detection, and imaging at the cellular and deep tissue levels, facilitating drug delivery, and serving as versatile therapeutic agents. Molecular medicine is currently focused on creating new and innovative tools for early-stage disease diagnosis and point-of-care diagnostics. The goal is to develop advanced techniques that can detect diseases at an early stage and provide faster and more convenient diagnostic options. Personalized medicine is achieving a lot of attention, and the integration of nanotechnology has the potential to bring about some amazing outcomes. In the coming years, multifunctional nanoparticles are expected to play a vital role in biomedical applications, such as disease diagnosis and drug delivery. This could even lead to changes in the traditional business model of pharmaceutical industries (Vallabani and Singh, 2018).

Potential Innovations in Nasal Drug Delivery

Nasal delivery is an area for innovation and advancement. Advancements in nanotechnology are unfolding within an environment characterized by swift technological advancements. For small and medium-sized enterprises , which are often the birthplace of early-stage innovations, it is challenging to stay abreast of the relentless stream of research and information that is pertinent to their process of innovation (Kraegeloh et al., 2018). Researchers are actively developing innovative liquid and powder nasal drug delivery systems. Formulations need to address drug solubility, permeation, stability, and mucoadhesive properties. Advancements in characterization methods are essential for nasal formulation development. Researchers explore techniques to assess drug behavior in vitro, ex vivo, and in vivo. Nasal drug delivery offers a direct route to the brain. Researchers investigate strategies for delivering therapeutics to treat neurological disorders (Garcia-Reyero et al., 2014). Nasal vaccines can stimulate mucosal immunity. Innovations aim to enhance vaccine effectiveness and patient compliance (Jabbal-Gill, 2010). Nasal delivery could be a game-changer for COVID-19 treatments. Researchers explore antiviral drugs and vaccines via this route. Rapid nasal delivery of emergency medications (e.g., for anaphylaxis) is gaining attention. Innovations focus on ease of use and precise dosing. Researchers investigate bypassing the blood-brain barrier and delivering drugs directly to the brain. This approach holds promise for treating neurological conditions. Nasal formulations for CNS disorders (e.g., migraine, Alzheimer's) are being explored. Innovations aim to improve drug availability and patient adherence. Tailoring nasal drug delivery to individual patients is an exciting frontier. Innovations may include patient-specific formulations or dosing regimens (Illum, 2002).

Conclusion

Nasal delivery is considered a promising technique for its various advantages. It allows for lower doses, quicker attainment of therapeutic blood levels, quicker onset of pharmacological activity, and drug delivery directly to the brain via the olfactory nerve. Nanoparticles for nasal administration have better physical and chemical properties that enhances their bioavailability. This innovative delivery system can be utilized to enhance the effectiveness of drug delivery by ensuring precise dosing and improving patient compliance. Moreover, it is a targeted approach that can optimize efficacy and minimize unwanted impacts. The next years will see a range of new products in the market. Researchers are actively developing innovative liquid and powder nasal drug delivery systems. This technique will be a gateway to further innovations which may include patient-specific formulations or dosing regimens and the treatment will be patient-oriented instead of drug-oriented. In the coming years, multifunctional nanoparticles are expected to play a major role in biomedical applications, such as disease diagnosis and drug delivery.

REFERENCES

Abdelkawi, A., Slim, A., Zinoune, Z., and Pathak, Y. (2023). Surface Modification of Metallic Nanoparticles for Targeting Drugs. *Coatings*, *13*(9), 1660.

Aurora, J. (2002). Development of nasal delivery systems: a review. *Drug Deliv Technology*, *2*(7), 1-8.

Baig, A. M., and Khan, N. A. (2014). Novel chemotherapeutic strategies in the management of primary amoebic meningoencephalitis due to Naegleria fowleri. *CNS Neuroscience and Therapeutics*, *20*(3), 289.

Baron, A., Szewieczek, D., and Nowosielski, R. (2007). Selected manufacturing techniques of nanomaterials. *Journal of Achievements in Materials and Manufacturing Engineering*, *20*(1-2), 83-86.

Batts, A. H., Marriott, C., Martin, G. P., Wood, C. F., and Bond, S. W. (1990). The effect of some preservatives used in nasal preparations on the mucus and ciliary components of mucociliary clearance. *Journal Pharm Pharmacology*, *42*(3), 145-151. https://doi.org/10.1111/j.2042-7158.1990.tb05374.x

Brewer, E., Coleman, J., and Lowman, A. (2011). Emerging technologies of polymeric nanoparticles in cancer drug delivery. *Journal of Nanomaterials*, *2011*, 1-10.

Chien, Y. W., and Chang, S.-F. (1987). Intranasal drug delivery for systemic medications. *Critical Reviews in Therapeutic Drug Carrier Systems*, *4*(2), 67-194.

Costantino, H. R., Illum, L., Brandt, G., Johnson, P. H., and Quay, S. C. (2007). Intranasal delivery: physicochemical and therapeutic aspects. *International Journal of Pharmaceutics*, *337*(1-2), 1-24.

De Jong, W. H., and Borm, P. J. (2008). Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine*, *3*(2), 133-149.

De Oliveira, J. L., Campos, E. V. R., Bakshi, M., Abhilash, P. C., and Fraceto, L. F. (2014). Application of nanotechnology for the encapsulation of botanical insecticides for sustainable agriculture: prospects and promises. . *Biotechnology Advances*, *32*(8), 1550-1561.

Dhuria, S. V., Hanson, L. R., and Frey, W. H., 2nd. (2010). Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *Journal Pharmacy Science*, *99*(4), 1654-1673. https://doi.org/10.1002/jps.21924

Fransén, N. (2008). *Studies on a novel powder formulation for nasal drug delivery* Acta Universitatis Upsaliensis].

Fubini, B., Ghiazza, M., and Fenoglio, I. (2010). Physico-chemical features of engineered nanoparticles relevant to their toxicity. *Nanotoxicology*, *4*(4), 347-363.

Fujiwara, H., Yamauchi, K., Wada, T., Ishihara, H., and Sasaki, K. (2021). Optical selection and sorting of nanoparticles according to quantum mechanical properties. *Science Advances*, *7*(3), eabd9551.

Garcia-Reyero, N. l., Kennedy, A. J., Escalon, B. L., Habib, T., Laird, J. G., Rawat, A., Wiseman, S., Hecker, M., Denslow, N., and Steevens, J. A. (2014). Differential effects and potential adverse outcomes of ionic silver and silver nanoparticles in vivo and in vitro. *Environmental Science and Technology*, *48*(8), 4546-4555.

Ghori, M. U., Mahdi, M. H., Smith, A. M., and Conway, B. R. (2015). Nasal drug delivery systems: An overview. *American Journal of Pharmacological Sciences*, *3*(5), 110-119.

Gizurarson, S. (2015). The effect of cilia and the mucociliary clearance on successful drug delivery. *Biological and Pharmaceutical Bulletin*, *38*(4), 497-506. https://doi.org/https://doi.org/10.1248/bpb.b14-00398

Goldberg, D. S., Vijayalakshmi, N., Swaan, P. W., and Ghandehari, H. (2011). G3. 5 PAMAM dendrimers enhance transepithelial transport of SN38 while minimizing gastrointestinal toxicity. *Journal of Controlled Release*, *150*(3), 318-325.

Guerreiro, A. R., Chianella, I., Piletska, E., Whitcombe, M. J., and Piletsky, S. A. (2009). Selection of imprinted nanoparticles by affinity chromatography. *Biosensors and Bioelectronics*, *24*(8), 2740-2743.

Guo, D., Xie, G., and Luo, J. (2013). Mechanical properties of nanoparticles: basics and applications. *Journal of physics D: applied physics*, *47*(1), 013001.

Illum, L. (1987). Drug delivery systems for nasal application. *STP Pharma*, *3*(7), 594-598.

Illum, L. (2002). Nasal drug delivery: new developments and strategies. *Drug Discovery Today*, *7*(23), 1184-1189.

Illum, L. (2004). Is nose-to-brain transport of drugs in man a reality? *Journal of Pharmacy and Pharmacology*, *56*(1), 3-17.

Illum, L. (2012). Nasal drug delivery—Recent developments and future prospects. *Journal of Controlled Release*, *161*(2), 254-263.

Jabbal-Gill, I. (2010). Nasal vaccine innovation. *Journal of Drug Targeting*, *18*(10), 771-786.

Jadhav, K. R., Gambhire, M. N., Shaikh, I. M., Kadam, V. J., and Pisal, S. S. (2007). Nasal drug delivery system-factors affecting and applications. *Current Drug Therapy*, *2*(1), 27-38.

Jansson, B. (2004). *Models for the transfer of drugs from the nasal cavity to the central nervous system* Acta Universitatis Upsaliensis].

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931.

Khan, S., and Hossain, M. K. (2022). Classification and properties of nanoparticles. In *Nanoparticle-based Polymer Composites* (pp. 15-54). Elsevier.

Kim, J. U., and O'Shaughnessy, B. (2002). Morphology selection of nanoparticle dispersions by polymer media. *Physical Review Letters*, *89*(23), 238301.

Kraegeloh, A., Suarez-Merino, B., Sluijters, T., and Micheletti, C. (2018). Implementation of safe-by-design for nanomaterial development and safe innovation: why we need a comprehensive approach. *Nanomaterials*, *8*(4), 239.

Krishnamoorthy, R., and Mitra, A. K. (1998). Prodrugs for nasal drug delivery. *Advanced Drug Delivery Reviews*, *29*(1-2), 135-146.

Kromhout, D., Menotti, A., Bloemberg, B., Aravanis, C., Blackburn, H., Buzina, R., Dontas, A. S., Fidanza, F., Giaipaoli, S., and Jansen, A. (1995). Dietary saturated and transfatty acids and cholesterol and 25-year mortality from coronary heart disease: the seven countries study. *Preventive Medicine*, *24*(3), 308-315.

Lalan, M., Tandel, H., Lalani, R., Patel, V., and Misra, A. (2019). Inhalation drug therapy: Emerging trends in nasal and pulmonary drug delivery. *Novel Drug Delivery Technologies: Innovative Strategies for Drug Re-positioning*, 291-333.

Lata, S., Sharma, G., Joshi, M., Kanwar, P., and Mishra, T. (2017). Role of nanotechnology in drug delivery. *International Journal Nanotechnology Nanoscience*, *5*, 1-29.

Lee, J. W., Park, J. H., and Robinson, J. R. (2000). Bioadhesive-based dosage forms: the next generation. *Journal Pharmacy Science*, *89*(7), 850-866. https://doi.org/10.1002/1520-6017(200007)89:7<850::Aid-jps2>3.0.Co;2-g

Ller, R. H. M., Schwitzer, J., and Bushrab, F. N. (2006). Manufacturing of nanoparticles by milling and homogenization

techniques. *A Series of Textbooks and Monographs*, 21.

Marttin, E., Schipper, N. G. M., Verhoef, J. C., and Merkus, F. W. H. M. (1998). Nasal mucociliary clearance as a factor in nasal drug delivery. *Advanced Drug Delivery Reviews*, *29*(1), 13-38. https://doi.org/https://doi.org/10.1016/S0169-409X(97)00059-8

Mathison, S., Nagilla, R., and Kompella, U. B. (1998). Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? *Journal of Drug Targeting*, *5*(6), 415-441.

Merkus, P., Ebbens, F. A., Muller, B., and Fokkens, W. J. (2006). The 'best method' of topical nasal drug delivery: comparison of seven techniques. *Rhinology*, *44*(2), 102-107.

Naidu, S., Sawhney, R., and Li, X. (2008). A methodology for evaluation and selection of nanoparticle manufacturing processes based on sustainability metrics. *Environmental Science and Technology*, *42*(17), 6697-6702.

Natarajan, S. K., and Selvaraj, S. (2014). Mesoporous silica nanoparticles: importance of surface modifications and its role in drug delivery. *RSC Advances*, *4*(28), 14328-14334.

Nongjai, R., Khan, S., Asokan, K., Ahmed, H., and Khan, I. (2012). Magnetic and electrical properties of In doped cobalt ferrite nanoparticles. *Journal of Applied Physics*, *112*(8).

Peng, K., Fu, L., Yang, H., and Ouyang, J. (2016). Perovskite LaFeO3/montmorillonite nanocomposites: synthesis, interface characteristics and enhanced photocatalytic activity. *Scientific Reports*, *6*(1), 19723.

Proctor, D. F., and Andersen, I. H. P. (1982). *The nose: upper airway physiology and the atmospheric environment*. Elsevier Biomedical Press Amsterdam.

Reger, M., Watson, G., Frey Ii, W., Baker, L., Cholerton, B., Keeling, M., Belongia, D., Fishel, M., Plymate, S., and Schellenberg, G. (2006). Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiology of Aging*, *27*(3), 451-458.

Saad, M. Z. H., Jahan, R., and Bagul, U. (2012). Nanopharmaceuticals: a new perspective of drug delivery system. *Asian Journal of Biomedical and Pharmaceutical Sciences*, *2*(14), 11.

Salamat-Miller, N., Chittchang, M., and Johnston, T. P. (2005). The use of mucoadhesive polymers in buccal drug delivery. *Advance Drug Deliv Review*, *57*(11), 1666-1691. https://doi.org/10.1016/j.addr.2005.07.003

Shinde, N. C., Keskar, N. J., and Argade, P. D. (2012). Nanoparticles: Advances in drug delivery systems. *Research Journal Pharmacy Biology Chemistry Science*, *3*(1), 922-929.

Singh, S., Pandey, V. K., Tewari, R. P., and Agarwal, V. (2011). Nanoparticle based drug delivery system: advantages and applications. *Indian Journal Science Technology*, *4*(3), 177-180.

Singh, V., Yadav, P., and Mishra, V. (2020). Recent advances on classification, properties, synthesis, and characterization of nanomaterials. *Green Synthesis of Nanomaterials for Bioenergy Applications*, 83-97.

Stuen, S., Oppegaard, A. S., Bergström, K., and Moum, T. (2005). Anaplasma phagocytophilum infection in north Norway. The first laboratory confirmed case. *46*(3), 1-5.

Sur, S., Rathore, A., Dave, V., Reddy, K. R., Chouhan, R. S., and Sadhu, V. (2019). Recent developments in functionalized polymer nanoparticles for efficient drug delivery system. *Nano-Structures and Nano-Objects*, *20*, 100397.

Thorne, R., Pronk, G., Padmanabhan, V., and Frey Ii, W. (2004). Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience*, *127*(2), 481-496.

Thorne, R. G., Emory, C. R., Ala, T. A., and Frey II, W. H. (1995). Quantitative analysis of the olfactory pathway for drug delivery to the brain. *Brain Research*, *692*(1-2), 278-282.

Vallabani, N. S., and Singh, S. (2018). Recent advances and future prospects of iron oxide nanoparticles in biomedicine and diagnostics. *3 Biotech*, *8*(6), 279.

Vauthier, C., and Bouchemal, K. (2009). Methods for the preparation and manufacture of polymeric nanoparticles. *Pharmaceutical research*, *26*, 1025-1058.

Vllasaliu, D., Fowler, R., and Stolnik, S. (2014). PEGylated nanomedicines: recent progress and remaining concerns. *Expert Opin Drug Deliv*, *11*(1), 139-154. https://doi.org/10.1517/17425247.2014.866651

Wilczewska, A. Z., Niemirowicz, K., Markiewicz, K. H., and Car, H. (2012). Nanoparticles as drug delivery systems. *Pharmacological Reports*, *64*(5), 1020-1037.

Xu, D., Song, X.-J., Chen, X., Wang, J.-W., and Cui, Y.-L. (2024). Advances and future perspectives of intranasal drug delivery: A scientometric review. *Journal of Controlled Release*, *367*, 366-384.

Zhao, Y., Lin, K., Zhang, W., and Liu, L. (2010). Quantum dots enhance Cu2+-induced hepatic L02 cells toxicity. *Journal of Environmental Sciences*, *22*(12), 1987-1992.

Chapter 03

Application of Nanotechnology in Combating Bovine Mastitis

Mona Mohamed Hassan Soliman*, Nagwa Sayed Ata, Amany Ahmed Arafa and Mai Mohamed Kandil

Department of Microbiology and Immunology, National Research Centre, Egypt
*Corresponding author: mona_nrc.micro@yahoo.com

ABSTRACT

Mastitis is considered the costliest illness on dairy industry and also adversely influences animal welfare. As treatment and prevention of mastitis depend intensely on antibiotics, there are increasing attention in veterinary and human medicine regarding the emergence of antimicrobial resistance. Diverse strains of bacteria, fungus, and algae are capable of causing mastitis. Bacteria are the main cause of bovine mastitis causing destruction to the udder parenchyma. Antibiotics are the main strategy for treatment of mastitis. In any case, long-term utilize of antibiotics in mastitis treatment has caused the emergence of resistant pathogens. Researchers have looked for alternative therapeutic ways to antibiotics for mastitis treatment. Researcher's efforts together with the innovative invention of nanotechnology are crowned with success in mastitis therapy and management. As a result, nanotechnology may become the principal sort of mastitis treatment in the near future. The current chapter will discuss the role nanoparticles in controlling mastitis in dairy cow herds.

KEYWORDS
Nanotechnology, Bovine mastitis, Nanoantibiotics, Drug delivery, Antibiotic resistance

Received: 22-May-2024
Revised: 12-Jul-2024
Accepted: 19-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Soliman MMH, Ata NS, Arafa AA and Kandil MM, 2024. Application of nanotechnology in combating bovine mastitis. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 19-26. https://doi.org/10.47278/book.CAM/2024.117

INTRODUCTION

Bovine mastitis (BM) is considered the most common and economically significant infectious illness that can affect dairy farms worldwide as it can raise treatment, labor, and culling expenses, which may lead to large financial losses (Kotb et al., 2021). Over 40% from the 1.489 million cows that are supposed to exist worldwide suffer from some form of BM (Zhylkaidar et al., 2021).

The average annual cost of failure resulting from BM is projected to be 147 per cow worldwide. Each cow experiences yearly losses of 11–18% due to culling and decreased milk output (Hogeveen et al., 2019). The United States losses billion-dollar annual costs as a result of declining milk supply and quality, which has a major impact on animal husbandry, growing veterinary care costs, and rising farm management expenditures (Hertl et al., 2014). Indeed, BM is significant ailment because of the disease's greater impact worldwide and also output expense (Shaheen et al., 2015).

Mastitis also affects the milk's quality, which has implications that extend outside of the dairy farm. Although BM was primarily a problem for dairy farmers and producers, worries about antibiotic residues, antimicrobial resistance, milk quality, and animal welfare have made it a problem for consumers and society as a whole (Hogeveen et al., 2011).

Traditionally, BM has been defined as inflammation of the mammary glands, mostly due to bacterial infection. There are 137 distinct pathogenic bacteria in BM, the most common ones being *Streptococcus* species, *Escherichia coli* (*E. coli*), and *Staphylococcus aureus* (*S. aureus*) (Elbayoumy et al., 2024).

The elevated incidence and increased treatment rate of such very costly and possibly deadly malady are alarming for both the dairy industry and policymakers. Preventive ways, immunization programs and treatment of diseased animals are all required for the control of bacterial diseases in BM. A number of treatment and prevention programs have been established, with varying fruitful rates (Sharma and Jeong, 2013).

In spite of the reality that antibiotics are still the most commonly used treatment for BM, worries concerning the emergence of antibiotic-resistant bacteria are growing. This chapter will discuss an overview of diagnosis, control, antimicrobial drug delivery and remedy of BM using nanotechnology.

History of Nanotechnology Application in Veterinary Field

Nanotechnology alludes to dealing with the structure of materials, chemicals, or components at the nanoscale level, generating particles between1.0 nm and 100 nm (Ianiski et al., 2021).

In 1959, Ricahard Feynman fist illustrated the idea of nanomaterials within the lecture Plenty of Room in the Bottom at Nobel Prize, suggesting that arranging the atoms the way we want would be possible (Feynman, 1960). Kroto et al. (1985) discovered the fullerenes while Iijima (1991) succeed in synthesis of carbon nanotubes, nanotechnology and nanoscience –

once considered as fiction – was viewed as a practical technology (Ferreira and Rangel, 2009).

In 1991, a preparation technique that included molecular atomic control was proposed (Ferreira and Rangel, 2009). Subsequently, several areas of activity made contributions to nanotechnology. Chemistry, science, atomic material field, computer technology, fabric science, and mechanical and electrical building were some of them (Roco, 2011). A new field known as nanomedicine has emerged as a result of growing interest in the therapeutic uses of nanotechnology (Ianiski et al., 2021).

According to Feugang et al. (2019), nanotechnology is expected to have a significant impact on the livestock business in particular in the twenty-first century. Commercially available veterinary medicine products nowadays include scientifically approved nanoparticle medicines (Underwood and Van Eps, 2012). That explains how nanotechnology practice is becoming more and more relevant to veterinary field. The study of nanoparticles holds great promise for the diagnosis, control, and treatment of BM.

Infection Diagnosis and Antimicrobial Resistance Detection Assisted by Nanotechnology

Detection of infection and antimicrobial resistance can be performed using nanotechnology. Conventional diagnostic techniques used for microbial illnesses need sample preparation and take a long period of time to readout, despite the fact that microorganisms exhibit high sensitivity and repeatability (Kaittanis et al., 2010).

Newly nanoparticles with known magnetic, electrical, luminescent, and catalytic features can quickly, accurately, and affordably detect antimicrobial medications as well as quickly judge if they are resistant or susceptible to them (Rosi and Mirkin, 2005; Jain, 2007).

Antibody-coated nanoparticles have been shown to be able to start the signals needed to count and do bioanalysis of extremely dangerous bacteria, including *E. Coli* O157:H7. This enables the very easy, rapid, and highly focused identification of a single bacteria in a lab environment in roughly 20 minutes (Look et al., 2010).

Research showed that in microarray-based systems, nanoparticles with specific Raman spectroscopic signatures could be utilized to identify antibiotic-resistant bacterial strains, as MRSA (Methicillin Resistant *Staph aureus*), from non-resistant isolates using single-nucleotide polymorphisms (Li et al., 2009).

Magnetic nanoparticles can be extremely effective and sensitive techniques for diagnosis of bacterial manifestations. With the use of super-magnetic iron oxide nanoprobes, *Mycobacterium avium* species, paratuberculosis (MAP) in milk and blood has been quantified quickly and extremely sensitive (Basu et al., 2004).

Moreover, recent advances in nanotechnology have made it possible to create pharmacological and biopharmaceutical diagnostics for microbial infection that are both quick and accurate, eliminating the need to prepare samples in opaque media like milk or blood (Grossman et al., 2004; Tully et al., 2006).

Every branch of medicine has undergone a revolution due to the emergence of new nanotechnology techniques, including diagnosis, vaccine development, and treatment. Recent diagnostic techniques for the precise and timely detection of mastitis have been made possible by the quick advancement of nanotechnology. Utilizing nano-biosensors, a special class of analytical methods for mastitis identification, is one of these primary diagnostic methods. A biosensor is a device that binds a physical nano-transducer with bioreceptors specific to the antigen or chemical that is under investigation (Driskell and Tripp 2009).

These sensors look for specific biological substances using electric impulses. Based on the target molecule's characteristics, the type of transductor used, the signaling and recognition system, and the nanoparticle used, there are many different kinds of biosensors (Martins et al., 2019).

Nanotechnology in Prevention and Treatment of Infectious Illnesses

Several researches have been done on the use of nanoparticles as new medicines, colloidal vaccine carriers, and adjuvants. Particulate systems exhibit a distinct similarity in size of microbes. The immune system may easily identify the microbe and nanoparticles as they are nearly similar in size to bacteria and viruses (Peek et al., 2008). Varied special vaccine carrier characteristics as size, chemical structure, charge, and surface features can also be modified to improve phagocytosis with mononuclear phagocytic system (MPS), which promotes the immunological presentation of antigens and the activation of antigen-presenting cells (APs) (Singh et al., 2007; Rice-Ficht et al., 2010).

Studies conducted in vivo investigated combinations of nanoemulsions containing proteins (as, recombinant *Bacillus anthracis* [*B. anthracis*] protective antigens) or entire viruses, such as the influenza virus, as possible vaccines (Myc et al., 2003; Bielinska et al., 2007). This vaccine can be delivered by mucosal routes and does not require cold storage, making it especially appropriate for immunization in many underdeveloped nations.

Effective Antimicrobial Medication Delivery using Nanoparticles

Liposomes: They are vesicles that are nano- to micro-sized, aqueous-cored and made of a phospholipid bilayer. Following the FDA's 1995 approval of Doxil as the first liposomal medication, liposomes have been investigated as a potentially effective therapeutically acceptable drug, protein, and enzyme delivery system (Lian and Ho, 2001; Torchilin, 2005).

Liposomes are widely used as antimicrobial drug delivery vehicles due to their lipid bilayer structure which resembles a cell membrane that readily fuses with the infectious microorganisms (Zhang et al., 2010).

Moreover, without undergoing chemical changes, lipophilic and hydrophilic antimicrobial medications may be

encapsulated and kept within the phospholipid bilayer and the aqueous core, correspondingly. The application of liposomes as antimicrobial drug delivery tools should take into account a number of factors, including the physico-chemical properties of lipids, the drugs to be loaded, the liposomes' particle size and polydispersity, surface charge (zeta-potential), stability in storage (shelf-life), repeatability, and viability in large-scale production (Lasic, 1998).

Increased in vivo stability was the outcome of conjugating liposomes with stealth compounds like polyethylene glycol, or PEG, on their surface. The platform can also be coupled with different targeted ligands, such as tiny compounds, aptamers, peptides, antibodies, and antibody fragments, for the purpose of targeted administration of antimicrobial medicines (Maruyama et al., 1990; Pinto-Alphandary et al., 2000).

Benzyl penicillin-encapsulating cationic liposomes was found to totally prevent the growth of *S. aureus* strain in one study, when compared to free medicines, with shorter exposure periods and lower drug concentrations (Kim and Jones, 2004).

Liposomal amikacin investigated changes in tissue distribution and notably prolonged half-life (tissue 63–465 h, blood 24.5 h) (Gangadharam et al., 1991). Extended blood circulation and improved localization were demonstrated by liposomal gentamicin and ceftazidime at the infection site (Bakker-Woudenberg et al., 1995). Significantly more intracellular MRSA infection was eliminated when vancomycin and teicoplanin-encapsulated liposomes were used (Onyeji et al., 1994).

Traditional antibiotics are not very efficient in treating cow mastitis, even though the bacteria are susceptible to them in vitro as the drugs are not well absorbed into the cells, especially by the phagocytes of the udder (Jain and Banerjee, 2008).

Antibiotics and other antimicrobial medications could be delivered utilizing liposomes and nanoparticles that can both protect the drug from the physiological milieu of bovines and help in its cellular uptake. Antibiotics have been added to polymeric nanoparticles, liposomes, and drug-loaded delivery vehicles, all of which have been shown to improve antibiotic intracellular delivery (Alving, 1988; Gruet et al., 2001).

Antibiotics from different families can be combined in nanoparticulate formulations (Müller, 1991). In order to prolong the release and prevent drug degradation. Because of all these qualities, using nanoparticles to treat bovine mastitis is a very suitable option. It has been demonstrated that solid lipid, metal, and polymeric nanoparticles are useful in the treatment and detection of bacterial infections causing mastitis in cows (Henry-Michelland et al., 1987; Spain et al., 2011; Mujawar et al., 2013).

Examples of Nanomaterials used in Antimicrobial Dosage form

There is increase in using nanoparticles in the veterinary, pharmaceutical, and medical fields due to their unique characteristics. The most developing scientific field in the world is nanotechnology. Nanomaterials have special properties both physically and chemically, and due to its large surface area compared to volume, they can be used to treat illnesses like mastitis in dairy cows (Algharib et al. 2020).

A new study had assured that bacteria shouldn't acquire antimicrobial resistance against metal nanoparticles. Apart from treating microbes with nanoparticle materials, the nanoparticles can also be synthesized using bacterial cells or enzymes. Current research has explored the production of metallic nanoparticles, such as gold [Au] and silver [Ag], either extracellularly or intracellularly, utilizing enzymes or microbes to produce biosynthetic nanoparticles (Holmes et al., 1995; Saravanan and Nanda, 2010).

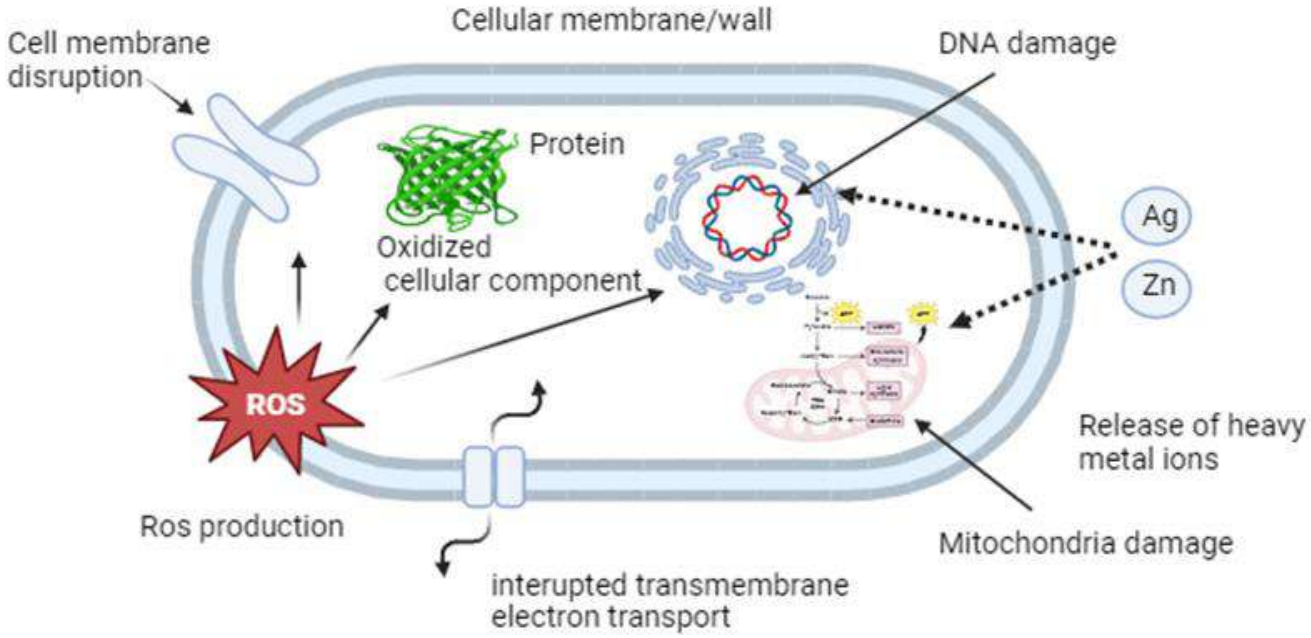


Fig. 1: Antimicrobial mechanisms of nanoparticles.

As seen in (Fig. 1), the antibacterial nanoparticles can destruct bacterial via a variety of methods as described by (Maness et al., 1999 and Rabea et al., 2003).

1) The generation of reactive oxygen species (ROS) via photocatalysis, which harms viral and cellular constituents.
2) Compromising the cell wall and membrane of the bacteria.
3) The transmission of energy is interrupted.
4) Reduction of DNA synthesis and the activity of enzymes.

Silver NPs

Silver (Ag) nanoparticles have been shown to be the most efficient against viruses, bacteria, and many other eukaryotic microbes among the varied kinds of metallic and metal oxide nanoparticles (Sharma et al., 2009; Chamundeeswari et al., 2010). Silver (Ag) nanoparticles release silver ions that boost antibacterial action while simultaneously gaining access to cell division and, the respiratory chain which ultimately cause cellular death (Klasen, 2000). The size of silver (Ag) nanoparticles has an inverse relationship with their antibacterial activity (Sondi and Salopek-Sondi, 2004; Raimondi et al., 2005). When silver (Ag) nanoparticles and antibiotics including amoxicillin, penicillin G, vancomycin, and erythromycin are used together, the antibacterial actions against both Gram-negative and Gram-positive bacteria are enhanced and work in concert, such as *E. coli* and *S. aureus* (Shahverdi et al., 2007; Fayaz et al., 2010). Moreover, green synthesized Ag NPs gave highly significant results against isolates of *Candida* species. and *Aspergillus* species isolated from mastitic cow milk (Hasanin et al., 2022).

Zinc Oxide (ZnO) NPs

Certain metal oxide nanoparticles, like zinc oxide, can withstand harsh manufacturing conditions and exhibit specific bacterial toxicity while having minimal impact on animal and human cells. The antibacterial activity of zinc oxide nanoparticles, or ZnO NPs, against important food-borne pathogens such enterotoxigenic *E. coli* and *E. coli* O157:H7 is being investigated as a potential medication carrier, and because they are biocompatible and relatively harmless to humans (Roselli et al., 2003; Brayner et al., 2006). In compared with silver nanoparticles (Ag NPs), it is more favorable in a number of ways, including cheap manufacturing expenses, UV-blocking properties, and a white look that contributes to light reflection characteristics that are helpful in sunscreen usage (Dastjerdi and Montazer, 2010). Additionally, it's thought that ZnO nanoparticles damage the lipids and proteins in the bacterial cell membrane, causing intracellular contents to seep out and the final death of the bacteria (Sawai, 2003).

Titanium Dioxide (TiO2) NPs

Of all the metal, metal oxide, and sulfur dioxide nanoparticles, titanium dioxide nanoparticles have been researched the most for photocatalytic antibacterial activity (Gelover et al., 2006). Strong antibacterial action is displayed by TiO2 nanoparticles when exposed to UV-A and near-UV beams. The required concentration needed to kill microbes is between 100 and 1000 parts per million. The strength of antimicrobial effect is dependent on the size, intensity, and wavelength of the light source of the TiO2 nanomaterials. According to a novel study, *E. coli* > *P. aeruginosa* > *S. aureus* > *E. faecium* > *C. albicans* is the decreasing order in which TiO2 nanoparticles' antimicrobial activity is recorded. The antimicrobial activity depends mainly on the density and the complexity of the cell wall or membrane of the targeted microbe. Furthermore, it was observed that the photocatalytic antibacterial efficacy of TiO2 nanoparticles was mostly dependent on the thickness of the cellular membrane or sheath structure of the microbe, and decreased in the following order: virus > bacterial wall > bacterial spore (Kühn et al., 2003). The generation of ROS, like peroxide and free hydroxyl radicals, is primarily responsible for the photocatalytic antibacterial action of TiO2 (Choi et al., 2007).

Gold (Au) NPs

By irradiating with the appropriate wavelengths, a range of nanoparticles, including near infrared light-absorbing gold (Au) nanoparticles, nanoshells, nanorods, and nanocages, have been employed to treat bacterial illness (Sekhon and Kamboj, 2010). Strong electrostatic attractions to the negatively charged cell membrane bilayer are the primary mechanism by which gold nanoparticles (Au NPs) exhibit antimicrobial activity (Johnston et al., 2010). To find selective antimicrobial effects, gold nanoparticles (Au NPs) conjugated with antimicrobial agents and antibodies have been studied. For example, gold nanoparticles (Au NPs) combined with anti-protein A-antibodies that target the bacterial surface, have been found to selectively destruct *S. aureus* (Pissuwan et al., 2010). Bacteria were efficiently harmed by the process of strong laser-induced hyperthermic actions that were followed by bubble arrangement around clustered gold nanoparticles (Au NPs). Strong antimicrobial agent effects by gold/drug nanocomposites, such as gold nanoparticles coated with antibiotics like streptomycin, neomycin, and gentamicin, have been reported in numerous studies against both Gram-positive and Gram-negative bacteria, as well as antibiotic-resistant strains (Grace and Pandian, 2007).

Chitosan

Many different types of bacteria, fungi, and yeasts can be inhibited by chitosan through various processes that are not all fully understood (Guarnieri et al., 2022). The most straightforward mode of action includes electrostatic interactions between the negatively charged microbial cell membranes and the positively charged NH3+ sites of chitosan. Intracellular

material is released as a result of the contact changing the microbial cell's permeability (Tsai and Su, 1999). Chitosan's binding to microbial enzymes and nucleotides can cause disruptions in the cell structure of *S. aureus* and *E. coli,* as demonstrated by Chung and Chen (2008). Chitosan displays antibacterial action in its polycationic shape against both Gram-positive and Gram-negative bacteria, with its mode of action differing based on the special cell membrane structure. While the negatively charged peptidoglycan and teichoic acidsare found in the cell wall layer of Gram-positive bacteria, chitosan directly interacts with these negatively charged structures in Gram-negative bacteria. These anionic structures include lipopolysaccharides and proteins (Nikaido and Vaara, 1985). There is no accurate information regarding on which bacteria the chitosan is more effective against. Indeed, some researchers as Chung et al. (2004) and Devlieghere et al. (2004) reported a more potent bactericidal effect on Gram-negative bacteria, whilst other writers (No et al., 2002; Fernandez-Saiz et al., 2009) showed a more potent effect on Gram-positive bacteria.

Nanoemulsion

An interfacial coating of surfactant molecules stabilizes a thin oil dispersion in water, forming nanoemulsions. The concentration, content, and mechanical energy of surfactants can affect the mean droplet size, which can range from 0.1 to 600 nm. By encapsulating the active compounds, nanoemulsions offer protection and stability to those compounds, as well as increasing the penetration power of the target compounds for more effective application (Machado et al., 2020). The antimicrobial activities of nanoemulsions have been highly studied in several studies, and the results show how effective they work to distribute and intensify the effect of antimicrobial drugs. For example, nanoemulsions including essential oils, as citral, have shown noteworthy antibacterial action. It has been found that the antimicrobial action of nanoemulsions are greatly affected by their configuration, underscoring the need of comprehending the physicochemical features of these systems (Gırgın and Nadaroglu, 2024).

Conclusion

The incidence of mastitis is incredibly increasing in farm animals as buffaloes and cows. To control mastitis, more strategic study in this area is needed. Veterinarians and mastitis researchers continue to face significant challenges due to bovine mastitis. When treating infectious disorders like mastitis, the emergence of antibiotic resistance caused by microbial variations poses a significant risk. Pharmaceutical corporations and academic researchers alike are addressing the global concern of antibiotic resistance development. The distinct physicochemical characteristics of diverse nanomaterials hold the potential to enhance the efficacy of current antimicrobial drugs and provide novel avenues for antibacterial agent development. It appears that using the characteristics of nanoparticles as antibiotic carriers appears to be one way to combat antimicrobial resistance. Numerous nanoparticles have been investigated as effective nanoantibiotics and antibiotic delivery systems that shield antimicrobial medications from resistance mechanisms. The importance nanoparticles in diagnosis, control, antimicrobial drug delivery and treatment of bovine mastitis was discussed in this chapter. Most significantly, using numerous independent and perhaps synergistic techniques on the same platform to boost antibacterial action is possible by nanoparticles and also can defeat antibiotic resistance. In an era where antibiotic resistance is growing, finding effective, safe, affordable, and tailored therapy for bovine mastitis necessitates interdisciplinary understanding and cutting-edge techniques from the fields of microbiology, immunology, biomaterials, polymers, and nanotechnology.

REFERENCES

Algharib, S. A., Dawood, A., and Xie, S. (2020). Nanoparticles for treatment of bovine Staphylococcus aureus mastitis. *Drug Delivery, 27*(1), 292-308.

Alving, C. R. (1988). Macrophages as targets for delivery of liposome-encapsulated antimicrobial agents. *Advanced Drug Delivery Reviews, 2*(1), 107-128.

Bakker-Woudenberg, I. A., Ten Kate, M. T., Stearne-Cullen, L. E. T., and Woodle, M. C. (1995). Efficacy of gentamicin or ceftazidime entrapped in liposomes with prolonged blood circulation and enhanced localization in Klebsiella pneumoniae-infected lung tissue. *Journal of Infectious Diseases, 171*(4), 938-947.

Basu, M., Seggerson, S., Henshaw, J., Jiang, J., del A Cordona, R., Lefave, C., and Basu, S. (2004). Nano-biosensor development for bacterial detection during human kidney infection: use of glycoconjugate-specific antibody-bound gold NanoWire arrays (GNWA). *Glycoconjugate Journal, 21*, 487-496.

Bielinska, A. U., Janczak, K. W., Landers, J. J., Makidon, P., Sower, L. E., Peterson, J. W., and Baker Jr, J. R. (2007). Mucosal immunization with a novel nanoemulsion-based recombinant anthrax protective antigen vaccine protects against Bacillus anthracis spore challenge. *Infection and Immunity, 75*(8), 4020-4029.

Brayner, R., Ferrari-Iliou, R., Brivois, N., Djediat, S., Benedetti, M. F., and Fiévet, F. (2006). Toxicological impact studies based on Escherichia coli bacteria in ultrafine ZnO nanoparticles colloidal medium. *Nano Letters, 6*(4), 866-870.

Chamundeeswari, M., Sobhana, S. L., Jacob, J. P., Kumar, M. G., Devi, M. P., Sastry, T. P., and Mandal, A. B. (2010). Preparation, characterization and evaluation of a biopolymeric gold nanocomposite with antimicrobial activity. *Biotechnology and Applied Biochemistry, 55*(1), 29-35.

Choi, J. Y., Kim, K. H., Choy, K. C., Oh, K. T., and Kim, K. N. (2007). Photocatalytic antibacterial effect of TiO2 film formed on

Ti and TiAg exposed to Lactobacillus acidophilus. Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of the Society for Biomaterials, *The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 80*(2), 353-359.

Chung, Y. C., and Chen, C. Y. (2008). Antibacterial characteristics and activity of acid-soluble chitosan. *Bioresource Technology, 99*(8), 2806-2814.

Chung, Y. C., Su, Y. P., Chen, C. C., Jia, G., Wang, H. L., Wu, J. G., and Lin, J. G. (2004). Relationship between antibacterial activity of chitosan and surface characteristics of cell wall. *Acta Pharmacologica Sinica, 25*(7), 932-936.

Dastjerdi, R., and Montazer, M. (2010). A review on the application of inorganic nano-structured materials in the modification of textiles: focus on anti-microbial properties. *Colloids and Surfaces B: Biointerfaces, 79*(1), 5-18.

Devlieghere, F., Vermeulen, A., and Debevere, J. (2004). Chitosan: antimicrobial activity, interactions with food components and applicability as a coating on fruit and vegetables. *Food Microbiology, 21*(6), 703-714.

Driskell, J. D., and Tripp, R. A. (2009). Emerging technologies in nanotechnology-based pathogen detection. *Clinical Microbiology Newsletter, 31*(18), 137-144.

Elbayoumy, M. K., Allam, A. M., Ghazy, A. A., and Nasr, S. M. (2024). Advances in Controlling Bacterial Mastitis in Dairy Cows. *Egyptian Journal of Veterinary Sciences, 55*(1), 1-21.

Fayaz, A. M., Balaji, K., Girilal, M., Yadav, R., Kalaichelvan, P. T., and Venketesan, R. (2010). Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. *Nanomedicine: Nanotechnology, Biology and Medicine, 6*(1), 103-109.

Fernandez-Saiz, P., Lagaron, J. M., and Ocio, M. J. (2009). Optimization of the film-forming and storage conditions of chitosan as an antimicrobial agent. *Journal of Agricultural and Food Chemistry, 57*(8), 3298-3307.

Ferreira, H. S., and Rangel, M. D. C. (2009). Nanotechnology: general aspects and potential applications in catalysis. *Química Nova, 32*, 1860-1870. Available from: <https://www.scielo.br/scielo. php?script=sci_arttextandpid=S0100-40422009000700033>. doi: 10.1590/S0100-40422009000700033.

Feugang, J. M., Rhoads, C. E., Mustapha, P. A., Tardif, S., Parrish, J. J., Willard, S. T., and Ryan, P. L. (2019). Treatment of boar sperm with nanoparticles for improved fertility. *Theriogenology, 137*, 75-81. Available from: <https://pubmed.ncbi.nlm. nih.gov/31204016/>. doi: 10.1016/j. theriogenology.2019.05.040.

Feynman, R. P. (1960). There's plenty of room at the bottom. *Engineering and Science, 23*, 22–36. Available from: < https://resolver.caltech.edu/CaltechES:23.5.1960Bottom >.

Gangadharam, P. R., Ashtekar, D. A., Ghori, N., Goldstein, J. A., Debs, R. J., and Düzgünes, N. (1991). Chemotherapeutic potential of free and liposome encapsulated streptomycin against experimental Mycobacterium avium complex infections in beige mice. *Journal of Antimicrobial Chemotherapy, 28*(3), 425-435.

Gelover, S., Gómez, L. A., Reyes, K., and Leal, M. T. (2006). A practical demonstration of water disinfection using TiO2 films and sunlight. *Water research, 40*(17), 3274-3280.

Gırgın, H., and Nadaroglu, H. (2024). Exploring the Synthesis of Nanoemulsions and Assessing Their Antimicrobial Effects. *Pharmata, 4*(2), 49-57.

Goy, R. C., Britto, D. D., and Assis, O. B. (2009). A review of the antimicrobial activity of chitosan. *Polímeros, 19*, 241-247.

Grace, A. N., and Pandian, K. (2007). Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles—A brief study. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 297*(1-3), 63-70.

Grossman, H. L., Myers, W. R., Vreeland, V. J., Bruehl, R., Alper, M. D., Bertozzi, C. R., and Clarke, J. (2004). Detection of bacteria in suspension by using a superconducting quantum interference device. *Proceedings of the National Academy of Sciences, 101*(1), 129-134.

Gruet, P., Maincent, P., Berthelot, X., and Kaltsatos, V. (2001). Bovine mastitis and intramammary drug delivery: review and perspectives. *Advanced Drug Delivery Reviews*, 50(3), 245-259. https://doi.org/10.1016/s0169-409x(01)00160-0

Guarnieri, A., Triunfo, M., Scieuzo, C., Ianniciello, D., Tafi, E., Hahn, T., and Falabella, P. (2022). Antimicrobial properties of chitosan from different developmental stages of the bioconverter insect Hermetia illucens. *Scientific Reports, 12*(1), 8084.

Hasanin, M. S., Emam, M., Soliman, M. M., Latif, R. R. A., Salem, M. M., El Raey, M. A., and Eisa, W. H. (2022). Green silver nanoparticles based on Lavandula coronopifolia aerial parts extract against mycotic mastitis in cattle. *Biocatalysis and Agricultural Biotechnology, 42*, 102350.

Henry-Michelland, S., Alonso, M. J., Andremont, A., Maincen, P., Sauzieres, J., and Couvreur, P. (1987). Attachment of antibiotics to nanoparticles: preparation, drug-release and antimicrobial activity in vitro. *International Journal of Pharmaceutics, 35*(1-2), 121-127.

Hertl, J. A., Schukken, Y. H., Welcome, F. L., Tauer, L. W., and Gröhn, Y. T. (2014). Effects of pathogen-specific clinical mastitis on probability of conception in Holstein dairy cows. *Journal of Dairy Science*, 97(11), 6942-6954. https:// doi.org/10.3168/jds.2014-8203

Hogeveen, H., Pyorala, S., Waller, K. P., Hogan, J. S., Lam, T. J., Oliver, S. P., and Hillerton, J. E. (2011). Current status and future challenges in mastitis research. In *Proceedings of the 50th Annual Meeting of the National Mastitis Council, 23-26 January, 2011, Arlington, USA* (pp. 36-48).

Hogeveen, H., Steeneveld, W., and Wolf, C. A. (2019). Production diseases reduce the efficiency of dairy production: A review of the results, methods, and approaches regarding the economics of mastitis. *Annual Review of Resource*

Economics, 11, 289-312. https://doi.org/10.1146/ annurev-resource-100518-093954

Holmes, J. D., Smith, P. R., Evans-Gowing, R., Richardson, D. J., Russell, D. A., and Sodeau, J. R. (1995). Energy-dispersive X-ray analysis of the extracellular cadmium sulfide crystallites of Klebsiella aerogenes. *Archives of Microbiology, 163*, 143-147.

Ianiski, L. B., Rodrigues, F. D. S., Stibbe, P. C., Weiblen, C., Pereira, D. I. B., Santurio, J. M., and Botton, S. D. A. (2021). Nanotechnology in veterinary medicine: a review. *Ciência Rural, 52,* e20210195.

Iijima, S. (1991). Helical microtubules of graphitic carbon. *Nature, 354*(6348), 56-58. Available from: <https://www.nature.com/articles/354056a0>. doi: 10.1038/354056a0.

Jain, D., and Banerjee, R. (2008). Comparison of ciprofloxacin hydrochloride-loaded protein, lipid, and chitosan nanoparticles for drug delivery. *Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 86*(1), 105-112.

Jain, K. K. (2007). Applications of nanobiotechnology in clinical diagnostics. *Clinical Chemistry, 53*(11), 2002-2009.

Johnston, H. J., Hutchison, G., Christensen, F. M., Peters, S., Hankin, S., and Stone, V. (2010). A review of the in vivo and in vitro toxicity of silver and gold particulates: particle attributes and biological mechanisms responsible for the observed toxicity. *Critical Reviews in Toxicology, 40*(4), 328-346.

Kaittanis, C., Santra, S., and Perez, J. M. (2010). Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. *Advanced Drug Delivery Reviews*, 62(4-5), 408-423.

Kim, H. J., and Jones, M. N. (2004). The delivery of benzyl penicillin to Staphylococcus aureus biofilms by use of liposomes. *Journal of Liposome Research, 14*(3-4), 123-139.

Klasen, H. J. (2000). Historical review of the use of silver in the treatment of burns. I. Early uses. *Burns, 26*(2), 117-130.

Kotb, E. E., M EL Sawah, A., E Kortam, L., A Abd El Fattah, O., and M Barghooth, W. (2021). Evaluation of using different adjuvants used for preparation of Staphylococcus aureus mastitis vaccine on the immune response. *Journal of Applied Veterinary Sciences*, 6(1), 9-17. https://doi.org/10.21608/ javs.2021.140065

Kroto, H. W., Heath, J. R., O'Brien, S. C., Curl, R. F., and Smalley, R. E. (1985). C60: Buckminsterfullerene. *Nature*, 318(6042), 162-163. Available from: https://garfield.library.upenn.edu/classics1993/A1993LT56300001.pdf. doi: 10.1038/318162a0.

Kühn, K. P., Chaberny, I. F., Massholder, K., Stickler, M., Benz, V. W., Sonntag, H. G., and Erdinger, L. (2003). Disinfection of surfaces by photocatalytic oxidation with titanium dioxide and UVA light. *Chemosphere, 53*(1), 71-77.

Lasic, D. D. (1998). Novel applications of liposomes. *Trends in Biotechnology, 16*(7), 307-321.

Li, M., Hu, B., Li, J., Chen, R., Zhang, X., and Chen, H. (2009). Extractive electrospray ionization mass spectrometry toward in situ analysis without sample pretreatment. *Analytical Chemistry, 81*(18), 7724-7731.

Lian, T., and Ho, R. J. (2001). Trends and developments in liposome drug delivery systems. *Journal of Pharmaceutical Sciences, 90*(6), 667-680.

Look, M., Bandyopadhyay, A., Blum, J. S., and Fahmy, T. M. (2010). Application of nanotechnologies for improved immune response against infectious diseases in the developing world. *Advanced Drug Delivery Reviews, 62*(4-5), 378-393.

Machado, G. T. P., Veleirinho, M. B., Honorato, L. A., and Kuhnen, S. (2020). Formulation and evaluation of anti-MRSA nanoemulsion loaded with Achyrocline satureioides: a new sustainable strategy for the bovine mastitis. *Nano Express, 1*(3), 030004.

Maness, P. C., Smolinski, S., Blake, D. M., Huang, Z., Wolfrum, E. J., and Jacoby, W. A. (1999). Bactericidal activity of photocatalytic TiO2 reaction: toward an understanding of its killing mechanism. *Applied and Environmental Microbiology, 65*(9), 4094-4098.

Martins, S. A., Martins, V. C., Cardoso, F. A., Germano, J., Rodrigues, M., Duarte, C., and Freitas, P. P. (2019). Biosensors for on-farm diagnosis of mastitis. *Frontiers in Bioengineering and Biotechnology, 7*, 186.

Maruyama, K., Kennel, S. J., and Huang, L. (1990). Lipid composition is important for highly efficient target binding and retention of immunoliposomes. *Proceedings of the National Academy of Sciences, 87*(15), 5744-5748.

Mujawar, L. H., Moers, A., Norde, W., and van Amerongen, A. (2013). Rapid mastitis detection assay on porous nitrocellulose membrane slides. *Analytical and Bioanalytical Chemistry, 405*, 7469-7476.

Müller, R. H. (1991). Colloidal carriers for controlled drug delivery and targeting: Modification, characterization and in vivo distribution. Taylor and Francis.

Myc, A., Kukowska-Latallo, J. F., Bielinska, A. U., Cao, P., Myc, P. P., Janczak, K., and Baker Jr, J. R. (2003). Development of immune response that protects mice from viral pneumonitis after a single intranasal immunization with influenza A virus and nanoemulsion. *Vaccine, 21*(25-26), 3801-3814.

Nikaido, H., and Vaara, M. (1985). Molecular basis of bacterial outer membrane permeability. *Microbiological Reviews, 49*(1), 1-32.

No, H. K., Park, N. Y., Lee, S. H., and Meyers, S. P. (2002). Antibacterial activity of chitosans and chitosan oligomers with different molecular weights. *International Journal of Food Microbiology, 74*(1-2), 65-72.

Onyeji, C. O., Nightingale, C. H., and Marangos, M. N. (1994). Enhanced killing of methicillin-resistant Staphylococcus aureus in human macrophages by liposome-entrapped vancomycin and teicoplanin. *Infection, 22*, 338-338.

Peek, L. J., Middaugh, C. R., and Berkland, C. (2008). Nanotechnology in vaccine delivery. *Advanced Drug Delivery Reviews, 60*(8), 915-928.

Pinto-Alphandary, H., Andremont, A., and Couvreur, P. (2000). Targeted delivery of antibiotics using liposomes and nanoparticles: research and applications. *International Journal of Antimicrobial Agents, 13*(3), 155-168.

Pissuwan, D., Cortie, C. H., Valenzuela, S. M., and Cortie, M. B. (2010). Functionalised gold nanoparticles for controlling pathogenic bacteria. *Trends in Biotechnology, 28*(4), 207-213.

Rabea, E. I., Badawy, M. E. T., Stevens, C. V., Smagghe, G., and Steurbaut, W. (2003). Chitosan as antimicrobial agent: applications and mode of action. *Biomacromolecules, 4*(6), 1457-1465.

Raimondi, F., Scherer, G. G., Kötz, R., and Wokaun, A. (2005). Nanoparticles in energy technology: examples from electrochemistry and catalysis. *Angewandte Chemie International Edition*, 44(15), 2190-2209.

Rice-Ficht, A. C., Arenas-Gamboa, A. M., Kahl-McDonagh, M. M., and Ficht, T. A. (2010). Polymeric particles in vaccine delivery. *Current Opinion in Microbiology, 13*(1), 106-112.

Roco, M. C. (2011). The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. *Journal of Nanoparticle Research, 13*, 427-445. Available from: <https://link.springer.com/article/10.1007/s11051-010-0192-z>. doi: 10.1007/s11051-010-0192-z.

Roselli, M., Finamore, A., Garaguso, I., Britti, M. S., and Mengheri, E. (2003). Zinc oxide protects cultured enterocytes from the damage induced by Escherichia coli. *The Journal of Nutrition, 133*(12), 4077-4082.

Rosi, N. L., and Mirkin, C. A. (2005). Nanostructures in biodiagnostics. *Chemical Reviews, 105*(4), 1547-1562.

Saravanan, M., and Nanda, A. (2010). Extracellular synthesis of silver bionanoparticles from Aspergillus clavatus and its antimicrobial activity against MRSA and MRSE. Colloids *and Surfaces B: Biointerfaces, 77*(2), 214-218.

Sawai, J. (2003). Quantitative evaluation of antibacterial activities of metallic oxide powders (ZnO, MgO and CaO) by conductimetric assay. *Journal of Microbiological Methods*, 54(2), 177-182.

Sekhon, B. S., and Kamboj, S. R. (2010). Inorganic nanomedicine—part 2. *Nanomedicine: Nanotechnology, Biology and Medicine, 6*(5), 612-618.

Shaheen, M., Ha, T. and Su, N. (2015). A treatise on bovine mastitis: disease and disease economics, etiological basis, risk factors, impact on human health, therapeutic management, prevention and control strategy. *Advances in Dairy Research, 4*, 1–10. https://doi.org/10.4172/2329-888X.1000150.

Shahverdi, A. R., Fakhimi, A., Shahverdi, H. R., and Minaian, S. (2007). Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphylococcus aureus and Escherichia coli. *Nanomedicine: Nanotechnology, Biology and Medicine, 3*(2), 168-171.

Sharma, N., and Jeong, D. K. (2013). Stem cell research: a novel boulevard towards improved bovine mastitis management. *International Journal of Biological Sciences, 9*(8), 818. https:// doi.org/10.7150/ijbs.6901

Sharma, V. K., Yngard, R. A., and Lin, Y. (2009). Silver nanoparticles: green synthesis and their antimicrobial activities. *Advances in Colloid and Interface Science*, 145(1-2), 83-96.

Singh, M., Chakrapani, A., and O'Hagan, D. (2007). Nanoparticles and microparticles as vaccine-delivery systems. *Expert Review of Vaccines, 6*(5), 797-808.

Sondi, I., and Salopek-Sondi, B. (2004). Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria. *Journal of Colloid and Interface Science, 275*(1), 177-182.

Spain, E., Kojima, R., Kaner, R. B., Wallace, G. G., O'Grady, J., Lacey, K., and Forster, R. J. (2011). High sensitivity DNA detection using gold nanoparticle functionalised polyaniline nanofibres. *Biosensors and Bioelectronics, 26*(5), 2613-2618.

Torchilin, V. P. (2005). Recent advances with liposomes as pharmaceutical carriers. *Nature Reviews Drug Discovery*, 4(2), 145-160.

Tsai, G. J., and Su, W. H. (1999). Antibacterial activity of shrimp chitosan against Escherichia coli. *Journal of Food Protection, 62*(3), 239-243.

Tully, E., Hearty, S., Leonard, P., and O'Kennedy, R. (2006). The development of rapid fluorescence-based immunoassays, using quantum dot-labelled antibodies for the detection of Listeria monocytogenes cell surface proteins. *International Journal of Biological Macromolecules, 39*(1-3), 127-134.

Underwood, C., and Van Eps, A. W. (2012). Nanomedicine and veterinary science: The reality and the practicality. *The Veterinary Journal*, 193(1), 12-23. Available from: <https://pubmed.ncbi.nlm.nih. gov/22365842/>. doi: 10.1016/j. tvjl.2012.01.002.

Zhang, L., Pornpattananangkul, D., Hu, C. M., and Huang, C. M. (2010). Development of nanoparticles for antimicrobial drug delivery. *Current Medicinal Chemistry, 17*(6), 585-594.

Zhylkaidar, A., Oryntaev, K., Altenov, A., Kylpybai, E., and Chayxmet, E. (2021). Prevention of bovine mastitis through vaccination. *Archives of Razi Institute, 76*(5), 1381. https:// doi.org/10.22092/ari.2021.356008.1764

Chapter 04

Use of Nanoparticles for Drug Delivery in Cancer Treatment

Sofia Qasim[1], Ahmed Faraz[2], Madeeha Arshad[1], Muhammad Muazim Sharif[3], Adil Jamal[4], Muhammad Madni[5], Kashif Hussain Mangi[6], Ifrah Tahir[7], David Atuahene[8] and Adil Munir[9]

[1]Department of Zoology, Division of Science and Technology, University of Education Lahore, Faisalabad campus, Pakistan
[2]Faculty of Pharmacy, Master in Pharmaceutical Sciences, University of Cyberjaya
[3]Department of Zoology, Islamia University of Bahawalpur, Pakistan
[4]Sciences and Research, College of Nursing, Umm Al Qura University, Makkah Saudi Arabia
[5]Department of Chemistry, Government College University Faisalabad Layyah Campus, Pakistan
[6]Department of Chemical Engineering, Quaid-e-Awam University of Engineering Science and Technology Nawabshah, Pakistan
[7]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[8]Department of Veterinary Sciences, School of Agriculture and Veterinary Medicine, University of Turin, 10095 Grugliasco, Italy.
[9]School of Chemistry, Faculty of Basic Science and Mathematics, Minhaj University Lahore, Pakistan
*Corresponding author: Ifrahtahir999@gmail.com

ABSTRACT

Enhancing treatment techniques against cancer is highly promising due to the rapid advancement of nanotechnology in the invention of nanomedicine agents. The recently discovered method for injecting medications into cancer cells with the least amount of drug leakage into healthy cells is using Nanoparticles (NPs). A highly effective therapeutic strategy for treating cancer disorders is the coupling of NPs with ligands of tumor biomarkers unique to cancer. The ideal size and surface properties of NPs have been engineered to enhance their biodistribution and maintain their blood circulation. Nanotherapeutics make use of the distinct pathology of tumors, which includes increased permeability and retention effects, to precisely deliver active drugs to cancer cells. Apart from the passive targeting method, the efficacy of these pharmaceutical NPs is enhanced by active targeting tactics that employ ligands or antibodies that are directed against specific tumor sites. Different nanostructures have been studied as carriers in drug delivery systems, including polymer compounds, dendrimers, silicon or carbon compounds, magnetic NPs, and liposomes. This chapter addresses the use of NPs as delivery vehicles for anticancer medication compounds. Drug carrier systems and target specificity have been investigated for a range of NPs with varying structural and chemical compositions.

KEYWORDS
Nanoparticles, Cancer, Drug delivery

Received: 24-May-2024
Revised: 11-Jul-2024
Accepted: 15-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Qasim S, Faraz A, Arshad M, Sharif MM, Jamal A, Madni M, Mangi KH, Tahir I, Atuahene D and Munir A, 2024. Use of nanoparticles for drug delivery in cancer treatment. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 27-33. https://doi.org/10.47278/book.CAM/2024.184

INTRODUCTION

Every year, about 10 million new instances of cancer are diagnosed, making it one of the most deadly diseases in the world (Stewart et al., 2003). However, in the last two years, death has decreased as a result of technological developments in diagnostic tools and therapies as well as an improved understanding of cancer. Surgical procedures, radiation therapy, and chemotherapy are being used to treat cancer. These therapies frequently result in the death of healthy cells and damage to the patient. The non-specific distribution of conventional chemotherapeutic agents in the body limits their ability to influence both cancerous and normal cells. This leads to suboptimal treatment outcomes because of excessive toxicities and a lack of targeted action within tumor cells (Ross et al., 2004).

In the world, cancer is the second-greatest cause of mortality and one of the major public health issues. By the conclusion of 2021, 1.9 million new cases are expected, as estimated by the American Cancer Society (Gavas et al., 2021). Many nanotherapeutic medications have been developed and are now extensively marketed as a result of breakthroughs in nanotechnology, and since 2010, numerous more have reached the clinical stage. Drug combinations and the repression of mechanisms that contribute to drug resistance are two areas where nanotherapeutic medicines have made advances in the domains of drug delivery methods and anti-cancer multidrug resistance (Palazzolo et al., 2018). The capacity to operate at the atomic, molecular, and supramolecular levels (on a scale of around 1-100 nm) is known as nanotechnology.

It allows us to develop and comprehend material structures, devices, and systems with essentially unique characteristics and capabilities due to their microscopic structure (Roco et al., 2000). Due to nanotechnology, we can now create materials with whole new and desirable properties. The benefits and scientific limits of using NPs as medication delivery methods are being thoroughly studied worldwide. The development of the use of NPs as efficient medication delivery methods has advanced remarkably throughout the past ten years. Currently being researched are a variety of nanoparticle forms that can be used as drug delivery systems, such as ceramic NPs, polymeric micelles, dendrimers, liposomes, and polymeric biodegradable NPs, including nanospheres and nanocapsules (Yih et al., 2006). This chapter will focus on the various types and characteristics of NPs, their application as vehicles for drug delivery to more effectively kill cancer cells and remove drug resistance, and how advancements in nanoparticle technology in the future will improve the efficacy of their therapy and utility in cancer treatments.

Nanoparticles

According to scientific definitions, NPs are single-dimensional particles smaller than 100 nm with special qualities typically absent from larger amounts of the same substance (Boisseau et al., 2011). NPs can be categorized as 0D, 1D, 2D, or 3D, depending on their overall shape (Laurent et al., 2008). The relatively complicated fundamental composition of NPs is made up of the surface stratum and core which is basically the center of the nanoparticle and is often known as the nanoparticle itself (Tiwari et al., 2012). Due to their remarkable characteristics, such as their high surface-to-volume ratio, difference, sub-micron size, and improved targeting mechanism, these materials have become increasingly important in interdisciplinary sectors. Permeability and absorbance (EPR) impact is said to be enhanced by NPs' deep tissue penetration. Moreover, the surface characteristics effectively overcome epithelial fenestration, which affects solubility and half-life (Shin et al., 2016).

Delivery of Nanoparticles with Selectivity

For anticancer medications to be successful in the treatment of cancer, they should ideally be able to pass through the body's barriers and reach the targeted tumor tissues with the least amount of volume loss or blood circulation activity. Second, medications should be able to attack cancer cells only while avoiding normal cells once they have reached their target. Because these two fundamental strategies immediately decrease dose-limiting toxicities and increase medication intracellular concentration, they are also linked to increases in patient lifespan and quality of life.

Characteristics of Nanoparticles Surfaces and sizes

For NPs to effectively carry medication to the target cancer tissue, they must be able to sustain extended circulation without being eliminated from the bloodstream. Both conventionally coated and unmodified NPs are frequently absorbed in the blood through the system of reticuloendothelial cells, including the liver and spleen, based on their dimensions and surface features (Moghimi et al., 2001). The surface features of NPs play a crucial role in dictating their life cycle and fate in the bloodstream concerning being engulfed by macrophages. For NPs to avoid being captured by macrophages, their surface should ideally be hydrophilic (Moghimi et al., 2003). This may be done in two ways: either hydrophilic polymers, such as Peg, are coated on the surface of the NPs to prevent opsonization, or blocking copolymers with hydrophobic and hydrophilic domains can be used to produce the NPs (Harris et al., 2001). Nanomaterials employed in drug administration must be large sufficient to before medications from spilling into the blood vessels too quickly, but they should also be small enough to evade capture by stable macrophages found in the liver and spleen, as well as other retinal endothelial system organs. In contrast, gaps between endothelial cells that exist in the leaky vasculature of tumors can have a diameter of 100 to 600 nm. The sinusoidal structures in the spleen's wall or the Kupffer cells in the liver are 150 to 200 nm in size. NPs need not be larger than 100 nm for them to get beyond these two distinct circulatory systems and into cancerous tissues (Wisse et al., 1996).

Types of Nanoparticles that are used in Drug Delivery Systems

In drug delivery systems, three types of NPs are frequently used: hybrid, organic, and inorganic NPs. Drug delivery methods with NPs submicron-sized particles (between 3 and 200 nm), systems that may be created utilizing a range of materials such as viruses (viral NPs), polymers (polymeric NPs), lipids (liposomes), and even organometallic compounds.

Organic Nanoparticles Polymeric-based Drug Delivery Systems

Natural polymers, including albumin, chitosan, and heparin, have long been used to carry medications as well as oligonucleotides, DNA, and proteins. To treat metastatic breast cancer, paclitaxel nanoparticle formulations have recently been used in clinical settings. According to Gradishar et al. (2005), this formulation uses nanometer-sized albumin-bound paclitaxel or serum albumin as a carrier. Polygl-glutamic acid (PGA) is the first environmentally friendly polymer utilized for the synthesis of conjugate. This was followed by polyethylene glycol (PEG), polystyrene-maleic anhydride copolymer, and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) (Li et al., 2002).

The method used to create a polymeric-based drug distributor determines whether the drug is covalently bucked to the polymer matrix or physically ensnared within it (Rawat et al., 2006). The resultant molecules might be amphiphilic core/shell polymeric micelles, capsule-shaped NPs of polymeric materials polymer-drug conjugates, or hyperbranched

macromolecules. Two types of polymers are employed as drug conjugates: natural polymers and synthetic polymers. According to a study, indomethacin-loaded nanocapsules significantly reduced tumor growth and increased survival in a rat model of xenograft glioma (Andronescu et al., 2017).

Dendrimers

There is a clear hyperbranched structure to the round polymeric macromolecules called dendrimers. A very branching architecture is what makes dendrimers unique. Dendrimers synthesis is often initiated by a reaction between acrylic acid and an ammonia core. This process yields a "tri-amine" GO product when it reacts with ethylenediamine to form a "tri-acid" molecule. According to Wang et al. (2008), this product undergoes another interaction with acrylic acid and generates the hexa-acid, which then generates "hexa amine", ET so off. Dendrimer's size ranges from 1 to 10 nm on average. However, according to Kim et al. (2017), it may be the size of up to 15 nm. The particular arrangement, which includes a set molecular weight, changeable branching, bioavailability, and charge, makes them useful for targeting nucleic acids. According to Lim et al. (2013), some frequently used dendrimers are Polyamidoamine (PAMAM), polyethyleneglycol, polypropylene imine (PPI), and triethanolamine, (TEA). To accomplish MDR management, a PAMAM dendrimer was first created. Many descriptions exist of PAMAM dendrimers assembled by DNA. The synthesized dendrimers considerably slowed the growth of epithelial carcinoma xenograft in mice treated with single-agent chemotherapy.

mAb Nanoparticles

Monoclonal antibodies have a specific targeting characteristic that makes them useful in cancer therapy (Kukowska-Latallo et al., 2005). These days, NPs and these mAbs are combined to form antibody-drug conjugates or ADCs. Compared to cytotoxic drugs or mAb alone, these have been demonstrated to be significantly more compelling and selective. In HER2+ mammary epithelial cell control, for instance, an antibody-drug NP with an outer layer modified by trastuzumab and a paclitaxel core showed better antitumor efficacy and less toxicity than either paclitaxel alone or as a single agent (Sievers et al., 2013).

Drug Delivery Systems based on Lipids

Liposomes

One of the earliest nanoparticle platforms used in medicine was liposomes, which were originally reported in 1965 (Bangham et al., 1993). More than 11 forms are now approved for use in clinical trials, while several others are being developed in preclinical and clinical stages. Liposomes are close colloidal shapes made of spherical lipid two layers with an outer lipid bilayer encircling a central aqueous region (Torchilin et al., 2005). Better kinetics and biodistribution are frequently found in drugs with liposomal compositions. Currently, this lipid-based technology is being applied to many types of cancer medications using a diversity of preparation procedures. Between them, liposomal forms of anthracyclines doxorubicin and daunorubicin were licensed for the treatment of the spread widely breast cancer and the Kaposi's sarcoma associated with AIDS (Markman et al., 2006).

Viral Nanoparticles

A wide range of viruses, including bacteriophages, canine parvovirus, the cowpea mosaic virus, and the cowpea chlorotic mottle virus, have been developed for usage in medical and nano utilization, including drug delivery and the process of tissue targeting. Using pharmacologic or genetic techniques, a wide range of targeted chemicals and peptides can be expressed on the viral surface in a physiologically significant fashion. Consequently, several ligands or antibodies, such as folic acid, transferrin, and single-chain immune globulin have been affixed to viruses to specifically target specific tumors in vivo (Hofheinz et al., 2005).

To optimize specificity, target cells should have higher levels of antigens or receptor surface markers compared to normal cells. To efficiently transport liposomes that to B-cell receptors using anti-CD19 monoclonal antibodies (mAb), for instance, the number of receptors should be around 104 and 105 copies per cell. It is less effective to target individuals with a lower density (Harris et al., 2001).

Receptor-mediated absorption is commonly needed for nano distributors to transport medicine in the cells and is caused by the way certain ligands react with their respective receptors (Alonso et al., 2004). An even more noteworthy therapeutic outcome was observed, for instance, if immunoliposomes target B-cell lymphoma, which is a kind of blood-related cancer, were tagged with an absorbing anti-CD19 ligand rather than a non-internalizing anti-CD20 ligand (Torchilin et al., 2005). Nevertheless, targeting nanocarriers towards non-internalizing receptors can sometimes be advantageous in solid tumors because of the effect of bystanders, which enables carriers to attach to surrounding cells and deliver medication to kill cells lacking the target receptor (Hobbs et al., 1998).

Inorganic Nanoparticles

Carbon Nanoparticle

Carbon is the building block of carbon NPs. They have found widespread use in health applications because of their mechanical ad optical, and electrical biocompatible characteristics (Swaminathan et al., 2010). Drugs can be encapsulated by carbon NPs via π-π stacking because of their intrinsic hydrophobic character (Ou et al., 2016). One can further classify

carbon NPs (NPs) into graphene, fullerenes, carbon nanohorns, carbon nanotubes, and graphene. Their form, morphology, and characteristics differ, even though they are all carbon-based.

Carbon nanotubes are cylinders that were originally discovered in the late 1980s; they are also referred to as rolls of graphite. There are two types of CNTs: single-walled and multi-walled. They may communicate with immune system cells to generate an immunological reaction, which will halt the tumor's growth because they are carbon-based. They were previously used as the DNA vector transport devices and in heat therapy of ablation. To target colon cancer cells, for example, a fluorescent single-walled CNT containing a mAb enclosing doxorubicin is employed. These CNTs combine to produce a complex that the cancer cells efficiently absorb, releasing doxorubicin intracellular while keeping the CNTs in their cytoplasm (Tabata et al., 1997)(Fig.1).

Quantum Dots

Biological imaging uses quantum dots extensively because they are semiconductors at the nanoscale scale that have a large variety of absorption, limited emission bands, and quality photostability (Heister et al., 2009). The three groups into which they are divided based on carbon are graphite quantum dots or carbon quantum dots, among others. Biological imaging with quantum dots is not the only application being explored by researchers. Cancer treatment is another. Graphene quantum dot quantum dots are the most widely used variety of quantum dots because they are rapidly eliminated from the body and are naturally biocompatible. Jamieson et al. (2007) reported that doxorubicin and quantum dots aptamer combo is effective against prostate cancer cells. However, the biggest obstacle is the absence of an ideal process for producing quantum dots.

Metallic Nanoparticles

Due to metallic NPs' exceptional optical, magnetic, and photothermal properties, they are being extensively investigated for "biological imaging" and focused DDS applications. Among the majority often utilized kinds of metallic NPs are those based on copper, iron, silver, and gold. According to (Bagalkot et al. 2007), NPs of gold (NPs) are utilized as internally extended drug carriers due to their easily controlled surface and size properties.

Magnetic Nanoparticles

When using metallic or metallic oxide-based medication delivery systems or magnetic resonance imaging (MRI), NPs with magnetic properties (NPs) are frequently employed. It is usually bound with the organic ingredients as fatty acids or polymers and increases their biocompatibility and durability (Castaneda et al., 2011). Breast cancer can be detected and visualized with the help of supermagnetic NPs of iron oxide and LHRH (Basoglu et al., 2018).

Nanoparticles of Calcium Phosphate

The substance known as "calcium phosphate NPs" is biodegradable, compatible with biology, and does not have any negative side effects. For this reason, they are employed as a delivery system for growth hormones, insulin, antibiotics, and birth control (Maurya et al., 2019). They are used in the transportation of oligonucleotides and plasmid DNA (Khosravi et al., 2010). Calcium phosphate NPs have been effectively used as delivery vectors for viral or non-viral cellular gene transfer veterinarians. The "liposomal nanolipoplex mixture" and magnesium or glycerol were shown to have reduced poisoning and better transfiguration characteristics (Mozafari et al., 2007).

Silica Nanoparticles

Silica has been studied in biology very recently, despite being a key element found in numerous natural materials. Silica NPs, also known as NPs, are widely used for gene transfer because of their ability to enhance their exterior with amino-silicanes (Katragadda et al., 2021).

Nanoparticle-mediated passive targeting

Improved Retention and Permeability

NPs that meet those prerequisites for size and surface properties in order to avoid being captured by the reticuloendothelial system can circulate in the circulation for extended periods and have a higher probability of reaching the targeted tumor tissues. Macrophages, including NPs, can aggregate in tumor tissues with selectivity due to the distinct path physiologic features of tumor vasculature (Maeda et al., 2001). In order to give oxygen and nutrients to rapidly proliferating cancer cells, existing arteries must be rerouted or recruited (a process known as revascularization) close to the tumor mass (Carmeliet et al., 2000). Tumor arteries become highly disordered and dilated, and numerous apertures show greater gaps in the junction between the endothelial cells and limited lymphatic outflow due to the resulting imbalance in angiogenic regulators, including matrix metalloproteinases and growth factors. These characteristics are referred to as the improved permeability and retention effect, and they are a crucial mechanism that allows macromolecules including NPs with molecular weights greater than 50 kDa to concentrate in the tumor interstitium in a targeted manner.

Microenvironment of Tumor

The distinct environment surrounding tumor cells, which differs from the surroundings of normal cells, also plays a

role in passive targeting. Cancer cells that proliferate quickly have a rapid metabolism, and they typically cannot sustain this pace due to insufficient oxygen and nutrition supplies. As a result, an acidic environment is created when tumor cells employ glycolysis to get additional energy (Pelicano et al., 2006). Certain enzymes that are expressed and released by cancer cells include matrix metalloproteinases, which are involved in the mobility and survival of these cells (Deryugina et al., 2006).

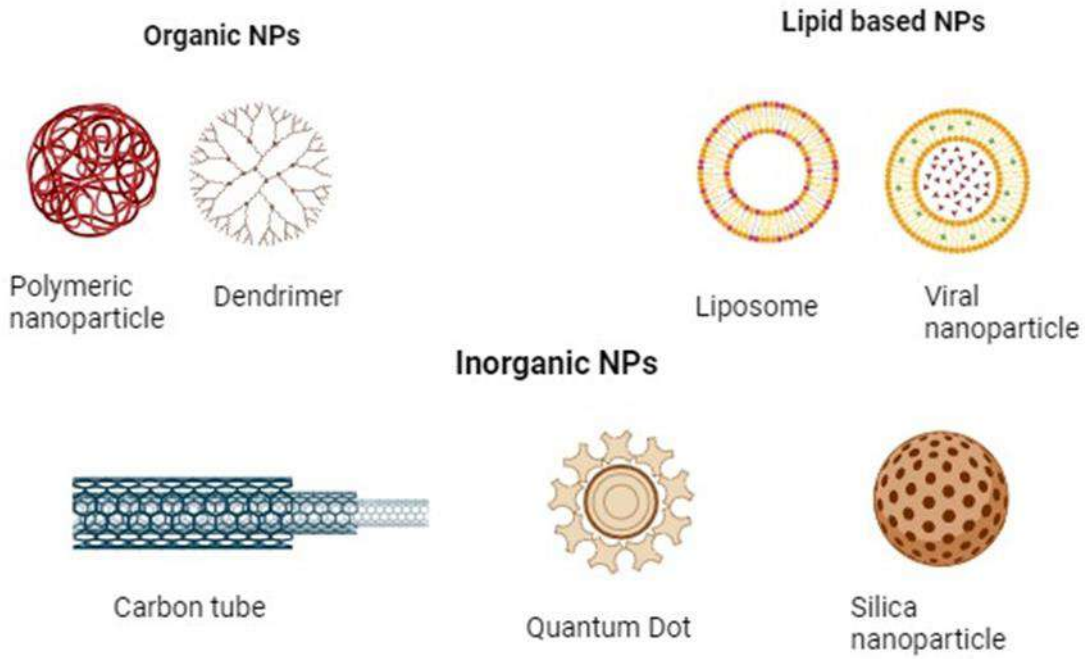


Fig 1: Types of NPs (Retrieved from Biorender).

Active Nanoparticle Targeting

There will inevitably be limitations to the selectivity of a drug administration strategy involving a two-conjugate or polymer medication combination it solely depends on the passive target techniques. One way to get around these restrictions is to add a targeted ligand or antibody to polymer-drug conjugates (Allen et al., 2002). An antibody and a medication were first tried to be directly conjugated. However, these early conjugates of antibodies and drugs have not demonstrated efficiency over a targeted delivery method for cancer treatment in clinical studies that have been carried out so far. This is due, in part, to the restricted quantity of molecules of drugs that may be incorporated into an antibody without compromising its ability to recognize immunological stimuli. Because a wide variety of liposomes and polymers have recently been discovered and introduced for use as drug delivery carriers, compared to previous antibody-drug conjugates, a bigger number of medications may be coupled with particular NPs without altering their targeting affinity. The ternary configuration of an antibody or ligand as the target moiety, an active chemotherapeutic drug as the carrier, and a polymer or lipid as the carrier is used by many recently identified targeted conjugates of drugs to take advantage of the wide range of transporters, targeting molecules, and medications available. Making ternary-structure NPs requires consideration of a few factors in order to produce more efficient delivery systems.

Expression of an Antigen or a Receptor

Antigens and receptors on the cell surface should ideally possess a number of characteristics that make them especially well-suited as targets unique to tumors. First, only tumor cells should exhibit them; normal cells should not express them. Secondly, on all targeted tumor cells, they need to express uniformly. Finally, antigens and receptors on the cell surface shouldn't leak into the bloodstream (Allen et al., 2002).

Targeted Conjugates Internalization

The ability of the intended conjugates to be internalized after adhering to the target cells is a crucial consideration when selecting the appropriate targeting ligand. Usually, internalization happens through endocytosis mediated by receptors. Using the foliate receptor as an example, an endosome is formed when the combination of the ligand and the receptor is encased in the invading plasma membrane after a foliate-targeted compound binds to the acid region on the cell surface. Target organelles get newly produced endosomes. When an endosome's pH level drops and enzymes are triggered, the drug exits the conjugation process. It reaches the cytoplasm if it possesses the necessary physical and chemical properties to cross the endosomal membrane. Depending on the substance, the target organelle will then trade the released medicines. As this is going on, the conjugate's released foliate receptor goes back to the cell surface and binds to fresh conjugates that target foliate to initiate a new round of transport (Leamon et al., 2004).

REFERENCES

Allen, T. M. (2002). Ligand-targeted therapeutics in anticancer therapy. *Nature Reviews Cancer*, *2*(10), 750-763.

Alonso, M. J. (2004). Nanomedicines for overcoming biological barriers. *Biomedicine and Pharmacotherapy*, *58*(3), 168-172.

American Cancer Society. (2007). *Breast cancer facts and figures*. American Cancer Society.

Andronescu, E., and Grumezescu, A. M. (2017). *Nanostructures for drug delivery*. Elsevier.

Bagalkot, V., Zhang, L., Levy-Nissenbaum, E., Jon, S., Kantoff, P. W., Langer, R., and Farokhzad, O. C. (2007). Quantum dot–aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence resonance energy transfer. *Nano Letters*, *7*(10), 3065-3070.

Bangham, A. D. (1993). Liposomes: the Babraham connection. *Chemistry and Physics of Lipids*, *64*(1-3), 275-285.

Basoglu, H., Goncu, B., and Akbas, F. (2018). Magnetic nanoparticle-mediated gene therapy to induce Fas apoptosis pathway in breast cancer. *Cancer Gene Therapy*, *25*(5), 141-147.

Boisseau, P., and Loubaton, B. (2011). Nanomedicine, nanotechnology in medicine. *Comptes Rendus Physique*, *12*(7), 620-636.

Carmeliet, P., and Jain, R. K. (2000). Angiogenesis in cancer and other diseases. *Nature*, *407*(6801), 249-257.

Castaneda, R. T., Khurana, A., Khan, R., and Daldrup-Link, H. E. (2011). Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. *JoVE (Journal of Visualized Experiments)*, (57), e3482.

Deryugina, E. I., and Quigley, J. P. (2006). Matrix metalloproteinases and tumor metastasis. *Cancer and Metastasis Reviews*, *25*, 9-34.

Gavas, S., Quazi, S., and Karpiński, T. M. (2021). NPs for cancer therapy: current progress and challenges. *Nanoscale Research Letters*, *16*(1), 173.

Gradishar, W. J., Tjulandin, S., Davidson, N., Shaw, H., Desai, N., Bhar, P., and O'Shaughnessy, J. (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *Journal of Clinical Oncology*, *23*(31), 7794-7803.

Harris, J. M., Martin, N. E., and Modi, M. (2001). Pegylation: a novel process for modifying pharmacokinetics. *Clinical Pharmacokinetics*, *40*, 539-551.

Harris, J. M., Martin, N. E., and Modi, M. (2001). Pegylation: a novel process for modifying pharmacokinetics. *Clinical Pharmacokinetics*, *40*, 539-551.

Heister, E., Neves, V., Tîlmaciu, C., Lipert, K., Beltrán, V. S., Coley, H. M., and McFadden, J. (2009). Triple functionalisation of single-walled carbon nanotubes with doxorubicin, a monoclonal antibody, and a fluorescent marker for targeted cancer therapy. *Carbon*, *47*(9), 2152-2160.

Hobbs, S. K., Monsky, W. L., Yuan, F., Roberts, W. G., Griffith, L., Torchilin, V. P., and Jain, R. K. (1998). Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. *Proceedings of the National Academy of Sciences*, *95*(8), 4607-4612.

Hofheinz, R. D., Gnad-Vogt, S. U., Beyer, U., and Hochhaus, A. (2005). Liposomal encapsulated anti-cancer drugs. *Anti-cancer Drugs*, *16*(7), 691-707.

Jamieson, T., Bakhshi, R., Petrova, D., Pocock, R., Imani, M., and Seifalian, A. M. (2007). Biological applications of quantum dots. *Biomaterials*, *28*(31), 4717-4732.

Katragadda C, Choudhury P, Murthy P (2021) NPs as non-viral gene delivery vectors. [online] Ijper.org. http://www.ijper.org/article/259. Accessed 30 July 2021

KHOSRAVI, D. K., Mozafari, M. R., Rashidi, L., and Mohammadi, M. (2010). Calcium based non-viral gene delivery: an overview of methodology and applications.

Kim, K. Y. (2017). Nanotechnology platforms and physiological challenges for cancer therapeutics. *Nanomedicine in Cancer*, 1-19.

Kukowska-Latallo, J. F., Candido, K. A., Cao, Z., Nigavekar, S. S., Majoros, I. J., Thomas, T. P., and Baker Jr, J. R. (2005). Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. *Cancer Research*, *65*(12), 5317-5324.

Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., and Muller, R. N. (2008). Magnetic iron oxide NPs: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical Reviews*, *108*(6), 2064-2110.

Leamon, C. P., and Reddy, J. A. (2004). Folate-targeted chemotherapy. *Advanced Drug Delivery Reviews*, *56*(8), 1127-1141.

Li, C. (2002). Poly (L-glutamic acid)–anticancer drug conjugates. *Advanced Drug Delivery Reviews*, *54*(5), 695-713.

Lim, J., Kostiainen, M., Maly, J., Da Costa, V. C., Annunziata, O., Pavan, G. M., and Simanek, E. E. (2013). Synthesis of large dendrimers with the dimensions of small viruses. *Journal of the American Chemical Society*, *135*(12), 4660-4663.

Maeda, H. (2001). The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. *Advan Enzyme Regul*, *41*, 1898-207.

Markman, M. (2006). Pegylated liposomal doxorubicin in the treatment of cancers of the breast and ovary. *Expert Opinion on Pharmacotherapy*, *7*(11), 1469-1474.

Maurya, A., Singh, A. K., Mishra, G., Kumari, K., Rai, A., Sharma, B., and Awasthi, R. (2019). Strategic use of nanotechnology in drug targeting and its consequences on human health: A focused review. *Interventional Medicine and Applied*

Science, *11*(1), 38-54.

Moghimi, S. M., and Szebeni, J. (2003). Stealth liposomes and long circulating NPs: critical issues in pharmacokinetics, opsonization and protein-binding properties. *Progress in Lipid Research*, *42*(6), 463-478.

Moghimi, S. M., Hunter, A. C., and Murray, J. C. (2001). Long-circulating and target-specific NPs: theory to practice. *Pharmacological Reviews*, *53*(2), 283-318.

Mozafari, M. R., Reed, C. J., and Rostron, C. (2007). Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, *62*(3), 205-209.

Ou, L., Song, B., Liang, H., Liu, J., Feng, X., Deng, B., and Shao, L. (2016). Toxicity of graphene-family NPs: a general review of the origins and mechanisms. *Particle and Fibre Toxicology*, *13*, 1-24.

Palazzolo, S., Bayda, S., Hadla, M., Caligiuri, I., Corona, G., Toffoli, G., and Rizzolio, F. (2018). The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric NPs, micelles, liposomes and exosomes. *Current Medicinal Chemistry*, *25*(34), 4224-4268.

Pelicano, H., Martin, D. S., Xu, R. A., and Huang, P. (2006). Glycolysis inhibition for anticancer treatment. *Oncogene*, *25*(34), 4633-4646.

Rawat, M., Singh, D., Saraf, S. A. S. S., and Saraf, S. (2006). Nanocarriers: promising vehicle for bioactive drugs. *Biological and Pharmaceutical Bulletin*, *29*(9), 1790-1798.

Roco, M. C., Williams, R. S., and Alivisatos, P. (Eds.). (2000). *Nanotechnology research directions: IWGN workshop report: vision for nanotechnology in the next decade*. Springer Science and Business Media.

Ross, J. S., Schenkein, D. P., Pietrusko, R., Rolfe, M., Linette, G. P., Stec, J., and Hortobagyi, G. N. (2004). Targeted therapies for cancer 2004. *American Journal of Clinical Pathology*, *122*(4), 598-609.

Shin, W. K., Cho, J., Kannan, A. G., Lee, Y. S., and Kim, D. W. (2016). Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO2 NPs for lithium-ion polymer batteries. *Scientific Reports*, *6*(1), 26332.

Sievers, E. L., and Senter, P. D. (2013). Antibody-drug conjugates in cancer therapy. *Annual Review of Medicine*, *64*, 15-29.

Stewart, B. W., and Kleihues, P. (Eds.). (2003). *World cancer report* (Vol. 57). Lyon: IARC press.

Swaminathan, S., Pastero, L., Serpe, L., Trotta, F., Vavia, P., Aquilano, D., and Cavalli, R. (2010). Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. *European Journal of Pharmaceutics and Biopharmaceutics*, *74*(2), 193-201.

Tabata, Y., Murakami, Y., and Ikada, Y. (1997). Photodynamic effect of polyethylene glycol–modified fullerene on tumor. *Japanese Journal of Cancer Research*, *88*(11), 1108-1116.

Tiwari, J. N., Tiwari, R. N., and Kim, K. S. (2012). Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. *Progress in Materials Science*, *57*(4), 724-803.

Torchilin, V. P. (2005). Recent advances with liposomes as pharmaceutical carriers. *Nature reviews Drug Discovery*, *4*(2), 145-160.

Wang, X., Yang, L., Chen, Z., and Shin, D. M. (2008). Application of nanotechnology in cancer therapy and imaging. *CA: a Cancer Journal for Clinicians*, *58*(2), 97-110.

Wisse, E., Braet, F., Luo, D., De Zanger, R., Jans, D., Crabbe, E., and Vermoesen, A. N. (1996). Structure and function of sinusoidal lining cells in the liver. *Toxicologic Pathology*, *24*(1), 100-111.

Wu, J., Liu, Q., and Lee, R. J. (2006). A folate receptor-targeted liposomal formulation for paclitaxel. *International Journal of Pharmaceutics*, *316*(1-2), 148-153.

Yih, T. C., and Al-Fandi, M. (2006). Engineered NPs as precise drug delivery systems. *Journal of Cellular Biochemistry*, *97*(6), 1184-1190.

Chapter 05

Role of Nanoparticles in the Treatment of Renal Cancer

Hassaan Bin Sajid[1], Amisha Naz[2], Laiba Naeem*[3], Bint-e-Zahra[3], Muhammad Zeeshan Haider[5], Safoora Murad[3], Hafiz Aamir Ali Kharl,[4] Muhammad Usama Javed[6] and Muhammad Ijaz Saleem[8]

[1]CABB Department, University of Agriculture, Faisalabad, Pakistan
[2]Department of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[3]Department of Chemistry, Faculty of Science, University of Agriculture, Faisalabad, Pakistan
[4]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
[5]Department of Human Nutrition and Dietetics, NIFSAT, University of Agriculture, Faisalabad, Pakistan
[6]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[7]Department of Parasitology, University of Agriculture, Faisalabad, Pakistan
[8]Department of Clinical Medicine and Surgery, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: laibanaeem401@gmail.com

ABSTRACT

The human urinary system consists of two kidneys which are amenable to filtering the blood and releasing metabolic waste in the form of urine through the renal glomerulus. The kidneys face major challenges due to the drug delivery system leading to treatment failure in multiple renal diseases. Since existing treatments for chronic kidney disease (CKD) are mostly unsuccessful, the condition has a significant impact on worldwide public health. Quick detection and appropriate therapy are important for the upcoming thwarting and emergence of CKD. Nanosystems having several physicochemical characteristics such as size, shape, density, surface, and charge with low cytotoxicity, compliant pharmacokinetics, cell internalization, and biodistribution, have shown positive results for renal therapy. Several forms of NPs have been utilized as drug carriers for renal treatment. Conversely, nanoparticles (NPs) having the size of 8nm cannot pass through the kidney. Still, all the nanostructures can be suitable and nontoxic if the nanoparticles' diameter is over the asymptotic value of 6nm for kidney filtration. As a result, the development of NPs in medicine has offered fresh approaches to the possible detection and management of kidney cancer.

KEYWORDS
Nanoparticles, Alternatives, CKD, Treatment, Cytotoxicity

Received: 05-Jun-2024
Revised: 21-Jul-2024
Accepted: 05-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Sajid HB, Naz A, Naeem L, Bint-e-Zahra, Haider MZ, Murad S, Kharl HAA, Javed MU and Saleem MI, 2024. Role of nanoparticles in the treatment of renal cancer. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 34-39. https://doi.org/10.47278/book.CAM/2024.277

INTRODUCTION

Cancer is a general term for a group of diseases defined as unbridled division and disruption of cells (Chandraprasad et al., 2022). Many years of intensive work have been devoted to identifying potential cancer risk factors. The genesis of some malignancies has been strongly linked to particular environmental variables including pollution and radiation but detrimental lifestyles like chronic stress, insufficient sleep, poor hygiene, consuming alcohol and sugary drinks, and unhealthy fats critically influence the cancer susceptibility assessment (Marino et al., 2024). Although these outside variables have been identified as important contributors to cancer, it has been difficult to determine how many proto-oncogene mutations, tumor suppressor gene expression patterns, and DNA repair genes are involved (Chen et al., 2020). Exclusively, 5-10% of instances of cancer are caused by genetic factors. Aging also contributes to many distinct cancer forms (Klein, 2021).

In the past few years, the number of renal suffers has greatly grown. Chronic kidney disease (CKD) and acute kidney injury (AKI) are the two main types of renal disorders (Liu et al., 2021). Moreover, it is considered that AKI and CKD are intimately related. In the modern world, the prevalence of renal pelvis and kidney cancer has increased dramatically (Cassell III et al., 2021). Renal cell carcinoma, also known as RCC, is a sneaky tumor that causes around 2% of cancer cases and deaths globally, and its incidence is expected to rise (Padala et al., 2020). The majority of RCCs are found in the kidney's cortex, which is made up of the collecting duct, tubular apparatus, and glomerulus. In terms of histology and behavior, malignancies of the renal pelvises are similar to urothelial (bladder) cancer. Hematuria, flank discomfort, and palpable masses are the "classic triad" of symptoms that just 10% of patients have at first. Additional typical symptoms include weight loss, leukocytosis, and fever. Moreover, around 20% of patients have a range of

paraneoplastic syndromes, such as hypertension brought on by an excess of renin, polycythemia from erythropoietin, Cushing's syndrome from adrenocorticotropic hormone (ACTH), and hypercalcemia from parathyroid-related hormone peptide (Satwikananda et al., 2023). Sometimes, because of tumor involvement and occlusion of the left-side renal vein, a diagnosis of left-sided varicocele raises the possibility of RCC. Surgical resection and ablation of the neoplasm or percutaneous biopsies with immunohistochemistry (IHC) staining are the two methods used to determine systemic therapy, depending on the patient's features and the severity of the illness (Vasiniotis Kamarinos et al., 2022). The immunohistochemical stain for programmed death ligand-1 (PDL1), an immunosuppressive marker, has gained significant predictive power because PD-1 inhibitors, such as pembrolizumab and nivolumab, have been used as the first-line treatment for PDL1-positive metastatic illness (Sekino et al., 2023). About 8.2% of patients had PDL1-positive disease, which is linked to more advanced illness and a worse chance of survival (Cabezón-Gutiérrez et al., 2021). Radiation and chemotherapy are extremely resistant to even PDL1-negative diseases. Various targeted treatments (such as sunitinib, a VEGF tyrosine kinase inhibitor) and immunotherapies (like aldesleukin (IL-2)) are commonly used in the treatment of metastatic illness.

Based on GLOBOCAN statistics from 2018, an estimated 403,000 individuals receive a diagnosis of kidney neoplasms a year, accounting for 2.2% of the total number of cancer diagnoses. From these, about 148,800 cases are ascertained in females and 254,500 in males, indicating an about 1.7 relative risk (RR) difference between men and women. Men and women have a cumulative worldwide risk of 0.69% and 0.35%, respectively, of acquiring the condition. As a result, the age-standardized rate (ASR) for men and women is 6.0 and 3.1, with a global average of 4.4. Belarus is the state in the world with the predominant cases of about 16.8/100,000 but the effective incidence in several countries in central Africa is close to or equal to 0. In the developed world, RCC is the seventh utmost type of neoplasm. According to the surveillance, epidemiological research, and results, around 74,000 new cases of renal cancer were detected in the US in 2019, making up 4.2% of all cancer diagnoses. The first reported rate of prevalence was 7.1/100,000 in 1975. Moreover, this led to a 4.9/100,000 incidence rate in 2016. This consistent increase has made renal cancer one of the rapidly growing cancers (Padala et al., 2020).

The primary methods for treating cancer are chemotherapy, irradiation, and surgical excision (Debela et al., 2021). The use of these conventional methods relies on the cancer type and maturation level of the cancer. The core treatment method is chemotherapy used for restricted and metastatic types of cancer which can be applied alone or concocted with the rest of therapies. Although, there are some drawbacks to conventional chemotherapy (Pedziwiatr-Werbicka et al., 2021). Foremost among them is limited aqueous solubility because most chemotherapeutics, whether synthetic or derived from plants, are hydrophobic and need solvents to manufacture the dose form, they can be quite hazardous. The second one is the nondiscrimination of anticancer drugs which can harm quickly reproducing normal cells and are non-selective for tumor cells. Another drawback is multidrug resistance or MDR which is mostly caused by elevated efflux pumps in the cell membrane, such as P-glycoprotein (Pgp), which are in charge of removing different anticancer medications from cells (Catalano et al., 2022).

In the last few years, strong tools for the diagnosis, imaging, and treatment of several illnesses and ailments have been revealed which are nanoparticles (NPs) and nanomedicines. The term "nanotechnology" refers to technology applied at the nanoscale. The ultrafine particles known as nanoscale/nanoparticles range in size from 1 nm to 1000 nm (Prerna and Ratan, 2021). When it comes to highly specialized medical intervention at the molecular level for illness detection, prevention, and therapy, nanomedicine is a significant field within nanotechnology. NPs have the potential to be utilized for molecular targeting and diagnostic imaging of many kidney disorders, such as AKI and CKD (Paluszkiewicz et al., 2021). Nanoparticles and Nanomedicines have specificity, diversity, and efficiency which could handle the difficulty of renal disease treatment. However, obstacles to their systemic administration and tailored distribution have hampered the implementation of nano-based therapies, despite their tremendous potential for treating renal disorders. These obstacles may arise during blood circulation, kidney entrance, or while traveling to specific kidney locations. Luckily, new research has indicated ways to enhance the movement of NPs from the bloodstream to the kidneys and their retention there, potentially resolving both issues.

Researchers conducted a groundbreaking study that demonstrated the ability of polymeric nanoparticles made of poly (methyl methacrylate) (PMMA) to enter renal tissue through systemic circulation. Renal-targeted drug delivery system (DDS) research began in the 1990s. In 1994, actinomycin D-loaded poly (isobutylcyanoacrylate) nanoparticles (NPs) localized in rat mesangial cells were used to describe the first targeted drug delivery method for glomerular mesangial cells. The exponential rise of nanomedicine as a whole has greatly accelerated subsequent research advancements in this area. Targeted nanoparticles (NPs) have emerged as a viable delivery system for tailored therapeutics in preclinical and clinical studies in laboratory settings, both in academia and industry (Oroojalian et al., 2020).

Nanoparticles in Renal Cancer Diagnosis

Evaluation of early and particular indicators is thought to be essential for forecasting the early development and course of nephropathy. Consequently, CKD might be avoided and consequences like infection, hypertension, anemia, and heart failure could be decreased with the use of an efficient intervention therapy (Kalantar-Zadeh et al., 2021). Nonetheless, the conventional diagnostic ways are currently accessible but have some drawbacks such as disruption and insensitivity. That’s why, NPs may be crucial for the rapid detection of CKD with substantial sensitivity. CKD can be detected

in two ways which include nanoimaging and nano-biomakers.

Nanoimaging

Kidney function is directly described by glomerular filtration rate (GFR). However, the contrast agent iohexol, which is used for this operation, might cause acute renal damage, making this form of detection uncomfortable. The CKD-epidemiology collaborative (CKD-EPI) formula, often known as eGFR, is frequently used by doctors to estimate GFR. However, tubular cells could absorb and secrete a small amount of creatinine, which reduced their ability to detect CKD in its early and late stages (González-Nicolás et al., 2024). In contrast, different fluorescent NPs, such as Q-dots, gold, and silica NPs, have been identified to offer four unique advantages over existing techniques in the assessment of GFR (Bhatt et al., 2024). Firstly, they did not produce any toxicity or disrupt in vivo metabolism. Secondly, the wavelengths of absorption and emission were in the visible range, with the near-infrared area being more favorable. Thirdly, glomeruli can completely filter them but cannot be absorbed and secreted through the tubules. NPs were convenient to develop and also affordable. Fluorescent semiconductor nanocrystals, or Q-dots, are examples of commercially accessible nanomaterials that have been extensively used in the biological area. Moreover, a variety of disorders, including cancer, have been extensively studied using extremely sensitive and reasonably priced near-infrared fluorescence imaging. However, preclinical research on noninvasive fluorescence imaging for renal insufficiency and staging is currently ongoing. Glutathione-coated gold nanoparticles (GS-AuNPs), which are renal-clearable and produce near-infrared light, have been employed by several scientists as a contrast agent in renal-function fluorescence imaging. In rats exhibiting unilateral ureteral obstruction (UUO), they discovered that this nanotechnology was effective for reporting the phases of kidney impairment and for noninvasively monitoring kidney disease (Huang, 2020). Additionally, they were able to pinpoint the malfunction that was present in kidney phases that corresponded with renal impairment as determined by pathological evidence. It is verified nowadays that both blood urea and serum creatinine are insufficient to identify renal impairment but nanomedicine can act as a potential identifier for this act. At first, they used GS-AuNPs to demonstrate that they were harmless and had no effect on metabolism in vivo by fluorescent imaging renal clearance kinetics in healthy mice. However, there are no structural changes and also discovered a very low deposition in the supporting tissues shown by the kidneys of mice. The visible and IR ranges having wavelengths of (~800nm) were emitted from gold NPs coated with glutathione. GS-AuNPs could be effectively eliminated from the body through the kidneys because of their smaller diameter (Ma et al., 2020). Currently, there are a variety of renal-clearable NPs accessible, including carbon dots, palladium nanosheets, iron oxide NPs, copper nanoparticles (CuNPs), silica NPs (SiNPs), and AuNPs, making the use of NPs in noninvasive-kidney-imaging-feasible. Significantly, NP imaging assesses renal tenderness and fibrosis as well as correctly identifies the phases of kidney failure, suggesting that this technique may be utilized in the future to both identify renal function and invasively study pathology (Paluszkiewicz et al., 2021).

Nano-Biomarkers

The risk factor for incident CKD and the advancement of CKD is albuminuria. The standard dipstick for urinalysis was only positive when the level of albumin in the urine was more than 30 mg/dL (Sumida et al., 2020). Urine albumin dipsticks or different specific antibody techniques can be used to test for microalbuminuria. However, these methods are inappropriate and insensitive. Raman spectrometers are readily accessible for purchase, and SERS offers several benefits including high sensitivity, easy sample preparation, quick analysis, and rapidity (Kołątaj et al., 2020). For instance, this method makes use of the analyte-absorbing silver NP surface, which might greatly increase the Raman signal. The minor value shows the authenticity of this procedure than any other conventional methods for tracking microalbuminuria. As previously reported, urine albumin may be detected relatively quickly and without the need for sample pre-processing. Currently, commercial tools that provide microalbuminuria point-of-care screening are accessible. The biological compatibility and conductivity of the newly developed disposable electrochemical immunosensor for point-of-care microalbuminuria testing were improved by the use of Au nanoparticles on the electrodes. Nowadays dielectrophoresis has been used to prepare new types of mixed Nps that are covalently attached to the antibodies. Another advantage of this technology is that you can take samples from anywhere even from the house of the patients and send data to the electronic machines for early CKD identification (Ma et al., 2020).

A revolutionary multianalyte point-of-care device based on nanotechnology may be used to test hemoglobin, serum albumin, urine creatinine, and glycosylated red blood cells in addition to microalbuminuria. It may also be expanded to monitor additional protein indicators such as glycated albumin and serum creatine. This gadget helps identify diabetic kidney disease early on by comparing test findings with laboratory data; in the future, it may be utilized in distant underdeveloped countries. Cystatin C (CysC), kidney injury molecule-1 (KIM-1), and N-acetyl- β-D-glucosaminidase (NAG) are promising biomarkers against CKD (Jana et al., 2022). Research on the use of NPs to enhance an immunosensor's response in the identification of these biomarkers is becoming more and more extensive. A sandwich-style assay was used to produce an inexpensive amperometric immunosensor to identify CysC in human serum. Researchers applied Au NPs layer-by-layer to check the CysC response and achieved excellent results. A new Ru (II) complex molecule having self-enhanced electrochemiluminescence (ECL) capabilities, called $[Ru(dcbpy)2dppz]^{2+}$-DPEA, was also recommended. When this molecule was introduced into the DNA duplex, it became brilliantly luminous (Ma et al., 2020). They discovered NAG, a unique biomarker of diabetic nephropathy, by using DNA nanotechnology in combination with an ECL self-enhanced

molecule to provide an effective signal amplification approach. Similarly, KIM-1 level biomarkers are being used along with ECL biosensors for early renal damage. Then, Pt NPs are pertinent to enhance the efficiency of electron transfer (Yu et al., 2022). So overall, nanotechnology is a very effective and sensitive instrument that has the potential to determine the early and accurate CKD diagnosis.

Nanoparticles in Renal Cancer Therapy

Quick advancements in nanotechnology for the creation of nanomedicine agents have enormous potential to enhance cancer treatment strategies. Products in the nanomedicine space provide the chance to develop complex targeting techniques and multifunctionality. New cancer treatments have been developed and improved using a broad variety of nanoparticles based on lipids, synthetic polymers, and organic, inorganic, or glycan substances (Aghebati-Maleki et al., 2020). They have been examined for the treatment of renal cancer, such as; Drug delivery systems, nano surgery, and gene nanotherapy.

Nanoparticles for Drug Delivery in Renal Cancer

NPs have been extensively studied for the transport of many kinds of medications because of their effective and safe specific drug delivery characteristic. NPs increased the medications' targetability, bioavailability, and pharmacokinetic qualities (Lee et al., 2023). Recently, it was demonstrated that thapsigargin NPs might effectively cure CKD by activating FoxO1 and Nrf2. Through the activation of Nrf2 and FoxO1, thapsigargin NPs prevented oxidative stress-induced cell death in human kidney tubular epithelial cells in vitro. Conversely, siRNA-mediated suppression of Nrf2 and FoxO1 increased the cytotoxicity caused by oxidative stress. It has been observed that thapsigargin NPs improved renal damage in an adenine diet-induced CKD rat model in vivo, suggesting that it is a viable treatment to stop or slow the course of CKD (Ma et al., 2020).

Natural polyphenol resveratrol has anti-inflammatory properties that help with several renal disorders. However, the poor pharmacological properties of the compound reduce its applications. Consequently, a unique technique was employed to get over these restrictions, and NPs loaded with resveratrol were created. For example, the KIM-1 antibody that is present in the epithelial cells of the kidney KIM-1 antibody was overloaded with coupled with NPs and improved targetability. Resveratrol-loaded nanoparticles (NPs) were used to treat HK-2. This led to decreased toxicity, prolonged and regulated drug release, and inhibition of the inflammasome NLRP3, and IL-1β, two key players in kidney inflammation (Zhao et al., 2021). Adenine-induced CKD mice had elevated BUN and creatinine levels. The treated patients have low creatinine levels and they recovered earlier as compared to the patients that are treated with simple drugs. Creatinine levels were lowered and tubulointerstitial damage was lessened in the CKD animals after being treated with resveratrol-loaded NPs or KIM-1-resveratrol-loaded NPs (Singh et al., 2022).

Numerous natural herbs have slowed the course of CKD and fibrosis, but their benefits were insufficient when used alone. A compound known as salvianolic acid B is derived from the conventional herb, and it is used to recover the epithelium of the human renal proximal tubular cell and suppress the cancer-producing cells (Liang et al., 2024). Studies have demonstrated that salvianolic acid B-phospholipid group encapsulation into nanoparticles (NPs) enhanced its oral bioavailability and intestinal absorption. That's why, CKD can be treated potentially by using nanotechnology in TCM herbal medicines. The initial treatment was ferrous sulfate ($FeSO_4$) for deficiency of iron. Moreover, the ferrous sulfate ($FeSO_4$) use had some limitations like poor bioavailability, low absorption rate, and adverse effects. Nonetheless, liposomal NPs are also applicable to the drug delivery process. Liposomal NPs improved the absorption of iron and resolved certain noncompliance issues. CKD was often associated with hyperphosphatemia. The phosphate binders have some disadvantages, including a significant risk of hypercalcemia, a high price tag, a low to moderate level of effectiveness, and unfavorable gastrointestinal side effects. To overcome these drawbacks, Fe (III) deposition methods and phosphate binders reliant on iron-ethylenediamine with nonporous silica (Fe-EDA-SAMMS) were selected for substrates. The Fe-EDA-SAMMS material had a greater capacity to bind phosphate, a faster rate of phosphate binding, a wider pH operating window, and was far less impacted by the other anions than other typical phosphate binders. Several nanodrugs, including sevelamer carbonate, have previously received approval from the US FDA (Food and Drug Administration) for use in hyperphosphatemia (Ma et al., 2020).

Nano Surgery

Femtosecond laser systems, nanotweezers, nanoneedles, and nano-knives are the nanodevices that are applicable to reduce the disruption of adjacent tissues at the stage of unitary cells (Paluszkiewicz et al., 2021). Nanoneedles can offer the appropriate and safe local dispatch of active materials through a transdermal way. The efficiency of anticancer treatment can be increased by directly delivering drugs into the cytoplasm of cells through the use of diamond nanoneedle arrays. Nano tweezers can control the both adjusting and operating of nanostructures. Silicon nano tweezers were used in medicine, for instance, to manipulate DNA molecules and make them easier to characterize. The nano-knives, which made a 20 nm incision, were a revolutionary tool in neurosurgery that made it possible to isolate and sever a single axon during peripheral nerve surgery. With its ability to irreversibly electroporate solid tumors, the nano-knife seems to be a breakthrough weapon in oncology.

The surgery processes mainly orthopedic and nano surgery are designed by the participation of NMs (Sedra et al.,

2021). Because of their superior biocompatibility, titanium-based NMs are utilized in the manufacture of implants, which can lessen postoperative discomfort and hasten the healing of wounds. NMs have been used in dentistry as well. Antibacterial silver, chitosan, copper oxide, or zinc oxide nanoparticles are great substrates for composite adhesives. Consequently, titanium oxide nanotubes make up the implant's surface (Liu et al., 2020).

Gene Nanotherapy

Gene therapy is another area of medicine that is quickly expanding because of nanotechnology; research in this field focuses on changing gene expression. The transfer of small interfering RNA (siRNA) to cells using nanocarriers such as lipid NPs is one method utilized to alter gene expression. Here, translation is prevented by siRNA's degradation of the target mRNA, which results in gene silence (Huang and Xiao, 2022). One such lipid-based nucleic acid-lipid nanoparticle that targets the growth factor for vascular endothelial cells is ALN-VSP (Alnylam). Using RNA interference, patients with advanced solid tumors have their production of KSP and VEGF downregulated when NPs are coupled with siRNAs that target these two proteins. Treatment for malignant conditions including brain tumors and neurodegenerative disorders can be greatly improved by targeted molecular therapy, which alters the expression of certain genes. Mutating the gene for P-glycoprotein, a protein that exports drugs out of cells and helps to remove numerous foreign substances, is another advantage of molecular targeted therapy that may help to solve the multi-drug resistance issue (Emran et al., 2022). The cytotoxicity of chemotherapeutic drugs towards cancer cell lines can be improved by developing a nanosystem for the simultaneous administration of siRNA (lowering the level of expression of P-glycoprotein genes) and an anti-cancer agent utilizing mesoporous silica NPs (Paris and Vallet-Regí, 2020).

Conclusion

A promising method for early CKD diagnosis and tracking the disease's course to ensure that treatment and preventative measures are implemented right away is nanotechnology. Nanosystems are better than other therapeutic and diagnostic methods because it provide invaluable insights by identifying and selecting specific disease areas. Some biomarkers, including hemoglobin, serum albumin, urine creatinine, glycosylated hemoglobin, CysC, NAG, and KIM-1, have been supplied using this technique. Additionally, effective signals have been enhanced using SERS, among other methods. Moreover, NP imaging can detect the kidney malfunctioning phases and also determine the fibrosis and inflammation of the kidney which could relegate the intrusive renal therapies eventually.

REFERENCES

Chandraprasad, M. S., Dey, A., and Swamy, M. K. (2022). Introduction to cancer and treatment approaches. In *Paclitaxel* (pp. 1-27). Academic Press.

Aghebati-Maleki, A., Dolati, S., Ahmadi, M., Baghbanzhadeh, A., Asadi, M., Fotouhi, A., and Aghebati-Maleki, L. (2020). Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *Journal of Cellular Physiology*, *235*(3), 1962-1972.

Bhatt, P., Kukkar, D., and Kim, K. H. (2024). Fluorescent nanomaterials for the detection of chronic kidney disease. *TrAC Trends in Analytical Chemistry*, 117572.

Cabezón-Gutiérrez, L., Custodio-Cabello, S., Palka-Kotlowska, M., Sanchez-Luis, S. M., and Khosravi-Shahi, P. (2021). Biomarkers of Pembrolizumab Efficacy in First-Line Advanced PD-L1≥ 50% Non-Small Cell Lung Cancer Treatment. *Journal of Cancer Immunology*, *3*(4), 188-195.

Cassell III, A., Manobah, B., and Willie, S. (2021). Diagnostic and therapeutic challenges of rare urogenital cancers: urothelial carcinoma of the renal pelvis, ureters and urethra. *World Journal of Oncology*, *12*(1), 20.

Catalano, A., Iacopetta, D., Ceramella, J., Scumaci, D., Giuzio, F., Saturnino, C., and Sinicropi, M. S. (2022). Multidrug resistance (MDR): A widespread phenomenon in pharmacological therapies. *Molecules*, *27*(3), 616.

Chen, L., Liu, S., and Tao, Y. (2020). Regulating tumor suppressor genes: post-translational modifications. *Signal Transduction and Targeted Therapy*, *5*(1), 90.

Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., and Manyazewal, T. (2021). New approaches and procedures for cancer treatment: Current perspectives. *SAGE Open Medicine*, *9*, 20503121211034366.

Emran, T. B., Shahriar, A., Mahmud, A. R., Rahman, T., Abir, M. H., Siddiquee, M. F. R., and Hassan, M. M. (2022). Multidrug resistance in cancer: understanding molecular mechanisms, immunoprevention, and therapeutic approaches. *Frontiers in Oncology*, *12*, 891652.

González-Nicolás, M. Á., González-Guerrero, C., Goicoechea, M., Boscá, L., Valiño-Rivas, L., and Lázaro, A. (2024). Biomarkers in Contrast-Induced Acute Kidney Injury: Towards A New Perspective. *International Journal of Molecular Sciences*, *25*(6), 3438.

Huang, J., and Xiao, K. (2022). Nanoparticles-based strategies to improve the delivery of therapeutic small interfering RNA in precision oncology. *Pharmaceutics*, *14*(8), 1586.

Huang, Y. (2020). Surface Charge-mediated Interactions and Transport of Ultrasmall Gold Nanoparticles in the Normal and Diseased Kidney (Doctoral dissertation).

Jana, S., Mitra, P., and Roy, S. (2022). Proficient novel biomarkers guide early detection of acute kidney injury: a

review. *Diseases*, *11*(1), 8.

Kalantar-Zadeh, K., Jafar, T. H., Nitsch, D., Neuen, B. L., and Perkovic, V. (2021). Chronic kidney disease. *The Lancet*, *398*(10302), 786-802.

Khan, A., Muhammad, L., Ali, S., Abdulhaq, A., and Rahman, Z. (2023). Efficacy of Ferrous Bis-Glycinate versus Ferrous Sulphate in Children with Iron Deficiency Anemia: Efficacy of Ferrous Bis-Glycinate versus Ferrous Sulphate. *Pakistan Journal of Health Sciences*, 39-43.

Klein, A. P. (2021). Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nature Reviews Gastroenterology and Hepatology*, *18*(7), 493-502.

Kołątaj, K., Krajczewski, J., and Kudelski, A. (2020). Plasmonic nanoparticles for environmental analysis. *Environmental Chemistry Letters*, *18*(3), 529-542.

Lee, J., Choi, M. K., and Song, I. S. (2023). Recent advances in doxorubicin formulation to enhance pharmacokinetics and tumor targeting. *Pharmaceuticals*, *16*(6), 802.

Liang, Q., Liu, X., Peng, X., Luo, T., Su, Y., Xu, X., and Xie, C. (2024). Salvianolic acid B in fibrosis treatment: a comprehensive review. *Frontiers in Pharmacology*, *15*, 1442181.

Liu, D., Du, Y., Jin, F. Y., Xu, X. L., and Du, Y. Z. (2021). Renal cell-targeted drug delivery strategy for acute kidney injury and chronic kidney disease: a mini-review. *Molecular Pharmaceutics*, *18*(9), 3206-3222.

Liu, J., Liu, J., Attarilar, S., Wang, C., Tamaddon, M., Yang, C., and Tang, Y. (2020). Nano-modified titanium implant materials: a way toward improved antibacterial properties. *Frontiers in Bioengineering and Biotechnology*, *8*, 576969.

Ma, Y., Cai, F., Li, Y., Chen, J., Han, F., and Lin, W. (2020). A review of the application of nanoparticles in the diagnosis and treatment of chronic kidney disease. *Bioactive Materials*, *5*(3), 732-743.

Marino, P., Mininni, M., Deiana, G., Marino, G., Divella, R., Bochicchio, I., and Sanseverino, F. (2024). Healthy lifestyle and cancer risk: modifiable risk factors to prevent cancer. *Nutrients*, *16*(6), 800.

Naseer, M. U., Iqbal, Z., and Aslam, B. (2022). In vitro Efficacy of Areca catechu against Cypermethrin Resistant Rhipicephalus microplus and its Phytochemical Analysis. *Pakistan Veterinary Journal*, *42*(3).

Oroojalian, F., Charbgoo, F., Hashemi, M., Amani, A., Yazdian-Robati, R., Mokhtarzadeh, A., and Hamblin, M. R. (2020). Recent advances in nanotechnology-based drug delivery systems for the kidney. *Journal of Controlled Release*, *321*, 442-462.

Padala, S. A., Barsouk, A., Thandra, K. C., Saginala, K., Mohammed, A., Vakiti, A., and Barsouk, A. (2020). Epidemiology of renal cell carcinoma. *World Journal of Oncology*, *11*(3), 79.

Paluszkiewicz, P., Martuszewski, A., Zaręba, N., Wala, K., Banasik, M., and Kepinska, M. (2021). The application of nanoparticles in diagnosis and treatment of kidney diseases. *International Journal of Molecular Sciences*, *23*(1), 131.

Paris, J. L., and Vallet-Regí, M. (2020). Mesoporous silica nanoparticles for co-delivery of drugs and n2ucleic acids in oncology: A review. *Pharmaceutics*, *12*(6), 526.

Pedziwiatr-Werbicka, E., Horodecka, K., Shcharbin, D., and Bryszewska, M. (2021). Nanoparticles in combating cancer: opportunities and limitations: a brief review. *Current Medicinal Chemistry*, *28*(2), 346-359.

Prerna, D. A., and Ratan, G. (2021). Nanoparticles: An Overview. *Drugs and Cell Therapies in Haematology*, *10*(1), 1487-1497.

Satwikananda, H., Wiratama, M. A., Putri, K. T. C., and Soebadi, D. M. (2023). Renal cell carcinoma in a patient with staghorn stones: A case report. *International Journal of Surgery Case Reports*, *110*, 108678.

Sedra, F., Shafafy, R., Sadek, A. R., Aftab, S., Montgomery, A., and Nadarajah, R. (2021). Perioperative optimization of patients with neuromuscular disorders undergoing scoliosis corrective surgery: a multidisciplinary team approach. *Global Spine Journal*, *11*(2), 240-248.

Sekino, M., Iwadate, M., Yamaya, Y., Matsumoto, Y., Suzuki, S., Mizunuma, H., and Suzuki, S. (2023). Analysis of Expression of Programmed Cell Death Ligand 1 (PD-L1) and BRAFV600E Mutation in Thyroid Cancer. *Cancers*, *15*(13), 3449.

Singh, S., Mazumder, R., Debnath, A., and Dutta, A. (2022). Kidney targeting approaches in the drug delivery arena. *NeuroQuantology*, *20*(8), 3424.

Sumida, K., Nadkarni, G. N., Grams, M. E., Sang, Y., Ballew, S. H., Coresh, J., and Chronic Kidney Disease Prognosis Consortium‡. (2020). Conversion of urine protein–creatinine ratio or urine dipstick protein to urine albumin–creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant–based meta-analysis. *Annals of Internal Medicine*, *173*(6), 426-435.

Vasiniotis Kamarinos, N., Vakiani, E., Gonen, M., Kemeny, N. E., Sigel, C., Saltz, L. B., and Sofocleous, C. T. (2022). Biopsy and margins optimize outcomes after thermal ablation of colorectal liver metastases. *Cancers*, *14*(3), 693.

Yu, X. A., Zhang, L., Zhang, R., Bai, X., Zhang, Y., Hu, Y., and Tian, J. (2022). Accurate identification of kidney injury progression via a fluorescent biosensor array. *Microchimica Acta*, *189*(8), 304.

Zhao, Y., Pu, M., Wang, Y., Yu, L., Song, X., and He, Z. (2021). Application of nanotechnology in acute kidney injury: From diagnosis to therapeutic implications. *Journal of Controlled Release*, *336*, 233-251.

Chapter 06

Evaluation of Anti-Bacterial Efficacy of Nanoparticles against Major Mastitis Associated Pathogens

Bilal Ahmed[1], Kainat[1], Abdul Baseer[2], Abdul Jabbar[3*], Asif Ali[4], Muhammad Mohsin Jamil[5], Maaz Anjum[6], Sami Ullah Khan[7], Muhammad Ashraf[5], Mansoor-Ul-Haq[8] and Ghulam Muhammad[8]

[1]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan
[2]Department of Veterinary Microbiology, Lasbela University of Agriculture Water and Marine Sciences, Uthal, Baluchistan, Pakistan
[3]University of Poonch, Rawalakot, Pakistan
[4]Department of Theriogenology, Faculty of Veterinary Science, University of Agriculture Faisalabad, Pakistan
[5]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
[6]Department of Clinical Medicine and Surgery, University of Agriculture Faisalabad, Pakistan
[7]Lasbela University of Agriculture Water and Marine Sciences, Uthal, Baluchistan, Pakistan
[8]Department of Veterinary Pathology, University of Agriculture Faisalabad, Pakistan
*Corresponding author: abduljabbar@upr.edu.pk

ABSTRACT

The physicochemical features of nanoparticles offer a novel method to combat bacterial infections and antibiotic resistance using nanotechnology. These particles, which have a size range of 1 to 100 nanometers, have improved surface areas, changed optical, chemical, and magnetic characteristics, and quantum effects. These features enable precision targeting and minimal toxicity in customized medicine. Silver, gold, copper, zinc oxide, and other metal and metal oxide nanoparticles have demonstrated exceptional antibacterial activity against a variety of diseases. Particularly noteworthy for their extraordinary properties are zinc oxide nanoparticles, which are used in healthcare, cosmetics, medicine, and agriculture. Customized nanoparticle patterns may be achieved by a variety of synthesis techniques, such as chemical reduction and green synthesis. The processes behind the antibacterial effect include rupture of cell membranes, formation of reactive oxygen species, and modification of enzyme activity, which are all affected by the size, shape, charge, and environment of nanoparticles. Additionally, membrane proteins that are affected by nanoparticles can denature proteins and cause cell death. The study's overall findings highlighted the advantages of nanoparticles antibacterial activity having more alone against some bacteria but in combination with traditional antibiotics were somehow reduced against bacteria. Some studies suggest that improving nanoparticle formulations could be an effective way to combat bacterial infections and address the growing issue of antibiotic-resistant bacteria. To sum up, nanoparticles are a viable tool for improving illness management and battling antibiotic resistance.

KEYWORDS
Nanoparticles, Antibacterial activity, Antibiotic resistance, Nanotechnology, Biofilm inhibition

Received: 15-Jun-2024
Revised: 13-Jul-2024
Accepted: 04-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Ahmed B, Kainat, Baseer A, Jabbar A, Ali A, Jamil MM, Anjum M, Khan SU, Ashraf M, Haq MU and Muhammad G, 2024. Evaluation of anti-bacterial efficacy of nanoparticals against major mastitis associated pathogens. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 40-46. https://doi.org/10.47278/book.CAM/2024.268

INTRODUCTION

A prevalent illness that commonly affects entire herds of cattle is bovine mastitis. Resistant bacteria with the ability to form biofilms are frequently the reason. Because of the remarkable qualities of nanoparticles, the quickly developing scientific field known as nano-biotechnology may be able to treat this sickness. The purpose of the study was to look at how treatment with copper and silver nanoparticles, either separately or in combination, inhibited the biofilms produced by mastitis pathogens (Pedersen et al., 2021).

New alternative treatments for cow mastitis may employ nanoparticles. We identified the nanoparticles' physicochemical characteristics, minimal inhibitory concentration, and interactions with the cell membrane, besides measuring the degree of biofilm reduction. According to the findings, out of all the nanomaterials examined, the silver–copper complex was the most active (biofilm was decreased by almost 100% at a concentration of 200ppm for each tested microorganism species). But individual silver nanoparticles were equally effective (biofilm was reduced by about 100% at

200ppm, but the level of decrease was less at 50 and 100ppm than for the complex) (Joshi et al., 2020).

A wide range of bacterial pathogen-caused illnesses, along with the emergence of multidrug resistance in their genes, necessitate the development of novel therapeutic compounds or new vectors for efficient drug administration and improved disease management. Nanoparticles have become a distinctive class of drugs in the last decade and are being utilized in a wide array of industrial domains, comprising medicines, cosmetics, healthcare, and agriculture (Mascarenhas-Melo et al., 2023).

Nanotechnology is an emerging field with the potential to completely transform various scientific disciplines. Because of their size and form, nanomaterial has a wide diversity of uses and are an important topic in both basic and applied sciences (Nasrollahzadeh et al., 2019).

Particles with a size series of 1 to 100 nanometers in at least one aspect are called nanoparticles. Materials like as metals, metal oxides, polymers, and carbon-based materials such as graphene can be castoff to create them. Because of their small size, these particles have special characteristics not seen in bulk materials, such as improved surface area, quantum effects, and changed chemical, optical, and magnetic assets (Rizwan et al., 2021).

Current investigation using metal nanoparticles like as silver, gold, copper, and iron as well as metal oxide nanoparticles such as ZnO, CuO, Ti_2O, and FeO nanoparticles remains to use nanoparticles as an antibacterial agent (Naseem et al., 2021).

Nanoparticles have a vast external area to bulk relation, which allows ligands to drag to the surface of the nanoparticle in large numbers and consequently interact with receptors on the surface of bacteria. Nanoparticles have strong antimicrobial action. The current effort focuses on the distinct mechanisms that numerous nanoparticles used to regulate bacteria, as well as their differential bond to the surfaces of Gram positive and Gram negative bacteria (Elbourne et al., 2019).

Kinds of Nanoparticles

Metal nanoparticles, which are prepared for metals such as iron, gold, silver, or platinum, have a wide range of usages in fields like electronics, environmental remediation, medicine, and catalysis.

Alkaline oxide nanoparticles, such iron oxide (Fe_2O_3), zinc oxide (ZnO), and titanium dioxide (TiO_2), are utilized as pigments, sunscreens, sensors, and catalysts.

Carbon nanoparticles—which include graphene, fullerenes, and carbon nanotubes (CNTs)—are used in a number of industries, including composites, electronics, energy storage, and medicinal research.

Polymeric nanoparticles, which come from either natural or synthetic polymers, are used in cosmetics, imaging agents, and medicine delivery.

Semiconductor nanoparticles, known as quantum dots, which have size-dependent optical and electrical characteristics, are essential parts of solar cells, displays, and biomedical imaging.

Lipid-based nanoparticles, which are composed of lipids or compounds that resemble lipids, are essential components of gene therapy and medication delivery systems (Soltys et al., 2021).

Various techniques are utilized in the creation of nanoparticles, each designed to provide particles with specific possessions, including size, shape, and composition. Here are a few typical techniques:

To create nanoparticles, chemical reduction involves reducing metal ions in a solution; for example, to make gold nanoparticles, reduce gold ions with agents such as citrate or sodium borohydride. The Sol-Gel Process, which is regularly used for metal oxide nanoparticles such as titania or silica, uses the hydrolysis and condensation of metal alkaline oxides or chlorides in a solution to make a colloidal suspension of nanoparticles.

In a limited micro emulsion system, micro emulsion permits for the founding of nanoparticles inside micelles, providing control over the size and disparity of the particles. By consuming a triggering agent to remove metal salts from a solution, precipitation makes nanoparticles. The size and form of the final product may be controlled by varying reaction parameters, such as pH, temperature, and concentration (Sharma et al., 2018).

Synthesis of Nanoparticles by Biologically

Green synthesis is an environmentally benign method of making nanoparticles with special features by reducing metal ions and creating nanoparticles from natural sources, such as plant extracts or microorganisms. Without the usage of chemical reduction agents, laser ablation creates nanoparticles via ablation of a target material in a liquid environment using a high-energy laser. By electrochemically reducing metal ions onto an electrode surface, electrochemical deposition generates nanoparticles with attractive control over their size and structure. By regulatory the size and form of nanoparticles during synthesis, templates such as porous materials or biological molecules are castoff in template-assisted synthesis to give further control over the possessions of the final product. These methods show numerous ways to the synthesis of nanoparticles, each with distinctive benefits and chances for modified nanoparticle design as shown in Fig. 1 (Roostaei et al., 2023).

This is only one of the numerous methods by which nanoparticles can be created. Scientists continually develop new techniques to modify nanoparticles for specific applications in medicine, electronics, biomedical imaging, and catalysis. The choice of production process is dependent upon several aspects, including cost-effectiveness, scalability, and preferred nanoparticle assets. Each approach has merits and demerits (Zahin et al., 2020).

Categorization of Nanoparticles

Various categorization techniques, comprising dynamic light scattering (DLS), energy-dispersive X-ray analysis (EDAX), atomic force microscopy (AFM), Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), UV–visible spectroscopy (UV–Vis), and X-ray diffraction spectroscopy (XRD), may be engaged to closely observe the figure, dimension, surface characteristics, and additional biological possessions. There are numerous imaging technologies existing for use in the medical industry nowadays. The most popular ones are ultrasonic (USI), optical, and magnetic resonance imaging (MRI). Magnetic and luminescent/fluorescent nanoparticles have made major contributions to the development of bio imaging techniques among these imaging instruments. Magnetic NPs are usually utilized for MRI, although fluorescent NPs, such AuNPs, are commonly employed for OI. Apart from inorganic nanoparticles like iron oxides and aurum, viral particles have also been shown to be useful for imaging. This section will cover the uses of these NPs for MRI and OI, as well as provide some examples of inorganic and organic NPs employed in these fields (Patil et al., 2022).

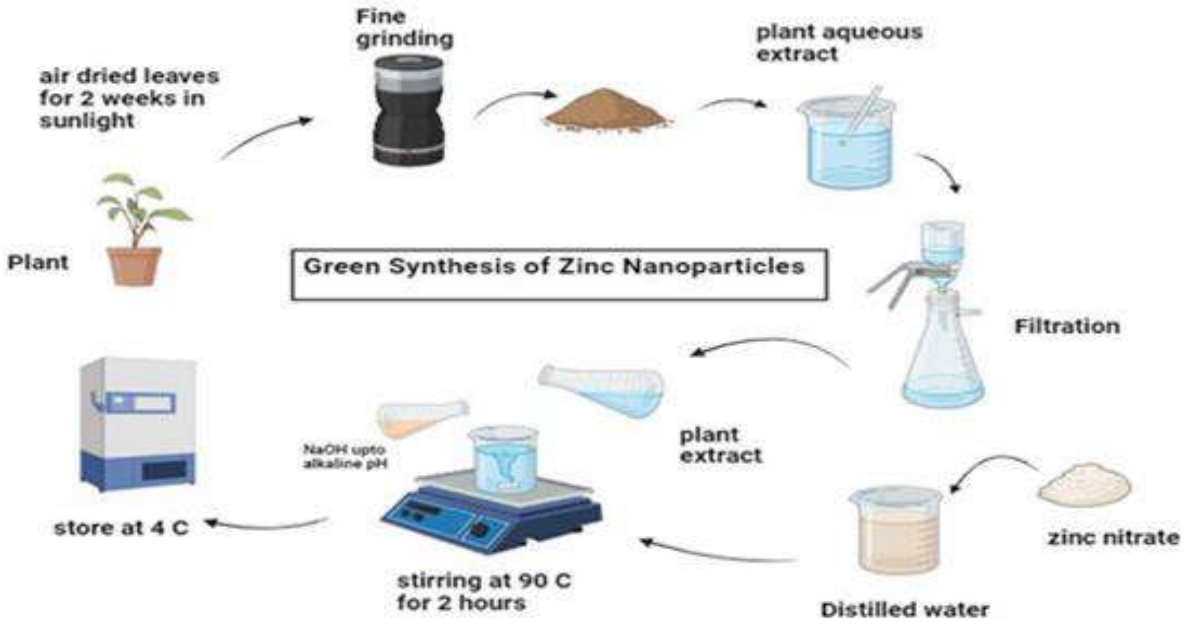


Fig.1: Biological synthesis of zinc oxide nanoparticles.

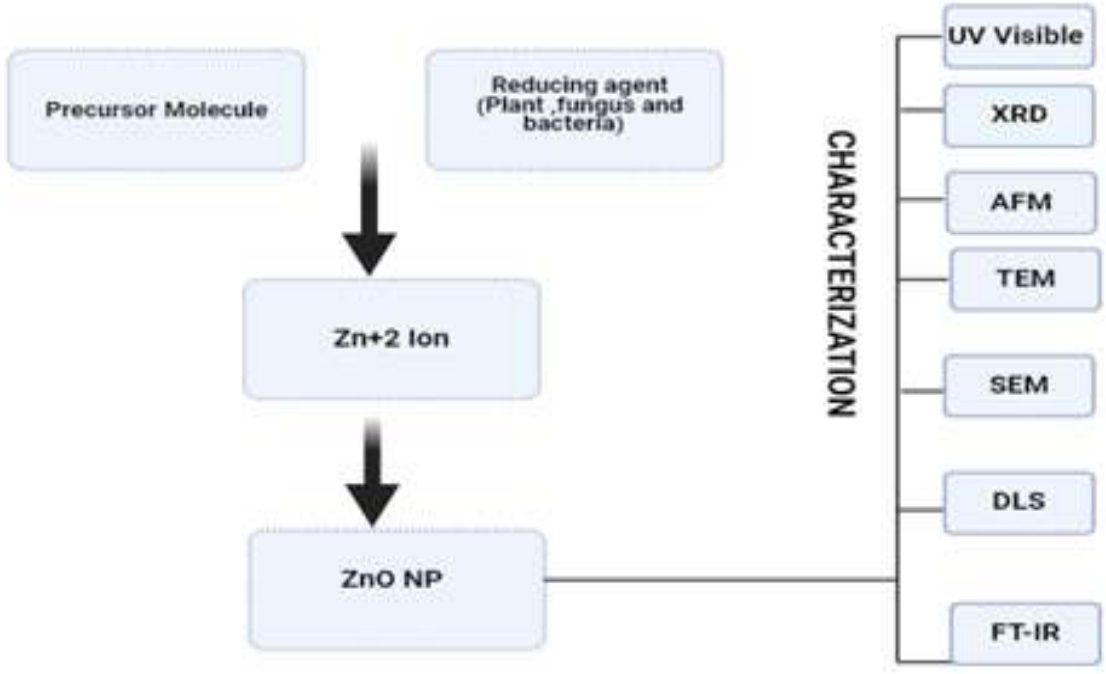


Fig. 2: Green synthesis of zinc nanoparticle and their characterization.

Kinetics of Nanoparticles

Some of the nanoparticle's physicochemical characteristics are changed by its form. The form of the nanoparticle determines how it interacts with the bacterial membrane. Its effective surface area and active facets are altered by the transition from a spherical to a rod-shaped to a triangular form. Compared to rod- or spherically shaped nanoparticles, triangle-shaped nanoparticles exhibit superior bacterial cell membrane contact and, thus, greater toxicity. The discharge of a Zn^{+2} ion from zincoxide nanopartical is also influenced by its shape. Shape has an impact on Zn^{+2} ion release and nanoparticle dissolubility in the water medium by influencing total surface area. When compared to rod-shaped ions, three dimension-shaped zinc-oxide nanoparticle releases Zn^{+2} ion additional efficiently (Agarwal et al., 2018).

Mechanism of Nanoparticles

The advancement of nanotechnology presents novel opportunities for managing microorganisms resistant to drugs as well as associated illnesses and infections. The wide range of organic phytochemicals surrounding green-synthesized nanoparticles helps them interact with various microbial surface receptors, such as proteins, lipids, phospholipids, and lipoteichoic acid. The bacterial complication of the nanoparticle stops the development and production of biofilms (Dua et al., 2023).

The current study also shows how many physiological characteristics of nanoparticles, such as their size, shape, surface charge, and concentration, affect their ability to prevent bacterial growth. It has also been shown how various working circumstances, such as temperature and pH, affect the antibacterial activity of nanoparticles (Pareek et al., 2018).

NPS have demonstrated effectiveness in substituting particular direct sick genes implicated in cancer, specific viral infections, and other genetic illnesses. They are also employed as gene delivery devices. Sadly, the immunological reactions that cationic nanoparticles can elicit restrict their application. Moreover, NPs have been applied to cellular imaging to identify alterations in cells both in vivo and in vitro. NPS can be more effectively targeted by conjugating them with moieties like antibodies and other ligands. Despite their potential proficiency as medicine or gene transporters, there are less NPs in medical usage than one would assume centered on the vast premedical investigations. This is mostly because of possible toxicity caused by poorly understood mechanisms, which is particularly true when NPS are taken on a long-term basis. Like any other substance or medication, the delivery technique and exposure to nanoparticles (NPS) dictate their toxicity. NPS can penetrate the body through the skin, be injected, swallowed, or breathed. The organ-specific toxicity of NPS upon exposure is determined by the injection method and systemic dispersion. Unintentional exposures include inhaling particulate particles from the environment or industry sites (Dionisi and Silva, 2016).

Nanoparticles have become highly effective antibacterial agents in the last ten years, providing tailored medication with low toxicity and precise targeting. They have demonstrated potential in the fight against bacteria resistant to antibiotics by obstructing their food supply or rupturing their cell membranes. Nanoparticles' high surface-area-to-volume ratio allows them to host a wide variety of ligands, which improves the targeting of harmful microorganisms. Silver, gold, copper, iron, zinc oxide, titanium oxide, and copper oxide are just a few of the alkali and alkaline oxide nanoparticle that have shown antibacterial qualities. Particularly zinc oxide nanoparticles have attracted a lot of interest because of their special optical, electrical, and therapeutic properties. Because of their quick electron transport kinetics and high degree of biocompatibility, ZnO nanoparticles are a good fit for biological membrane applications (Jiang et al., 2018).

Using plant components, bacteria, fungi, algae, and organic materials to create nanoparticles is known as "green synthesis" (Fig. 2). Plant metabolites function as both a reducing and stabilizing agent, hence no additional stabilizing agent is required. Phytochemicals are easily manipulated at the laboratory scale and may help to create specialized medicinal uses for nanoparticles. Because they have multiple pharmacologically energetic biological molecules coated on their exterior, which enables numerous ligand-based conjugation of the nanoparticles with receptors microbial membranes, nanoparticles synthesized through the green route, for example, typically display enhanced antimicrobial action than nanoparticles derived physically or chemically (Fadaka et al., 2021).

These biomolecules, which are mostly flavones, organic acids, amides, polysaccharides, ketone, aldehyde, and quinones, are recognized to have important therapeutic effects against a variety of human pathogens. A recent investigation against microbial pathogenic spp. *E. coli, S. aureus, B. subtillis*, and *K. pneumonia* showed that the biologically produced silver nanoparticle (AgNP) produced a greater zone of inhibition than the chemically generated one. Tri-sodium and lemon-synthesized silver nanoparticles showed comparable outcomes, with lemon manufactured silver nanoparticles exhibiting superior antimicrobial activity contrary to both G+ and G- microbes (Gurunathan, 2019).

Influence of zinc oxide nanoparticles size, numerous microorganisms may be controlled by zinc oxide nanoparticles. The antibacterial properties of zinc oxide nanoparticles diminish as their size increases. The presence of soluble Zn^{+2} ions or the pH shift brought on by ZnO NP dissolving in water are thought to be the causes of ZnO NP's antibacterial action. Because a nanoparticle's solubility and size are inversely correlated, there must be an effective Zn^{+2} ion present to limit bacterial growth as shown in Fig. 3 (Ali et al., 2018).

Pharmacodynamics of Nanoparticles

A number of mechanisms are employed by nanoparticles to function as antibacterial agents. Loss of cell membrane integrity brought on by phospholipid bilayer breakdown is regarded as one of the most significant mechanisms. The use of nanoparticles as Reactive oxygen species (ROS)-induced oxidative stress is yet another significant mechanism. By

preventing or changing the cycles of DNA replication, protein synthesis, nutrients metabolism, and respiration, this reactive oxygen species molecule contributes to additional cell demised (Sies and Jones, 2020).

Bacterial membranes are easily penetrated by smaller nanoparticles, which result in membrane leakage and cell death. It is believed that the chief contrivance of microbial reticence is the penetration of nanoparticles into bacterial cells, which is significantly influenced by the size of the particles. Since aggregation causes the particles to become larger as a whole, it may potentially affect the antibacterial activity of the nanoparticles. Aggregation also limits the dispersion capacity of nanoparticles in aqueous media, impairing their overall anti-microbial activity as well as their potential to interact with bacterial cells (Ogunsona et al., 2020).

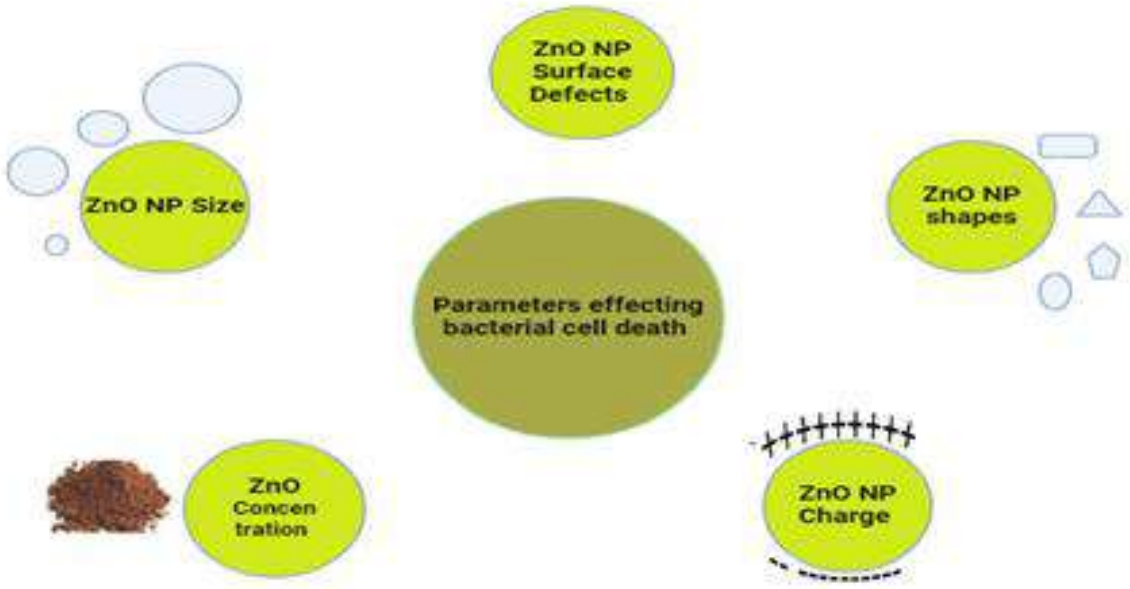


Fig. 3: Impact of shape and size of ZnO-NP.

The external charge Because of their stronger electrostatic attraction to negatively charged cell membrane surfaces, positively charged nanoparticles exhibit greater toxicity towards microorganisms. Influence of the operational environment (culture media pH and temperature) ZnO NP's antibacterial activity is supported by a high temperature and an acidic pH (4–5). The assertion is supported by the findings. An acidic pH promotes more nanoparticle dissolution in the medium. The nominal Zn^{+2} ion concentration in media and, consequently, the antimicrobial activity is increased by the increased solubility of nanoparticles. Similar outcomes were recorded in another experiment. In which the medium's Zn^{+2} ion content was raised by lowering the pH from 9 to 7 (Stanić and Tanasković, 2020).

Raising the temperature causes ZnO NP to become more soluble. Another way that temperature contributes to the growth of ZnO NP's antibacterial activity is through the increased production of reactive oxygen species (ROS) by bacterial cells when exposed to high temperatures. ZnO NP's have superior antibacterial feat than soluble zinc compounds like zinc chloride because of their vigorous directing perspective, capacity to produce ROS in the cell membrane and subsequently disrupt cell membrane integrity, and ability to further aid in protein, lipid, and DNA denaturation. As a result, Zinc chloride's antibacterial activity is mostly related to its capacity to oxidize thiol groups on glycolytic enzymes, hence suppressing the glycolytic process due to the Zn^{+2} ion's unique attraction for the S group (Godoy-Gallardo et al., 2021).

It is known that certain nanoparticles have efflux pump-inhibiting properties. Bacterial cell membranes include efflux pumps, which are involved in expelling waste products and hazardous substances from the cell. These pumps are also known to carry antibiotics out of the cell, extending the life of the cell. When excess Zn^{+2} ions inside the cell reach dangerous amounts, Zn^{+2} efflux trailer protein (cation diffusion facilitator and P-type ATPase) exports them out of the cell. Because the bacterial cell could not recover with nutritional replacement. And another report that ZnONP had a bactericidal rather than bacteriostatic impact on *C. jejuni* bacterial culture (Ogunsona et al., 2020).

ZnO-NPs Adjoining and its Movement Inside the Microbial Cell

The outer layer of the peptidoglycan, triple layer that makes up the cell walls of gram-positive bacteria contains porins. Ion channels called porins are found in the outer layer of peptidoglycan and help passive passage of nanoparticles throughout the cell. Porin has other functions that include recognition, cell-to-cell communication, and nutrition absorption by the cell. Shows the various strategies used by gram + and gram - bacteria for the attachment and internal transport of ZnO nanoparticles. Depending on their size and shape, ZnO NP can also be swallowed via membrane diffusion through membrane-based holes, nonspecific uptake, or endocytosis (David, 2021).

Zinc oxide nanoparticles have a tendency to liquefy in water solutions and release Zn^{+2} ions when a surface's free

energy changes. The electrostatic desirability of Zn^{+2} ions to negatively charged membranes is also deliberated to be a typical mechanism of nanoparticles addition to the cell surface. The concentration of Zn^{+2} rises in the microbial cytoplasm due to the native breakdown of linked zinc oxide nanoparticles, which results in membrane outflow and the loss of the proton motive force (Du et al., 2021).

Gram-negative bacteria are more vulnerable to the harmful effects of nanoparticles than gram-positive bacteria because the former have a thinner peptidoglycan layer and are less resistant to the interaction of nanoparticles with their cell membranes. Therefore, the first contact between nanoparticles and bacteria is significantly influenced by the thickness, content, and structure of the cell wall (Tavares et al., 2020).

Membrane permeability is reduced and cell death results from interactions between nanoparticles and membrane proteins that inactivate them. The morphology, size, and shape of the nanoparticle all influence its propensity to surround itself with a protein corona. They connect with a thiol group on this protein corona, which unfolds proteins and has the ability to denature them, ultimately resulting in cell death. Protein surface thiol or sulfhydryl (-SH) groups are reacted with by nanoparticles to generate a persistent S-metagroup, which inactivates the protein. Protein hydrogen ion loss reduces membrane permeability and results in cell death. Zn^{+2} release from the ZnO compound into the media containing bacteria and inhibition of enzymes is necessary for the basic metabolic processes that sustain life (Siddiqi et al., 2018).

Conclusion

Nanotechnology presents a revolutionary avenue for addressing bacterial infections and antibiotic resistance, with nanoparticles emerging as potent antibacterial agents due to their unique physicochemical properties. These nanoparticles, usually extending from 1 to 100 nanometers in size, display distinct characteristics such as greater surface area, quantum effects, and improved optical, chemical, and magnetic properties, allowing accurate targeting and negligible toxicity in personalized medicine. Alkali and alkaline oxide nanoparticles, containing silver, gold, copper, iron, zinc oxide, titanium oxide, and copper oxide, have confirmed significant antibacterial efficacy against a broad spectrum of pathogens. Amid these, zinc oxide nanoparticles (ZnO NPs) have gathered particular consideration for their excellent optical, electrical, and medicinal points, making them suitable for numerous applications in medicine, cosmetics, healthcare, and agriculture. The creation of nanoparticles hires various methods, such as chemical reduction, sol-gel process, micro emulsion, and precipitation, as well as ecologically friendly methods like green synthesis and laser ablation, each donation unique advantages for custom-made nanoparticle design. The antimicrobial action of nanoparticles are accredited to several mechanisms, including disruption of cell membrane integrity, generation of reactive oxygen species (ROS)-induced oxidative stress, inhibition of efflux pumps, and modulation of enzymatic action. The size, shape, surface charge, and operational echo of nanoparticles comedy crucial roles in defining their antimicrobial efficacy, with smaller nanoparticles exhibiting higher toxicity and positively charged nanoparticles representing improved electrostatic attraction to bacterial cell membranes. Additionally, nanoparticles intermingle with membrane proteins and induce protein corona formation, prominent to protein denaturation and following cell death. Inclusively, nanoparticles hold huge prospective as effective antimicrobial agents, proposing new avenues for opposing antibiotic-resistant pathogens and enlightening disease management.

REFERENCES

Agarwal, H., Menon, S., Kumar, S. V., and Rajeshkumar, S. J. C.-b. i. (2018). Mechanistic study on antibacterial action of zinc oxide nanoparticles synthesized using green route. *286*, 60-70.

Ali, A., Phull, A.-R., and Zia, M. J. N. R. (2018). Elemental zinc to zinc nanoparticles: Is ZnO NPs crucial for life? Synthesis, toxicological, and environmental concerns. *7*(5), 413-441.

David, O. M. (2021). The impact of nanoparticles on the proteome of cultured human cells.

Du, M., Zhao, W., Ma, R., Xu, H., Shan, C., Liu, K., and Jiao, Z. J. J. o. H. M. (2021). Visible-light-driven photocatalytic inactivation of S. aureus in aqueous environment by hydrophilic zinc oxide (ZnO) nanoparticles based on the interfacial electron transfer in S. aureus/ZnO composites. *418*, 126013.

Dua, S., Ahmed, H., and Arfin, N. (2023). Soft nanomaterials and their applications. In *Nanomaterials: the Building Blocks of Modern Technology: Synthesis, Properties and Applications* (pp. 27-68). Springer.

Dionisi, D. and I.M. Silva. 2016. Production of ethanol, organic acids and hydrogen: an opportunity for mixed culture biotechnology? Reviews in Environmental Science and Bio/Technology. 15:213-242.

Elbourne, A., Chapman, J., Gelmi, A., Cozzolino, D., Crawford, R. J., Truong, V. K. J. J. o. C., and Science, I. (2019). Bacterial-nanostructure interactions: The role of cell elasticity and adhesion forces. *546*, 192-210.

Fadaka, A. O., Sibuyi, N. R. S., Madiehe, A. M., and Meyer, M. J. P. (2021). Nanotechnology-based delivery systems for antimicrobial peptides. *13*(11), 1795.

Godoy-Gallardo, M., Eckhard, U., Delgado, L. M., de Roo Puente, Y. J., Hoyos-Nogués, M., Gil, F. J., and Perez, R. A. J. B. M. (2021). Antibacterial approaches in tissue engineering using metal ions and nanoparticles: From mechanisms to applications. *6*(12), 4470-4490.

Gurunathan, S. J. A. J. o. C. (2019). Rapid biological synthesis of silver nanoparticles and their enhanced antibacterial effects against Escherichia fergusonii and Streptococcus mutans. *12*(2), 168-180.

Jiang, J., Pi, J., Cai, J. J. B. c., and Applications. (2018). The advancing of zinc oxide nanoparticles for biomedical applications. *2018*.

Joshi, A. S., Singh, P., and Mijakovic, I. (2020). Interactions of gold and silver nanoparticles with bacterial biofilms: Molecular interactions behind inhibition and resistance. *International Journal of Molecular Sciences*, *21*(20), 7658.

Mascarenhas-Melo, F., Mathur, A., Murugappan, S., Sharma, A., Tanwar, K., Dua, K., and Biopharmaceutics. (2023). Inorganic nanoparticles in dermopharmaceutical and cosmetic products: Properties, formulation development, toxicity, and regulatory issues. *192*, 25-40.

Naseem, T., Durrani, T. J. E. C., and Ecotoxicology. (2021). The role of some important metal oxide nanoparticles for wastewater and antibacterial applications: A review. *3*, 59-75.

Nasrollahzadeh, M., Sajadi, S. M., Sajjadi, M., and Issaabadi, Z. (2019). An introduction to nanotechnology. In *Interface Science and Technology* (Vol. 28, pp. 1-27). Elsevier.

Ogunsona, E. O., Muthuraj, R., Ojogbo, E., Valerio, O., and Mekonnen, T. H. J. A. M. T. (2020). Engineered nanomaterials for antimicrobial applications: A review. *18*, 100473.

Pareek, V., Gupta, R., Panwar, J. J. M. S., and C, E. (2018). Do physico-chemical properties of silver nanoparticles decide their interaction with biological media and bactericidal action? A review. *90*, 739-749.

Patil, R. M., Deshpande, P. P., Aalhate, M., Gananadhamu, S., Singh, P. K. J. S., and Interfaces. (2022). An update on sophisticated and advanced analytical tools for surface characterization of nanoparticles. 102165.

Pedersen, R. R., Krömker, V., Bjarnsholt, T., Dahl-Pedersen, K., Buhl, R., and Jørgensen, E. (2021). Biofilm research in bovine mastitis. *Frontiers in Veterinary Science*, *8*, 656810.

Rizwan, M., Shoukat, A., Ayub, A., Razzaq, B., and Tahir, M. B. (2021). Types and classification of nanomaterials. In *Nanomaterials: synthesis, Characterization, Hazards and Safety* (pp. 31-54). Elsevier.

Roostaei, T., Rahimpour, M. R., Zhao, H., Eisapour, M., Chen, Z., Hu, J. J. A. i. C., and Science, I. (2023). Recent advances and progress in biotemplate catalysts for electrochemical energy storage and conversion. 102958.

Sharma, M., Pathak, M., and Kapoor, P. N. J. A. J. C. (2018). The sol-gel method: pathway to ultrapure and homogeneous mixed metal oxide nanoparticles. *30*(7), 1405-1412.

Siddiqi, K. S., ur Rahman, A., Tajuddin, n., and Husen, A. J. N. R. l. (2018). Properties of zinc oxide nanoparticles and their activity against microbes. *13*, 1-13.

Sies, H., and Jones, D. P. J. N. R. M. C. b. (2020). Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *21*(7), 363-383.

Soltys, L., Olkhovyy, O., Tatarchuk, T., and Naushad, M. J. M. (2021). Green synthesis of metal and metal oxide nanoparticles: Principles of green chemistry and raw materials. *7*(11), 145.

Stanić, V., and Tanasković, S. B. (2020). Antibacterial activity of metal oxide nanoparticles. In *Nanotoxicity* (pp. 241-274). Elsevier.

Tavares, T. D., Antunes, J. C., Padrão, J., Ribeiro, A. I., Zille, A., Amorim, M. T. P., and Felgueiras, H. P. J. A. (2020). Activity of specialized biomolecules against gram-positive and gram-negative bacteria. *9*(6), 314.

Zahin, N., Anwar, R., Tewari, D., Kabir, M. T., Sajid, A., Mathew, B., and Research, P. (2020). Nanoparticles and its biomedical applications in health and diseases: special focus on drug delivery. *27*, 19151-19168.

Chapter 07

Use of Nanotechnology to Treat Avian Influenza

Muhammad Ifham Naeem[1*], Farooq Hussain[2], Elif Sibel Aslan[3] Javeria Nousheen[4], Qamar un Nisa[5], Mobeen Sarwar[6], Minahal Fatima[7], Afifa Khanim[8], Waqar Younis[9] and Ghulam Murtaza[10]

[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS-Lahore, Pakistan
[2]Shaheed Benazir Bhutto University of Veterinary and Animal Sciences Sakrand, Pakistan
[3]Biruni University, Department of Molecular Biology and Genetics, Istanbul, Turkey
[4]Department of Epidemiology and Public Health University of Veterinary and Animal Sciences, Lahore, Pakistan
[5]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[6]Department of Livestock and Dairy Development, Provincial Diagnostic Laboratory, Lahore, Pakistan
[7]Department of Zoology, Wildlife and Fishries, University of Agriculture, Faisalabad, Pakistan
[8]School of Chemistry, Minhaj University Lahore, Pakistan
[9]Riphah International University, Lahore, Pakistan
[10]National Institute of Food Science and Technology (NIFSAT), University of Agriculture, Faisalabad, Pakistan
*Corresponding author: afhamnaim4@gmail.com

ABSTRACT

Avian influenza virus infection is a crucial challenge being faced by the poultry farmers in this day and age. The high rate of mortality and morbidity caused by this disease has resulted in a huge downturn in the economic situation of the poultry industry. Especially, recently there has been a rise in incidence of avian influenza virus strain that is highly pathogenic. Invasion of this strain leads to a higher mortality rate than the low pathogenic strain of AIV. Similarly, cases to zoonotic AIV infection from birds to humans have been also seen in recent years. This situation makes this virus a formidable foe for not only poultry birds but also human populations. This mandates proper research and analysis of viruses through new technological solutions like nanotechnology to formulate effective vaccines and better diagnostic tools. Once properly developed these tools can be used to control the spread of AIV hence preventing the economic and health losses it may cause.

KEYWORDS
Mortality, Morbidity, Pathogenic, Avian influenza virus, AIV

Received: 19-May-2024
Revised: 12-Jul-2024
Accepted: 08-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Naeem MI, Hussain F, Aslan ES, Nousheen J, Nisa QU, Sarwar M, Fatima M, Khanim A, Younis W and Murtaza G, 2024. Use of nanotechnology to treat avian influenza. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 47-54. https://doi.org/10.47278/book.CAM/2024.225

INTRODUCTION

A key role is attributed to poultry products in the production of food items and reduction in poverty status in case there is a shortage of other types of food products that are nutrient-rich (Hedman et al., 2020; Desta, 2021). Various crucial factors will determine the poultry industry's upcoming growth rate. The list of factors is comprised of but not limited to the immunity of poultry birds, health status and production capacity of birds being reared (Hafez and Attia, 2020). Diseases of poultry keep emerging continuously at a global level and are the main topic of concern for the stakeholders of the poultry industry (De Boeck et al., 2015). The most common and widespread diseases of poultry, all over the world, include Infectious bronchitis (IB), avian influenza (AI), Newcastle disease (ND), and Gumboro disease (Nkukwana, 2018; Yadav et al., 2019).

The disease of Avian influenza virus (AIV) is caused by a very notable virus of poultry birds belonging to the Orthomyxoviridae family. The infection of AIV leads to huge economic losses for the poultry farmers at global scale (Dhama et al., 2005; Parvin et al., 2018). The structure of AIV is made up of a segmented negative eight piece, single-stranded RNA encoding bases for around 11 proteins (Chen and Deng, 2009). Additionally, the Avian Influenza Virus is divided into subgroups depending upon the proteins found on the surface of the viral agent. These proteins include hemagglutinin (HA) and neuraminidase (NA) which assist the attachment and release of viral agent to the target surface, in the same order (Ducatez et al., 2008; Yang et al., 2016). The rearrangement of hemagglutinin and neuraminidase with various subgroups may result in severely rampant pandemics such as H1N1, H2N2, and H3N2 in humans (Blagodatski et al., 2021). AIV is classified depending upon the severity of clinical signs it may cause in its victim. This classification includes highly pathogenic avian influenza virus (HPAIV) and low pathogenic avian influenza virus (LPAIV) (Luo et al., 2021; Soda et al., 2021).

Vaccination failure in during production phase of poultry birds is quite common due to the co-circulation of the

existence of various strains of AIV. These subtypes include H5, H7, and H9 (Mansour et al., 2017). Hence it is essential to strive for the advancement of a polyvalent vaccine that can be used for inducing immunity against various serotypes simultaneously. When taken into account such factors indicate that there is a high risk for emergence of novel infectious diseases and serotypes for the human and livestock populations (Mohamed et al., 2019). Such an example from the past is the inclination of poultry production systems towards intense rearing systems for battling the losses caused by the rise of highly pathogenic H7N9 AIV. The increase in poultry stocking density and rise in populations has led to an increase in the transmission rate of the disease between humans and birds (Astill et al., 2018). Furthermore, the increase in the rate of evolution and immense pressure on the immunity of birds are limiting factors against the effectiveness of vaccination (Gilbert et al., 2017). Additionally, the utilization of antimicrobial agents as feed additives has increased the problem of drug residues and consequently antibiotic resistance. This is the main reason that led to the ban of antibiotic utilization at the sub-therapeutic level in all European countries since January 2006 (Manyi-Loh et al., 2018).

Nanotech

Classification of Avian influenza viruses (AIV) is partitioned into two classes one is the low pathogenic viruses and the other is of highly pathogenic viruses. The low pathogenic avian influenza also known as LPAI is a less virulent strain of viruses that produces mild clinical signs after infection and has low chances of affecting the reproductive system and affecting egg production capacity (Gonzales et al., 2012), other hand HPAI or high pathogenic avian influenza virus infection lead to cause massive outbreaks of influenza with high death rate in birds (Tiensin et al., 2005). However, the actual pathogenicity of low pathogenic capability Avian Influenza virus is determined by various internal and external factors of the hosting individual (França and Brown, 2014). In regions where both types of this virus are prevalent among poultry birds, the use of inactivated whole unit and vectored viral vaccines is preferred to minimize the risk and occurrence of Avian Influenza Virus (Swayne, 2012; Suarez and Pantin-Jackwood, 2017). The parenteral administration of these vaccines induces the immunity at systemic level and provides partial to full protection against the progression of disease. Still, these vaccines provide no assurance of preventing viral invasion and release of viral agent from already diseased birds (Costa et al., 2011; Kapczynski et al., 2016). This marks the requirement for researchers to look into immunogenicity and efficacy improvement methods for existing vaccines against AIV. Such a goal can be obtained through the selection of adjuvants having greater capabilities regarding the stimulation of innate and adaptive immunity (Gutjahr et al., 2016; Pizzolla et al., 2017). This adjuvant can be used effectively through the exploration of efficient vaccination routes (Hasegawa et al., 2007) and by adopting optimized methods of vaccine delivery (Vyas and Gupta, 2007; Jain et al., 2011; Singh et al., 2016).

Linked directly with profound sciences of physics, chemistry. biology, materials and medicine, nanotechnology is a fairly recent and under-development field of applied sciences. It includes several types of cutting-edge technological tools and applications that utilize the properties of nanomaterials form the physicochemical aspect to regulate their surface area, size, and shape to produce various types of nanomaterials with of different properties. Nanoparticles have been vastly utilized for development of nanoparticle-based drug carriers with a targeting nature, test kits for rapid pathogen detection or bio-molecular sensing systems and antiviral agents that with mechanism of action relying on their interference with viral infectious agents, especially during their attachment to cell surface and entry in the host cell (Miranda et al., 2010; Cao et al., 2011; Falanga et al., 2011).

Influenza

The last twenty years have proven to be a nightmare for avian health as the rise of highly pathogenic type A avian influenza virus (AIV) strains was witnessed. The emergence of this strain led to have development of disease with severe and incurred heavy losses causing an economic crash in the poultry industry. The victims of this strain included chickens and turkeys, but humans were also affected as a number of avian-human transmissions cases were observed. The highly pathogenic AIV strains were found to be the main reason behind high morbidity and mortality rates in poultry post-infection. This led to breakouts and epidemics with significant economic downturns. For instance, in early 2006, an infection with highly pathogenic H5N1 AIV at a poultry farm in Egypt resulted in high mortality of birds. Afterwards, this breakout the first human case of AIV was detected. Since that, the WHO has recorded more than a hundred cases of AIV infection in humans from birds and several deaths have also occurred due to this infection in Egypt (Cattoli et al., 2011).

The diversity in genotype and phenotype diversity of influenza viruses along with their divergence capabilities pose a significant threat to the technological development of diagnosis and therapeutic tools and techniques. AIVs are classified for diagnosis based on their subtypes according to their haemagglutinin (HA, H1-H16) decided upon their antigenic properties and through testing of surface glycoproteins neuraminidase (N1-N9). The only strains that are avian and have been reported as an etiologic agent in humans include H5, H7 and H9. The H5N1 is the very well-identified and highly pathogenic avian influenza virus strain (Leong et al., 2008). Currently the recent reporting subtype of AIV, H7N9 has gained attention from the researchers. On the basis of evidence obtained through genetic research most of the strains belonging to the influenza virus are found linked to the aquatic birds. The wild birds usually show little or no disease in case of infection with AIV hence they are assumed to serve as ‘reservoirs’ for these viruses. The appearance of genetic mutations or re-shuffling of these viral genes has led to high pathogenicity in these strains making them extremely virulent and adaptable to new species of hosts, such as birds (chicken), livestock (pigs) and human populations. Poultry birds and

livestock pigs have been reported to play their role as 'mixing vessels' for various subtypes of avian influenza virus. This mixing facilitates shuffling genetic material among the highly pathogenic subtypes of avian influenza. This shuffling ultimately led to the development of strains that caused severe disease outbreaks among human populations (Bengis et al., 2004; Sakoda et al., 2012; Jones et al., 2013; Beaudoin et al., 2014). Alterations in the situation of hosting individual, environmental conditions, or transmission agent can lead to rise in occurrence of virus invasion rate. Several viral maladies that emerged in the last few tens of years have recently become entangled among the population of humans all across the globe. Many important instances of these viral attacks include Chikungunya virus, Hantavirus, monkey-pox virus, Hendra virus, Zika virus, Nipah virus and SARS coronavirus, and the challenge of avian influenza virus pandemic from bird or pig sources. Climate change and the effects of activities of humans on the ecosystem are the main factors contributing to the dispersal of pathogens. Especially the presence of high genetic biodiversity among wild birds along with the lower genetic biodiversity level of the domestic birds leads to the encouragement of the quick spread of infections in densely populated farms and live poultry markets (Loth et al., 2010; Jones et al., 2013; Wang et al., 2014; Wu et al., 2014).

Diagnosis

Viral agents of Avian Influenza have been mostly distinguished through detection and assessment of particular proteins and nucleic acids and by the use of analysis techniques like polymerase chain reaction (PCR) (Esposito et al., 2010; Heger et al., 2014), enzyme-linked lectin assay (ELLA) and enzyme-linked immunosorbent assay (ELISA) (Westgeest et al., 2015). Although effective, these methods require a set of specific expensive tools and equipment under special controlled laboratory conditions only to be performed by expert personnel (Sun et al., 2001; Park et al., 2010; Esfandyarpour et al., 2013; Qasim et al., 2014). Generally, influenza virus infection was diagnosed through a series of tests starting from Western blot, protein and DNA microarrays or PCR which later on led to analysis through DNA sequencing. The AIV typing microarray tests can be used for detection purposes but are also helpful in the provision of supplemental information regarding the subtype identified in the symptomatically positive samples as compared to the ones detected with real-time PCR (Lung et al., 2012). Techniques of Lab-on-a-chip and full integration methods have been optimized for identification and differentiation of pathotypes, and characterization of the influenza A viruses, isolated from actual field samples, phylogenetically (Charlton et al., 2009).

Several types of ELISA tests including strip tests like immune-chromatographic tests (Watanabe et al., 2015) along with double antibody sandwich enzyme-linked immune-sorbent assay (DAS-ELISA) (Moulick et al., 2017), have been mainly utilized for the quick identification of H9 influenza virus subtypes and the specificity of attachment of receptors in various sample types. DAS-ELISA employs the use of two monoclonal antibodies with a lofty specificity value of 99.1% in its results and it has a 93.1% sensitivity percentage. The type of ELISA test that employs the use a special type of blocking that is dual-function with high sensitivity and a perfect 100% specificity in its results for a quicker confirmation of avian influenza virus invasion as compared to other time-taking tests like PCR. These diagnostics techniques are useful methods for AIV diagnosis besides the traditional approach through the haem-agglutination inhibition (HI) test. HI test is primarily used for the sorting of numerous samples. However, these tests have evidently more sensitivity and specificity in their results as compared to the HI test while also being quicker and more convenient for implementation of automatic systems (Comin et al., 2013; Li et al., 2013). Another method reported for the identification of AIV in samples is through immunofluorescence assay of magnetic nature. This test can be performed by a spectrometer with optical fibres and a chip of microfluidics with portability options (Zhang et al., 2013). A technique has been formulated to identify the zoonotic pathogen strain of avian influenza A/ H7N9 using the real-time PCR test in a set of limited detection range starting from 3.2×10^{-4} to 6.4×10^{-4} haem-agglutination units (HAUs) for the genes of H7 and N9, respectively (Fan et al., 2014; Kang et al., 2014). An idea of a polydimethylsiloxane-made microfluidics chip with the capability to detect real-time fluorescence for the quick detection of AIV H5 has been presented (Zhu et al., 2014). Microarrays of DNA and protein and DNA can be utilized for the multiplexed detection, sorting and typing of Avian Influenza Viruses that have been recently categorized as the H16 and N9 subtypes. These microarrays have opened a new channel of possibilities for diagnosis applications. However factors like practicality and economics still limit their use in diagnostic laboratories at large scale (Rodrigo et al., 2014; Zhao et al., 2015).

Nanotechnology-based Solutions

Various types of nano-sized materials are now being utilized as the appliances of interactions between the materials and the viral agents. This interaction enables the researchers to build bio-sensing analyzers that work effectively in theory based on the application of electro-analysis with a portable nature. It can perform nearly perfect identification of influenza virus (Moulick et al., 2017). The utilisation of vaccines based on nano-materials has several benefits that include but are not limited to increased storage viability time, the stabilisation of vaccines by encapsulating with nanoparticles of a polymeric nature that stay solid at room temperature, the provision of the possibility to administer the vaccine through an alternate route, and obtaining ability of precise discharge. Nanomaterial-based vaccines can also be used to release soluble antigens that can assist in the induction of two forms of immunity, i.e., humoral and cellular (Chen et al., 2017). In the same way, nanoparticles formulated from the chitosan derivatives are utilized for delivering an immune response upon administration through the mucosal entry sites of birds. Post-vaccination a reduction can be observed in the morbidity and mortality rates of infection. The viral load was also found reduced in chickens that were infected with IBV and AIV (Renu and Renukaradhya, 2020).

Nanobeads also known as magnetic beads are considered nanoparticles and are utilized at amplifion for the

identification of signals along with quartz crystal microbalance (QCM) apta sensors, the magnetic nano bead-amplified QCM immune sensors. These beads can be utilized for the detecting presence of the H5N1 proteins (Brockman, 2013). Magnetic nanoparticles composed of silver nanoparticles (AgNPs) and carbon-derivative materials are often used for the analysis and identification of various influenza virus subtypes. These particles are prepared on the well-researched methodologies readily available in reports of past researchers. (Mokhtarzadeh et al., 2017; Boroumand et al., 2021). Furthermore, the knowledge of well-known methods like the electrode-based well array, on-chip nano-membrane tubular sensors based on full integration and electrochemical quantitative systems, also assists the research and development of such nanoparticles (Krejcova et al., 2012; Cha et al., 2013).

Mesoporous nanoparticles like that of silica can perform various functions due to their amino group and being naturally attached to probiotics like quercetin and shikimic acid. These nanoparticles have developed into a novel formulation of antiviral nanoparticles that target the identification of highly pathogenic avian influenza H5N1 virus. These nanoparticles also induce a strong response from the immune system. These particles limit the cytokines (IL-1β and TNF-α) and nitric oxide (NO) production by half. When tested on a critical carrageenan-induced rat model these nanoparticles served an extremely efficient role in inducing the anti-inflammatory effect and then continued it in vivo (Neethirajan, 2017; AbouAitah et al., 2020). Thus, nano-scaled technology through the utilization of several types of NPs and as the nano-vaccines, nano-bodies and nano-medicine, along with the utilization of adjuvants, has a significant role in future as a biomedical application for controlling avian infectious diseases.

Conclusion

Avian Influenza Virus has been the arch-nemesis of the poultry production industry since it was reported. Infection of Avian Influenza virus spreads rapidly and has severe clinical signs with a high rate of mortality if the infecting agent is the highly pathogenic strain of AIV. These factors make it a major risk for the progress of the poultry industry. Additionally, the recent discovery regarding the zoonosis potential of this disease has led to a rise of concern among public health researchers. This situation called for immediate action so now a number of researchers are exploiting cutting-edge innovations to counter AIV. One such innovation is the nanotechnology. Nanotechnology is being researched for its use for effective vaccination against AIV, its control and proper diagnosis. These advancements in nanotechnology have given mankind hope that this pandemic can be controlled. Control over AIV will not only reduce poultry losses but it will also bring a sense of security for public health.

REFERENCES

AbouAitah, K., Swiderska-Sroda, A., Kandeil, A., Salman, A. M., Wojnarowicz, J., Ali, M. A., and Lojkowski, W. (2020). Virucidal action against avian influenza H5N1 virus and immunomodulatory effects of nanoformulations consisting of mesoporous silica nanoparticles loaded with natural prodrugs. *International Journal of Nanomedicine*, 5181-5202. https://doi.org/10.2147/IJN.S247692

Astill, J., Dara, R. A., Fraser, E. D., and Sharif, S. (2018). Detecting and predicting emerging disease in poultry with the implementation of new technologies and big data: A focus on avian influenza virus. *Frontiers in Veterinary Science*, *5*, 263. https://doi.org/https://doi.org/10.3389/fvets.2018.00263

Beaudoin, A., Kitikoon, P., Schreiner, P., Singer, R., Sasipreeyajan, J., Amonsin, A., and Bender, J. (2014). Risk Factors for Exposure to Influenza A Viruses, Including Subtype H 5 Viruses, in T hai Free-Grazing Ducks. *Transboundary and Emerging Diseases*, *61*(4), 362-374. https://doi.org/https://doi.org/10.1111/tbed.12043

Bengis, R., Leighton, F., Fischer, J., Artois, M., Morner, T., and Tate, C. (2004). The role of wildlife in emerging and re-emerging zoonoses. *Revue Scientifique et Technique-office International des Epizooties*, *23*(2), 497-512.

Blagodatski, A., Trutneva, K., Glazova, O., Mityaeva, O., Shevkova, L., Kegeles, E., and Khavina, E. (2021). Avian influenza in wild birds and poultry: dissemination pathways, monitoring methods, and virus ecology. *Pathogens*, *10*(5), 630. https://doi.org/https://doi.org/10.3390/pathogens10050630

Boroumand, H., Badie, F., Mazaheri, S., Seyedi, Z. S., Nahand, J. S., Nejati, M., and Ghandali, M. (2021). Chitosan-based nanoparticles against viral infections. *Frontiers in Cellular and Infection Microbiology*, *11*, 643953. https://doi.org/10.3389/fcimb.2021.643953

Brockman, L. (2013). *QCM aptasensor for rapid and specific detection of avian influenza virus* (Publication Number 789) [Graduate Theses and Dissertations, University of Arkansas, Fayetteville]. Fayetteville. https://scholarworks.uark.edu/etd/789/

Brownlie, R., Zhu, J., Allan, B., Mutwiri, G. K., Babiuk, L. A., Potter, A., and Griebel, P. (2009). Chicken TLR21 acts as a functional homologue to mammalian TLR9 in the recognition of CpG oligodeoxynucleotides. *Molecular Immunology*, *46*(15), 3163-3170. https://doi.org/https://doi.org/10.1016/j.molimm.2009.06.002

Calderon-Nieva, D., Goonewardene, K. B., Gomis, S., and Foldvari, M. (2017). Veterinary vaccine nanotechnology: pulmonary and nasal delivery in livestock animals. *Drug Delivery and Translational Research*, *7*, 558-570. https://doi.org/10.1007/s13346-017-0400-9

Cao, C., Gontard, L. C., Thuy Tram, L. L., Wolff, A., and Bang, D. D. (2011). Dual enlargement of gold nanoparticles: from mechanism to scanometric detection of pathogenic bacteria. *Small*, *7*(12), 1701-1708. https://doi.org/10.1002/

smll.201100294

Carroll, E. C., Jin, L., Mori, A., Munoz-Wolf, N., Oleszycka, E., Moran, H. B., and Agger, E. M. (2016). The vaccine adjuvant chitosan promotes cellular immunity via DNA sensor cGAS-STING-dependent induction of type I interferons. *Immunity*, *44*(3), 597-608. https://doi.org/http://dx.doi.org/10.1016/j.immuni.2016.02.004

Cattoli, G., Fusaro, A., Monne, I., Coven, F., Joannis, T., Abd El-Hamid, H. S., and Mancin, M. (2011). Evidence for differing evolutionary dynamics of A/H5N1 viruses among countries applying or not applying avian influenza vaccination in poultry. *Vaccine*, *29*(50), 9368-9375. https://doi.org/https://doi.org/10.1016/j.vaccine.2011.09.127

Cha, M. S., Lee, J. K., Cho, S. H., Park, J. G., Lee, H. Y., Lim, S. H., and Yoon, Y. R. (2013). Quantitative analysis of H5N1 DNA hybridization on nanowell array electrode. *Journal of Nanoscience and Nanotechnology*, *13*(8), 5245-5249. https://doi.org/https://doi.org/10.1166/jnn.2013.7531

Chadwick, S., Kriegel, C., and Amiji, M. (2010). Nanotechnology solutions for mucosal immunization. *Advanced Drug Delivery Reviews*, *62*(4-5), 394-407. https://doi.org/https://doi.org/10.1016/j.addr.2009.11.012

Charlton, B., Crossley, B., and Hietala, S. (2009). Conventional and future diagnostics for avian influenza. *Comparative Immunology, Microbiology and Infectious Diseases*, *32*(4), 341-350. https://doi.org/10.1016/j.cimid.2008.01.009

Chen, J., and Deng, Y.-M. (2009). Influenza virus antigenic variation, host antibody production and new approach to control epidemics. *Virology Journal*, *6*, 1-3. https://doi.org/10.1186/1743-422X-6-30

Chen, Y. C., Cheng, H. F., Yang, Y. C., and Yeh, M. K. J. V. R., Croatia: InTech. (2017). Biotechnologies applied in biomedical vaccines. In A. Farhat, H. Hassan, and O. Hani (Eds.), *Vaccines* (pp. 97-110). Books on Demand. https://dx.doi.org/10.5772/intechopen.69547

Comin, A., Toft, N., Stegeman, A., Klinkenberg, D., and Marangon, S. (2013). Serological diagnosis of avian influenza in poultry: is the haemagglutination inhibition test really the 'gold standard'? *Influenza and Other Respiratory Viruses*, *7*(3), 257-264. https://doi.org/10.1111/j.1750-2659.2012.00391.x

Costa, T. P., Brown, J. D., Howerth, E. W., Stallknecht, D. E., and Swayne, D. E. (2011). Homo-and heterosubtypic low pathogenic avian influenza exposure on H5N1 highly pathogenic avian influenza virus infection in wood ducks (Aix sponsa). *PLOS one*, *6*(1), e15987. https://doi.org/10.1371/journal.pone.0015987

De Boeck, C., Kalmar, I., Dumont, A., and Vanrompay, D. (2015). Longitudinal monitoring for respiratory pathogens in broiler chickens reveals co-infection of Chlamydia psittaci and Ornithobacterium rhinotracheale. *Journal of Medical Microbiology*, *64*(5), 565-574. https://doi.org/10.1099/jmm.0.000047

De Geus, E. D., and Vervelde, L. (2013). Regulation of macrophage and dendritic cell function by pathogens and through immunomodulation in the avian mucosa. *Developmental and Comparative Immunology*, *41*(3), 341-351. https://doi.org/10.1016/j.dci.2013.03.008

Desta, T. T. (2021). Indigenous village chicken production: a tool for poverty alleviation, the empowerment of women, and rural development. *Tropical Animal Health and Production*, *53*(1), 1. https://doi.org/10.1007/s11250-020-02433-0

Dhama, K., Chauhan, R., Kataria, J., Mahendran, M., and Tomar, S. (2005). Avian influenza: the current perspectives. *Journal of Immunology and Immunopathology*, *7*(2), 1-33.

Ducatez, M., Webster, R., and Webby, R. (2008). Animal influenza epidemiology. *Vaccine*, *26*, D67-D69. https://doi.org/10.1016/j.vaccine.2008.07.064

Esfandyarpour, R., Esfandyarpour, H., Javanmard, M., Harris, J. S., and Davis, R. W. (2013). Microneedle biosensor: A method for direct label-free real time protein detection. *Sensors Actuators B: Chemical*, *177*, 848-855. https://doi.org/10.1016/j.snb.2012.11.064

Esposito, S., Molteni, C. G., Daleno, C., Valzano, A., Tagliabue, C., Galeone, C., and Principi, N. (2010). Collection by trained pediatricians or parents of mid-turbinate nasal flocked swabs for the detection of influenza viruses in childhood. *Virology Journal*, *7*, 1-4. https://doi.org/10.1186/1743-422X-7-85

Falanga, A., Vitiello, M. T., Cantisani, M., Tarallo, R., Guarnieri, D., Mignogna, E., and Galdiero, S. (2011). A peptide derived from herpes simplex virus type 1 glycoprotein H: membrane translocation and applications to the delivery of quantum dots. *Nanomedicine: Nanotechnology, Biology and Medicine*, *7*(6), 925-934. https://doi.org/10.1016/j.nano.2011.04.009

Fan, J., Cui, D., Lau, S., Xie, G., Guo, X., Zheng, S., and Huo, Z. (2014). Detection of a novel avian influenza A (H7N9) virus in humans by multiplex one-step real-time RT-PCR assay. *BMC Infectious Diseases*, *14*, 1-9. https://doi.org/10.1186/1471-2334-14-541

França, M. S., and Brown, J. D. (2014). Influenza pathobiology and pathogenesis in avian species. In R. Compans and M. Oldstone (Eds.), *Influenza Pathogenesis Control* (Vol. 1, pp. 221-242). Springer. https://doi.org/10.1007/82_2014_385

Ghotbi, Z., Haddadi, A., Hamdy, S., Hung, R. W., Samuel, J., and Lavasanifar, A. (2011). Active targeting of dendritic cells with mannan-decorated PLGA nanoparticles. *Journal of Drug Targeting*, *19*(4), 281-292. https://doi.org/10.3109/1061186X.2010.499463

Gilbert, M., Xiao, X., and Robinson, T. P. (2017). Intensifying poultry production systems and the emergence of avian influenza in China: a 'One Health/Ecohealth'epitome. *Archives of Public Health*, *75*, 1-7. https://doi.org/10.1186/s13690-017-0218-4

Gizurarson, S. (2015). The effect of cilia and the mucociliary clearance on successful drug delivery. *Biological and Pharmaceutical Bulletin*, *38*(4), 497-506. https://doi.org/10.1248/bpb.b14-00398

Gonzales, J., Elbers, A., Van der Goot, J., Bontje, D., Koch, G., De Wit, J., and Stegeman, J. (2012). Using egg production data

to quantify within-flock transmission of low pathogenic avian influenza virus in commercial layer chickens. *Preventive Veterinary Medicine*, *107*(3-4), 253-259. https://doi.org/10.1016/j.prevetmed.2012.06.010

Gupta, S. K., Deb, R., Dey, S., and Chellappa, M. M. (2014). Toll-like receptor-based adjuvants: enhancing the immune response to vaccines against infectious diseases of chicken. *Expert Review of Vaccines*, *13*(7), 909-925. https://doi.org/10.1586/14760584.2014.920236

Gutjahr, A., Tiraby, G., Perouzel, E., Verrier, B., and Paul, S. (2016). Triggering intracellular receptors for vaccine adjuvantation. *Trends in Immunology*, *37*(9), 573-587. https://doi.org/10.1016/j.it.2016.07.001

Hafez, H. M., and Attia, Y. A. (2020). Challenges to the poultry industry: current perspectives and strategic future after the COVID-19 outbreak. *Frontiers in veterinary science*, *7*, 516. https://doi.org/10.3389/fvets.2020.00516

Hasegawa, H., Ichinohe, T., Tamura, S.-i., and Kurata, T. (2007). Development of a mucosal vaccine for influenza viruses: preparation for a potential influenza pandemic. *Expert Review of Vaccines*, *6*(2), 193-201. ttps://doi.org/10.1586/14760584.6.2.193

Hedman, H. D., Vasco, K. A., and Zhang, L. (2020). A review of antimicrobial resistance in poultry farming within low-resource settings. *Animals*, *10*(8), 1264. https://doi.org/10.3390/ani10081264

Heger, Z., Cernei, N., Gumulec, J., Masarik, M., Eckschlager, T., Hrabec, R., and Kizek, R. (2014). Determination of common urine substances as an assay for improving prostate carcinoma diagnostics. *Oncology Reports*, *31*(4), 1846-1854. https://doi.org/10.3892/or.2014.3054

Hemmi, H., Takeuchi, O., Kawai, T., Kaisho, T., Sato, S., Sanjo, H., and Takeda, K. (2000). A Toll-like receptor recognizes bacterial DNA. *Nature*, *408*(6813), 740-745. https://doi.org/10.1038/35047123

Jain, S., O'Hagan, D. T., and Singh, M. (2011). The long-term potential of biodegradable poly (lactideco-glycolide) microparticles as the next-generation vaccine adjuvant. *Expert Review of Vaccines*, *10*(12), 1731-1742. https://doi.org/10.1586/erv.11.126

Jones, B. A., Grace, D., Kock, R., Alonso, S., Rushton, J., Said, M. Y., and McDermott, J. (2013). Zoonosis emergence linked to agricultural intensification and environmental change. *Proceedings of the National Academy of Sciences*, *110*(21), 8399-8404. https://doi.org/10.1073/pnas.1208059110

K Garg, N., Mangal, S., Khambete, H., K Sharma, P., and K Tyagi, R. (2010). Mucosal delivery of vaccines: role of mucoadhesive/biodegradable polymers. *Recent Patents on Drug Delivery and Formulation*, *4*(2), 114-128. https://doi.org/10.2174/187221110791185015

Kang, M. L., Cho, C. S., and Yoo, H. S. (2009). Application of chitosan microspheres for nasal delivery of vaccines. *Biotechnology Advances*, *27*(6), 857-865. https://doi.org/10.1016/j.biotechadv.2009.06.007

Kang, X., Wu, W., Zhang, C., Liu, L., Feng, H., Xu, L., and Xu, B. (2014). Detection of avian influenza A/H7N9/2013 virus by real-time reverse transcription-polymerase chain reaction. *Journal of Virological Methods*, *206*, 140-143. https://doi.org/10.1016/j.jviromet.2014.01.026

Kapczynski, D. R., Tumpey, T. M., Hidajat, R., Zsak, A., Chrzastek, K., Tretyakova, I., and Pushko, P. (2016). Vaccination with virus-like particles containing H5 antigens from three H5N1 clades protects chickens from H5N1 and H5N8 influenza viruses. *Vaccine*, *34*(13), 1575-1581. https://doi.org/10.1016/j.vaccine.2016.02.011

Klinman, D. M., Klaschik, S., Tomaru, K., Shirota, H., Tross, D., and Ikeuchi, H. (2010). Immunostimulatory CpG oligonucleotides: Effect on gene expression and utility as vaccine adjuvants. *Vaccine*, *28*(8), 1919-1923. https://doi.org/10.1016/j.vaccine.2009.10.094

Krejcova, L., Hynek, D., Adam, V., Hubalek, J., and Kizek, R. (2012). Electrochemical sensors and biosensors for influenza detection. *International Journal of Electrochemical Science*, *7*(11), 10779-10801. https://doi.org/10.1016/S1452-3981(23)16902-1

Kunisawa, J., Fukuyama, S., and Kiyono, H. (2005). Mucosa-associated lymphoid tissues in the aerodigestive tract: their shared and divergent traits and their importance to the orchestration of the mucosal immune system. *Current Molecular Medicine*, *5*(6), 557-572. https://doi.org/10.2174/1566524054863924

Leong, H. K., Goh, C. S., Chew, S. T., Lim, C. W., Lin, Y. N., Chang, S. F., and Chua, S. B. (2008). Prevention and control of avian influenza in Singapore. *Annals Academy of Medicine Singapore*, *37*(6), 504. http://dx.doi.org/10.47102/annals-acadmedsg.V37N6p504

Li, J., Zou, M., Chen, Y., Xue, Q., Zhang, F., Li, B., and Yang, Y. (2013). Gold immunochromatographic strips for enhanced detection of Avian influenza and Newcastle disease viruses. *Analytica Chimica Acta*, *782*, 54-58. https://doi.org/10.1016/j.aca.2013.04.022

Loth, L., Gilbert, M., Osmani, M. G., Kalam, A. M., and Xiao, X. (2010). Risk factors and clusters of highly pathogenic avian influenza H5N1 outbreaks in Bangladesh. *Preventive Veterinary Medicine*, *96*(1-2), 104-113. https://doi.org/10.1016/j.prevetmed.2010.05.013

Lung, O., Beeston, A., Ohene-Adjei, S., Pasick, J., Hodko, D., Hughes, K. B., and Deregt, D. (2012). Electronic microarray assays for avian influenza and Newcastle disease virus. *Journal of Virological Methods*, *185*(2), 244-253. https://doi.org/10.1016/j.jviromet.2012.07.005

Luo, S., Xie, Z., Li, M., Li, D., Xie, L., Huang, J., and Fan, Q. (2021). Survey of low pathogenic avian influenza viruses in live poultry markets in Guangxi Province, Southern China, 2016–2019. *Scientific Reports*, *11*(1), 23223. https://doi.org/10.1038/s41598-021-02639-8

Lycke, N. (2012). Recent progress in mucosal vaccine development: potential and limitations. *Nature Reviews Immunology*, *12*(8), 592-605. https://doi.org/10.1038/nri3251

Ma, T., Wang, L., Yang, T., Ma, G., and Wang, S. (2014). M-cell targeted polymeric lipid nanoparticles containing a toll-like receptor agonist to boost oral immunity. *International Journal of Pharmaceutics*, *473*(1-2), 296-303. https://doi.org/10.1016/j.ijpharm.2014.06.052

Mansour, S. M., Mohamed, F. F., Eid, A. A., Mor, S. K., and Goyal, S. M. (2017). Co-circulation of paramyxo-and influenza viruses in pigeons in Egypt. *Avian Pathology*, *46*(4), 367-375. https://doi.org/10.1080/03079457.2017.1285391

Manyi-Loh, C., Mamphweli, S., Meyer, E., and Okoh, A. (2018). Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules*, *23*(4), 795. https://doi.org/10.3390/molecules23040795

Miranda, O. R., Creran, B., and Rotello, V. M. (2010). Array-based sensing with nanoparticles:'chemical noses' for sensing biomolecules and cell surfaces. *Current Opinion in Chemical Biology*, *14*(6), 728-736. https://doi.org/10.1016/j.cbpa.2010.07.021

Mohamed, M., Ahmed, H., Erfan, A., Abdelkarim, L., and Awadallah, M. (2019). Endemic status and zoonotic potential of avian influenza viruses in Egypt, 2006-2019. *Advances in Animal and Veterinary Sciences*, *7*(s2), 154-162. http://dx.doi.org/10.17582/journal.aavs/2019/7.s2.154.162

Mokhtarzadeh, A., Eivazzadeh-Keihan, R., Pashazadeh, P., Hejazi, M., Gharaatifar, N., Hasanzadeh, M., and de la Guardia, M. (2017). Nanomaterial-based biosensors for detection of pathogenic virus. *Trends in Analytical Chemistry*, *97*, 445-457. https://doi.org/10.1016/j.trac.2017.10.005

Moulick, A., Richtera, L., Milosavljevic, V., Cernei, N., Haddad, Y., Zitka, O., and Adam, V. (2017). Advanced nanotechnologies in avian influenza: current status and future trends–a review. *Analytica Chimica Acta*, *983*, 42-53. https://doi.org/10.1016/j.aca.2017.06.045

Neethirajan, S. (2017). Recent advances in wearable sensors for animal health management. *Sensing and Bio-Sensing Research*, *12*, 15-29. https://doi.org/10.1016/j.sbsr.2016.11.004

Nkukwana, T. (2018). Global poultry production: Current impact and future outlook on the South African poultry industry. *South African Journal of Animal Science*, *48*(5), 869-884. https://doi.org/10.4314/sajas.v48i5.7

Park, M., Cella, L. N., Chen, W., Myung, N. V., and Mulchandani, A. (2010). Carbon nanotubes-based chemiresistive immunosensor for small molecules: Detection of nitroaromatic explosives. *Biosensors and Bioelectronics*, *26*(4), 1297-1301. https://doi.org/10.1016/j.bios.2010.07.017

Parvin, R., Begum, J. A., Nooruzzaman, M., Chowdhury, E. H., Islam, M. R., and Vahlenkamp, T. W. (2018). Review analysis and impact of co-circulating H5N1 and H9N2 avian influenza viruses in Bangladesh. *Epidemiology and Infection*, *146*(10), 1259-1266. https://doi.org/10.1017/S0950268818001292

Pawar, D., Mangal, S., Goswami, R., and Jaganathan, K. (2013). Development and characterization of surface modified PLGA nanoparticles for nasal vaccine delivery: effect of mucoadhesive coating on antigen uptake and immune adjuvant activity. *European Journal of Pharmaceutics and Biopharmaceutics*, *85*(3), 550-559. https://doi.org/10.1016/j.ejpb.2013.06.017

Pizzolla, A., Smith, J. M., Brooks, A. G., and Reading, P. C. (2017). Pattern recognition receptor immunomodulation of innate immunity as a strategy to limit the impact of influenza virus. *Journal of Leucocyte Biology*, *101*(4), 851-861. https://doi.org/10.1189/jlb.4MR0716-290R

Qasim, M., Lim, D.-J., Park, H., and Na, D. (2014). Nanotechnology for diagnosis and treatment of infectious diseases. *Journal of Nanoscience and Nanotechnology*, *14*(10), 7374-7387. https://doi.org/https://doi.org/10.1166/jnn.2014.9578

Renu, S., and Renukaradhya, G. J. (2020). Chitosan nanoparticle based mucosal vaccines delivered against infectious diseases of poultry and pigs. *Frontiers in Bioengineering and Biotechnology*, *8*, 558349. https://doi.org/10.3389/fbioe.2020.558349

Rodrigo, M. A. M., Zitka, O., Krejcova, L., Hynek, D., Masarik, M., Kynicky, J., and Kizek, R. (2014). Electrochemical microarray for identification pathogens: a review. *International Journal of Electrochemical Science*, *9*(7), 3431-3439. https://doi.org/10.1016/S1452-3981(23)08021-5

Rose, M. A., Zielen, S., and Baumann, U. (2012). Mucosal immunity and nasal influenza vaccination. *Expert Review of Vaccines*, *11*(5), 595-607. https://doi.org/10.1586/erv.12.31

Sakoda, Y., Ito, H., Uchida, Y., Okamatsu, M., Yamamoto, N., Soda, K., and Sunden, Y. (2012). Reintroduction of H5N1 highly pathogenic avian influenza virus by migratory water birds, causing poultry outbreaks in the 2010–2011 winter season in Japan. *Journal of General Virology*, *93*(3), 541-550. https://doi.org/10.1099/vir.0.037572-0

Sinani, G., Sessevmez, M., Gök, M. K., Özgümüş, S., Okyar, A., Alpar, H. O., and Cevher, E. (2017). Nasal vaccination with poly (β-amino ester)-poly (d, l-lactide-co-glycolide) hybrid nanoparticles. *International Journal of Pharmaceutics*, *529*(1-2), 1-14. https://doi.org/10.1016/j.ijpharm.2017.06.053

Singh, S. M., Alkie, T. N., Hodgins, D. C., Nagy, É., Shojadoost, B., and Sharif, S. (2015). Systemic immune responses to an inactivated, whole H9N2 avian influenza virus vaccine using class B CpG oligonucleotides in chickens. *Vaccine*, *33*(32), 3947-3952. https://doi.org/10.1016/j.vaccine.2015.06.043

Singh, S. M., Alkie, T. N., Nagy, É., Kulkarni, R. R., Hodgins, D. C., and Sharif, S. (2016). Delivery of an inactivated avian influenza virus vaccine adjuvanted with poly (D, L-lactic-co-glycolic acid) encapsulated CpG ODN induces protective

immune responses in chickens. *Vaccine*, *34*(40), 4807-4813. https://doi.org/10.1016/j.vaccine.2016.08.009

Soda, K., Yamane, M., Hidaka, C., Miura, K., Ung, T. T., Nguyen, H. L., and Ito, T. (2021). Prior infection with antigenically heterologous low pathogenic avian influenza viruses interferes with the lethality of the H5 highly pathogenic strain in domestic ducks. *Journal of Veterinary and Medical Science*, *83*(12), 1899-1906. https://doi.org/10.1292/jvms.21-0515

Suarez, D. L., and Pantin-Jackwood, M. J. (2017). Recombinant viral-vectored vaccines for the control of avian influenza in poultry. *Veterinary Microbiology*, *206*, 144-151. https://doi.org/10.1016/j.vetmic.2016.11.025

Sun, W., Jiao, K., and Zhang, S. (2001). Electrochemical ELISA for the detection of cucumber mosaic virus using o-pheneylenediamine as substrate. *Talanta*, *55*(6), 1211-1218. https://doi.org/10.1016/S0039-9140(01)00530-6

Swayne, D. E. (2012). Impact of vaccines and vaccination on global control of avian influenza. *Avian Diseases*, *56*(4s1), 818-828. https://doi.org/10.1637/10183-041012-Review.1

Tan, Z., Liu, W., Liu, H., Li, C., Zhang, Y., Meng, X., and Xing, Y. (2017). Oral Helicobacter pylori vaccine-encapsulated acid-resistant HP55/PLGA nanoparticles promote immune protection. *European Journal of Pharmaceutics and Biopharmaceutics*, *111*, 33-43. https://doi.org/10.1016/j.ejpb.2016.11.007

Thomas, C., Rawat, A., Hope-Weeks, L., and Ahsan, F. (2011). Aerosolized PLA and PLGA nanoparticles enhance humoral, mucosal and cytokine responses to hepatitis B vaccine. *Molecular pharmaceutics*, *8*(2), 405-415. https://doi.org/10.1021/mp100255c

Tiensin, T., Chaitaweesub, P., Songserm, T., Chaisingh, A., Hoonsuwan, W., Buranathai, C., and Gilbert, M. (2005). Highly pathogenic avian influenza H5N1, Thailand, 2004. *Emerging Infectious Diseases*, *11*(11), 1664. https://doi.org/10.3201%2Feid1111.050608

Vyas, S. P., and Gupta, P. N. (2007). Implication of nanoparticles/microparticles in mucosal vaccine delivery. *Expert Review of Vaccines*, *6*(3), 401-418. https://doi.org/10.1586/14760584.6.3.401

Wang, C., Wang, J., Su, W., Gao, S., Luo, J., Zhang, M., . . . Chen, Y. (2014). Relationship between domestic and wild birds in live poultry market and a novel human H7N9 virus in China. *The Journal of Infectious Diseases*, *209*(1), 34-37. https://doi.org/10.1093/infdis/jit478

Watanabe, Y., Ito, T., Ibrahim, M. S., Arai, Y., Hotta, K., Phuong, H. V. M., and Poetranto, E. D. (2015). A novel immunochromatographic system for easy-to-use detection of group 1 avian influenza viruses with acquired human-type receptor binding specificity. *Biosensors and Bioelectronics*, *65*, 211-219. https://doi.org/10.1016/j.bios.2014.10.036

Wattrang, E. (2009). Phosphorothioate oligodeoxyribonucleotides induce in vitro proliferation of chicken B-cells. *Veterinary Immunology and Immunopathology*, *131*(3-4), 218-228. https://doi.org/10.1016/j.vetimm.2009.04.013

Westgeest, K. B., Bestebroer, T. M., Spronken, M. I., Gao, J., Couzens, L., Osterhaus, A. D., and de Graaf, M. (2015). Optimization of an enzyme-linked lectin assay suitable for rapid antigenic characterization of the neuraminidase of human influenza A (H3N2) viruses. *Journal of Virological Methods*, *217*, 55-63. https://doi.org/10.1016/j.jviromet.2015.02.014

Wu, X., Tian, H., Zhou, S., Chen, L., and Xu, B. (2014). Impact of global change on transmission of human infectious diseases. *Science China Earth Sciences*, *57*, 189-203. https://doi.org/10.1007/s11430-013-4635-0

Yadav, M. P., Singh, R. K., and Malik, Y. S. (2019). Epidemiological perspective in managing viral diseases in animals. *Recent Advances in Animal Virology*, 381-407. https://doi.org/10.1007/978-981-13-9073-9_20

Yang, H., Carney, P. J., Mishin, V. P., Guo, Z., Chang, J. C., Wentworth, D. E., and Stevens, J. (2016). Molecular characterizations of surface proteins hemagglutinin and neuraminidase from recent H5Nx avian influenza viruses. *Journal of Virology*, *90*(12), 5770-5784. https://doi.org/10.1128/jvi.00180-16

Zhang, R.-Q., Liu, S.-L., Zhao, W., Zhang, W.-P., Yu, X., Li, Y., and Zhang, Z.-L. (2013). A simple point-of-care microfluidic immunomagnetic fluorescence assay for pathogens. *Analytical Chemistry*, *85*(5), 2645-2651. https://doi.org/10.1021/ac302903p

Zhao, Y., Wang, X., Chen, P., Zeng, X., Bao, H., Wang, Y., and Li, G. (2015). Detection of antibodies against avian influenza virus by protein microarray using nucleoprotein expressed in insect cells. *Journal of Veterinary Medical Science*, *77*(4), 413-419. https://doi.org/10.1292/jvms.14-0207

Zheng, M., Qu, D., Wang, H., Sun, Z., Liu, X., Chen, J., and Chen, Z. (2016). Intranasal administration of chitosan against influenza A (H7N9) virus infection in a mouse model. *Scientific Reports*, *6*(1), 28729. https://doi.org/10.1038/srep28729

Zhu, L., Zhu, C., Deng, G., Zhang, L., Zhao, S., Lin, J., and Liu, Y. (2014). Rapid identification of H5 avian influenza virus in chicken throat swab specimens using microfluidic real-time RT-PCR. *Analytical Methods*, *6*(8), 2628-2632. hhttps://doi.org/10.1039/C3AY42126K

Chapter 08

Use of Nanotechnology to Treat Infectious Bronchitis in Poultry

Muhammad Ifham Naeem[1], Farooq Hussain[2], Hina Faiqa[3], Sadia Asghar[4], Qamar un Nisa[5], Muhammad Umair Saleem[6], Minahal Fatima[7], Kinza Fatima[8], Noman Yousaf[9] and Waqar Younis[10]

[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS-Lahore, Pakistan
[2]Shaheed Benazir Bhutto University of Veterinary & Animal Sciences, Sakrand, Pakistan
[3]Department of Epidemiology and Public Health University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Institute of Molecular Biology and Biotechnology, University of Lahore, Pakistan
[5]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[6]Institute of Animal and Dairy Science, University of Agriculture, Faisalabad, Pakistan.
[7]Department of Zoology, Wildlife and Fishries, University of Agriculture, Faisalabad, Pakistan
[8]National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing, China
[9]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
[10]Riphah International University, Lahore, Pakistan
*Corresponding author: afhamnaim4@gmail.com

ABSTRACT

Poultry industry has played a major role in managing food security and combating poverty for populations with food insecurities. For this purpose, it is important for the farmers to develop controls against diseases that can affect poultry production. One such control measure is vaccination. However, there are some diseases that can still lead to reduction in productivity despite vaccination. An example of one such disease is Infectious Bronchitis (IB). It is mainly a respiratory tract disease caused by the Infectious Bronchitis Virus (IBV) that can cause a decline in production of poultry birds irrespective of their status of vaccination. Hence, researchers observed that this was a disease that needed further control strategies to limit its impact. As it is a viral disease, use of antibiotics was ruled out. Another idea presented by researchers was use of innovative medicinal agents such nanoparticles to combat the disease. Since then several techniques and strategies have been outlined by researchers specifically for battling IB.

KEYWORDS
Infectious Bronchitis, Vaccination, Poultry production, Antibiotics, Nanoparticles

Received: 23-May-2024
Revised: 17-July-2024
Accepted: 15-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Naeem MI, Hussain F, Faiqa H, Asghar S, Nisa QU, Saleem MU, Fatima M, Fatima K, Yousaf N and Younis W, 2024. Use of nanotechnology to treat infectious bronchitis in poultry. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 55-60. https://doi.org/10.47278/book.CAM/2024.226

INTRODUCTION

Poultry products are an integral part of our regular food consumption list and a tool for poverty alleviation when there is a lack of other suitable and nutritious food options (Hedman et al., 2020; Desta, 2021). Various crucial components like health, immunity, and production, capability of poultry birds are the main factors determining the future progress of poultry farming (Immunivt, 1998; Hafez and Attia, 2020). At the global level, new diseases of poultry birds are always being reported and become the main topic of concern in the poultry farming industry (De Boeck et al., 2015). Diseases like Infectious bronchitis (IB) have become a problem of common occurrence in poultry birds all over the world (Nkukwana, 2018; Yadav et al., 2019; Legnardi et al., 2020). Despite significant attention being paid to controlling infectious diseases for economic loss aversion, these ailments continuously begin to occur and reoccur (Ali et al., 2021). Infectious bronchitis develops due to the Avian Infectious Bronchitis Virus (IBV) infection. IBV belongs to the *Gammacoronavirus* genus and is a unique virus. IBV pioneered coronavirus when it was identified in 1993 by isolation from poultry. It was also assumed to be a crucial pathogenic virus of livestock (Schalk and Hawn, 1931). IBV belongs to the family of viruses that are enveloped and have non-segmented, single-stranded, positive-sense RNA (Wu et al., 2020).

Currently, IBV has become a pathogen of major concern for domestic poultry from an economic perspective as its infection leads to significant mortality and losses in production irrespective of the vaccination status of birds (Cavanagh, 2007). Many researchers reported global pandemics of IBV in chickens and other avian species that were marked by high rates of death, and disease, and with lowered production in terms of eggs and meat (Mansour et al., 2021; Parvin et al.,

2021). The use of conventional treatment options like antivirals against IBV leads to the development of resistance most of the time. Additionally, it can also produce side effects, and the re-emergence of the viral agent (Legnardi et al., 2020). Presently, vaccines of live attenuated nature are being mainly used for the control and prevention of IBV infections (Sultan et al., 2019; Toro, 2021). Despite the efforts to curb IBV, the higher rate of viral genetic diversity, composition and the occurrence of novel viral strains leads to a reduction in the efficacy of vaccination (Franzo et al., 2016; Sultan et al., 2019).

The utilization of antimicrobial agents as feed additives has led to a rise in the problem of drug residues. Drug residues consequently form the basis of antibiotic resistance in the pathogen. That is why the use of antibiotics at the sub-therapeutic level has been banned in Europe since January 2006 (Manyi-Loh et al., 2018). Hence, researchers must initiate the development of new strategies for controlling these diseases. To achieve this goal, attention is being diverted towards the development of antiviral herbs for useful combinations to get formulations with the least adverse effects on the health of birds and humans (Fuzimoto and Isidoro, 2020; Tagde et al., 2021). The effect of innovative and non-traditional medicine on the immune system and a reduction in the prevalence of unprecedented disasters can be very effective for defense against infectious diseases caused by viral agents (Hoang et al., 2020). It has been reported in previous research that some derivatives of plants and substances added to poultry feed including plant extract, prebiotics, probiotics, enzymes, and yeast, have an immunity-enhancing impact (Soccol et al., 2010; Gadde et al., 2017). The effects of these extracts and additives include improvement in metabolism, reduced physiological stress, prevention of cytokine expedition by macrophages, and antibacterial action, thus improving immune functionality (Al-Harthy, 2015; Patra et al., 2019). Mammal antibodies (Sastry et al., 2003) can be utilized for the purpose of diagnosis and therapy against the infection of various pathogens (Immunivt, 1998), however, the antibodies of mammals can be only obtained through the application of invasive extraction tactics. That is why avian eggs are considered the best alternate option to produce antibodies for the sake of diagnosis and therapy purposes against infection of pathogens (Pereira et al., 2019; El-Kafrawy et al., 2021).

Among the different useful applications including a number of nanoparticles which are used to enhance the interaction between the virus and molecules, and also helps the researchers to build a electroanalytical biosensing analyzer which is portable and which helps in the detection of the virus effectively (Neethirajan, 2017; Power et al., 2018) and the production of nano-based vaccine against viruses. Usually, there are first-generation vaccines which are developed by killing the organisms or inactivation of living organisms or by live attenuation of organisms while on the other hand second and third-generation vaccines are prepared using subunits of either RNA or DNA (Saha et al., 2013; Scallan et al., 2013). In comparison to conventionally developed vaccines, subunit- based vaccines have more advantages including low cost and high proficiency of vaccine to develop immune response against the pathogens (Brisse et al., 2020). The cons of subunit-based vaccines include poor or low immunogenicity, adverse effects, and in in-vivo conditions they are unstable in addition to multiple boosters. So in comparison to conventional vaccines, nanotechnology is the best way to deal with the shortcomings of the vaccines and helps to provide better immune response and produce vaccines that work along with adjuvant and protect the host from the pathogens (Yan et al., 2020). Genomic assortment along with the massive outbreaks of such infectious diseases can lead to an epidemic which results in the spread of adverse side effects globally which not only affects poultry industry but also disturbs human health (Shao et al., 2017; Blagodatski et al., 2021).

Nanotechnology vs Infectious Bronchitis

The word nano originated from the Latin word “nanus” meaning a small object, lesser, dwarf, minute unit that is around 1 nm or 10^{-9} m (Youssef et al., 2019). Nanotechnology is one of the innovative skills that have an unmatched potential of being utilized with regards to a socio-economic prospective in the poultry industry all across the globe (Abd El-Ghany et al., 2021). Nanotechnology has progressed the field of biomedical sciences, with a huge number of NPs of various kinds and capabilities in terms of diagnostics and therapy against infectious viral ailments (Ramos et al., 2017; Krishnan et al., 2021). Investigation has been done to check the antiviral effects of nanocomposites of G-Ag against IBV and Feline CoV (Chen et al., 2016a; Wu et al., 2020). Li et al. (Li et al., 2018) found help in preparing a vaccine on the basis of BIV-flagellin self- assembled protein nanoparticles (SAPNs) which are used against IBV by using spike protein as an adjuvant with the flagellin. Chicken infected with IBV were administered with nano-vaccine which we mentioned above and the results show the enhanced antibody action which confirms the role of the vaccine giving protective immunity. Chandrasekar et al., shows that another adjuvant-based nano-carriers of Quil-A and chitosan (QAC) were developed having the size of less than 100 nm (Chandrasekar et al., 2020).

Other than that some procedures are also done to make encapsulation with plasmid DNA (pQACN) vaccine and coding nucleocapsid which were then given through the intranasal route. The results show increased immunogenic and protective outcomes in both humoral and cellular immunity against IBV infections. Furthermore, it is observed that the rate of viral load decreases and the severity of symptoms also reduces. Polymeric carbonized nano-gels (CNGs) are considered as effective therapeutic agents against IBV. CNGs work by prohibiting the S1 and S2 glycoproteins to interact with cells of the host as the infection proceeds, CNGs are vulnerable to viruses as they are very much absorbent on the virus. In the process of development of CNGs, a very high temperature is required to make these nano-gels, due to the high temperature formation the CNGs exhibit a positive charge. This positive charge helps CNGs to neutralize the charge present on the IBV which reduces the level of pathogenicity of virus (Liu et al., 2020). Chou et al. (Chou et al., 2021) proposed that if amalgamation of the CNGs using pyrolysis method is done with lysine hydrochloride, this may prohibit the virus against IBV. CNGs were administered at a very low concentration of 30ug/ml in IBV-infected chicken embryos and

the efficacy was determined as it shows an inhibitory effect >98%. Many uses of full NP to detect and trace virus has been demonstrated as the NP was based on magnetic and gold quantum dots (QDs) (Kang et al., 2021). Ahmed et al. (Ahmed et al., 2018) suggested a new technique in which he links anti-IBV Abs with QDs and produced an immune-link of chiral-QDs. This immune-link is referred to as a chiro-immuno-sensor for IBV collected from chicken's blood samples.

In addition, a nanostructure was made for the limit which was self-assembled, used for the detection and targeting the virus while using the EID (egg infection dose) 47.91/50ml was very efficient in the process of examination of targeting virus (Ahmed et al., 2017). Virus-like particles (VLPs) have been studied widely and used as a transportation tool for many compounds especially medicines, proteins (peptides), RNA/DNA, antibiotics, and vaccines. They work as an adjuvant or antigen nano-carriers to help immune cells to exhibit humoral immune response and protection against viruses (Nasrollahzadeh et al., 2020). Surface protein S used to bind with the receptor which triggers the body to respond against it and shows an immune response (Kato et al., 2019). Chen et al. (Chen et al., 2016b) have demonstrated a technique for the usage of CoV VLPs-based S protein in which the incubation of 100-nm gold np was done with optimal concentration of viral proteins. The finding of the study was the impulsive production of proteins with the installment of virus-like nanostructure assembly with fundamental particles having viral antigen coating. In addition, the results of VLPs from this study was come to the conclusion that validate the successful production of synthetic VLPs (sVLPs) from NP (Liu et al., 2013; Wang et al., 2017).

Encapsulation of the IB live attenuated vaccine using chitosan nanoparticles has been demonstrated to show brilliant results in enhancing the antibodies responses and cell mediated responses. This specially includes increased level of IgA at mucosa and enhanced the expression of genes (interferon gamma related genes) especially at the sites where virus replicates primarily (Lopes et al., 2018). Saponins were used as immunostimulant in this study which was further recognized in several studies later. Berezin et al. (Berezin et al., 2013) determined the noticeable improvement in antibody (IgG, IgM and IgA) and cell mediated (IFN-gamma and IL2) immune responses. Single dose of intranasal immunization using saponins and delivery system was used against influenza. After that, Yu et al. (Yu et al., 2015) demonstrated the use of saponins (oral ginseng stem-leaf saponins) to increase the response of vaccine in chicken especially with immunosuppression. Hence both the chitosan and saponins are used for dual purpose including as an adjuvant or as an immunomodulator to enhance the immune responses (Greenland and Letvin, 2007).

AgNps and *P. betle*

Attributed to their astonishing antimicrobial properties, AgNps drew the attention of the researchers. These nanoparticles are usually present in less than 100 nanometers in size, and contain a large surface area available for the interaction with viruses (Karna et al., 2023). The special properties possessed by the AgNPs makes them unique against many viruses, especially those against viruses which cause bronchitis. These nanoparticles are very effective against some common bronchitis viruses for example respiratory syncytial virus and influenza virus (Nefedova et al., 2021). Several studies have demonstrated that the use of AgNPs at the early stages of infection can inhibit the infection while interacting with the viral envelope (Saadh et al., 2021; Saadh, 2022; Saadh, 2023a). The mechanism of action of AgNPs is to disrupt the viral envelope in response to which virus is not able to enter in the host cells and start replication itself (Saadh et al., 2021). Furthermore, another unique property of AgNPs is that they do not induce viral resistance so used as an effective solution for long term use against viruses (Saadh, 2022; Saadh, 2023a). For centuries *P. betle* leaves have been used in cultural practices and as a traditional medicine. The leaves of *P. betle* are contains a rich amount of several bioactive compounds polyphenols including acetyl eugenol, transisoeugenol, chavicol, chavibetol acetate, chavibetol, and allyl pyrocatechol diacetate (Saadh, 2023b). These polyphenols have been used for the production of silver nanoparticles (AgNPs) which is one of the potential uses of these polyphenols which gathered the attention of various industries (Saadh, 2023b). These polyphenols present on the *P. betle* leaves act as reducing and capping agents when present on the surface of silver nanoparticles. This property of these polyphenols inhibits the aggregation of nanoparticles which in turn reduces the size of AgNPs giving several benefits including increasing the stability of nanoparticles and improving their performance (Saadh, 2023b). AgNPs perform their action through the disruption of viral envelope while attaching with the viral genome. After disruption, the virus is no longer capable of causing infection in the host cell and cannot replicate. The contact of viruses with AgNPs is enhanced due to the small size and increased surface area of these nanoparticles (Saadh, 2023b).

Conclusion

Since time of its introduction chicken has become an integral part of food in terms of culture and nutrition. With introduction of new farming techniques poultry overshadowed other meat producing industries by many levels. However, this progress came with its own problems. Soon it was found that various diseases affected poultry flocks leading to high mortality rates, inefficient FCR and low production. One of such diseases is Infectious Bronchitis. It is a viral respiratory tract infection caused by Infectious Bronchitis Virus (IBV). IB is one of the viral diseases that severely affect production and viability of poultry flocks and effect the economical horizon of agricultural market. This disease reportedly affects the production of birds irrespective of the vaccination status. Such dire straits demanded development of a new weapon for defense against IB. Such a weapon was presented by researchers in form of nanotechnology. Nanoparticles of silver and other material when given alone of integrated into vaccine, were proved to

be supremely effective. Hence this technology has emerged as a beacon of hope for poultry farmers that can help them control IB and limit its effects at the same time.

REFERENCES

Abd El-Ghany, W. A., Shaalan, M., and Salem, H. M. (2021). Nanoparticles applications in poultry production: an updated review. *World's Poultry Science Journal*, *77*(4), 1001-1025.

Ahmed, S. R., Kang, S. W., Oh, S., Lee, J., and Neethirajan, S. (2018). Chiral zirconium quantum dots: a new class of nanocrystals for optical detection of coronavirus. *Heliyon*, *4*(8).

Ahmed, S. R., Nagy, É., and Neethirajan, S. (2017). Self-assembled star-shaped chiroplasmonic gold nanoparticles for an ultrasensitive chiro-immunosensor for viruses. *RSC Advances*, *7*(65), 40849-40857.

Al-Harthy, M. (2015). Schwarzkümmelsamenöl als alternative zu antibiotischen leistungsförderern bei masthühnern. *European Poultry Science*, *79*, 1-13.

Ali, R. N., Rubin, H., and Sarkar, S. (2021). Countering the potential re-emergence of a deadly infectious disease—Information warfare, identifying strategic threats, launching countermeasures. *PLOS one*, *16*(8), e0256014.

Berezin, V., Bogoyavlenskiy, A., Turmagambetova, A., Alexuk, P., Zaitceva, I., Omirtaeva, E., and Sokolova, N. (2013). Nanoparticles from plant saponins as delivery system for mucosal influenza vaccine. *American Journal of Infectious Diseases and Microbiology*, *1*, 1-4.

Blagodatski, A., Trutneva, K., Glazova, O., Mityaeva, O., Shevkova, L., Kegeles, E., and Khavina, E. (2021). Avian influenza in wild birds and poultry: dissemination pathways, monitoring methods, and virus ecology. *Pathogens*, *10*(5), 630.

Brisse, M., Vrba, S. M., Kirk, N., Liang, Y., and Ly, H. (2020). Emerging concepts and technologies in vaccine development. *Frontiers in Immunology*, *11*, 583077.

Cavanagh, D. (2007). Coronavirus avian infectious bronchitis virus. *Veterinary Research*, *38*(2), 281-297.

Chandrasekar, S. S., Kingstad-Bakke, B., Wu, C.-W., Suresh, M., and Talaat, A. M. (2020). A novel mucosal adjuvant system for immunization against avian coronavirus causing infectious bronchitis. *Journal of Virology*, *94*(19), 10.1128/jvi. 01016-01020.

Chen, H. W., Huang, C. Y., Lin, S. Y., Fang, Z. S., Hsu, C. H., Lin, J. C., and Hu, C. M. J. (2016b). Synthetic virus-like particles prepared via protein corona formation enable effective vaccination in an avian model of coronavirus infection. *Biomaterials*, *106*, 111-118.

Chen, Y. N., Hsueh, Y. H., Hsieh, C. T., Tzou, D. Y., and Chang, P. L. (2016a). Antiviral activity of graphene–silver nanocomposites against non-enveloped and enveloped viruses. *International Journal of Environmental Research and Public Health*, *13*(4), 430.

Chou, D.-L., Mao, J.-Y., Anand, A., Lin, H.-J., Lin, J. H.-Y., Tseng, C.-P., and Wang, H.-Y. (2021). Carbonized lysine-nanogels protect against infectious bronchitis virus. *International Journal of Molecular Sciences*, *22*(11), 5415.

De Boeck, C., Kalmar, I., Dumont, A., and Vanrompay, D. (2015). Longitudinal monitoring for respiratory pathogens in broiler chickens reveals co-infection of Chlamydia psittaci and Ornithobacterium rhinotracheale. *Journal of Medical Microbiology*, *64*(5), 565-574.

Desta, T. T. (2021). Indigenous village chicken production: a tool for poverty alleviation, the empowerment of women, and rural development. *Tropical Animal Health and Production*, *53*(1), 1.

El-Kafrawy, S. A., Abbas, A. T., Sohrab, S. S., Tabll, A. A., Hassan, A. M., Iwata-Yoshikawa, N., and Azhar, E. I. (2021). Immunotherapeutic efficacy of IgY antibodies targeting the full-length spike protein in an animal model of middle east respiratory syndrome coronavirus infection. *Pharmaceuticals*, *14*(6), 511.

Franzo, G., Tucciarone, C. M., Blanco, A., Nofrarías, M., Biarnés, M., Cortey, M., and Cecchinato, M. (2016). Effect of different vaccination strategies on IBV QX population dynamics and clinical outbreaks. *Vaccine*, *34*(46), 5670-5676.

Fuzimoto, A. D., and Isidoro, C. J. (2020). The antiviral and coronavirus-host protein pathways inhibiting properties of herbs and natural compounds-Additional weapons in the fight against the COVID-19 pandemic? *Journal of Traditional and Complementary Medicine*, *10*(4), 405-419.

Gadde, U., Kim, W., Oh, S., and Lillehoj, H. S. J. (2017). Alternatives to antibiotics for maximizing growth performance and feed efficiency in poultry: a review. *Animal Health Research Reviews*, *18*(1), 26-45.

Greenland, J. R., and Letvin, N. L. (2007). Chemical adjuvants for plasmid DNA vaccines. *Vaccine*, *25*(19), 3731-3741.

Hafez, H. M., and Attia, Y. A. (2020). Challenges to the poultry industry: current perspectives and strategic future after the COVID-19 outbreak. *Frontiers in Veterinary Science*, *7*, 516.

Hedman, H. D., Vasco, K. A., and Zhang, L. (2020). A review of antimicrobial resistance in poultry farming within low-resource settings. *Animals*, *10*(8), 1264.

Hoang, B. X., Shaw, G., Fang, W., and Han, B. J. (2020). Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection. *Journal of Global Antimicrobial Resistance*, *23*, 256-262.

Immunivt, I. (1998). Mechanisms of protective immunity (Infection and Immunity Group). *Immunology*, *95*, 34-38.

Kang, J., Tahir, A., Wang, H., and Chang, J. (2021). Applications of nanotechnology in virus detection, tracking, and infection mechanisms. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *13*(4), e1700.

Karna, S., Kavitha, R., and Damodharan, N. (2023). Anticancer activity of silver nanoparticle of prodigiosin on lung cancer. *International Journal of Applied Pharmaceutics*, *15*(1), 264-268.

Kato, T., Takami, Y., Deo, V. K., and Park, E. Y. (2019). Preparation of virus-like particle mimetic nanovesicles displaying the S protein of Middle East respiratory syndrome coronavirus using insect cells. *Journal of Biotechnology*, *306*, 177-184.

Krishnan, S., Dusane, A., Morajkar, R., Venkat, A., and Vernekar, A. A. (2021). Deciphering the role of nanostructured materials in the point-of-care diagnostics for COVID-19: a comprehensive review. *Journal of Materials Chemistry B*, *9*(30), 5967-5981.

Legnardi, M., Tucciarone, C. M., Franzo, G., and Cecchinato, M. (2020). Infectious bronchitis virus evolution, diagnosis and control. *Veterinary Sciences*, *7*(2), 79.

Li, J., Helal, Z. H., Karch, C. P., Mishra, N., Girshick, T., Garmendia, A., and Khan, M. I. (2018). A self-adjuvanted nanoparticle based vaccine against infectious bronchitis virus. *PLOS one*, *13*(9), e0203771.

Liu, G., Lv, L., Yin, L., Li, X., Luo, D., Liu, K., and Cao, Y. (2013). Assembly and immunogenicity of coronavirus-like particles carrying infectious bronchitis virus M and S proteins. *Vaccine*, *31*(47), 5524-5530.

Liu, J., Li, R., and Yang, B. (2020). Carbon dots: a new type of carbon-based nanomaterial with wide applications. *ACS Central Science*, *6*(12), 2179-2195.

Lopes, P. D., Okino, C. H., Fernando, F. S., Pavani, C., Casagrande, V. M., Lopez, R. F., and Montassier, H. J. (2018). Inactivated infectious bronchitis virus vaccine encapsulated in chitosan nanoparticles induces mucosal immune responses and effective protection against challenge. *Vaccine*, *36*(19), 2630-2636.

Mansour, S. M., ElBakrey, R. M., Mohamed, F. F., Hamouda, E. E., Abdallah, M. S., Elbestawy, A. R., and Eid, A. A. (2021). Avian paramyxovirus type 1 in Egypt: epidemiology, evolutionary perspective, and vaccine approach. *Frontiers in Veterinary Science*, *8*, 647462.

Manyi-Loh, C., Mamphweli, S., Meyer, E., and Okoh, A. (2018). Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules*, *23*(4), 795.

Nasrollahzadeh, M., Sajjadi, M., Soufi, G. J., Iravani, S., and Varma, R. S. (2020). Nanomaterials and nanotechnology-associated innovations against viral infections with a focus on coronaviruses. *Nanomaterials*, *10*(6), 1072.

Neethirajan, S. (2017). Recent advances in wearable sensors for animal health management. *Sensing and Bio-Sensing Research*, *12*, 15-29.

Nefedova, E., Koptev, V., Bobikova, A. S., Cherepushkina, V., Mironova, T., Afonyushkin, V., and Sigareva, N. (2021). The infectious bronchitis coronavirus pneumonia model presenting a novel insight for the SARS-CoV-2 dissemination route. *Veterinary Sciences*, *8*(10), 239.

Nkukwana, T. (2018). Global poultry production: Current impact and future outlook on the South African poultry industry. *South African Journal of Animal Science*, *48*(5), 869-884.

Parvin, R., Begum, J. A., Nooruzzaman, M., Kabiraj, C. K., and Chowdhury, E. H. (2021). Circulation of three genotypes and identification of unique mutations in neutralizing epitopes of infectious bronchitis virus in chickens in Bangladesh. *Archives of Virology*, *166*, 3093-3103.

Patra, A. K., Amasheh, S., and Aschenbach, J. R. J. (2019). Modulation of gastrointestinal barrier and nutrient transport function in farm animals by natural plant bioactive compounds–a comprehensive review. *Critical Reviews in Food Science and Nutrition*, *59*(20), 3237-3266.

Pereira, E., Van Tilburg, M., Florean, E., and Guedes, M. (2019). Egg yolk antibodies (IgY) and their applications in human and veterinary health: A review. *International Immunopharmacology*, *73*, 293-303.

Power, A. C., Gorey, B., Chandra, S., and Chapman, J. (2018). Carbon nanomaterials and their application to electrochemical sensors: a review. *Nanotechnology Reviews*, *7*(1), 19-41.

Ramos, A. P., Cruz, M. A., Tovani, C. B., and Ciancaglini, P. (2017). Biomedical applications of nanotechnology. *Biophysical Reviews*, *9*(2), 79-89.

Saadh, M. (2022). Potent antiviral effect of green synthesis silver nanoparticles on Newcastle disease virus. *Arabian Journal of Chemistry*, *15*(7), 103899.

Saadh, M. J. (2023a). Silver nanoparticles inhibit goatpox virus replication. *Archives of Virology*, *168*(1), 32.

Saadh, M. J. (2023b). Green synthesis of silver nanoparticles using Piper betle exhibit high antimicrobial activity against Salmonella enteritidis and E. coli. *Iraqi Journal of Veterinary Sciences*, *37*(3), 759-763.

Saadh, M. J., Aggag, M. M., Alboghdadly, A., Kharshid, A. M., Aldalaen, S. M., and Abdelrazek, M. A. (2021). Silver nanoparticles with epigallocatechingallate and zinc sulphate significantly inhibits avian influenza A virus H9N2. *Microbial Pathogenesis*, *158*, 105071.

Saha, A., Chowdhury, M. I., Nazim, M., Alam, M. M., Ahmed, T., Hossain, M. B., and Qadri, F. (2013). Vaccine specific immune response to an inactivated oral cholera vaccine and EPI vaccines in a high and low arsenic area in Bangladeshi children. *Vaccine*, *31*(4), 647-652.

Sastry, M., Ahmad, A., Khan, M. I., and Kumar, R. (2003). Biosynthesis of metal nanoparticles using fungi and actinomycete. *Current Science*, 162-170.

Scallan, C. D., Tingley, D. W., Lindbloom, J. D., Toomey, J. S., and Tucker, S. N. (2013). An adenovirus-based vaccine with a double-stranded RNA adjuvant protects mice and ferrets against H5N1 avian influenza in oral delivery models. *Clinical and Vaccine Immunology*, *20*(1), 85-94.

Schalk, A. F., and Hawn, M. C. (1931). An apparently new respiratory disease of baby chicks. *Journal of the American Veterinary Medical Association*, *78* 413-423.

Shao, W., Li, X., Goraya, M. U., Wang, S., and Chen, J.-L. (2017). Evolution of influenza a virus by mutation and re-assortment. *International Journal of Molecular Sciences*, *18*(8), 1650.

Soccol, C. R., Vandenberghe, L. d. S., Spier, M. R., Medeiros, A. B. P., Yamaguishi, C. T., Lindner, J. D. D., and Thomaz-Soccol, V. (2010). The potential of probiotics: a review. *Food Technology and Biotechnology*, *48* (4), 413–434.

Sultan, H. A., Ali, A., El Feil, W. K., Bazid, A. H. I., Zain El-Abideen, M. A., and Kilany, W. H. J. (2019). Protective efficacy of different live attenuated infectious bronchitis virus vaccination regimes against challenge with IBV variant-2 circulating in the Middle East. *Frontiers in Veterinary Science*, *6*, 341.

Tagde, P., Tagde, S., Tagde, P., Bhattacharya, T., Monzur, S. M., Rahman, M. H., and Abdel-Daim, M. M. (2021). Nutraceuticals and herbs in reducing the risk and improving the treatment of COVID-19 by targeting SARS-CoV-2. *Biomedicines*, *9*(9), 1266.

Toro, H. (2021). Global control of infectious bronchitis requires replacing live attenuated vaccines by alternative technologies. *Avian Diseases*, *65*(4), 637-642.

Wang, C., Zheng, X., Gai, W., Zhao, Y., Wang, H., Wang, H., and Li, N. (2017). MERS-CoV virus-like particles produced in insect cells induce specific humoural and cellular imminity in rhesus macaques. *Oncotarget*, *8*(8), 12686.

Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Song, Z.-G., and Pei, Y.-Y. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265-269.

Yadav, M. P., Singh, R. K., and Malik, Y. S. (2019). Epidemiological perspective in managing viral diseases in animals. *Recent Advances in Animal Virology*, 381-407.

Yan, X., Zhou, M., Yu, S., Jin, Z., and Zhao, K. (2020). An overview of biodegradable nanomaterials and applications in vaccines. *Vaccine*, *38*(5), 1096-1104.

Youssef, F. S., El-Banna, H. A., Elzorba, H. Y., and Galal, A. M. (2019). Application of some nanoparticles in the field of veterinary medicine. *International Journal of Veterinary Science and Medicine*, *7*(1), 78-93.

Yu, J., Shi, F., and Hu, S. (2015). Improved immune responses to a bivalent vaccine of Newcastle disease and avian influenza in chickens by ginseng stem-leaf saponins. *Veterinary Immunology and Immunopathology*, *167*(3-4), 147-155.

Chapter 09

Use of Nanoparticles in Elimination of Ectoparasites in Companion Animals

Mehroz Latif[1*], Muhammad Numair Ahmad[1], Muhammad Saad Arshad[1], Muhammad Ahmad Sannan[1], Zubair Qamber[1], Nehsoon Tahir Sharif[2], Muhammad Mobashar[3] and Muhammad Ghufran Shahbaz[1]

[1]Faculty of Veterinary Sciences, Bahauddin Zakariya University, Multan – Pakistan
[2]Sustainable Development Study Center (SDSC), Government College University, Lahore
[3]Department of Animal Nutrition, University of Agriculture, Peshawar, Pakistan
*Corresponding author: mehrozlatif3321@gmail.com

ABSTRACT

Companion animals, including pets and working animals, are susceptible to various ectoparasites. The companion animals are mostly affected by fleas, lice, mites, ticks, and flies. These parasites present a significant challenge for the health and well-being of animals. These parasites also pose the zoonotic risk by spreading various zoonotic pathogens from animals to humans. The use of different chemical (organophosphates, carbamates, pyrethriods, macrocyclic lactones etc.), mechanical (grooming) and environmental methods (biological control, sanitation, and environmental modifications) are considered as traditional methods in control of ectoparasites. However these control methods exhibit limitations such as variable efficacy and toxicity concerns. Similarly, the repeated use of these acaricides has led to environmental pollution, resistance development and increase in the treatment cost. The promising approaches to ectoparasite management can be found in the growing field of nanotechnology. Owing to their small size, nanoparticles provide opportunity for the targeted distribution and continuous release of active substances. Different metallic and polymeric nanoparticles employs mechanisms such as cell membrane damage and oxidative stress induction against ectoparasites. Various formulations, including topical treatments, environmental applications, and controlled-release formulations demonstrate effectiveness in ectoparasite elimination. Overall, nanoparticle-based ectoparasite control shows promise in providing safer, more effective, and sustainable solutions for companion animal healthcare, enhancing their health and well-being globally.

KEYWORDS
Companion animals, Ectoparasite control, Nanoparticles, Nanotechnology, Sustainable healthcare

Received: 29-May-2024
Revised: 29-Jul-2024
Accepted: 14-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Latif M, Ahmad MN, Arshad MS, Sannan MA, Qamber Z, Sharif NT, Mobashar M and Shahbaz MG, 2024. Use of nanoparticles in elimination of ectoparasites in companion animals. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 61-67. https://doi.org/10.47278/book.CAM/2024.124

INTRODUCTION

Companion animals, ranging from beloved household pets to essential working animals, play a significant role in the lives of millions of people globally (Overgaauw et al., 2020). Ensuring their health and well-being is vital, yet they are often affected by a variety of ectoparasites, including fleas, ticks, mites, and others. These ectoparasites not only cause discomfort and irritation to the animals but also pose significant health risks, including the transmission of diseases to both animals and humans (Rafiqi et al., 2016). The current methods of ectoparasite control, such as topical and oral medications, environmental management, and mechanical methods like grooming, although effective to some extent, are not without limitations. These limitations include variable efficacy, potential toxicity, and the development of resistance among ectoparasites, presenting ongoing challenges in the management of ectoparasitic infestations (Leone and Han, 2020). In recent years, the emerging field of nanotechnology has offered promising solutions to these challenges. Nanoparticles, defined as particles with dimensions typically ranging from 1 to 100 nanometers, possess unique properties that make them highly suitable for applications in animal healthcare. With their small size and large surface area, nanoparticles offer enhanced capabilities for targeted delivery, sustained release of active ingredients, and improved efficacy in ectoparasite elimination (Najahi-Missaoui et al., 2020).

This chapter aims to explore the potential of nanoparticles in ectoparasite control in companion animals. This chapter will delve into the properties and mechanisms of action of nanoparticles, categorize different types of nanoparticles being explored for this purpose, and discuss the advantages and limitations of each type. Furthermore, it will examine the factors influencing the effectiveness of nanoparticle-based treatments and explore their application in various formulations, including topical treatments, environmental applications, and controlled-release formulations. By shedding light on the

innovative potential of nanotechnology in ectoparasite control, this chapter seeks to pave the way for the development of safer, more effective, and sustainable solutions for the management of ectoparasitic infestations in companion animals, ultimately enhancing their health and well-being.

Types of Ectoparasites in Companion Animals

Companion animals are affected by ectoparasites such as fleas, ticks, lice, and mites, which can lead to various health issues. Fleas, belonging to the order *Siphonaptera* with over 2500 species (Bourne et al., 2018), include cat fleas (*Ctenocephalides felis*) and dog fleas (*Ctenocephalides canis*) that transmit bacterial pathogens like *Bartonella* and *Rickettsia* (Durden and Hinkle, 2019). They can cause diseases like flea-borne spotted fever, murine typhus, and cat scratch fever (*Bartonella henselae*) (Rust, 2017), as well as flea allergy dermatitis (FAD) (Farrell et al., 2023). Fleas also carry *Mycoplasma haemoplasma* species causing hemolytic anemia (Bourne et al., 2018) and can transmit *Yersinia pestis*, the plague bacterium (Rust, 2017). Additionally, fleas are intermediate hosts for the tapeworm *Dipylidium caninum*, causing pruritis and digestive issues in pets (Bourne et al., 2018). Ticks are haematophagous invertebrates with over 900 species in the families *Ixodidae* and *Argasidae* (Boulanger et al., 2019). Species like *Rhipicephalus sanguineus*, *R. haemaphysaloides*, and *Haemaphysalis longicornis* affect pets (Nelder et al., 2021), transmitting diseases such as Lyme disease, Q fever, spotted fever rickettsioses, and babesiosis, and can cause tick paralysis and allergic reactions (Kopsco et al., 2021; Buczek et al., 2020).

Lice are wingless insects in the orders *Mallophaga* (chewing lice) and *Anoplura* (sucking lice) (Shiferaw, 2018). Dogs are infested by *Trichodectes canis*, *Linognathus setosus*, and *Heterodoxus spiniger*, while cats are infested by *Felicola subrostratus* (Little, 2021). Infestations cause dermatological lesions, anemia, and alopecia due to scratching and biting (Kumsa et al., 2019). Mites belong to orders *Astigmata* and *Prostigmata*, with families like *Sarcoptidae*, *Psoroptidae*, *Psorergatidae*, *Demodicidae*, and *Cheyletiellidae* (Benti et al., 2020). Dogs can be infested with *Cheyletiella yasguri*, *Demodex canis*, *D. injai*, *Sarcoptes scabiei*, and *Otodectes cynotis*. Cats may host *Cheyletiella blakei*, *Demodex cati*, *D. gatoi*, *Notoedres cati*, and *O. cynotis* (Little and Cornitas, 2021). Mite infestations can result in dermatitis, pruritis, skin allergies, and severe illness by invading internal organs (Olivry and Mueller, 2019).

Current Methods in Ectoparasites Control

Chemical Methods

The drugs and chemicals which are used against ectoparasites are known as ectoparasiticides (Sharma et al., 2021). Various types of chemicals are used for this purpose including organophosphates, carbamates, pyrethroids, insect growth regulators, macrocyclic lactones, phenylpyrazoles, chloronicotinyl nitroguanidines, spinosad and the isoxazolines (Staffored and Coles, 2017). They are utilized in a variety of ways, including macrocyclic lactones (Ivermectin, Doramectin-subcutaneous injection), organophosphates (Malathion, Dichlorvos as dip, spray, pour on), carbamates (Carbaryl, Propoxur as dip, dust, spray), formamidines (Amitraz as dip, spray), and pyrethroids (Cypermethrin, Permethrin, Deltamethrin, etc. as dip, spray, spot on, and pour on). Synthetic hormones and arthropod enzymes, such methoprene and pyriproxyfen, can slow the development and proliferation of parasites. These are used in oral preparations as well as in combination with other drugs (Rust, 2020; Jamil et al., 2022). Isoxazolines, a recently developed class of insecticides, have the ability to strongly inhibit GABA-gated channels and have an impact on L-glutamate-gated chloride channels. In addition to killing adult cat fleas, they can also destroy triatomine bugs, ticks, mites, lice, mosquitoes, biting flies, and sea lice (Jamil et al., 2022). Fipronil containing collars are also available for dogs and cats which protect them from ticks, mites and lice (Paily et al., 2021).

Environmental Control

Environmental control includes the strategies like biological control, sanitation, and environmental modifications (Rust, 2020). Biological controls are used in the form of essential oils, entomopathogenic fungus, and Spider venom peptides. Azadirachtin a naturally occurring compound is used as an insecticide against agricultural pests which is very effective in biological controls (Jamil et al., 2022). Sanitation of carpets and surfaces can be done by treating with 0.4% dimeticone spray, IGRs and pyrethroids to control immature stages of insects. Vacuuming can also remove eggs and larva from the surface and carpets (Elsheikha, 2017; Rust, 2020). Environmental modification involves provision of adequate nutrition, removal of manures, hygienic food provision and keeping the animal stress free (Sharma et al., 2021).

Mechanical Methods

Many animals use mechanical defenses such as grooming to avoid or to mitigate the occurrences of infection by ectoparasites (Horn and Luong, 2019). Various types of grooming practices are done by domestic animals such as stimulus–response grooming (immediate immune response) and programmed grooming (response in form of bouts), or scratch and scan grooming (Kupfer and Fessler, 2018). Self-grooming may be energetically costly, comprises future resistance and other energy costs (Horn and Luong, 2019). Animals self-groom themselves by scratching, picking with their digits, or by using the mouth to remove ectoparasites (Kupfer and Fessler, 2018). Another mechanical method is bathing

which can be done with water, shampoo and chemicals (Frontline® Plus, Boehringer Ingelheim). Bathing can be performed every seven days and involves wetting the animal and apply the shampoo along the back, neck, belly and limbs (avoiding the eyes, nostrils and mouth). After waiting for five minutes clean it with warm water and dry the animal with the help of towel (Cruz et al., 2020).

Challenges and Limitations Associated with Existing Methods

Although there are different ways of fighting against parasitism, but these methods exhibit various limitations as well. These imitations include anthelmintic resistance and its prolonged use leads to worm refugia (Maqbool et al., 2017). Anthelmintic resistance is emerging as an important issue which develops due to irrational use of anthelmintic drugs, lack of knowledge about drug usage and lack of molecular diagnostic tests to detect anthelmintics resistance (Kotze et al., 2020). Use of biological control method has some limitations as it is not effective enough to remove infection. In addition, it is very slow acting, time consuming, gives unpredictable results, effective at one place and not effective at another similar place (Maqbool et al., 2017).

Nanoparticles

The use of technology at the nanoscale for the useful application in everyday life is known as nanotechnology. This includes manipulating physical, chemical, or biological systems down to the atom's submicron size and incorporating the resulting nanostructures into larger systems (Molento and Arenal, 2020). Nanoparticles (NPs) are particles characterized by dimensions typically falling within the range of 1 to 100 nanometers. Their properties vary based on size and surface characteristics. Due to their small size and expansive surface area, nanoparticles have wide range of applications in fields including cosmetics, electronics, as well as diagnostic and therapeutic medicine (Najahi-Missaoui et al., 2020). The practical application of nanotechnology has greatly accelerated the development of several sectors, most notably biomedical applications such as tissue engineering, drug transport, bio-imaging, and nano-diagnostics (Hikal et al., 2021).

There are major two categories of nanomaterials being used against the parasites i.e. Metallic and Polymeric Nanoparticles. Metallic NPs include silver, gold and copper nanoparticles. They exhibit antimicrobial and insecticidal properties due to their surface chemistry and small size. On the other hand, polymeric NPs include polymeric micelles, dendrimers, and nanocapsules. They are biocompatible, biodegradable and act as versatile carriers for controlled release of active ingredients (Begines et al., 2020; Hikal et al., 2021). The nanoparticles mainly work by entering the body of parasite resulting into cell membrane damage, ribosome disassembly, protein denaturation and oxidative stress. The oxidative stress and denaturation of the protein results in mitochondrial and DNA damage. This leads to the death of the parasite (AlGabbani, 2023). However, nanoparticles also offer various other ways to eliminate the parasites from the body of the host. These particles offers the methods to address the shortcomings of conventional drug delivery systems (Aljabali et al., 2018). In order to fight ectoparasites, nanoparticles use a variety of strategies, the most common of which are controlled release of active chemicals and physical disruption. Sharp-edged or spiked nanoparticles cause structural damage to the cellular membranes of ectoparasites when they come into direct contact with them. Moreover, nanoparticles are effective dispersants of insecticidal or acaricidal substances, allowing for their slow release over time (Banu et al., 2023).

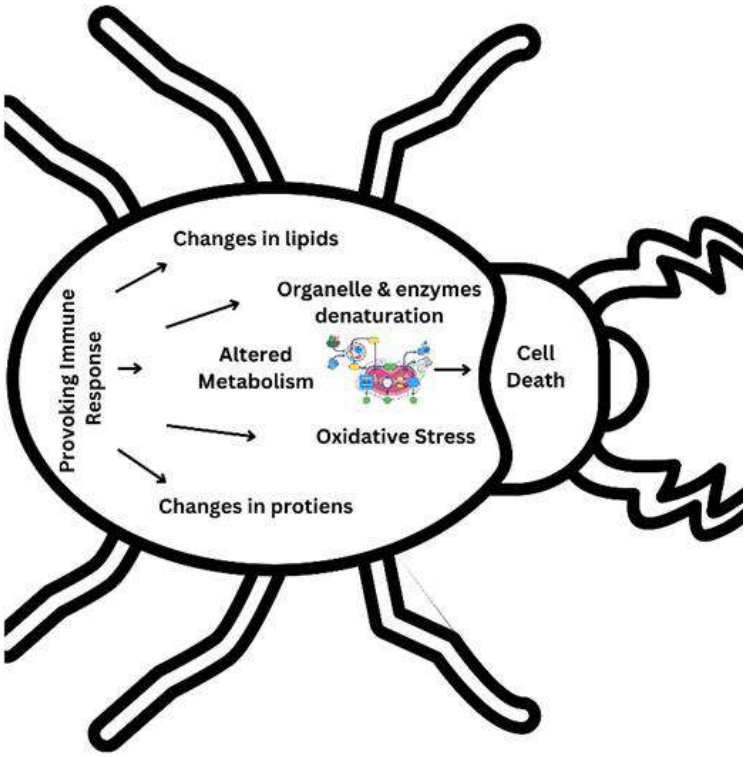


Fig. 1: General Mechanism of Nanoparticles against ectoparasites

Application of Nanoparticles in Ectoparasite Control

The use of nanoparticles in diverse formulations for direct and environmental treatments is a viable route for controlling ectoparasites (Zaheer et al., 2022).

A. Topical Formulations

i) Nanoparticles in Spot-on Treatments: Spot-on treatments represent a common method for administering ectoparasiticides directly onto the skin of companion animals (Ferrer, 2021). Nanoparticles integrated into spot-on formulations enhance efficacy through several mechanisms. Firstly, nanoparticles can serve as carriers for active ingredients, protecting them from degradation and facilitating their controlled release over time. This sustained release ensures prolonged exposure of ectoparasites to the insecticidal or acaricidal compounds, thereby enhancing efficacy while reducing the frequency of application. Additionally, nanoparticles with specific surface modifications can improve adhesion to the skin, prolonging the duration of action and minimizing product runoff (Pavoni et al., 2019; Prasad et al., 2021).

ii) Nanoparticles in Shampoos and Sprays: Shampoos and sprays are alternative topical formulations commonly used for ectoparasite control in companion animals (Gorman, 2016). Integration of nanoparticles into these formulations offers several advantages (Pereira-Silva et al., 2022). Nanoparticles can enhance the penetration of active ingredients through the ectoparasite's cuticle, increasing their bioavailability and efficacy. Moreover, nanoparticles can confer stability to formulations, preventing degradation of active compounds and ensuring consistent performance over time (Molento and Arenal, 2020).

B. Environmental Applications

Nanoparticles are embedded in fabrics, beddings and household sprays. Ectoparasites often reside in the environment surrounding companion animals, including their bedding and living areas (Kocoń and Nowak-Chmura, 2017). Nanoparticles can be incorporated into fabrics, household sprays and bedding materials to create a hostile environment for ectoparasites (Chatha et al., 2019). Metallic nanoparticles, such as silver nanoparticles, exhibit potent antimicrobial properties and can be impregnated into textiles to inhibit the growth of ectoparasites and prevent transmission between animals (Qu et al., 2023). Additionally, sprays can be applied to surfaces frequented by companion animals, such as floors, carpets, and furniture, to eliminate ectoparasites and their eggs (Elsheikha et al., 2018).

C. Controlled-Release Formulations

Nanoparticles offer the protection by controlled release formulations. These products maintain therapeutic concentrations for an extended duration by encapsulating insecticidal or acaricidal chemicals within nanoparticles, therefore ensuring a continuous supply of the active ingredient. This long-lasting impact lessens the need for frequent treatment, improving animal owners' convenience and guaranteeing efficient ectoparasite management (Danyaro et al., 2023; Najitha Banu et al., 2023).

Efficacy and Safety of Nanoparticle based Ectoparasite Control

Nano-particles are very efficient in the control of ectoparasites as repeated use of acaricides has led to environmental pollution, resistance development and increase in the treatment cost (Abdel-Ghany et al., 2022). Different types of nano-particles have developed for this purpose such as silver NPs, titanium dioxide NPs, zinc oxide NPs, nickel NPs, copper NPs and magnesium NPs (Benelli et al., 2017). Zinc Oxide nanoparticles and cypermethrin-coated nanoparticles of ZnO (C-ZnO NPs) and ZnS (C-ZnS NPs) are very effective against many *Rhipicephalus* ticks as well as *Hyalommma* ticks (Zaheer et al., 2023). Zein nano-particles associated with cypermethrin (CYPE) + chlorpyrifos (CHLO) + a plant compound (citral, menthol or limonene) have high efficacy against *Rhipicephalus microplus* ticks as compared to other acaricides. This formulation lowers the nematodes toxicity and has long period of residual activity (Figueiredo et al.,2023). Similarly, iron oxide and iron sulphides NPs coated on pyrethroids (cypermethrin and deltamethrin) can control the major life stages of *Hyalomma* ticks (Zaheer et al., 2024). Hence, nano-particles have low efficacy and short shelf-life but nanopaticles-based drug delivery system effectively targets the acaricidal drugs into the sites of infection as well as enhances the efficacy of the acaricides (Najitha Banu et al., 2023).

The nanoparticles have no safety concerns (safe in use) and also reduce the adverse effects of various drug but some nanoparticles have toxic profile (Bajwa et al., 2022). Treatment with silver nanoparticles has caused DNA damage and morphological abnormalities in a variety of vertebrate and invertebrate creatures. It has also negatively impacted the enzymatic activities of a number of non-target species (Benelli, 2018). The toxicological evaluation of these nanoparticles is an important factor to reduce its negative effect on non-target species (Figueiredo et al., 2023). However, these NPs should have excellent chemical and physical structures, should be non-toxic and should be evaluated at every cellular level during their preparation. This evaluation will help to reduce their toxic effects (Bajwa et al., 2022).

Compared with traditional method (use of chemical, environmental managements, biological and mechanical means), nano-particles have more environmental safety and low pesticide resistance (Nie et al., 2023). Nano-particles coated on acaricides have led to development of drug delivery system which could increase the efficacy and performance of previous acaricidal drugs by targeting the site of infections. These NPs are also water soluble and have no effect on the environment as compared to various chemicals used in traditional methods (Athanassiou et al., 2018). NPs based acaricidal formulations

will enhance stability, action and duration of insecticidal activity. It will also remove harmful organic solvents which are not removed in commonly used acaricides (Zaheer et al., 2022).

Conclusion

In conclusion, the field of nanotechnology presents a promising avenue for revolutionizing the control of ectoparasites in companion animals. Ectoparasites pose significant health risks to both animals and humans, and current control methods are often limited by variable efficacy, toxicity concerns, and the development of resistance. The application of nanoparticles in various formulations, including topical treatments, environmental applications, and controlled-release formulations, offers diverse and effective strategies for combating ectoparasites. Nanoparticles integrated into spot-on treatments, shampoos, and sprays enhance efficacy by improving adhesion to the skin and penetration through the ectoparasite's cuticle. Furthermore, nanoparticles embedded in fabrics and household sprays create a hostile environment for ectoparasites in the animal's surroundings. Despite the numerous advantages of nanoparticle-based ectoparasite control, it is essential to consider safety concerns and environmental implications. Overall, nanoparticle-based ectoparasite control offers a promising solution to the ongoing challenges faced in companion animal healthcare. By leveraging the innovative potential of nanotechnology, we can develop safer, more effective, and sustainable strategies for managing ectoparasitic infestations, ultimately enhancing the health and well-being of companion animals worldwide.

REFERENCES

Abdel-Ghany, H. S., Abdel-Shafy, S., Abuowarda, M. M., El-Khateeb, R. M., Hoballah, E. M., and Fahmy, M. M. (2022). Acaricidal efficacy of biosynthesized zinc oxide nanoparticles against Hyalomma dromedarii (Acari: Ixodidae) and their toxic effects on Swiss albino mice. *Acta Parasitologica*, *67*(2), 878-891.

AlGabbani, Q. (2023). Nanotechnology: A promising strategy for the control of parasitic infections. *Experimental Parasitology*, 108548.

Aljabali, A. A., Akkam, Y., Al Zoubi, M. S., Al-Batayneh, K. M., Al-Trad, B., Abo Alrob, O., and Evans, D. J. (2018). Synthesis of gold nanoparticles using leaf extract of Ziziphus zizyphus and their antimicrobial activity. *Nanomaterials*, *8*(3), 174.

Athanassiou, C. G., Kavallieratos, N. G., Benelli, G., Losic, D., Usha Rani, P., and Desneux, N. (2018). Nanoparticles for pest control: current status and future perspectives. *Journal of Pest Science*, *91*, 1-15.

Bajwa, H. U. R., Khan, M. K., Abbas, Z., Riaz, R., Rehman, T. U., Abbas, R. Z., and Alouffi, A. (2022). Nanoparticles: Synthesis and their role as potential drug candidates for the treatment of parasitic diseases. *Life*, *12*(5), 750.

Begines, B., Ortiz, T., Pérez-Aranda, M., Martínez, G., Merinero, M., Argüelles-Arias, F., and Alcudia, A. (2020). Polymeric nanoparticles for drug delivery: Recent developments and future prospects. *Nanomaterials*, *10*(7), 1403.

Benelli, G. (2018). Mode of action of nanoparticles against insects. *Environmental Science and Pollution Research*, *25*(13), 12329-12341.

Benelli, G., Maggi, F., Romano, D., Stefanini, C., Vaseeharan, B., Kumar, S., and Canale, A. (2017). Nanoparticles as effective acaricides against ticks—a review. *Ticks and Tick-borne Diseases*, *8*(6), 821-826.

Benti, E., Sori, T., Degu, T., and Fesseha, H. (2020). Mange mites infestation in small ruminants in Ethiopia-review. *World Applied Science Journal*, *38*, 395-403.

Boulanger, N., Boyer, P., Talagrand-Reboul, E., and Hansmann, Y. (2019). Ticks and tick-borne diseases. *Medecine et Maladies Infectieuses*, *49*(2), 87-97.

Bourne, D., Craig, M., Crittall, J., Elsheikha, H., Griffiths, K., Keyte, S., and Wilson, A. (2018). Fleas and flea-borne diseases: biology, control and compliance. *Companion Animal*, *23*(4), 204-211.

Buczek, A., and Buczek, W. (2020). Importation of ticks on companion animals and the risk of spread of tick-borne diseases to non-endemic regions in Europe. *Animals*, *11*(1), 6.

Chatha, S. A. S., Asgher, M., Asgher, R., Hussain, A. I., Iqbal, Y., Hussain, S. M., and Iqbal, H. M. (2019). Environmentally responsive and anti-bugs textile finishes–Recent trends, challenges, and future perspectives. *Science of the Total Environment*, *690*, 667-682.

Cruz, B. C., Teixeira, W. F. P., Gomes, L. V. C., Maciel, W. G., Felippelli, G., Buzzulini, C., and da Costa, A. J. (2020). Does bathing affect tick and flea burdens and ectoparasiticide effectiveness of a spot-on formulation (fipronil+(S)-methoprene) for dogs?. *Veterinary Parasitology*, *283*, 109192.

Danyaro, A. M., Tijjani, H., Kalra, S. J. S., and Olatunde, A. (2023). Nanoparticles for Antiparasitic Drug Delivery. *Parasitic Infections*: *Immune Responses and Therapeutics*, 303-327.

Durden, L. A., and Hinkle, N. C. (2019). Fleas (siphonaptera). In *Medical and Veterinary Entomology* (pp. 145-169). Academic Press.

Elsheikha, H. (2017). Ectoparasites: Preventive plans and innovations in treatment. *Veterinary Times*, *47*(14), 6-12.

Elsheikha, H., Wright, I., and McGarry, J. (2018). *Parasites and pets: A Veterinary Nursing Guide*. CABI.

Farrell, S., McGarry, J., Noble, P. J. M., Pinchbeck, G. J., Cantwell, S., Radford, A. D., and Singleton, D. A. (2023). Seasonality and other risk factors for fleas infestations in domestic dogs and cats. *Medical and Veterinary Entomology*, *37*(2), 359-370.

Ferrer, L. (2021). Ectoparasite infestation–treatment and prophylaxis. In *BSAVA Manual of Canine and Feline Dermatology* (pp. 70-75). BSAVA Library.

Figueiredo, A., Anholeto, L. A., Cola, D. F., Fantatto, R. R., Gainza, Y. A., Dos Santos, I. B., and de Souza Chagas, A. C. (2023). Acaricides containing zein nanoparticles: A tool for a lower impact control of the cattle tick Rhipicephalus microplus. *Veterinary Parasitology*, *318*, 109918.

Gorman, C. (2016). Evolution of ectoparasiticide formulations and strategies. *Companion Animal*, *21*(2), 79-88.

Hikal, W. M., Bratovcic, A., Baeshen, R. S., Tkachenko, K. G., and Said-Al Ahl, H. A. (2021). Nanobiotechnology for the detection and control of waterborne parasites. *Open Journal of Ecology*, *11*(3), 203-223.

Horn, C. J., and Luong, L. T. (2019). Current parasite resistance trades off with future defenses and flight performance. *Behavioral Ecology and Sociobiology*, *73*, 1-10.

Jamil, M, Idrees, A., Qadir, Z. A., Elahi, M. E., Imran, F., Qasim, M. and Sadia, B. I. (2022). Medical and Veterinary Ectoparasites' Importance: An Insight on Alternative Control. *Pakistan Journal of Medical and Health Sciences*, *16*(01), 667.

Kocoń, A., and Nowak-Chmura, M. (2017). Skin ectoparasites of domestic animals. *Annales Universitatis Paedagogicae Cracoviensis Studia Naturae*, (2), 137-158.

Kopsco, H. L., Duhaime, R. J., and Mather, T. N. (2021). An analysis of companion animal tick encounters as revealed by photograph-based crowdsourced data. *Veterinary Medicine and Science*, *7*(6), 2198-2208.

Kotze, A. C., Gilleard, J. S., Doyle, S. R., and Prichard, R. K. (2020). Challenges and opportunities for the adoption of molecular diagnostics for anthelmintic resistance. *International Journal for Parasitology: Drugs and Drug Resistance*, *14*, 264-273.

Kumsa, B., Abiy, Y., and Abunna, F. (2019). "Ectoparasites infesting dogs and cats in Bishoftu, central Oromia, Ethiopia." *Veterinary Parasitology: Regional Studies and Reports* 15 (2019): 100263.

Kupfer, T. R., and Fessler, D. M. (2018). Ectoparasite defence in humans: relationships to pathogen avoidance and clinical implications. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *373*(1751), 20170207.

Leone, F., and Han, H. S. (2020). Ectoparasitic diseases. *Feline Dermatology*, 405-436.

Little, S. E. (2021). Fleas and lice. In *Greene's Infectious Diseases of the Dog and Cat* (pp. 1324-1337). WB Saunders.

Little, S. E., and Cortinas, R. (2021). Mites. In *Greene's Infectious Diseases of the Dog and Cat* (pp. 1378-1398). WB Saunders.

Maqbool, I., Wani, Z. A., Shahardar, R. A., Allaie, I. M., and Shah, M. M. (2017). Integrated parasite management with special reference to gastro-intestinal nematodes. *Journal of Parasitic Diseases*, *41*(1), 1-8.

Molento, M. B., and Arenal, A. (2020). The breakthrough of nanotechnology to veterinary parasitology research. LALIOTIS, GP Current research in agriculture and veterinary science. London: Publisher International, 71-77.

Najahi-Missaoui, W., Arnold, R. D., and Cummings, B. S. (2020). Safe nanoparticles: are we there yet?. *International Journal of Molecular Sciences*, *22*(1), 385.

Najitha Banu, A., Kudesia, N., Rana, N., Sadaf, D., and Raut, A. M. (2023). Antiparasitic Activity of Nanomaterials. In *Nanomaterials for Sustainable Development: Opportunities and Future Perspectives* (pp. 173-205). Singapore: Springer Nature Singapore.

Najitha Banu, A., Kudesia, N., Rana, N., Sadaf, D., and Raut, A. M. (2023). Antiparasitic Activity of Nanomaterials. In Nanomaterials for Sustainable Development: Opportunities and Future Perspectives (pp. 173-205). Singapore: Springer Nature Singapore.

Nelder, M. P., Russell, C. B., Dibernardo, A., Clow, K. M., Johnson, S., Cronin, K., and Lindsay, L. R. (2021). Monitoring the patterns of submission and presence of tick-borne pathogens in Ixodes scapularis collected from humans and companion animals in Ontario, Canada (2011–2017). *Parasites and Vectors*, *14*(1), 260.

Nie, D., Li, J., Xie, Q., Ai, L., Zhu, C., Wu, Y., and Tan, W. (2023). Nanoparticles: a potential and effective method to control insect-borne diseases. *Bioinorganic Chemistry and Applications*, *2023*.

Olivry, T., and Mueller, R. S. (2019). Critically appraised topic on adverse food reactions of companion animals (8): storage mites in commercial pet foods. *BMC Veterinary Research*, *15*, 1-5.

Overgaauw, P. A., Vinke, C. M., van Hagen, M. A., and Lipman, L. J. (2020). A one health perspective on the human–companion animal relationship with emphasis on zoonotic aspects. *International Journal of Environmental Research and Public Health*, *17*(11), 3789.

Pavoni, L., Pavela, R., Cespi, M., Bonacucina, G., Maggi, F., Zeni, V., and Benelli, G. (2019). Green micro-and nanoemulsions for managing parasites, vectors and pests. *Nanomaterials*, *9*(9), 1285.

Pereira-Silva, M., Martins, A. M., Sousa-Oliveira, I., Ribeiro, H. M., Veiga, F., Marto, J., and Paiva-Santos, A. C. (2022). Nanomaterials in hair care and treatment. *Acta Biomaterialia*, *142*, 14-35.

Prasad, R. D., Charmode, N., Shrivastav, O. P., Prasad, S. R., Moghe, A., Sarvalkar, P. D., and Prasad, N. R. (2021). A review on concept of nanotechnology in veterinary medicine. *ES Food and Agroforestry*, *4*, 28-60.

Qu, L. Y., Liu, J. L., Liu, Y. Y., Zhang, G. Q., Xu, Y. J., Zhu, P., and Wang, Y. Z. (2023). Anchoring silver nanoparticles using catechol-derived resins: an efficient and versatile approach for producing durable antimicrobial fabrics. *Progress in Organic Coatings*, *176*, 107397.

Rafiqi, S. I., Kumar, S., Chaudhary, R., Farooq, U., and Kirthika, P. (2016). Ectoparasites of companion animals and their control. *International Journal Animal Veterinary Science*, *3*, 15-18.

Rust, M. K. (2017). The biology and ecology of cat fleas and advancements in their pest management: a review. *Insects*, *8*(4), 118.

Rust, M. K. (2020). Recent advancements in the control of cat fleas. *Insects*, *11*(10), 668.

Saleh, M. N., Allen, K. E., Lineberry, M. W., Little, S. E., and Reichard, M. V. (2021). Ticks infesting dogs and cats in North America: biology, geographic distribution, and pathogen transmission. *Veterinary Parasitology*, *294*, 109392.

Sharma, S., Sharma, D., Pathak, V., and Singh, E. (2021). Ectoparasites of cattle and their control strategies. *Indian Farmer*, *8*, 242-246.

Shiferaw, S. (2018). An overview of ectoparasites on domestic animals in Ethiopia. *Journal Veterinary Science Medicine*, *6*(1), 1-5.

Stafford, K. A., and Coles, G. C. C. (2017). Drug resistance in ectoparasites of medical and veterinary importance. *Antimicrobial Drug Resistance: Mechanisms of Drug Resistance, Volume 1*, 735-744.

Zaheer, T., Abbas, R. Z., Perveen, N., Sparagano, O. A., Khan, S. R., Rehman, T. U., and Arshad, M. I. (2023). Application of cypermethrin-coated ZnS and ZnO nanoparticles against rhipicephalus ticks. *Pathogens*, *12*(6), 807.

Zaheer, T., Abbas, R. Z., Rehman, T. U., Khan, M. K., and Arshad, M. I. (2024). Novel insights regarding the safety and efficacy of pyrethroid-coated nanoparticles against Hyalomma ticks. *Toxicology Mechanisms and Methods*, *34*(2), 148-163.

Zaheer, T., Ali, M. M., Abbas, R. Z., Atta, K., Amjad, I., Suleman, A., and Aqib, A. I. (2022). Insights into nanopesticides for ticks: the superbugs of livestock. *Oxidative Medicine and Cellular Longevity*, *2022*

Chapter 10

Green Nanoparticles; Sustainable Approaches and Applications in Veterinary Medicine

Ume Habiba Firdous[1], Sehrish Kiran[2], Muhammad Umair Waqas[3], Abdullah Saghir Ahmad[4], Salena Ahmad[5], Atif Rehman[3], Amina Iqbal[1], Idrees Raza[3], Muhammad Hamza Muneer[3] and Ali Haider[3]*

[1]Department of Zoology, Wildlife and Fisheries, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, 66000, Multan, Punjab, Pakistan
[2]Department of Chemistry, Faculty of Science and Technology, Lahore College for Women University, Jail Road, Lahore, Pakistan
[3]Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, Multan, Punjab, Pakistan
[4]Department of Parasitology, Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
[5]Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
*Corresponding author: ali.haider@mnsuam.edu.pk

ABSTRACT

Nanoscience and nanotechnology has gain massive attention in several research areas, including nano-medicine, biotechnology, biomedical sciences and veterinary medicine. A relatively new branch of research called "green nanotechnology" focuses on using biological processes to produce nanoparticles from live cells. The biological routes need application of either plants or microorganisms (bacteria, fungus, yeast, and algae, etc.) for synthesis. Using microorganisms poses higher risk due to pathogenicity and large-scale culture management. Nanoparticles have several applications in medicine, drug and gene transport, cell imaging, bio sensing, wound healing, dental care, x-ray imaging, and activation of antibacterial, antifungal, anti-inflammatory, anticancer, and antifouling properties. Use of green technology in animal husbandry and veterinary care is relatively novel. Recently veterinary medicine has gain remarkable advancements in health care technologies. Animal production and growth are being improved with the application of current state and advances in nanotechnology. Therefore, nanoparticles are alternative antimicrobial agent for identification of pathogenic bacteria and to counteract the misuse of antibiotic. Additionally, nanoparticles are utilized as drug delivery agents to create new drug and vaccine candidates with enhanced properties and performance, as well as for diagnostic and therapeutic purposes.

KEYWORDS
Nanotechnology, Nanoparticle, Green technology, Antibacterial, Veterinary medicine

Received: 23-May-2024
Revised: 19-Jul-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Firdous UH, Kiran S, Waqas MU, Ahmad AS, Ahmad S, Rehman A, Iqbal A, Raza I, Muneer MH and Haider A, 2024. Green nanoparticles; sustainable approaches and applications in veterinary medicine. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 68-78. https://doi.org/10.47278/book.CAM/2024.231

INTRODUCTION

Presently, nanotechnology has gained a lot of attention as one of the vital disciplines due to its technological advancement in several fields of science including physics, biology, chemistry, medicine, pharmacy, material science and environment (Nicolas et al., 2013). Nanotechnology refer towards investigation and manipulation of materials with an objective of achieving a dimension falling within range of 1–100 nm (Ahmad et al., 2017). A Professor Norio Taniguchi of Tokyo Science University first used the word "nanotechnology" in 1974 to refer the precise process of creating materials (Taniguchi, 1974). The word "nano" is derived from Greek word "nanos" meaning dwarf and "nanometer" (10^{-9}) meaning the length of three atoms aligned in a single pattern, or one billionth of a meter (Thakkar et al., 2010).

Importance of Nanotechnology

Nanotechnology plays an imperative role in several technical domains owing to its pre-established superstructures. This field pertains towards the manipulation of atoms or molecules in order to create structures with desired shape and characteristics. Its health and environmental applications involve efficient drug delivery and solar energy harvesting. Additionally, it contributes towards reduction of industrial chemical use and creation of better, healthier, and more livable environment. Moreover, it contain applications in water filtration, cancer treatment, and food packaging (Khan et

al., 2019). Nanomaterials (NMs) possess numerous unique properties because of their greater surface area to volume ratio, specific size, composition, shape and concentration of individual constituents. These properties also makes possible the application of particles in different fields as catalysts, drug/gene delivery system, nano-magnets, quantum dots for electronic devices, water disinfectants and pollutant remediating agents (Khin et al., 2012; Tang et al., 2014; Gong et al., 2018).

Nanoparticles

Nanoparticles (NPs) are solid particles with size of few nanometers, created at molecular or atomic level containing unique or superior physical properties that are not possible for bulk solids. These NPs exhibit the properties of unified cohesive entity (Sharma et al., 2019). Because of their unique characteristics over their bulk counterparts, NPs are created in variety of sizes and shapes. Nanoscale materials possessing high surface to volume ratios vary significantly because of their mechanical properties, biological activity, light absorption, thermal conductivity, melting points and catalytic properties (Mandhata et al., 2022).

Classification of Nanomaterials

Numerous classifications of nanomaterials have been established, based on following factors:

(I) **The structure:** Dendrimers carbon tubes, liposomes, nanoclusters, nanotubes, micelles and fibers (Abdullaeva, 2017).

(II) **The dimension:** The size of NPs ranges from 1 to 100 nm; smaller particles containing larger surfaces, affects both toxicity and functioning (Saleh, 2020; Lang et al., 2021).

(III) **The morphology:** NPs might be manufactured in a variety of shapes, including cubes, triangles, wires, helices, stars, hooks, plates and spheres (Buzea and Pacheco, 2017).

(IV) **The application:** NPs can be used in nutritional, medicinal, diagnostic, theranostic and vaccine manufacturing purposes.

(V) **The surface modifications:** It refers to surface functionalization of NPs by adding thiols, fatty acids, anionic chemicals, or by carboxylation, PEGylation, or amination linking to functional groups. It also refers to adjustment of surface charge, either negative or positive (Saleh, 2020).

(VI) **The composition:** In order to overcome limitations of single-component NPs, improve their properties, and accomplish multiple functionalities. A NMs can be synthesized using a single material or composite of at least two different NPs (Buzea and Pacheco, 2017; Ma, 2019; Du and Yuan, 2020).

(VII) **The nature:** NPs can be divided into three categories: carbon, organic and inorganic (Ealia et al., 2017). Metals or metal oxides make up inorganic NPs. Gold, silver (Ag), copper, cadmium, iron, aluminium, cobalt and zinc are materials used to make metal NPs (Reverberi et al., 2016). Because iron (Fe) NPs are very reactive and quickly oxidize to Fe_2O_3 in the presence of oxygen at ambient temperature, coating FeNPs is recommended to maintain them stable and to stop aggregation (Ali et al., 2016). Because of their higher reactivity and efficiency, metal-oxide NPs are mostly produced (Tai et al., 2007). Carbon-based NPs should be categorized into, black carbon, fullerenes, carbon nanofibers, carbon nanotubes and graphene (Bhaviripudi et al., 2007). Proteins, liposomes, and peptide-based NPs are examples of organic NPs (Osama et al., 2020). They are biodegradable, biocompatible and non-toxic. Nano-capsules, as liposomes and micelles, are an excellent alternative for sustained release and drug administration due to their outside shell and empty internal portion (Abd El-Ghany et al., 2021).

Green Nanotechnology

NPs produced using environmentally friendly techniques are often devoid of harmful substances and compatible with living organisms due to absence of reducing agents or external coatings in their synthesis methods. That's why they are less harmful than nanoparticles synthesized chemically (Porzani et al., 2021). Biologically produced nanoparticles have provided a modern approach for developing an alternative technology (Ebrahimzadeh et al., 2020). The advantages of biological synthesis compared to traditional physiochemical techniques are its cost-efficiency and eco-friendliness (Duran et al., 2016).

In addition, biological engineering enables creation of nanoparticles with exact dimensions and shape by controlling several factors, including pH, temperature, incubation time, as well as concentration and developmental settings of biological agent used (Gericke and Pinches, 2006a; Gericke and Pinches, 2006b). Green synthesis of several nanoparticles from different plants, including *Solanum nigrum*, *Ocimum basilicum*, *Azadirachta*, *Camellia sinensis*, *Mangiferaindica* and green tea have been reported recently (Majidi et al., 2016).

Green Nanoparticles Production Methods

Green nanoparticles (GNPs) are synthesized using various components and bio-chemicals derived from plants acting as stabilizing and reducing agents. Green synthesized technologies are more durable, economical, non-toxic, and eco-friendly compared to other physical, biological, and chemical techniques (Mustapha et al., 2022). The procedure of synthesizing NPs from plant extract is cost effective and yields higher products since, extract contains large amount of phytochemical components that can be used as stabilizing and reducing agents to transform metal ions into metal NPs (Venkataraman, 2022).

Variations in Green Synthesis of Nanoparticles

Diverse factors, as temperature, pH, reaction time, and reactant concentration, might be adjusted according to requirements of environmentally friendly production of NPs for their morphological analysis. These features primarily recognize the impact of extrinsic variables on synthesis of NPs, and they might have pivotal part in improving the efficiency of producing metallic NPs (Zhang et al., 2020).

Biological Methods

Biological techniques are acquiring ubiquity due to their reduced impairment, ease of application, eco-friendliness, and effectiveness compared to traditional treatments. This method employs microorganisms (as bacteria, viruses, and fungi) or extracts from plants or algae as direct substitutes for chemical and physical procedures (Eszenyi et al., 2011; Abdelnour et al., 2021). The extracts include polyphenols, terpenoids, sugars, proteins, and other components that function as reducers to maintain minerals in reduced state throughout production (Marappan et al., 2017). Biological techniques have several limits when it comes to retrieving NPs, as time required to manufacture them and need to maintain culture medium and conditions (Abdelnour et al., 2021).

Synthesis using Plant Extract

Numerous phytochemical substances with oxidation-reduction properties, as flavonoids, phenolics, terpenoids and polysaccharides are found in plants. Therefore, they are ideally used in eco-friendly synthesis of NPs (Widatalla et al., 2022). The synthetic GNPs have an impact on several components of plants, including roots, stems, leaves, seeds, and fruits, due to availability of important phytochemicals (Parmar and Sanyal, 2022). Various techniques for synthesizing plant-mediated NPs include: (i) employing specific phytochemicals (Ivask et al., 2014), (ii) using plant extracts externally (extracellularly), and (iii) using plant extracts internally (intracellularly). Several plants contain the capacity to accumulate metals and subsequently convert them into NPs within their cells. Numerous key biomolecules present in plants, as proteins, polysaccharides, alkaloids, phenolics, aldehydes, ketones, terpenoids, saponins, tannins, flavones, and vitamins, play a crucial role in reducing metals (Nath and Banerjee, 2013). Fig. 1 indicate green fabrication process of metal NPs mediated by plants.

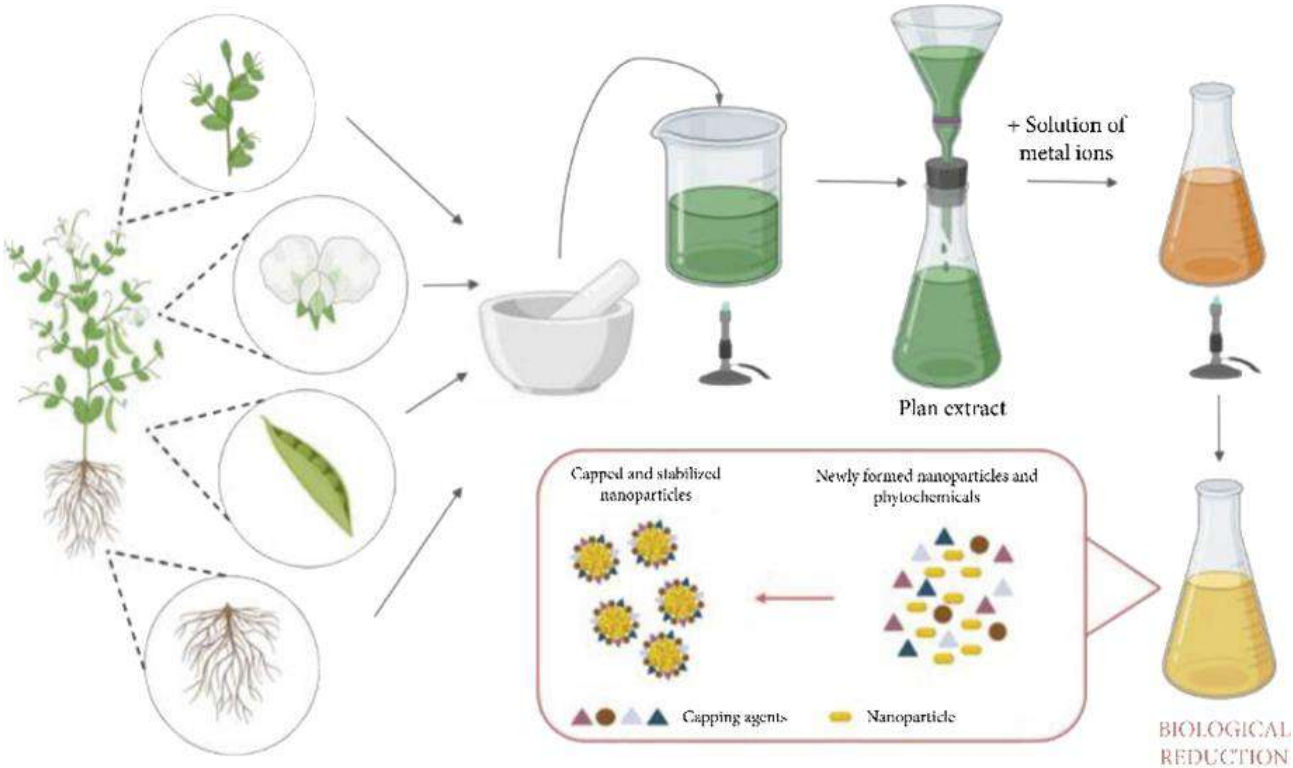


Fig. 1: The typical process of plant-mediated green synthesis of metal nanoparticles Copyright © 2021 (Ronavari et al., 2021).

Biosynthesis using Microorganisms

Microorganisms like bacteria, fungi, and yeast are showing huge interest for synthesis of NPs however, lack of control over NP size, extensive procedures, and culture contamination pose threats to the method. Microbial-derived NPs can often be categorized into several types based on the particular environment within which they are synthesized (Li et al., 2011).

Bacteria

Bacterial species have been extensively used in several commercial biotechnological applications, as genetic engineering, bioremediation and bioleaching (Gericke and Pinches, 2006). Bacteria are vital prospects for NPs manufacturing due to their ability to reduce metal ions (Iravani, 2014). Numerous bacterial species are employed in synthesis of metallic and other new NPs. Actinomycetes and prokaryotic bacteria are often used in the production of metal/metal oxide NPs (Singh et al., 2018).

Fungi

Fungi that synthesize metal/metal oxide NPs provide very effective method for producing well-dispersed NPs with distinct morphologies due to their diverse intracellular enzymes. They are highly efficient in producing metal and metal oxide NPs (Chen et al., 2009). Proficient fungus have higher NPs production rates than bacteria (Mohanpuria et al., 2008).

Viruses

Viruses, which are not regarded as entire living beings, are also utilized in process of producing nanomaterials. Plant virus capsids in particular are helpful bio-template for synthesis of NPs (Young et al, 2008; Banik and Sharma, 2011; Love et al., 2014). A few plant viruses, including red clover necrotic mosaic virus, cowpea mosaic virus, and tobacco mosaic virus, have been utilized to create Fe–Pt, Co–Pt, Co–Fe, and Cd–Se alloy NPs (Tsukamoto et al., 2007; Loo et al., 2007; Shah et al., 2009).

Yeast

The single-celled microorganisms known as yeasts are found in eukaryotic cells containing about 1500 known species (Yurkov et al., 2011). Yeast strains have various advantages over bacteria, including the ability to synthesize several enzymes, rapid development using inexpensive resources, efficient mass production, and easy regulation in laboratory settings (Kumar et al., 2011).

Comparison of Plant-based Green Synthesis over Microorganism-based Methods

Reaction rates in synthesis methods based on plant extracts are relatively high. Depending on kind and number of plants involved, this process may take a few minutes to many hours. In microorganism-based techniques, microbe cultivation requires significant amount of time, sometimes several days. This indicates time-consuming nature of this approach. Some of bacteria in addition to these are highly dangerous and could threaten human health. However, *Pseudomonas*, *Fusarium* and *Escherichia coli* are safest and most benign bacteria to produce nanoparticles. In nature, there are numerous plants especially evergreens, which are almost constantly present. In contrast to microbes, herbal extracts usually produce metal nanoparticles at ambient temperature without heating the reaction mixture or culture medium. Broadly, plant extracts are more suitable for industrial scale synthesis than microbes (Noruzi, 2015).

Applications of Green Nanoparticles

i. **Agriculture;** GNPs made from different plants, decrease harmful emissions of nitrous oxide, carbon dioxide and methane. This is an important idea of employing green nanotechnology in agriculture to reduce detrimental environmental consequences and high cost of fertilizers. GNPs have potential to alleviate health problems among farmers while simultaneously increasing agricultural output (Raja et al., 2022).

ii. **Detoxifying agent;** Plants naturally contain wide variety of phytochemical constituents which, are affordable and environmentally beneficial. Green synthesized NPs are subjected to substantial significance and detoxification of environmental heavy metal. Because heavy metals contaminate soil and water in large quantities, green nanoparticles can help reduce metallic toxicity in the environment (Jadoun et al., 2022).

iii. **Energy;** The energy sector is core area where green nanotechnology offer opportunities as addition of NMs to solar cells can increase their ability to absorb light and convert it into electricity, creating cleaner and more effective energy sources (Cuong et al., 2022).

iv. **Biosensor;** The visual characteristics of gold NPs produced by algae have demonstrated exceptional performance and might be valuable in biological sensing applications as determining kind and quantity of hormones present in human body, particularly in cancer diagnosis. Algal-produced Au-Ag demonstrated exceptional electro-catalytic activity against 2-butanone at room temperature, and might be used as substrate to create biosensors for cancer detection and to identify presence of malignant cells (Anvar et al., 2023). A new and practical method for creating nano-biosensing instruments to target environmental contaminants is use of biosynthesized Ag-NPs. The Ag-NPs produced from *Anacardium occidentale* leaf extract have been utilized as a sensing probe to find Cr (VI) in tap water (Balavigneswaran et al., 2014). Green-synthesized NPs, including Ag-NPs, CuO-NPs, ZnO-NPs and NiO-NPs, show antibacterial activity through several mechanisms. Ag-NPs possess ability to rupture bacterial cells by creating holes in their membrane (Annamalai and Nallamuthu, 2016), resulting disruption in DNA replication, ATP production, protein denaturation and loss of proton motive force (Shao et al., 2018; Jemilugba et al., 2019). NPs contain ability to damage polymer components of cell membranes found in both pathogenic and non-pathogenic microorganisms, including peptidoglycan in cell walls. Increasing the concentration of NPs can increase permeability of membrane and cause cell wall rupture (Dakal et al., 2016).

The primary characteristic of NPs with small sizes that may lead to cell wall damage is their large surface area (Janthima et al., 2018).

v. **Antifungal agent;** Numerous medical applications of green synthesized NPs are presented in Fig. 2. The development of effective, new and potent antifungal medicines is very promising, as fungal infections have become a critical public health concern due to drug resistance and restricted access to antifungal treatment. Fantastic antifungal efficacy is demonstrated by NPs, which may offer a novel treatment option for fungal illnesses. The most potent antifungals that can be produced through green methods are silver nanoparticles. For example mechanism involved in biocidal effects of *Nostoc* Bahar_and *Desertifilum* sp. IPPAS B-1220 against *Candida albicans* attributed to their capacity to interfere along with fungal cell structures and stimulate oxidative stress, assisting them to be utilized as robust antimycotic agent (Hamida et al., 2021).

vi. **Anti-inflammatory agent;** Anti-inflammatory mechanism of various NPs may be applicable for targeting, drug designing, in food and cosmetic industry , as well as offers feasible solution for treatment of several types of inflammations with minimal side-effects (Agarwal et al., 2019). Selenium (Se) an crucial trace element that perform critical role in counteracts chronic inflammation and immune functions by regulating signal-transduction pathways and inflammatory gene expression in triggered macrophages (Narayan et al., 2015). The roles of Se in immunity and inflammation have been recognized, and can reduces risk of cardiovascular diseases and rheumatoid arthritis (Huang et al., 2012). It has been reported that silver NPs demonstrate anti-gastric ulcer properties (Sreelakshmy et al., 2016) and solid lipid NPs (Sun et al., 2017) and anti-peptic ulcer assets of chitosan NPs (Goncalves et al., 2014).

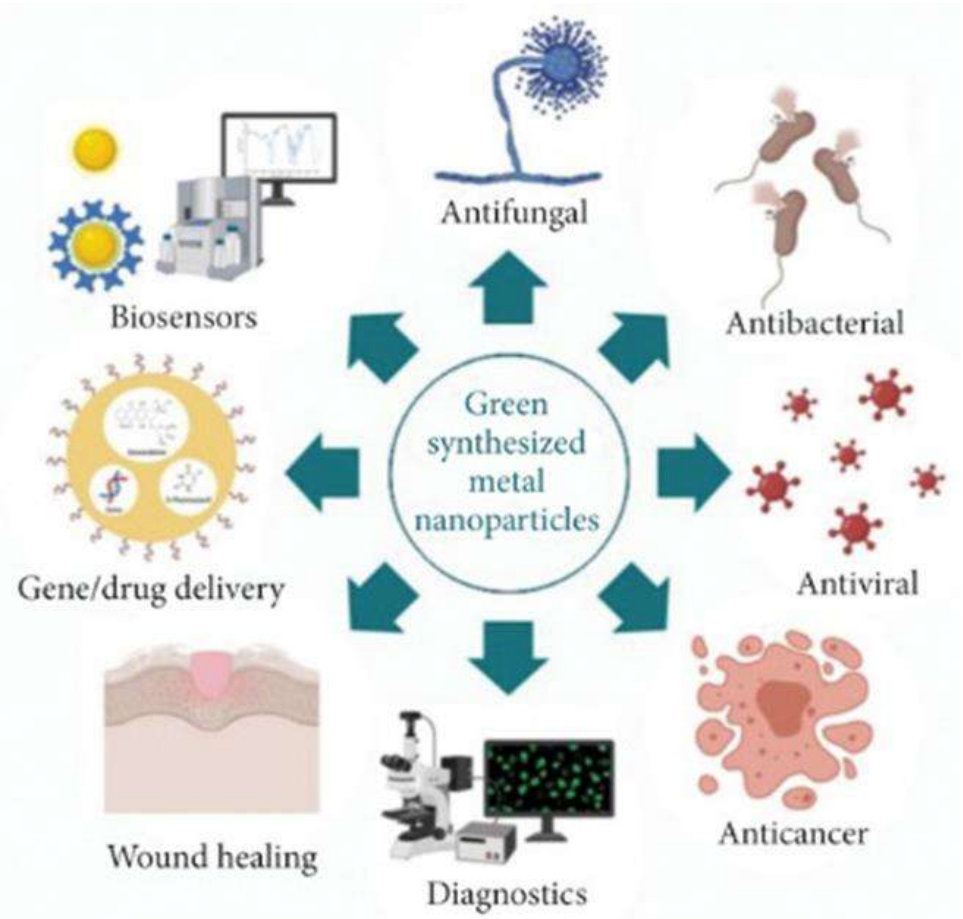


Fig. 2: Green-synthesized metal nanoparticles' medical applications Copyright © 2021 (Ronavari et al., 2021).

vii. **Anticancer;** Synthesized silver NPs derived from several plants, such as *Ficus religiosa* (Antony et al., 2013) and microorganisms such as *Deinococcus radioduran* (Kulkarni et al., 2015), *Streptomyces rochei* MHM13 (Abd-Elnaby et al., 2016) have demonstrated *in-vitro* anticancer actions towards different cancer cell lines. The synthesized silver NPs from *Indigofera tinctoria* leaf extract revealed cytotoxicity against lung cancer cell line A549. It was discovered that the cytotoxic effects of silver NPs were dose-dependent and more distinct than those of leaf extract administered as a placebo (Vijayan et al., 2018).

Application of Nanotechnology in Veterinary Medicine

❖ NMs are very beneficial in biomedical applications because of their small size, which makes them compatible with a wide range of biological organisms as shown in Fig. 3. Nanotechnology contain significant potential for resolving wide range of issues in veterinary medicine and veterinary-sanitary inspection (Patil et al., 2009). Many applications, such as

medicine administration, gene transfer, imaging, parasitology, tissue engineering and pest control, might be revolutionized by nano-biotechnologies (Rai et al., 2009; Heng et al., 2013; Amerasan et al., 2016). Recently, garlic oil nano-emulsion has emerged as promising technique that may be greatest antibiotic substitute in chicken farms. Because application of garlic nano-emulsion greatly decreases gene expression levels of multi drug resistant (MDR) *P. aeruginosa* in broiler farms, it is great choice for therapy as an alternative to antibiotics (El-Oksh et al., 2022). In the animal model of atopic dermatitis (AD), nano-sized zinc oxide significantly decreased pro-inflammatory cytokines, exhibiting stronger anti-inflammatory effects than bZnO (IL-10, IL-13, IFN-, and Th2 cytokines) (Yousaf et al., 2024).

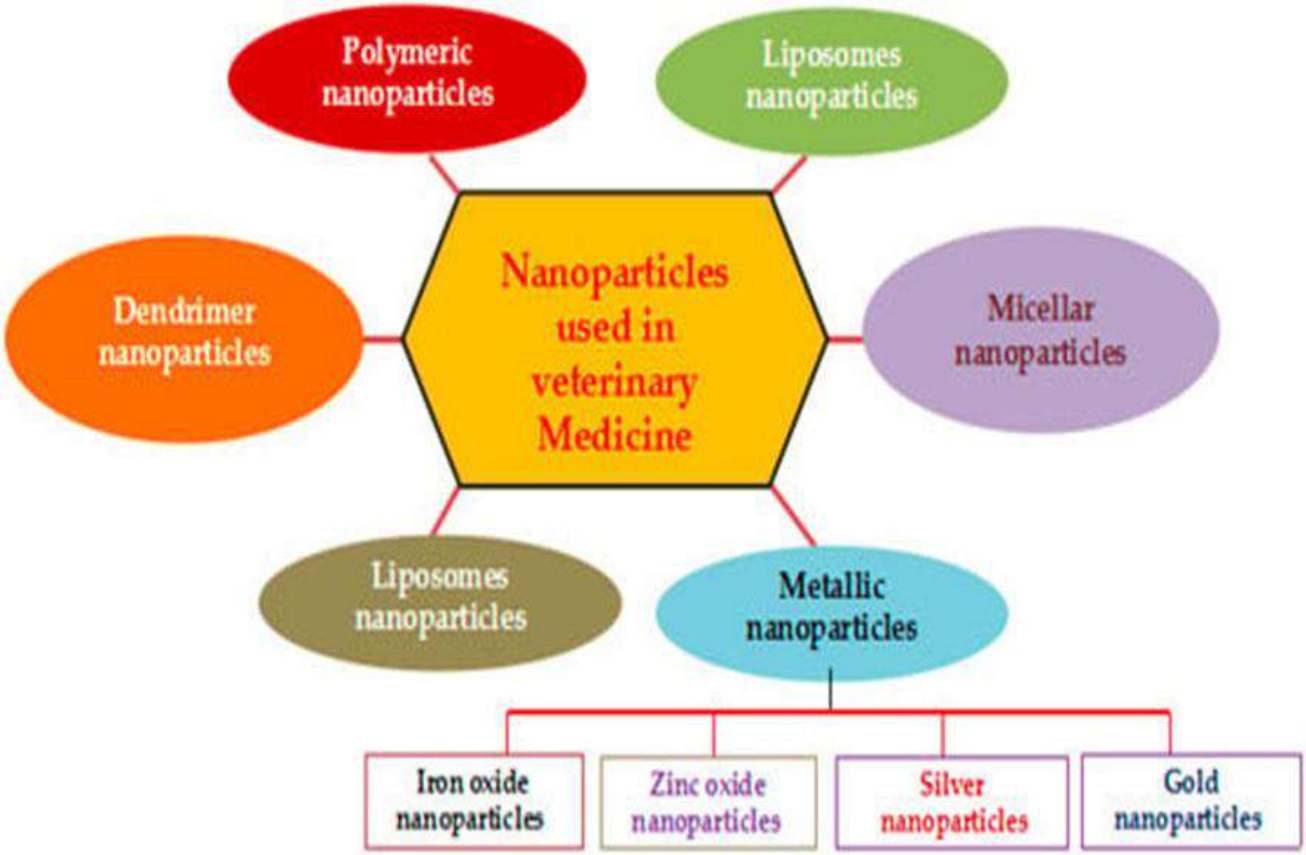


Fig. 3: Type of nanoparticles used in application of veterinary medicine and animal production (Bai et al., 2018).

❖ The hydrogel of silver NPs made from *Arnebia nobilis* root extract demonstrated effective wound healing activity in an animal excision model. The antibacterial qualities of biosynthesized silver NPs are correlated with their therapeutic effects in wound treatment (Garg et al., 2014).

❖ A substance termed timicosin contain semisynthetic characteristics. Broiler chicks were given three different kinds of micellar NPs as lipid-core nanocapsules, solid lipid NPs, and nanostructured lipid carriers-pills. Improved medication bioavailability and pharmacokinetics were the goals of their utilization. The pharmacokinetic properties and bioavailability of the medication were improved in three separate batches of lipid NPs administered to broiler chickens (Al-Qushawi et al., 2016).

Diagnostics

Bio-imaging plays vital role in disease diagnosis, particularly in identification of cancer and tumors, as well as in recognition of forms, structures and pathways inside organisms. Gold, iron-based NPs and quantum dots are being used in various biomedical imaging techniques as magnetic resonance imaging (MRI), photo-acoustic (PA) imaging, computed tomography (CT), contrast-enhanced dual-energy mammography (DEM), high-order multiphoton luminescence (HOMPL) microscopy for cancer and tumor detection (Nune et al., 2009; Chou et al., 2016).

Certain NMs (e.g., magnetic, fluorescent and catalytic) can be used as probes for various imaging and diagnostic applications because of their essential physicochemical qualities and biocompatibility. Biochips for early diagnosis of animal illnesses have been developed and effectively implemented. These chips are made from silicon pools that have hundreds or thousands of small recombinant Deoxyribonucleic acid (DNA) strands grafted on them (Hanafy, 2018). Molecular diagnostic methods are becoming more common in diagnostic laboratories these days. Immune diagnostic probe integration with NMs significantly increase the specificity and sensitivity of antibody-based

immunodiagnostic techniques and provide strong impetus for their development. More biocompatible, stable, and sensitive to target antigens are the antibodies conjugated to NPs (Vrublevskaya et al., 2017).

Therapeutic usage of Green Nanotechnology

Drug Delivery

Higher binding affinity for biomolecules, decreased oxidative stress and inflammation in tissues have demonstrated by nano-medicines. Thousands of unique nano-medicines have been created over time, each with different use for handling of different diseases. Many more are in the clinical testing phase and very few have been authorized for use in clinical settings. Different kinds of NPs were found based on therapeutic need as shown in Fig. 4, depending on their origin and use. Iron oxide NPs, polymeric proteins, liposomes and metal-based materials have all become highly effective (Dikshit et al., 2021). They have notable advantages in terms of improving drug stability inside the body as well as bioavailability, pharmacological activity, toxicity protection, distribution, solubility and resistance to degradation from both physical and chemical sources (Zoroddu et al., 2014).

It offers a platform for development of therapeutic NMs or nano-medicines. Numerous opportunities in medical sciences, particularly in area of drug delivery systems, have been made possible by development of nano-medicines. Because of their structural qualities, they have great way to target particular locations and enter cells or sick areas quickly (Luque-Michel et al., 2017). Nano-medicines have shown greater ability to cooperate with biomolecules and to lower oxidative stress and inflammation in tissues (Dikshit et al., 2021).

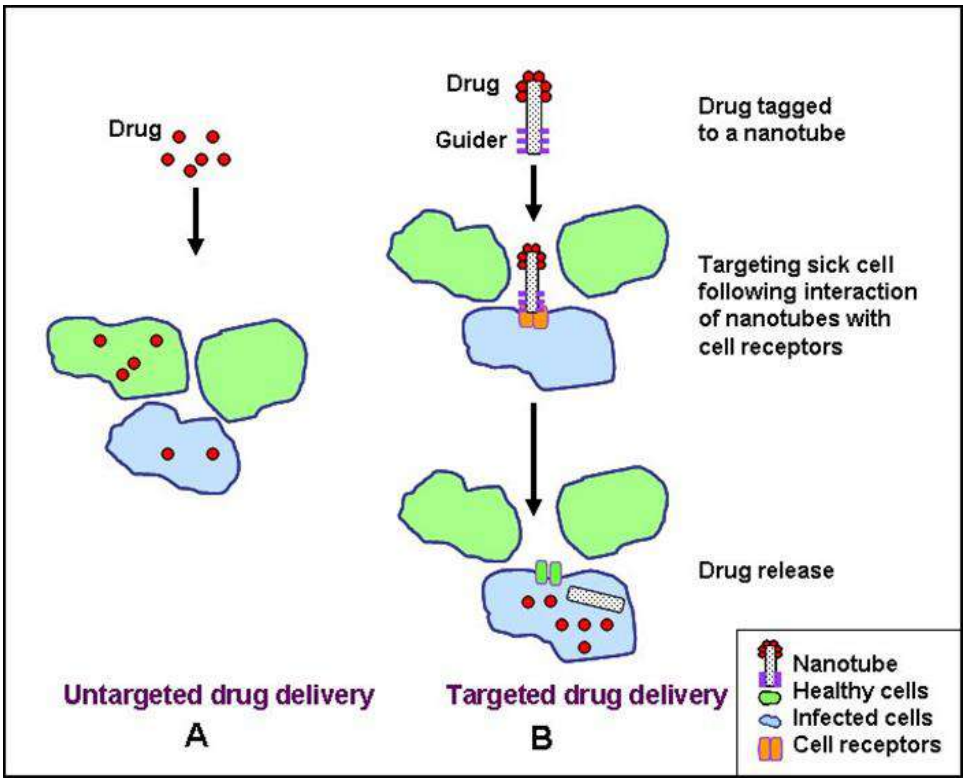


Fig. 4: Targeted drug delivery of nanotubes (Suri et al., 2007).

Future Perspectives

The development of innovative nano-drugs and delivery systems using non-toxic nanoparticles such dendrimers, polymeric nanoparticles, liposomes, and metal nanoparticles is now more possible because to recent developments in nanotechnology. The unique characteristics of each form of nanoparticle are employed to improve the therapeutic indices of the integrated pharmaceuticals in a number of ways as prolonged release, bioavailability, retention time, and protection of the entrapped agent from the internal body environment. Additional metallic nanoparticles are being thoroughly investigated for a range of biomedical uses as "nanotheranostics." In addition to being widely used as diagnostic, therapeutic, imaging, and nanocarrier agents in veterinary medicine, metallic nanoparticles serve as artificial platforms for multimodal imaging approach to the detection and treatment of degenerative illnesses, including cancer in humans. For veterinary illnesses, targeted drug delivery via various metallic nanoparticles holds out a lot of potential for both immediate and long-term therapy plans (Bai et al., 2018).

While, taking into account their manufacturing capabilities and enhancing their size, stability and lifespans, it is crucial to guarantee the quality and safety criteria of green NPs. Despite a vast extent of research, only a little amount of NP-based drugs are in use nowadays, and the bulk are still in the experimental stage. In order to enable functional nanotechnology design, further study is required to comprehend toxicity, cellular and physiological factors that affects

distribution of medications via NPs, improved permeability and retention impact and pharmacokinetic mechanisms in human body (Hosseingholian et al., 2023).

Crucially, to utilize all of the tools derived from a variety of nanomaterials towards being beneficial instruments for different diseases and therapies in veterinary animals, like humans, further in-depth pre-clinical investigations are urgently needed to realize the bright future of veterinary medicine. Predicting future risks to biological systems and the environment therefore necessitates ongoing, thorough research into the short- and long-term impacts of such materials in vivo as well as a thorough grasp of molecular mechanisms. Utilizing nanoparticle-mediated drug delivery broadly is crucial in veterinary medicine as it holds great promise for more effective medication delivery to specific target sites and for overcoming biological obstacles (Bai et al., 2018).

Conclusion

The most significant application of nanotechnology in tissue engineering is regenerative medicine, which has potential to revolutionize the design of scaffolds and transplants with tissue-regenerative qualities. Creating perfect nanomaterials that can communicate with damaged or sick cells and tissues to start regeneration process is still difficult. Similar to this, as regenerative medicine is still in its early stages of development, there is great deal of concern regarding safety of using nanomaterials on animals. Ultimately, strong collaboration between scientists and veterinary physicians is critical to comprehending underlying principles of cell-biomaterial interactions at nanoscale level and being able to convert findings from bench to bedside. Additionally, research is crucial to the animal production sector, especially in identifying gaps in applications and knowledge.

REFERENCES

Abd-Elnaby, H. M., Abo-Elala, G. M., Abdel-Raouf, U. M., and Hamed, M. M. (2016). Antibacterial and anticancer activity of extracellular synthesized silver nanoparticles from marine Streptomyces rochei MHM13. *The Egyptian Journal of Aquatic Research*, *42*(3), 301-312.

Abd El-Ghany, W. A., Shaalan, M., and Salem, H. M. (2021). Nanoparticles applications in poultry production: an updated review. *World's Poultry Science Journal*, *77*(4), 1001-1025.

Abdelnour, S. A., Alagawany, M., Hashem, N. M., Farag, M. R., Alghamdi, E. S., Hassan, F. U., and Attia, Y. A. (2021). Nanominerals: fabrication methods, benefits and hazards, and their applications in ruminants with special reference to selenium and zinc nanoparticles. *Animals*, *11*(7), 1916.

Abdullaeva, Z. (2017). *Nano-and biomaterials: compounds, properties, characterization, and applications*. John Wiley and Sons.

Agarwal, H., Nakara, A., and Shanmugam, V. K. (2019). Anti-inflammatory mechanism of various metal and metal oxide nanoparticles synthesized using plant extracts: A review. *Biomedicine and Pharmacotherapy*, *109*, 2561-2572.

Ahmed, S., Chaudhry, S. A., and Ikram, S. (2017). A review on biogenic synthesis of ZnO nanoparticles using plant extracts and microbes: a prospect towards green chemistry. *Journal of Photochemistry and Photobiology B: Biology*, *166*, 272-284.

Al-Qushawi, A., Rassouli, A., Atyabi, F., Peighambari, S. M., Esfandyari-Manesh, M., Shams, G. R., and Yazdani, A. (2016). Preparation and characterization of three tilmicosin-loaded lipid nanoparticles: physicochemical properties and in-vitro antibacterial activities. *Iranian Journal of Pharmaceutical Research: IJPR*, *15*(4), 663.

Ali, A., Zafar, H., Zia, M., ul Haq, I., Phull, A. R., Ali, J. S., and Hussain, A. (2016). Synthesis, characterization, applications, and challenges of iron oxide nanoparticles. *Nanotechnology, Science and Applications*, 49-67.

Amerasan, D., Nataraj, T., Murugan, K., Panneerselvam, C., Madhiyazhagan, P., Nicoletti, M., and Benelli, G. (2016). Myco-synthesis of silver nanoparticles using Metarhizium anisopliae against the rural malaria vector Anopheles culicifacies Giles (Diptera: Culicidae). *Journal of Pest Science*, *89*, 249-256.

Anvar, S. A. A., Nowruzi, B., and Afshari, G. (2023). A review of the application of nanoparticles biosynthesized by microalgae and cyanobacteria in medical and veterinary sciences.

Annamalai, J., and Nallamuthu, T. (2016). Green synthesis of silver nanoparticles: characterization and determination of antibacterial potency. *Applied Nanoscience*, *6*, 259-265.

Antony, J. J., Sithika, M. A. A., Joseph, T. A., Suriyakalaa, U., Sankarganesh, A., Siva, D., and Achiraman, S. (2013). In vivo antitumor activity of biosynthesized silver nanoparticles using Ficus religiosa as a nanofactory in DAL induced mice model. *Colloids and Surfaces B: Biointerfaces*, *108*, 185-190.

Bai, D. P., Lin, X. Y., Huang, Y. F., and Zhang, X. F. (2018). Theranostics aspects of various nanoparticles in veterinary medicine. *International Journal of Molecular Sciences*, *19*(11), 3299.

Bai, D.-P., Lin, X.-Y., Huang, Y.-F. and Zhang, X.-F. (2018). Theranostics aspects of various nanoparticles in veterinary medicine. *International Journal of Molecular Sciences,* 19:3299.

Balavigneswaran, C. K., Sujin Jeba Kumar, T., Moses Packiaraj, R., and Prakash, S. (2014). Rapid detection of Cr (VI) by AgNPs probe produced by Anacardium occidentale fresh leaf extracts. *Applied Nanoscience*, *4*(3), 367-378.

Banik, S., and Sharma, P. (2011). Plant pathology in the era of nanotechnology. *Indian Phytopathol*, *64*(2), 120-127.

Bhaviripudi, S., Mile, E., Steiner, S. A., Zare, A. T., Dresselhaus, M. S., Belcher, A. M., and Kong, J. (2007). CVD synthesis of single-walled carbon nanotubes from gold nanoparticle catalysts. *Journal of the American Chemical Society*, *129*(6), 1516-1517.

Buzea, C., and Pacheco, I. (2017). Nanomaterials and their classification. *EMR/ESR/EPR Spectroscopy for Characterization of Nanomaterials*, 3-45.

Chen, Y. L., Tuan, H. Y., Tien, C. W., Lo, W. H., Liang, H. C., and Hu, Y. C. (2009). Augmented biosynthesis of cadmium sulfide nanoparticles by genetically engineered Escherichia coli. *Biotechnology Progress*, *25*(5), 1260-1266.

Chou, S. W., Liu, C. L., Liu, T. M., Shen, Y. F., Kuo, L. C., Wu, C. H., and Chou, P. T. (2016). Infrared-active quadruple contrast FePt nanoparticles for multiple scale molecular imaging. *Biomaterials*, *85*, 54-64.

Cuong, H. N., Pansambal, S., Ghotekar, S., Oza, R., Hai, N. T. T., Viet, N. M., and Nguyen, V. H. (2022). New frontiers in the plant extract mediated biosynthesis of copper oxide (CuO) nanoparticles and their potential applications: A review. *Environmental Research*, *203*, 111858.

Dakal, T. C., Kumar, A., Majumdar, R. S., and Yadav, V. (2016). Mechanistic basis of antimicrobial actions of silver nanoparticles. *Frontiers in Microbiology*, *7*, 1831.

Dikshit, P. K., Kumar, J., Das, A. K., Sadhu, S., Sharma, S., Singh, S., and Kim, B. S. (2021). Green synthesis of metallic nanoparticles: Applications and limitations. *Catalysts*, *11*(8), 902.

Du, Y., and Yuan, X. (2020). Coupled hybrid nanoparticles for improved dispersion stability of nanosuspensions: a review. *Journal of Nanoparticle Research*, *22*(9), 261.

Durán, N., Nakazato, G., and Seabra, A. B. (2016). Antimicrobial activity of biogenic silver nanoparticles, and silver chloride nanoparticles: an overview and comments. *Applied Microbiology and Biotechnology*, *100*, 6555-6570.

Ealia, S. A. M., and Saravanakumar, M. P. (2017). A review on the classification, characterisation, synthesis of nanoparticles and their application. In *IOP conference series: materials science and engineering* (Vol. 263, No. 3, p. 032019). IOP Publishing.

Ebrahimzadeh, M. A., Naghizadeh, A., Amiri, O., Shirzadi-Ahodashti, M., and Mortazavi-Derazkola, S. (2020). Green and facile synthesis of Ag nanoparticles using Crataegus pentagyna fruit extract (CP-AgNPs) for organic pollution dyes degradation and antibacterial application. *Bioorganic Chemistry*, *94*, 103425.

El-Oksh, A. S., Elmasry, D. M., and Ibrahim, G. A. (2022). Effect of garlic oil nanoemulsion against multidrug resistant Pseudomonas aeruginosa isolated from broiler. *Iraqi Journal of Veterinary Sciences*, *36*(4), 877-888.

Eszenyi, P., Sztrik, A., Babka, B., and Prokisch, J. (2011). Elemental, nano-sized (100-500 nm) selenium production by probiotic lactic acid bacteria. *International Journal of Bioscience, Biochemistry and Bioinformatics*, *1*(2), 148.

Garg, S., Chandra, A., Mazumder, A., and Mazumder, R. (2014). Green synthesis of silver nanoparticles using Arnebia nobilis root extract and wound healing potential of its hydrogel. *Asian Journal of Pharmaceutics (AJP)*, *8*(2).

Gericke, M., and Pinches, A. (2006). Biological synthesis of metal nanoparticles. *Hydrometallurgy*, *83*(1-4), 132-140.

Gericke, M., and Pinches, A. (2006). Microbial production of gold nanoparticles. *Gold Bulletin*, *39*(1), 22-28.

Gong, X., Huang, D., Liu, Y., Peng, Z., Zeng, G., Xu, P., and Wan, J. (2018). Remediation of contaminated soils by biotechnology with nanomaterials: bio-behavior, applications, and perspectives. *Critical Reviews in Biotechnology*, *38*(3), 455-468.

Gonçalves, I. C., Henriques, P. C., Seabra, C. L., and Martins, M. C. L. (2014). The potential utility of chitosan micro/nanoparticles in the treatment of gastric infection. *Expert Review of Anti-infective Therapy*, *12*(8), 981-992.

Hamida, R. S., Ali, M. A., Goda, D. A., and Redhwan, A. (2021). Anticandidal potential of two cyanobacteria-synthesized silver nanoparticles: Effects on growth, cell morphology, and key virulence attributes of Candida albicans. *Pharmaceutics*, *13*(10), 1688.

Hanafy, M. H. (2018). Myconanotechnology in veterinary sector: Status quo and future perspectives. *International Journal of Veterinary Science and Medicine*, *6*(2), 270-273.

Heng, M. Y., Tan, S. N., Yong, J. W. H., and Ong, E. S. (2013). Emerging green technologies for the chemical standardization of botanicals and herbal preparations. *TrAC Trends in Analytical Chemistry*, *50*, 1-10.

Hosseingholian, A., Gohari, S. D., Feirahi, F., Moammeri, F., Mesbahian, G., Moghaddam, Z. S., and Ren, Q. (2023). Recent advances in green synthesized nanoparticles: From production to application. *Materials Today Sustainability*, 100500.

Huang, Z., Rose, A. H., and Hoffmann, P. R. (2012). The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. *Antioxidants and Redox Signaling*, *16*(7), 705-743.

Iravani, S. (2014). Bacteria in nanoparticle synthesis: current status and future prospects. *International Scholarly Research Notices*, *2014*(1), 359316.

Ivask, A., Kurvet, I., Kasemets, K., Blinova, I., Aruoja, V., Suppi, S., and Kahru, A. (2014). Size-dependent toxicity of silver nanoparticles to bacteria, yeast, algae, crustaceans and mammalian cells in vitro. *PloS one*, *9*(7), e102108.

Jadoun, S., Chauhan, N. P. S., Zarrintaj, P., Barani, M., Varma, R. S., Chinnam, S., and Rahdar, A. (2022). Synthesis of nanoparticles using microorganisms and their applications: a review. *Environmental Chemistry Letters*, *20*(5), 3153-3197.

Janthima, R., Khamhaengpol, A., and Siri, S. (2018). Egg extract of apple snail for eco-friendly synthesis of silver nanoparticles and their antibacterial activity. *Artificial Cells, Nanomedicine, and Biotechnology*, *46*(2), 361-367.

Jemilugba, O. T., Parani, S., Mavumengwana, V., and Oluwafemi, O. S. (2019). Green synthesis of silver nanoparticles using Combretum erythrophyllum leaves and its antibacterial activities. *Colloid and Interface Science Communications*, *31*, 100191.

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931.

Khin, M. M., Nair, A. S., Babu, V. J., Murugan, R., and Ramakrishna, S. (2012). A review on nanomaterials for environmental remediation. *Energy and Environmental Science*, *5*(8), 8075-8109.

Kulkarni, R. R., Shaiwale, N. S., Deobagkar, D. N., and Deobagkar, D. D. (2015). Synthesis and extracellular accumulation of silver nanoparticles by employing radiation-resistant Deinococcus radiodurans, their characterization, and determination of bioactivity. *International Journal of Nanomedicine*, 963-974.

Kumar, D., Karthik, L., Kumar, G., and Roa, K. B. (2011). Biosynthesis of silver nanoparticles from marine yeast and their antimicrobial activity against multidrug resistant pathogens. *Pharmacologyonline*, *3*, 1100-1111.

Lang, C., Mission, E. G., Fuaad, A. A. H. A., and Shaalan, M. (2021). Nanoparticle tools to improve and advance precision practices in the Agrifoods Sector towards sustainability-A review. *Journal of Cleaner Production*, *293*, 126063.

Li, X., Xu, H., Chen, Z. S., and Chen, G. (2011). Biosynthesis of nanoparticles by microorganisms and their applications. *Journal of Nanomaterials*, *2011*(1), 270974.

Love, A. J., Makarov, V., Yaminsky, I., Kalinina, N. O., and Taliansky, M. E. (2014). The use of tobacco mosaic virus and cowpea mosaic virus for the production of novel metal nanomaterials. *Virology*, *449*, 133-139.

Loo, L., Guenther, R. H., Lommel, S. A., and Franzen, S. (2007). Encapsidation of nanoparticles by red clover necrotic mosaic virus. *Journal of the American Chemical Society*, *129*(36), 11111-11117.

Luque-Michel, E., Imbuluzqueta, E., Sebastián, V., and Blanco-Prieto, M. J. (2017). Clinical advances of nanocarrier-based cancer therapy and diagnostics. *Expert Opinion on Drug Delivery*, *14*(1), 75-92.

Ma, D. (2019). Hybrid nanoparticles: an introduction. In *Noble metal-metal oxide hybrid nanoparticles* (pp. 3-6). Woodhead Publishing.

Majidi, S., et al., *Artife Cell Nanomed.* B, 2016. 44: p. 722-34.

Mandhata, C. P., Sahoo, C. R., and Padhy, R. N. (2022). Biomedical applications of biosynthesized gold nanoparticles from cyanobacteria: An overview. *Biological Trace Element Research*, *200*(12), 5307-5327.

Marappan Gopi, M. G., Beulah Pearlin, B. P., Kumar, R. D., Muthuvel Shanmathy, M. S., and Govindasamy Prabakar, G. P. (2017). Role of nanoparticles in animal and poultry nutrition: modes of action and applications in formulating feed additives and food processing.

Mohanpuria, P., Rana, N. K., and Yadav, S. K. (2008). Biosynthesis of nanoparticles: technological concepts and future applications. *Journal of Nanoparticle Research*, *10*, 507-517.

Mustapha, T., Misni, N., Ithnin, N. R., Daskum, A. M., and Unyah, N. Z. (2022). A review on plants and microorganisms mediated synthesis of silver nanoparticles, role of plants metabolites and applications. *International Journal of Environmental Research and Public Health*, *19*(2), 674.

Nath, D., and Banerjee, P. (2013). Green nanotechnology–a new hope for medical biology. *Environmental Toxicology and Pharmacology*, *36*(3), 997-1014.

Narayan, V., Ravindra, K. C., Liao, C., Kaushal, N., Carlson, B. A., and Prabhu, K. S. (2015). Epigenetic regulation of inflammatory gene expression in macrophages by selenium. *The Journal of Nutritional Biochemistry*, *26*(2), 138-145.

Nicolas, J., Mura, S., Brambilla, D., Mackiewicz, N., and Couvreur, P. (2013). Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. *Chemical Society Reviews*, *42*(3), 1147-1235.

Noruzi, M. (2015). Biosynthesis of gold nanoparticles using plant extracts. *Bioprocess and Biosystems Engineering*, *38*(1), 1-14.

Nune, S. K., Gunda, P., Thallapally, P. K., Lin, Y. Y., Laird Forrest, M., and Berkland, C. J. (2009). Nanoparticles for biomedical imaging. *Expert Opinion on Drug Delivery*, *6*(11), 1175-1194.

Osama, E., El-Sheikh, S. M., Khairy, M. H., and Galal, A. A. (2020). Nanoparticles and their potential applications in veterinary medicine. *Journal of Advanced Veterinary Research*, *10*(4), 268-273.

Patil, S. S., Kore, K. B., and Kumar, P. (2009). Nanotechnology and its applications in veterinary and animal science. *Veterinary World*, *2*(12), 475-477.

Parmar, M., and Sanyal, M. (2022). Extensive study on plant mediated green synthesis of metal nanoparticles and their application for degradation of cationic and anionic dyes. *Environmental Nanotechnology, Monitoring and Management*, *17*, 100624.

Porzani, S. J., Lima, S. T., Metcalf, J. S., and Nowruzi, B. (2021). In vivo and in vitro toxicity testing of cyanobacterial toxins: A mini-review. *Reviews of Environmental Contamination and Toxicology Volume 258*, 109-150.

Rai, M., Yadav, A., and Gade, A. (2009). Silver nanoparticles as a new generation of antimicrobials. *Biotechnology Advances*, *27*(1), 76-83.

Raja, R. K., Hazir, S., Balasubramani, G., Sivaprakash, G., Obeth, E. S. J., Boobalan, T., and Arun, A. (2022). Green nanotechnology for the environment. In *Handbook of Microbial Nanotechnology* (pp. 461-478). Academic Press.

Reverberi, A. P., Kuznetsov, N. T., Meshalkin, V. P., Salerno, M., and Fabiano, B. (2016). Systematical analysis of chemical methods in metal nanoparticles synthesis. *Theoretical Foundations of Chemical Engineering*, *50*, 59-66.

Rónavári, A., Igaz, N., Adamecz, D. I., Szerencsés, B., Molnar, C., Kónya, Z., and Kiricsi, M. (2021). Green silver and gold nanoparticles: Biological synthesis approaches and potentials for biomedical applications. *Molecules*, *26*(4), 844.

Saleh, T. A. (2020). Nanomaterials: Classification, properties, and environmental toxicities. *Environmental Technology and Innovation*, *20*, 101067.

Sharma, G., Kumar, A., Sharma, S., Naushad, M., Dwivedi, R. P., ALOthman, Z. A., and Mola, G. T. (2019). Novel development of nanoparticles to bimetallic nanoparticles and their composites: A review. *Journal of King Saud University-Science*, *31*(2), 257-269.

Shah, S. N., Steinmetz, N. F., Aljabali, A. A., Lomonossoff, G. P., and Evans, D. J. (2009). Environmentally benign synthesis of virus-templated, monodisperse, iron-platinum nanoparticles. *Dalton Transactions*, (40), 8479-8480.

Shao, Y., Wu, C., Wu, T., Yuan, C., Chen, S., DIng, T., and Hu, Y. (2018). Green synthesis of sodium alginate-silver nanoparticles and their antibacterial activity. *International Journal of Biological Macromolecules*, *111*, 1281-1292.

Singh, J., Dutta, T., Kim, K. H., Rawat, M., Samddar, P., and Kumar, P. (2018). 'Green'synthesis of metals and their oxide nanoparticles: applications for environmental remediation. *Journal of Nanobiotechnology*, *16*, 1-24.

Sreelakshmy, V., Deepa, M. K., and Mridula, P. (2016). Green synthesis of silver nanoparticles from Glycyrrhiza glabra root extract for the treatment of gastric ulcer. *Journal Dev Drugs*, *5*(2), 152.

Sun, Q., Li, W., Li, H., Wang, X., Wang, Y., and Niu, X. (2017). Preparation, characterization and anti-ulcer efficacy of sanguinarine loaded solid lipid nanoparticles. *Pharmacology*, *100*(1-2), 14-24.

Suri, S. S., Fenniri, H., and Singh, B. (2007). Nanotechnology-based drug delivery systems. *Journal of Occupational Medicine and toxicology*, *2*, 1-6.

Tai, C. Y., Tai, C. T., Chang, M. H., and Liu, H. S. (2007). Synthesis of magnesium hydroxide and oxide nanoparticles using a spinning disk reactor. *Industrial and Engineering Chemistry Research*, *46*(17), 5536-5541.

Tang, W. W., Zeng, G. M., Gong, J. L., Liang, J., Xu, P., Zhang, C., and Huang, B. B. (2014). Impact of humic/fulvic acid on the removal of heavy metals from aqueous solutions using nanomaterials: a review. *Science of the Total Environment*, *468*, 1014-1027.

Taniguchi, N. (1974). On the basic concept of'nano-technology'. In *Proc. Intl. Conf. Prod. Eng. Tokyo, Part II, 1974*. Japan Society of Precision Engineering.

Thakkar, K. N., Mhatre, S. S., and Parikh, R. Y. (2010). Biological synthesis of metallic nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *6*(2), 257-262.

Tsukamoto, R., Muraoka, M., Seki, M., Tabata, H., and Yamashita, I. (2007). Synthesis of CoPt and FePt3 nanowires using the central channel of tobacco mosaic virus as a biotemplate. *Chemistry of Materials*, *19*(10), 2389-2391.

Venkataraman, S. (2022). Plant molecular pharming and plant-derived compounds towards generation of vaccines and therapeutics against coronaviruses. *Vaccines*, *10*(11), 1805.

Vijayan, R., Joseph, S., and Mathew, B. (2018). Indigofera tinctoria leaf extract mediated green synthesis of silver and gold nanoparticles and assessment of their anticancer, antimicrobial, antioxidant and catalytic properties. *Artificial Cells, Nanomedicine, and Biotechnology*, *46*(4), 861-871.

Vrublevskaya, V. V., Afanasyev, V. N., Grinevich, A. A., Skarga, Y. Y., Gladyshev, P. P., Ibragimova, S. A., and Morenkov, O. S. (2017). A sensitive and specific lateral flow assay for rapid detection of antibodies against glycoprotein B of Aujeszky's disease virus. *Journal of Virological Methods*, *249*, 175-180.

Widatalla, H. A., Yassin, L. F., Alrasheid, A. A., Ahmed, S. A. R., Widdatallah, M. O., Eltilib, S. H., and Mohamed, A. A. (2022). Green synthesis of silver nanoparticles using green tea leaf extract, characterization and evaluation of antimicrobial activity. *Nanoscale Advances*, *4*(3), 911-915.

Youssef, F. S., Ismail, S. H., Fouad, O. A., and Mohamed, G. G. (2024). Green synthesis and Biomedical Applications of Zinc Oxide Nanoparticles. Review. *Egyptian Journal of Veterinary Sciences*, *55*(1), 287-311.

Young, M., Debbie, W., Uchida, M., and Douglas, T. (2008). Plant viruses as biotemplates for materials and their use in nanotechnology. *Annual Review Phytopathology*, *46*(1), 361-384.

Yurkov, A. M., Kemler, M., and Begerow, D. (2011). Species accumulation curves and incidence-based species richness estimators to appraise the diversity of cultivable yeasts from beech forest soils. *PLoS One*, *6*(8), e23671.

Zhang, D., Ma, X. L., Gu, Y., Huang, H., and Zhang, G. W. (2023). Green Synthesis of Metallic Nanoparticles and Their Potential Applications to Treat Cancer.

Zoroddu, M. A., Medici, S., Ledda, A., Nurchi, V. M., Lachowicz, J. I., and Peana, M. (2014). Toxicity of nanoparticles. *Current Medicine Chemistry*, *21*(33), 3837-3853

Chapter 11

Nanoparticles in Targeted Drug Delivery and Therapeutics

Amina Iqbal[1], Ume Habiba Firdous[1], Iram Shahzadi[2], Kashif Hussain[3], Abdullah Saghir Ahmad[4], Sehrish Kiran[5], Salena Ahmad[6], Muhammad Usman[3], Idrees Raza[3], Rana Muhammad Shahbakht[3], Muhammad Umair Waqas[3] and Ali Haider[3]*

[1]Department of Zoology, Wildlife and Fisheries, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, 66000, Multan, Punjab, Pakistan
[2]School of Pharmacy, University of Management and Technology, Lahore, Punjab, Pakistan
[3]Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, 66000, Multan, Punjab, Pakistan
[4]Department of Parasitology, Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
[5]Department of Chemistry, Faculty of Science and Technology, Lahore College for Women University, Jail Road, Lahore, Pakistan
[6]Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
*Corresponding author: ali.haider@mnsuam.edu.pk

ABSTRACT

Numerous scientific domains can benefit greatly from nanotechnology. Nanoparticles are fundamental building components of nanotechnology. Recent developments in nanotechnology have demonstrated enormous potential of nanoparticles in medicinal applications. Because of their high carrier capacity, capacity to establish ligand-stabilized connections, and ease of obligatory molecules that are both hydrophilic and hydrophobic, nanoparticles are an advantageous platform for targeted and monitored administration disease-related micro and macromolecules treatment. The problems by conventional therapy are solved when therapeutic chemicals are mixed with nanoparticles (protein, nanogels, carbon nanotubes, quantum dots, nano-medicines); however, some issues as toxicity and side effects are still up for debate and should be carefully considered before being used in biological systems. Therefore, it's critical to comprehend unique characteristics of medicinal nanoparticles as well as methods of distribution. Here, we give an explanation of the special qualities that nanoparticles in biological systems possess. In this discussion, we will focus on the kind of therapeutically utilized nanoparticles, their specificity for therapeutic purposes, and their current delivery approaches for various illnesses like infectious, cancer, and cardiovascular, autoimmune, neurological, pulmonary, and ophthalmic disorders. Acquiring knowledge about properties of nanoparticles and how they interact with the biological environment can help us develop new approaches for analysis, treatment, and prevention of many ailments, especially those that are incurable.

KEYWORDS
Nanoparticles, Targeted delivery, Therapeutic NP, Disease, Treatment

Received: 17-May-2024
Revised: 18-Jul-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Iqbal A, Firdous UH, Hussain K, Ahmad AS, Kiran S, Ahmad S, Usman M, Raza I, Shahbakht RM, Waqas MU and Haider A, 2024. Nanoparticles in targeted drug delivery and therapeutics. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 79-93. https://doi.org/10.47278/book.CAM/2024.232

INTRODUCTION

The features of nanoparticles (1–100 nm) make them appropriate for use in medicine. These substances are sufficiently tiny to get into the appropriate tissues within the body, bind selectively to the target cell, and circulate with ease. The main aim of producing nanoparticles as provision system is to transmit active therapeutic compounds during treatment by controlling the particle size, surface characteristics, and effective release without causing side effects. The ability to construct multifunctional nano systems for simultaneous diagnosis and treatment is made possible by availability of nanoparticles known as thermo nucleic nanoparticles exhibiting both therapeutic and diagnostic properties concurrently (Anani et al.,2021; Kandasamy and Maity, 2021; Lu, 2022). Theranostic nanoparticles are perfect for biomedical applications because of number of attributes, including sufficient drug delivery, fast clearance, no negative effects on other organs, precise and rapid distribution, and comprehensive morphological and biochemical properties of targeted spot (Jokerst and Gambhir, 2011).

Drug efficacy and side effect reduction can be achieved through nanoparticle engineering with unique surface characteristics that allow them to aim for diseased cells, avoiding those that are healthy (Huang et al., 2010). Furthermore, nanoparticles can be engineered to release their contents in an appropriate manner, enabling long-term, continuous

medication delivery (Bajpai et al., 2018). The utilization of nanoparticles (NPs) in the pharmaceutical sector has experienced a significant surge in past few years. This can be attributed to their smaller size, which facilitates their easy penetration of cellular plasma membranes through cellular endocytic mechanisms (Zhang et al., 2015; Torrano et al., 2016). Numerous nanomaterials and nano-carriers have had their anticancer capabilities investigated in recent years. Old nano-medicine based cancer treatments are still in use to cause unwanted immunotherapeutic and photochemical effects (e.g., responses to inflammation, both acute and chronic) despite the previously mentioned properties, benefits, medical uses and NPs' improvements in cancer diagnosis and therapy that is, if NPs are not effectively functionalized for medicinal purposes (Braakhuis et al., 2014; Jeong et al., 2022). Preclinical and clinical research continues to recommend a comprehensive examination of NPs prior to their regular therapeutic usage (Desai, 2012; N.-Y. Lee et al., 2019; Ramos et al., 2022).

Recent advances in biomedical science have successfully improved the design of therapeutic medicines for the treatment of disease. The transport of therapeutic chemicals towards target location stands in the way of effectiveness of treating numerous diseases. Common therapeutic drugs have drawbacks including inadequate bio-distribution, unfavorable side effects, minimal efficacy, and non-selectivity (Kadam et al., 2012). Thus, the design of multifunctional, well-controlled delivery systems is main focus of current research efforts.

Delivering a variety of compounds to specific parts of the body through the association of therapeutic medicines with nanoparticles that have distinctive biologic and physicochemical characteristics engineering their paths for appropriate directing is auspicious strategy (Jahan et al., 2017). Delivering a variety of compounds to specific parts of the body through the association of therapeutic medicines with nanoparticles that have distinctive physicochemical and biologic characteristics and engineering their paths for appropriate targeting is a promising strategy. By improving the therapeutic agents' efficacy and/or tolerance in biological systems, raising their concentration at the target area also raises their therapeutic index. Combining water-insoluble medicinal compounds with nanoparticles can enhance their bioavailability and shield them from physiological obstacles. Conversely, when therapeutic nanoparticles are associated with contrast agents, it becomes possible to monitor their delivery location and track their journey in in vivo systems. The preceding advantages make it possible to use targeted therapeutic nanoparticles in a variety of medical specialties. In this paper, we outlined the physicochemical characteristics of nanoparticles that make them essential tools in nanomedicine and reviewed the past ten years of research on therapeutic nanoparticles and their targeted delivery uses in a range of illnesses, including cancer and neurological diseases (Yetisgin et al., 2020).

Nanoparticles as Nano-medicines

Numerous domains within nano-medicine, including medication and imaging, diagnostics, and gene delivery have included nanotechnology (Thakur et al., 2015; Martinho et al., 2011). The term "drug delivery" (DD) describes the procedures, formulations, technologies, and methods used to move pharmacological substances through body in order to provide intended therapeutic effect (Mohammad et al., 2017). It includes methods of delivering medication to both humans and animals in order to achieve therapeutic efficacy. The focus of recent advancements in drug delivery systems (DDSs) has mostly been on smart DDSs, which aim to administer drugs at the right time, dosage, and place for optimal safety and efficacy (Thakur et al., 2015).

The use of personalized medication designs and dosage adjustments in precision medicine has significantly altered the context of cancer treatment. It is possible to precisely alter a medication's absorption properties, how it behaves in target and nontarget tissues, and how it is administered in therapeutic combinations that work well together (Manzari et al., 2021). Among the intriguing uses of NPs in precision medicine include suppression or immuno-activation, intracellular targeting, genome engineering (Mitchell et al., 2021). Targeted-delivery nano-medicines can be made with varied variety of nanoparticles (NPs), due to their conjugated polymers, polymeric micelles, distinctive structural characteristics, polymeric, liposomes, and dendrimers. Particularly in the context of cancer treatment, numerous issues pertaining to drug-targeting techniques for irrefutable application have been found, studied, and determined. Integrating knowledge with technical advancements and multidisciplinary research could pave the path for the introduction of safer nano-medicine (Tewabe et al., 2021).

Types of Therapeutic Nanoparticles

Metallic Nanoparticles (NPs)

Therapeutic agents can be disseminated in a polymer carrier matrix, encased in a polymer shell, covalently bonded or adsorbed to the particle surface, or contained within a structure in solid colloidal particles with sizes ranging from 10 to 1000 nm are known as metallic nanoparticles for drug delivery (Brigger et al., 2002; Kroll et al., 2009; Sahoo and Labhasetwar, 2003). By avoiding multidrug resistance, site specificity, effectively delivering therapeutic agents and enhancing, metallic nanoparticles aim to raise the therapeutic index of pharmaceuticals (Brannon-Peppas and Blanchette, 2004; Byrne et al., 2008).

Metallic nanoparticles can carry large doses of drugs, outcomes in great concentrations of anticancer medications at the targeted location. This avoids harmfulness and other painful side effects that arise from high drug concentrations in other parts of the body, and is the main reason why metallic nanoparticles are useful as cancer therapy probes (A. H. Lu et al., 2007). Cancer therapy might be carried out both within cells and within sub cells with use of metallic nanoparticles, which would significantly boost therapeutic efficacy and decrease adverse effects (M. Z. Ahmad et al., 2010).

Bimetallic Nanoparticles

Numerous uses for bimetallic nanoparticles have been reported in the medical field, including bio-imaging, cancer therapy, antibacterial, antioxidant, and anti-diabetic medication delivery. Because of their strong magnetic characteristics, gold based Au–Fe and nickel based Ni–Co bimetallic nanoparticles suitable for use as contrast agents in CT and MRI imaging tests for diagnosis and prognosis (Amendola et al., 2014) and a tumor-targeting theranostic agent (Y. Lu et al., 2022). Cu–Fe has also been applied to improved chemodynamic treatment (Koo et al., 2022), Ag-Cu, Au-Pt, Pd-Pt, and Au-Co have all been utilized for anticancer activities and cancer therapies (Garfinkel et al., 2022; H. Yang et al., 2022; Koyyati et al., 2022; Oladipo et al., 2020; Seifi et al., 2020). Additionally, Au-Bi has been utilized to suppress tumor cells (He et al., 2021). Human health concerns have been raised by heavy metal ion contamination of water sources and dye emission from numerous industries worldwide. It is well recognized that dyes released by companies are harmful to human organs like the liver and kidney (Ge et al., 2018). But water bodies must be cleaned up and made free of many kinds of pollution. For this, bimetallic nanoparticles have been employed (Idris and Roy, 2023). Nano-chips, nano-sensors, nano-coating, and nano semiconductors, have all been created using bimetallic nanoparticles. For instance, bimetallic nanoparticles of Pd–Au, Au–Cu, Pd–Ru, Fe–Mn, Co–Ni, Ag–Cu, Au–Pt, Au–Ag, Cu–Sn, and Ag–Cu have been utilized to create biosensors and detectors that are able to detect dimethoate (Ansari et al., 2018), evaluate milk samples for Salmonella typhimurium (Sohrabi et al., 2022), and hydrazine (Amiripour et al., 2018) as well as anti-inflammatory drug 4-aminoantipyrine (Saeed et al., 2022), anti-cancer drug (Sravani et al., 2022), favipiravir (Mehmandoust et al., 2021), luteolin (Tang et al., 2022), diclofenac (Eteya et al., 2019), coal mine gases sensor (W. Zhang et al., 2022), and glucose in serum (Huan et al., 2022).

Green Nanoparticles

Emerging uses for green synthesized metal and metal oxide nanoparticles in biomedical field include immunotherapy, regenerative medicine, dentistry, wound healing, tissue treatment, and bio sensing platforms (Pandit et al., 2022). Significantly more beneficial impacts of silver nanoparticles include their anticancer characteristics, broad spectrum antibacterial response, non-toxicity, and other therapeutic uses (Cadinoiu et al., 2022; Safaya and Rotliwala, 2022; Y. Yang et al., 2022). Natural form Au nanoparticles produced using green synthesis. Complementing photosensitizers with gold-based nanoparticles can enable photodynamic antimicrobial chemotherapy (Hossain et al., 2022; Shivaramakrishnanet al., 2017). Furthermore, a different study found that elemental mercury was removed from soil and air by using green synthesized selenium nanoparticles, which also work to remove heavy metals (zinc, copper, and nickel) from soil (Ramezani et al., 2021; X. Wang et al., 2018; Zohra et al., 2021). Medicine using selenium nanoparticles is a significant bio therapeutic agent that has no negative effects (Hosnedlova et al., 2018).

Polymeric Nanoparticles

Lipid-based compounds like liposomes and polymeric-based particles like polymeric micelles, dendrimers, and polymer/drug composites make up the majority of drug-delivery nanoparticles (Jokerst and Gambhir, 2011; Lin et al., 2019). Due to the discovery of the special qualities of polymer nanoparticles, polymeric nanoparticles have gained favour over other nanoparticles in recent years. They are a good choice for creating theranostic nanosystems. The benefits of these nanoparticles include medication release control, biodegradability, biocompatibility, and flexibility for hydrophobic and hydrophilic payloads (Ferrari et al., 2018).

Uniform spherical shapes, polymer nanospheres range in size from 10 to 200 nm (Hosseini et al., 2023). Nanospheres are utilized as substitute carriers for the administration of imaging and anti-cancer medicines (Elkharraz et al., 2006; Grayson et al., 2005; Liu et al., 2009; Ranganath and Wang, 2008). It has been written that drug-loaded nanospheres can be modified with ligands for specific therapy. Nanospheres of wheat germ agglutinin (WGA), for instance, have been utilized to identify N-acetylglucosamine and sialic acid shown in prostate cancer cells (Xie et al., 2007). Typically, polymeric micelles have a size of less than 100 nm. Many studies have focused on polymeric micelles because of their ideal properties, which include tissue penetration, biocompatibility, nano-size, high stability, low toxicity, in physiological conditions, high drug concentration in the target site, high loading capacity, free control property, and the potential for ultimate functionalization of the group target ligand composition (Arshad et al., 2020; Rana and Sharma, 2019; Yadavet al., 2019; Y. Zhang et al., 2014). Novel type of polymeric materials known as dendrimers are huge molecules having a structure like a tree with branches or arms that are symmetrical in the center, interior portion, and external shell. These structures are composed of Units of symmetric branching that remain arranged around central linear polymer core or tiny molecule. Having just emerged as a class of nanoscale macromolecules utilized as carriers, their unique advantage in precision structural engineering makes their emerging applications in cancer treatment and bio imaging particularly noteworthy (Fréchet, 2003; Larson and Ghandehari, 2012; Pearson et al., 2012).

Micelles

Water-insoluble medicinal compounds are mostly delivered systemically by polymeric micelles. They form as aggregates in solution and have a size of less than 100 nm. Their excellent stability in physiological systems is ensured by their hydrophilic surface, which also helps to protect them against nonspecific uptake by reticulo-endothelial system. As a result, dynamic structure of polymeric micelles offers a significant therapeutic agent delivery

mechanism that enables a range of loading capacities, controlled ligand conjugation, and a decreased rate of dissolution (Z. Ahmad et al., 2014).

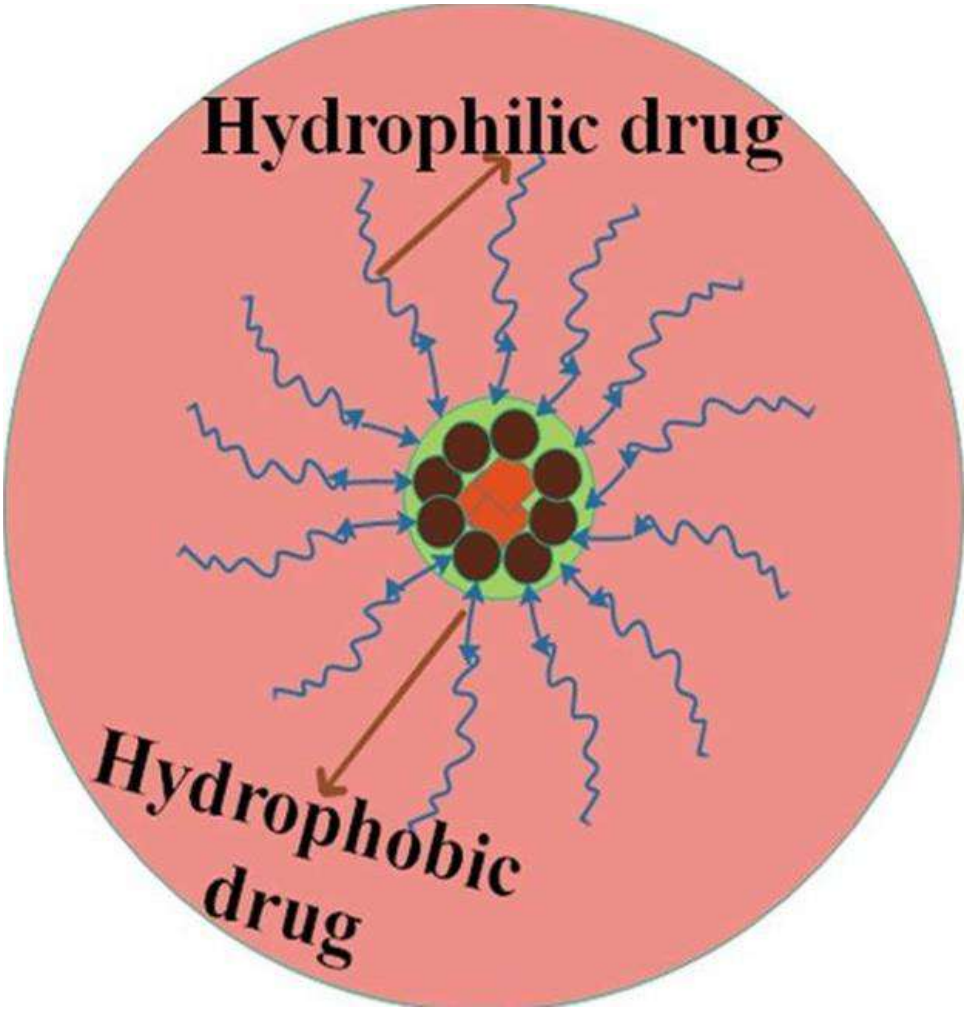


Fig. 1: Diagrammatic depiction of polymeric micelles structure

Nanosheets

The scientific world has been very interested in two-dimensional (2D) nanosheets ever since graphene was discovered in 2004 (Novoselov et al., 2004). Due to their special qualities, 2D nano-sheets can be helpful in several biological research areas, such as the transfer of nucleic acids for gene therapy (Choi et al., 2018). The first known carbon-based 2D nanomaterial is grapheme (Ge et al., 2018). To our knowledge, this work is the first that describes GO-based nano-carriers used for photo thermal and gene therapy was made by (Feng et al., 2013). Yin et al. introduced multifunctional GO nano-sheets that have the capacity to target cancer in addition to performing gene and photo thermal therapy concurrently (Yin et al., 2017).

Discovered in 2014, Black phosphorus (BP) is a recently discovered kind of 2D nano-sheet that has been thoroughly explored in the last few years (L. Li et al., 2014). Because of its biocompatibility, it has been thought to offer significant deal of potential for biological applications (Qian et al., 2017). Chemo/gene/photothermal therapy mediated by BP nano-sheets demonstrated a novel approach to overcome medication resistance in cancer (Kim et al., 2020).

Carbon Nanotubes

One way to characterize carbon nanostructures (CNSs) is as a very practical class of nanostructure. As a subset of smart nano-carriers made completely of carbon, carbon nanotubes (K. P. Loh et al., 2018). In addition to offering a wide range of potential advantages, such as the encapsulation of both hydrophobic and hydrophilic molecules, which improves drug stability and enables site-specific administration, nanostructures can be applied to the targeted delivery of pharmaceuticals (Niezabitowska et al., 2018). One important area of CNT use is functionalization in applications in biology through a variety of techniques. These techniques are crucial because they not only make the CNTs stable and biocompatible in the biological environment, but also allow them to combine or conjugate with different biomolecules, therapeutic agents, and diagnostic devices to produce accurate, cost-effective, and therapeutic systems (Kumar et al., 2014; Rogers-Nieman and Dinu, 2014). Using nanotubes as a drug delivery system, cancer is treated (Inoue et al., 2009). CNTs are frequently employed as nanocarriers for anti-tumor drugs, such as camptothecin, doxorubicin, methotrexate, and cisplatin. In particular, cisplatin has been utilized as a treatment for a number of conditions related to cancer (Saleemi et al., 2020).

These CNTs' primary function is to preserve the structural integrity of the pharmaceuticals, as encapsulation or "endohedral modification" frequently reduces the rate at which pharmacological substances degrade in order to maximize drug release under carefully monitored conditions (Perry et al., 2011). Because hydrophobic and capillary forces are what drive the encapsulation of pharmaceuticals, this technique works best with medications that have a lower surface tension. For instance, gold nanoparticles are used in the fabrication of oxidized carbon nano-bottles to inhibit the uncontrolled release of the medicine that is enclosed (cisplatin) (J. Li et al., 2012), as shown in Fig. 2.

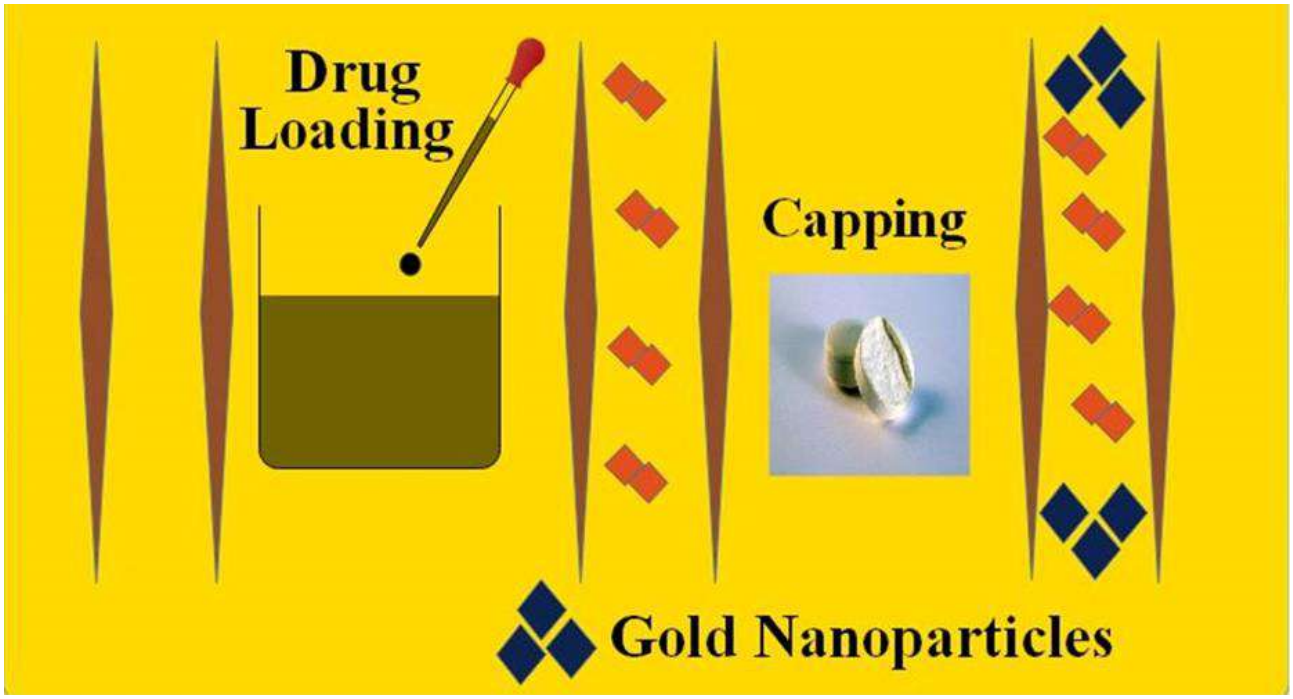


Fig. 2: Carbon nanobottle synthesis, in which the ends of the encased carbon nanotubes are made of gold nanoparticles.

Nanogels

Hydrogels with a sub micrometer particle size ranging from 20 to 250 nm and a three-dimensional (3D) tunable porous structure are known as nanogels, and they are a type of systemic drug delivery carrier. They are characterized by their particle size range of 1 to 350 μm, which sets them apart from hydrogels that develop in situ and facilitate local delivery (Jiang et al., 2014). Unlike ordinary nanoparticles (NPs), nanogels possess customizable particle size, shape, and sensitivity to various external stimuli such as temperature, pH, redox conditions, ionic strength, and others, which enables them to have excellent controlled drug release properties (Sahiner et al., 2006). One of the main obstacles to effective drug delivery to cancer cells and better clinical results in cancer therapy is drug resistance. Hyaluronate (HA) nanogels carrying doxorubicin and cisplatin have been developed to reverse drug resistance, according to (Ma et al., 2021). The purpose of the nanogel's design was to keep the cancer cells' medication concentrations at their ideal levels. The assessment of the nanogels demonstrated their potential for reversing drug resistance (Attama et al., 2022).

Quantum Dots

Due to their special qualities, Quantum dots (QDs), which are semiconductor nano-crystals, are a preferred nano-carrier for chemotherapeutic drugs above other kinds (Field et al., 2018). Because of its size and characteristics, QDs are widely used in therapeutic applications. Additionally, due to QDs' exceptional physical, optical, and exciting electrical properties, they are used in a variety of other applications, including tissue engineering, bio imaging, cancer treatment, photo thermal therapy, bio sensing, preventing bioterrorism, and most notably drug delivery (Duan et al., 2019). Numerous anticancer medications today exhibit undesirable traits in clinical trials, including inadequate targeting, toxicity, and lack of selectivity. It is anticipated that recent advancements in QDs, therapy-based multifunctional nanoparticle medicines, and their drug delivery to the target organ would have an impact on cancer detection and treatment (Badılı et al., 2020).

QDs are useful agents for medication delivery tailored to the microenvironment. For this reason, graphene QDs were assessed by (Wei et al., 2018). GQDs can be used to achieve classic cell visualization using tailored high quality PL colors and images but their lack of cell selectivity makes it difficult to extract cellular-level information from molecules. Targeted imaging was suggested by researchers as a possible substitute for cell identification and detection. This can be accomplished by adding specific groups and polymers to the surface of GQDs to increase their internalization efficiency. According to published research, the most popular cell targeting substances are arginine−glycine−aspartic acid (RGD), folic acid (FA), proteins, and even hyaluronic acid (HA) (D. Zhang et al., 2018; J.-E. Lee et al., 2013; S. Li et al., 2017; Zheng et al., 2013). Through endocytosis, FA demonstrates a strong affinity for folate receptor (FR) found upon the exterior of

different human cancerous cells (Biswas et al., 2021), as shown in Fig. 3. These nanoparticles have additional benefits in that they can be employed to the manufacture of sensitive sensors. For industrial and clinical research, the sensitive, selective, dependable, quick, and affordable drug analysis approach is essential (Badılı et al., 2020).

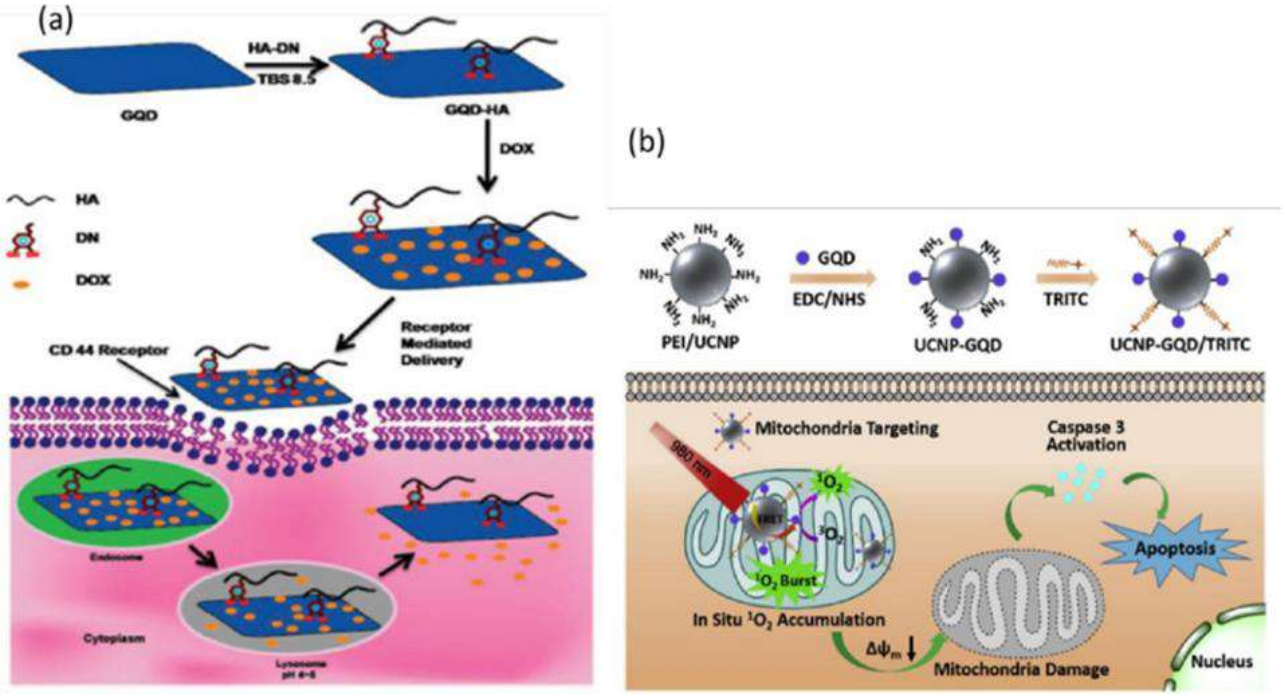


Fig. 3: a): Hyaluronic acid (HA) is used to target deliver GQDs, and the medicine is then released from the surface of the GQD into an environment of tumor cells. Copyright 2021 American Chemical Society. b): Diagram demonstrating the synthesis of UCNP-GQD/TRITC with mitochondria-targeting effectiveness. Tumor cell death can be triggered very effectively by an in situ $^1O_2$ burst in mitochondria upon laser irradiation. Copyright 2021 American Chemical Society.

Protein NP

Nanotechnology has shown enormous impending in the arena of medicine (Kamaly et al., 2012; Shi et al., 2011). The use of nanoparticle technology in protein delivery can: 1, shield proteins in the biological environment against early deterioration or denaturation; 2, increase the shelf life of proteins having poor pharmacokinetic properties in the circulatory system; 3, regulate an adaptable, steady release that keeps the drug's application inside medicinal range; and 4, target damaged cells, tissues, and intracellular spaces to increase the safety and effectiveness of biologic therapies. The investigation of nanoparticle technologies for protein delivery has been made possible by the notable success of small-molecule nanoparticle formulations of daunorubicin (DaunoXome), doxorubicin (Doxil and Myocet), amphotericin B (Ambisome), and paclitaxel (Abraxane) (Peer D et al., 2007).

Nanoparticles Characteristics for Therapeutics

New and improved nanomaterials for biomedical applications have been created attributable to advances in nanotechnology (Dessale et al., 2022). Because of their distinct qualities, NPs are used in variety of presentations (Machado et al., 2014). The capabilities of multifunctional nanoparticles (NPs) include transportation of hydrophobic compounds, active and passive targeting of disease cells, prolongation of drug circulation, enhancement of drug entry and accumulation at tumor sites, mitigation of drug resistance, augmentation of medication safety and tolerability, and advancement of other technological fields (Q. Yang et al., 2014; Zeineldin and Syoufjy, 2017).

Size

Another significant element influencing circulation and bio distribution of medicinal nanoparticles is size. Particles bigger than 200 nm may be removed by phagocytic cells in reticulo-endothelial system (RES), but smaller particles can be readily removed by physiological processes (percolation over kidney). As a result, therapeutic nanoparticles smaller than 100 nm circulate in the bloodstream over an extended duration. Numerous investigations revealed that because therapeutic nanoparticles in 20–200 nm size range are not recognized by RES and cannot be filtrated by kidney, exhibit a greater accumulation rate in tumors (Bhatia and Bhatia, 2016; Ernsting et al., 2013; W. Wu et al., 2018). In addition, compared to normal tissues, quantity and volume of blood vessels are greater in tumor sites. Therefore, increased permeability and retention (EPR) effect occurs when nanoparticles of the right size are able to enter the tumor area relatively quickly and remain there for a longer period of time (Nakamura et al., 2016; Fang et al., 2011).

Surface Charge

The expulsion and targeted delivery of therapeutic nanoparticles are significantly influenced by their surface charge. When associated to neutral or negatively charged nanoparticles, positively charged nanoparticles elicit stronger immunological response. Furthermore, it has been demonstrated that nanoparticles with an exterior potential of between -10 and +10 mV are less prone to non-specific interactions and phagocytosis (Bhatia and Bhatia, 2016; Ernsting et al., 2013). The substance of the nanoparticles, however, may determine the optimal range. The surface charge of nanoparticles and their sensitivity to pH are also strongly connected. These nanoparticles can be made to identify and localize themselves in particular cell partitions. To release their payload, acidic nanoparticles can be directed towards endosomes or lysosomes, which have a pH of less than 6.0 (Casey et al., 2010; W. Wu et al., 2018; C. Wang et al., 2017).

Surface Modifications

PEG is an ideal polymer for therapeutic nanoparticles because of its inherent physicochemical characteristics, which lessen phagocytic absorption and limit aggregation in non-target regions (Walkey et al., 2012). Therapeutic nanoparticle PEGylation should take into account factors that affect surface hydrophilicity and phagocytosis, such as PEG chain length, shape, and density. Target-specific delivery of PEGylated nanoparticles can be enhanced by conjugating targeting ligands to their surface; however, this also has an impact on the nanoparticles' bio-distribution (Yetisgin et al., 2020), as shown in Fig. 4.

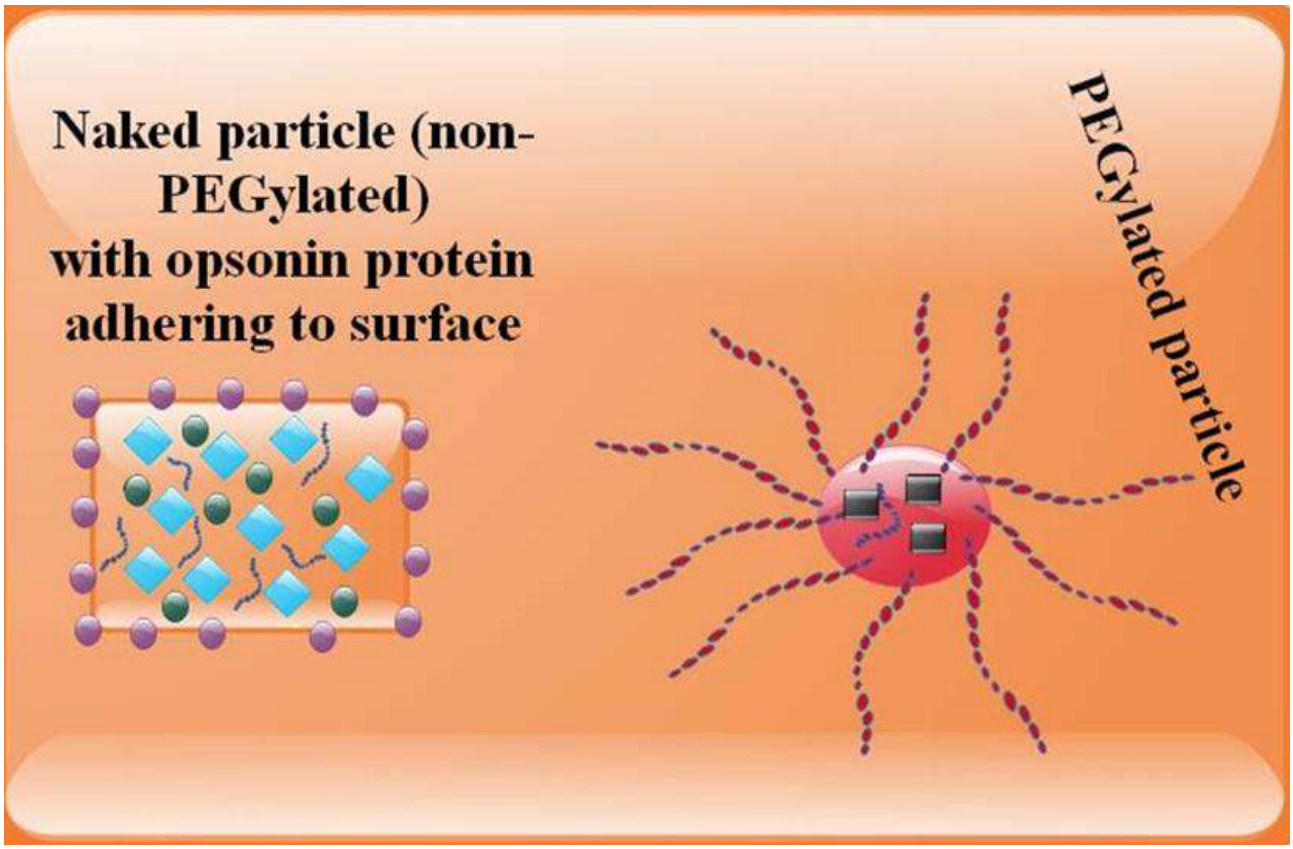


Fig. 4: PEG offers stealth. PEGylation of particles can be used to mask surface characteristics and balance the net charge, which will lessen the likelihood that opsonin proteins will bind to them and that macrophages will eventually clear them. This tactic can increase how long particles circulate within the body.

Nanoparticles Application in Therapeutics

Distinct advantages of nanotechnology for imaging, diagnostics, and medication administration, additionally its potential for developing synthetic vaccines, tiny medical devices, and therapeutic properties of certain nano-materials themselves, have made it increasingly popular for use in cancer treatment. Many therapeutic nanoparticle (NP) stages, including liposomes, polymeric micelles, and albumin NPs, have been accepted for use in the treatment of cancer (Shi et al., 2017). NPs are used in medical applications due to their unique properties, which include their quantum nature, higher surface-to-mass ratio than other particles, and ability to absorb and transport other molecules like proteins and drugs. The composition of NPs can vary greatly as they can start with dextran, chitosan, phospholipids, biological lipids, lactic acid, or other substances like metals, carbon, silica, or other polymers (Guo et al., 2013; Jani et al., 2020; Mukherjee and Bhattacharyya, 2020; Nikolova, 2020; Saxena et al., 2020).

Cancer

A major cause of death and burden on world health is cancer. By 2018, it was predicted that there would be 9.6 million cancer-related deaths and 18.1 million new cancer cases (Bray et al., 2018). Uncontrolled cell growth, which begins at one focal site and spreads to other parts of the body until it kills, is hallmark of disease known as cancer. Nanotechnology has yielded some promising results in detection and treatment of cancer, including the administration of medication (Hu et al., 2016), targeted therapy, molecular imaging, biomarker mapping, drug carriage, gene therapy, and detection and diagnostics (Tran et al., 2017).

One essential feature of nano-carriers for drug delivery is their ability to preferentially target cancer cells, which increases therapeutic efficiency while shielding healthy cells from damage. The two main categories of targeting mechanisms are passive targeting and active targeting (Yao et al., 2020). The purpose of passive targeting is to take advantage of distinctions between normal and tumor tissue. When medications are successfully transported to target site, they can function therapeutically. This is known as passive targeting. The neovascularization caused by high cancer cell proliferation and increased perm selectivity of tumor vasculature relative to normal vessels are caused by big vascular wall pores (Carmeliet and Jain, 2000). Active targeting uses direct interactions between ligands and receptors to target cancer cells in particular. To differentiate between targeted and healthy cells, ligands on surface of NPs are specifically designed to target molecules that are expressed on surface of tumor cells (Kamaly et al., 2012; Shi et al., 2011). Receptor-mediated endocytosis is triggered by interaction between ligands on NPs and receptors on surface of cancer cells. This process enables internalized NPs to effectively release therapeutic medicines (Farokhzad and Langer, 2009).

Infectious Diseases

Transmissible illnesses brought on by infectious pathogens, including bacteria, viruses, fungi, and parasites, are referred to as infectious diseases. One of main concerns for global public health is infectious diseases, which cause millions of deaths annually, the majority of which take place in developing nations (Markwalter et al., 2018). The primary treatment strategy for infectious diseases involves the utilization of antimicrobial medications (Hillaireau and Couvreur, 2009; Sendi and Proctor, 2009). Liposomes that increase antimicrobial activity of medications and polymer-based and non-polymeric nanoparticles are examples of nano-delivery applications for the treatment of infectious disorders (Zazo et al., 2016). A broad-spectrum antibiotic called ciprofloxacin is recommended to treat lung infections. With LipoquinTM, ciprofloxacin liposome formulation, systemic effects of the high-dose antibiotics are avoided because it is intended for inhalation and has a 24-hour sustained release (Yetisgin et al., 2020).Similar to this, amphotericin B's related toxicity is intended to be decreased by the anti-fungal liposomal transporter Ambisome® (Walsh et al., 1999).

Liposomal amphotericin B is appropriate for much disseminated histoplasmosis or immuno-compromised patients with HIV infection because of its minimal systemic toxicity (Cornely et al., 2007). Medical gadgets are also adorned with antimicrobial nano-drugs to prevent the production of biofilms (L. Wang et al., 2017), for example, Ag-NPs in central venous catheters CVCs (K. Wu et al., 2015). Additionally, some nanoparticles like Verigene®, Silverline®, Acticoat™, or Endorem™ SPIONs are employed as medical devices or in diagnosis (Beal et al., 2013; Bozzuto and Molinari, 2015; Weissig et al., 2014).

Pulmonary Disease

Asthma, pulmonary tuberculosis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and idiopathic pulmonary fibrosis (IPF) are examples of pulmonary lung illnesses (Sugawara and Nikaido, 2014). Delivery systems based on nanoparticles enable increased bioavailability, reduction in dosage, regulated release, and frequency of treatment. Natural polymeric nanoparticles including chitosan, gelatin, and alginate, as well as synthetic polymers like PLGA, poloxamer, and PEG, are frequently utilized in creation of nanomedicine inhalation formulations (Lim et al., 2016; Yhee et al., 2016). Furthermore, pulmonary inhalation of polyamidoamine (PAMAM) dendrimers combined with anti-asthma beclometasone dipropionate (BDP) proved to be an effective method (Nasr et al., 2014).

Regenerative Therapy

Regenerative therapy is centered on creation and utilization of biocompatible materials that can augment tissue regeneration and repair through their inherent biological mechanisms. Using stem cells in therapy is one way to encourage the body's own repair or regeneration process (Yetisgin et al., 2020). Interest in creating and administering therapeutic nanoparticles directly to support bone regeneration has grown over time (Gera et al., 2017). One of treatment techniques based on nanoparticles and stimulation of osteoblasts for bone formation is the delivery of several growth factors (Kong et al., 2014; Ortega-Oller et al., 2015; Park et al., 2016; S. Zhang et al., 2010). Furthermore, another therapeutic approach in bone tissue is the nano-delivery of synthetic chemicals, which may inhibit osteoclasts, cells that break down bone. Because they encourage osteoclast apoptosis, bisphosphonate medications are frequently used to treat osteoporosis. Bisphosphonate medications have been delivered via variety of metallic nanoparticles, either polymeric or non-polymeric (Giger et al., 2013; X. J. Loh et al., 2016). In bone tissue, another method for using therapeutic nanoparticles is to lessen inflammation, especially in cases of extensive wounds (Warabi et al., 2001; Gonçalves et al., 2015).

Targeted Drug Delivery Application of NP

Targeted delivery is efficient administration of medicinal substance with focus on target location of accumulation. After spending ideal amount of time in physiological system, drug-loaded system should evade immune system, target specific cell or tissue, and release loaded medicine (Colombo et al., 2012). At present, much research is being done on targeted nanoparticle delivery as a cancer treatment. In clinical trials or now being evaluated in clinics, more than 20 per cent of therapeutic nanoparticles were created with anti-cancer purposes in consideration. Moreover, related studies have focused on using nanoparticles to treat a range of other conditions, such as viral, neurodegenerative, and autoimmune diseases (Baranwal et al., 2023).

Limitations and Disadvantages

The application of nanoparticles shows promise in treatment of wide range of illnesses, including glaucoma and cancer. Regrettably, there are certain drawbacks and restrictions associated with nano-medical techniques that rely on nanoparticle technologies. When employing nanoparticles in living things, there are number of factors to carefully consider, including their toxicity, ability to elude phagocytic system, avoid physiological barrier, and incite an immunological response (Ferrari, M. 2005). The propensity of smaller nanoparticles to aggregate presents another challenge. For example, micelles, dendrimers, and QDs of smaller sizes are more likely to aggregate, which leads to inadequate bio distribution (Angra et al., 2011; D. Li and Kaner, 2006; Rizvi and Saleh, 2018; Sadauskas et al., 2009).

When pharmaceuticals that are currently utilized in medical applications are mixed with therapeutic nanoparticles, medications gain new functions and improve treatment effectiveness. However, Manzoor et al. (2012) discovered that the heterogeneities of vascular permeability may limit medication concentration and penetration into tumor regions utilizing nanoparticle-based drug delivery methods. To get around the issue, they proposed a controlled delivery method utilizing drug-loaded liposomes that release the medication *in vitro* when exposed to ambient heat (Manzoor et al., 2012).

Future Perspectives

Nanoparticle-based treatments is at the core of nano-medicine, which is the medical field of the future. But before affluence, there is still a long way to go. Above all, it is crucial to look into the nanoparticles' long-term safety and toxicity. In the meanwhile, research on disease causes and novel medications will pave the way for the inclusion of safer and more effective nanoparticle-based treatments in patient regimens (Yetisgin et al., 2020).

Conclusions

The creation of therapeutic drugs based on nanoparticles has been subject of much research during past ten years, and nano-delivery systems are crucial for precisely targeting intended location in treatment of numerous illnesses. Nowadays, polymers or lipids make up majority of nanoparticles utilized in the targeted delivery method, despite of the fact that polymeric nanoparticles show promise for treating diseases. In addition, expense of producing nanomedicine and doing it on a greater scale is a significant issue that requires attention. Thus, by comprehending properties of nanoparticles and their connections with biological environment such as their targeting of receptors or mechanisms of action in the pathophysiology of disease, we will be able to get around obstacles and develop novel approaches for the diagnosis, treatment, and prevention of wide range of diseases, especially incurable ones. Nano-medicines, future of medicine, will be built on therapeutics based on nanoparticles. Nanoparticle-based treatments will become safer and more effective in patient regimens as a result of new pharmaceuticals and discoveries about causes of diseases.

REFERENCES

Ahmad, M. Z., Akhter, S., Jain, G. K., Rahman, M., Pathan, S. A., Ahmad, F. J., and Khar, R. K. (2010). Metallic nanoparticles: technology overview and drug delivery applications in oncology. *Expert Opinion on Drug Delivery, 7*(8), 927-942.

Ahmad, Z., Shah, A., Siddiq, M., and Kraatz, H.-B. (2014). Polymeric micelles as drug delivery vehicles. *Rsc Advances, 4*(33), 17028-17038.

Amendola, V., Scaramuzza, S., Litti, L., Meneghetti, M., Zuccolotto, G., Rosato, A., and Anselmi, C. (2014). Magneto-plasmonic Au-Fe alloy nanoparticles designed for multimodal SERS-MRI-CT imaging. *Small, 10*(12), 2476-2486.

Amiripour, F., Azizi, S. N., and Ghasemi, S. (2018). Gold-copper bimetallic nanoparticles supported on nano P zeolite modified carbon paste electrode as an efficient electrocatalyst and sensitive sensor for determination of hydrazine. *Biosensors and Bioelectronics, 107*, 111-117.

Anani, T., Rahmati, S., Sultana, N., and David, A. E. (2021). MRI-traceable theranostic nanoparticles for targeted cancer treatment. *Theranostics, 11*(2), 579.

Angra, P. K., Rizvi, S. A. A., Oettinger, C. W., and D'Souza, M. J. (2011). Novel approach for preparing nontoxic stealth microspheres for drug delivery. *European Journal of Chemistry, 2*(2), 125-129.

Ansari, Z., Saha, A., Singha, S. S., and Sen, K. (2018). Phytomediated generation of Ag, CuO and Ag-Cu nanoparticles for dimethoate sensing. *Journal of Photochemistry and Photobiology A: Chemistry, 367*, 200-211.

Arshad, M., Pradhan, R. A., Zubair, M., and Ullah, A. (2020). Lipid-derived amphiphilic delivery, biopolymer-based nanocarriers renewable for drug formulations: biomedical and food applications. *Biopolymer-Based Formulations:*

Biomedical and Food Applications, 283.

Attama, A. A., Nnamani, P. O., Onokala, O. B., Ugwu, A. A., and Onugwu, A. L. (2022). Nanogels as target drug delivery systems in cancer therapy: A review of the last decade. *Frontiers in Pharmacology, 13*, 874510.

Badılı, U., Mollarasouli, F., Bakirhan, N. K., Ozkan, Y., and Ozkan, S. A. (2020). Role of quantum dots in pharmaceutical and biomedical analysis, and its application in drug delivery. *TrAC Trends in Analytical Chemistry, 131*, 116013.

Bajpai, V. K., Kamle, M., Shukla, S., Mahato, D. K., Chandra, P., Hwang, S. K., and Han, Y.-K. (2018). Prospects of using nanotechnology for food preservation, safety, and security. *Journal of Food and Drug Analysis, 26*(4), 1201-1214.

Baranwal, J., Barse, B., Di Petrillo, A., Gatto, G., Pilia, L., and Kumar, A. (2023). Nanoparticles in cancer diagnosis and treatment. *Materials, 16*(15), 5354.

Beal, S. G., Ciurca, J., Smith, G., John, J., Lee, F., Doern, C. D., and Gander, R. M. (2013). Evaluation of the nanosphere verigene gram-positive blood culture assay with the VersaTREK blood culture system and assessment of possible impact on selected patients. *Journal of Clinical Microbiology, 51*(12), 3988-3992.

Bhatia, S., and Bhatia, S. (2016). Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. *Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae*, 33-93.

Biswas, M. C., Islam, M. T., Nandy, P. K., and Hossain, M. M. (2021). Graphene quantum dots (GQDs) for bioimaging and drug delivery applications: a review. *ACS Materials Letters, 3*(6), 889-911.

Bozzuto, G., and Molinari, A. (2015). Liposomes as nanomedical devices. *International Journal of Nanomedicine*, 975-999.

Braakhuis, H. M., Park, M. V., Gosens, I., De Jong, W. H., and Cassee, F. R. (2014). Physicochemical characteristics of nanomaterials that affect pulmonary inflammation. *Particle and Fibre Toxicology, 11*(1), 1-25.

Brannon-Peppas, L., and Blanchette, J. O. (2004). Nanoparticle and targeted systems for cancer therapy. *Advanced Drug Delivery Reviews, 56*(11), 1649-1659.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians, 68*(6), 394-424.

Brigger, I., Morizet, J., Aubert, G., Chacun, H., Terrier-Lacombe, M.-J., Couvreur, P., and Vassal, G. (2002). Poly (ethylene glycol)-coated hexadecylcyanoacrylate nanospheres display a combined effect for brain tumor targeting. *Journal of Pharmacology and Experimental Therapeutics, 303*(3), 928-936.

Byrne, J. D., Betancourt, T., and Brannon-Peppas, L. (2008). Active targeting schemes for nanoparticle systems in cancer therapeutics. *Advanced Drug Delivery Reviews, 60*(15), 1615-1626.

Cadinoiu, A. N., Rata, D. M., Daraba, O. M., Ichim, D. L., Popescu, I., Solcan, C., and Solcan, G. (2022). Silver nanoparticles biocomposite films with antimicrobial activity: In vitro and in vivo tests. *International Journal of Molecular Sciences, 23*(18), 10671.

Carmeliet, P., and Jain, R. K. (2000). Angiogenesis in cancer and other diseases. *Nature, 407*(6801), 249-257.

Casey, J. R., Grinstein, S., and Orlowski, J. (2010). Sensors and regulators of intracellular pH. *Nature Reviews Molecular Cell Biology, 11*(1), 50-61.

Choi, J. R., Yong, K. W., Choi, J. Y., Nilghaz, A., Lin, Y., Xu, J., and Lu, X. (2018). Black phosphorus and its biomedical applications. *Theranostics, 8*(4), 1005.

Colombo, M., Carregal-Romero, S., Casula, M. F., Gutiérrez, L., Morales, M. P., Böhm, I. B., and Parak, W. J. (2012). Biological applications of magnetic nanoparticles. *Chemical Society Reviews, 41*(11), 4306-4334.

Cornely, O. A., Maertens, J., Bresnik, M., Ebrahimi, R., Ullmann, A. J., Bouza, E., and Boehme, A. (2007). Liposomal amphotericin b as initial therapy for invasive mold infection: a randomized trial comparing a high–loading dose regimen with standard dosing (AmBiLoad Trial). *Clinical Infectious Diseases, 44*(10), 1289-1297.

Desai, N. (2012). Challenges in development of nanoparticle-based therapeutics. *The AAPS Journal, 14*(2), 282-295.

Dessale, M., Mengistu, G., and Mengist, H. M. (2022). Nanotechnology: a promising approach for cancer diagnosis, therapeutics and theragnosis. *International Journal of Nanomedicine*, 3735-3749.

Duan, Q., Ma, Y., Che, M., Zhang, B., Zhang, Y., Li, Y., and Sang, S. (2019). Fluorescent carbon dots as carriers for intracellular doxorubicin delivery and track. *Journal of Drug Delivery Science and Technology, 49*, 527-533.

Elkharraz, K., Faisant, N., Guse, C., Siepmann, F., Arica-Yegin, B., Oger, J., and Siepmann, J. (2006). Paclitaxel-loaded microparticles and implants for the treatment of brain cancer: preparation and physicochemical characterization. *International Journal of Pharmaceutics, 314*(2), 127-136.

Ernsting, M. J., Murakami, M., Roy, A., and Li, S.-D. (2013). Factors controlling the pharmacokinetics, biodistribution and intratumoral penetration of nanoparticles. *Journal of Controlled Release, 172*(3), 782-794.

Eteya, M. M., Rounaghi, G. H., and Deiminiat, B. (2019). Fabrication of a new electrochemical sensor based on AuPt bimetallic nanoparticles decorated multi-walled carbon nanotubes for determination of diclofenac. *Microchemical Journal, 144*, 254-260.

Fang, J., Nakamura, H., and Maeda, H. (2011). The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced Drug Delivery Reviews, 63*(3), 136-151.

Farokhzad, O. C., and Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano, 3*(1), 16-20.

Feng, L., Yang, X., Shi, X., Tan, X., Peng, R., Wang, J., and Liu, Z. (2013). Polyethylene glycol and polyethylenimine dual-functionalized nano-graphene oxide for photothermally enhanced gene delivery. *Small, 9*(11), 1989-1997.

Ferrari, R., Sponchioni, M., Morbidelli, M., and Moscatelli, D. (2018). Polymer nanoparticles for the intravenous delivery of anticancer drugs: The checkpoints on the road from the synthesis to clinical translation. *Nanoscale, 10*(48), 22701-22719.

Field, L. D., Walper, S. A., Susumu, K., Lasarte-Aragones, G., Oh, E., Medintz, I. L., and Delehanty, J. B. (2018). A quantum dot-protein bioconjugate that provides for extracellular control of intracellular drug release. *Bioconjugate Chemistry, 29*(7), 2455-2467.

Fréchet, J. M. (2003). Dendrimers and other dendritic macromolecules: From building blocks to functional assemblies in nanoscience and nanotechnology. *Journal of Polymer Science Part A: Polymer Chemistry, 41*(23), 3713-3725.

Garfinkel, D. A., Tang, N., Pakeltis, G., Emery, R., Ivanov, I. N., Gilbert, D. A., and Rack, P. D. (2022). Magnetic and Optical Properties of Au–Co Solid Solution and Phase-Separated Thin Films and Nanoparticles. *ACS Applied Materials and Interfaces, 14*(13), 15047-15058.

Ge, L., Wang, W., Peng, Z., Tan, F., Wang, X., Chen, J., and Qiao, X. (2018). Facile fabrication of Fe@ MgO magnetic nanocomposites for efficient removal of heavy metal ion and dye from water. *Powder Technology, 326*, 393-401.

Gera, S., Sampathi, S., and Dodoala, S. (2017). Role of nanoparticles in drug delivery and regenerative therapy for bone diseases. *Current Drug Delivery, 14*(7), 904-916.

Giger, E. V., Castagner, B., and Leroux, J.-C. (2013). Biomedical applications of bisphosphonates. *Journal of Controlled Release, 167*(2), 175-188.

Gonçalves, R. M., Pereira, A. C. L., Pereira, I. O., Oliveira, M. J., and Barbosa, M. A. (2015). Macrophage response to chitosan/poly-(γ-glutamic acid) nanoparticles carrying an anti-inflammatory drug. *Journal of Materials Science: Materials in Medicine, 26*, 1-12.

Grayson, A. C. R., Cima, M. J., and Langer, R. (2005). Size and temperature effects on poly (lactic-co-glycolic acid) degradation and microreservoir device performance. *Biomaterials, 26*(14), 2137-2145.

Guo, D., Xie, G., and Luo, J. (2013). Mechanical properties of nanoparticles: basics and applications. *Journal of Physics D: Applied Physics, 47*(1), 013001.

He, F., Ji, H., Feng, L., Wang, Z., Sun, Q., Zhong, C., and Lin, J. (2021). Construction of thiol-capped ultrasmall Au–Bi bimetallic nanoparticles for X-ray CT imaging and enhanced antitumor therapy efficiency. *Biomaterials, 264*, 120453.

Hillaireau, H., and Couvreur, P. (2009). Nanocarriers' entry into the cell: relevance to drug delivery. *Cellular and Molecular Life Sciences, 66*, 2873-2896.

Hosnedlova, B., Kepinska, M., Skalickova, S., Fernandez, C., Ruttkay-Nedecky, B., Peng, Q., and Zidkova, J. (2018). Nano-selenium and its nanomedicine applications: a critical review. *International Journal of Nanomedicine*, 2107-2128.

Hossain, M. M., Polash, S. A., Saha, T., and Sarker, S. R. (2022). Gold nanoparticles: a lethal nanoweapon against multidrug-resistant bacteria *Nano-strategies for addressing antimicrobial resistance: nano-diagnostics, nano-carriers, and nano-antimicrobials* (pp. 311-351): Springer.

Hosseini, S., Mohammadnejad, J., Salamat, S., Zadeh, Z. B., Tanhaei, M., and Ramakrishna, S. (2023). Theranostic polymeric nanoparticles as a new approach in cancer therapy and diagnosis: a review. *Materials Today Chemistry, 29*, 101400.

Hu, J., Huang, W., Huang, S., ZhuGe, Q., Jin, K., and Zhao, Y. (2016). Magnetically active Fe 3 O 4 nanorods loaded with tissue plasminogen activator for enhanced thrombolysis. *Nano Research, 9*, 2652-2661.

Huan, K., Li, Y., Deng, D., Wang, H., Wang, D., Li, M., and Luo, L. (2022). Composite-controlled electrospinning of CuSn bimetallic nanoparticles/carbon nanofibers for electrochemical glucose sensor. *Applied Surface Science, 573*, 151528.

Huang, Q., Yu, H., and Ru, Q. (2010). Bioavailability and delivery of nutraceuticals using nanotechnology. *Journal of Food Science, 75*(1), R50-R57.

Idris, D. S., and Roy, A. (2023). Synthesis of bimetallic nanoparticles and applications—an updated review. *Crystals, 13*(4), 637.

Inoue, K.-i., Koike, E., Yanagisawa, R., Hirano, S., Nishikawa, M., and Takano, H. (2009). Effects of multi-walled carbon nanotubes on a murine allergic airway inflammation model. *Toxicology and Applied Pharmacology, 237*(3), 306-316.

Jahan, S. T., Sadat, S., Walliser, M., and Haddadi, A. (2017). Targeted therapeutic nanoparticles: an immense promise to fight against cancer. *Journal of Drug Delivery, 2017*.

Jani, P., Subramanian, S., Korde, A., Rathod, L., and Sawant, K. K. (2020). Theranostic nanocarriers in cancer: dual capabilities on a single platform. *Functional Bionanomaterials: From Biomolecules to Nanoparticles*, 293-312.

Jeong, M.-J., Jeon, S., Yu, H.-S., Cho, W.-S., Lee, S., Kang, D., and Kim, S.-Y. (2022). Exposure to nickel oxide nanoparticles induces acute and chronic inflammatory responses in rat lungs and perturbs the lung microbiome. *International Journal of Environmental Research and Public Health, 19*(1), 522.

Jiang, Y., Chen, J., Deng, C., Suuronen, E. J., and Zhong, Z. (2014). Click hydrogels, microgels and nanogels: Emerging platforms for drug delivery and tissue engineering. *Biomaterials, 35*(18), 4969-4985.

Jokerst, J. V., and Gambhir, S. S. (2011). Molecular imaging with theranostic nanoparticles. *Accounts of Chemical Research, 44*(10), 1050-1060.

Kadam, R. S., Bourne, D. W., and Kompella, U. B. (2012). Nano-advantage in enhanced drug delivery with biodegradable nanoparticles: contribution of reduced clearance. *Drug Metabolism and Disposition, 40*(7), 1380-1388.

Kamaly, N., Xiao, Z., Valencia, P. M., Radovic-Moreno, A. F., and Farokhzad, O. C. (2012). Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. *Chemical Society Reviews, 41*(7), 2971-3010.

Kandasamy, G., and Maity, D. (2021). Multifunctional theranostic nanoparticles for biomedical cancer treatments-A comprehensive review. *Materials Science and Engineering: C, 127*, 112199.

Kim, N. Y., Blake, S., De, D., Ouyang, J., Shi, J., and Kong, N. (2020). Two-dimensional nanosheet-based photonic nanomedicine for combined gene and photothermal therapy. *Frontiers in Pharmacology, 10*, 1573.

Kong, Z., Lin, J., Yu, M., Yu, L., Li, J., Weng, W., and Wang, H. (2014). Enhanced loading and controlled release of rhBMP-2 in thin mineralized collagen coatings with the aid of chitosan nanospheres and its biological evaluations. *Journal of Materials Chemistry B, 2*(28), 4572-4582.

Koo, S., Park, O. K., Kim, J., Han, S. I., Yoo, T. Y., Lee, N., and Bae, J.-S. (2022). Enhanced chemodynamic therapy by Cu–Fe peroxide nanoparticles: tumor microenvironment-mediated synergistic Fenton reaction. *ACS nano, 16*(2), 2535-2545.

Koyyati, R., Kudle, K. R., Nagati, V., Merugu, R., and Padigya, P. R. M. (2022). *Extracellular Synthesis of Mono and Bimetallic Nanocomposites from Novel Strains of Rhodopseudomonas palustris and Evaluation of Their Biomedical Applications*. Paper presented at the Macromolecular Symposia.

Kroll, A., Pillukat, M. H., Hahn, D., and Schnekenburger, J. (2009). Current in vitro methods in nanoparticle risk assessment: limitations and challenges. *European journal of Pharmaceutics and Biopharmaceutics, 72*(2), 370-377.

Kumar, R., Dhanawat, M., Kumar, S., N Singh, B., K Pandit, J., and R Sinha, V. (2014). Carbon nanotubes: a potential concept for drug delivery applications. *Recent Patents on Drug Delivery and Formulation, 8*(1), 12-26.

Larson, N., and Ghandehari, H. (2012). Polymeric conjugates for drug delivery. *Chemistry of Materials, 24*(5), 840-853.

Lee, J.-E., In, I., Lee, H., Lee, K. D., Jeong, J. H., and Park, S. Y. (2013). Target delivery and cell imaging using hyaluronic acid-functionalized graphene quantum dots. *Molecular Pharmaceutics, 10*(10), 3736-3744.

Lee, N.-Y., Ko, W.-C., and Hsueh, P.-R. (2019). Nanoparticles in the treatment of infections caused by multidrug-resistant organisms. *Frontiers in Pharmacology, 10*, 1153.

Li, D., and Kaner, R. B. (2006). Shape and aggregation control of nanoparticles: not shaken, not stirred. *Journal of the American Chemical Society, 128*(3), 968-975.

Li, J., Yap, S. Q., Yoong, S. L., Nayak, T. R., Chandra, G. W., Ang, W. H., and Sheu, F.-S. (2012). Carbon nanotube bottles for incorporation, release and enhanced cytotoxic effect of cisplatin. *Carbon, 50*(4), 1625-1634.

Li, L., Yu, Y., Ye, G. J., Ge, Q., Ou, X., Wu, H., and Zhang, Y. (2014). Black phosphorus field-effect transistors. *Nature Nanotechnology, 9*(5), 372-377.

Li, S., Zhou, S., Li, Y., Li, X., Zhu, J., Fan, L., and Yang, S. (2017). Exceptionally high payload of the IR780 iodide on folic acid-functionalized graphene quantum dots for targeted photothermal therapy. *ACS Applied Materials and Interfaces, 9*(27), 22332-22341.

Lim, Y. H., Tiemann, K. M., Hunstad, D. A., Elsabahy, M., and Wooley, K. L. (2016). Polymeric nanoparticles in development for treatment of pulmonary infectious diseases. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 8*(6), 842-871.

Lin, Y., Xu, J., and Lan, H. (2019). Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. *Journal of Hematology and Oncology, 12*(1), 1-16.

Liu, J., Meisner, D., Kwong, E., Wu, X. Y., and Johnston, M. R. (2009). Translymphatic chemotherapy by intrapleural placement of gelatin sponge containing biodegradable paclitaxel colloids controls lymphatic metastasis in lung cancer. *Cancer Research, 69*(3), 1174-1181.

Loh, K. P., Ho, D., Chiu, G. N. C., Leong, D. T., Pastorin, G., and Chow, E. K. H. (2018). Clinical applications of carbon nanomaterials in diagnostics and therapy. *Advanced Materials, 30*(47), 1802368.

Loh, X. J., Lee, T.-C., Dou, Q., and Deen, G. R. (2016). Utilising inorganic nanocarriers for gene delivery. *Biomaterials Science, 4*(1), 70-86.

Lu, A. H., Salabas, E. E. L., and Schüth, F. (2007). Magnetic nanoparticles: synthesis, protection, functionalization, and application. *Angewandte Chemie International Edition, 46*(8), 1222-1244.

Lu, Y., Zhang, P., Lin, L., Gao, X., Zhou, Y., Feng, J., and Zhang, H. (2022). Ultra-small bimetallic phosphides for dual-modal MRI imaging guided photothermal ablation of tumors. *Dalton Transactions, 51*(11), 4423-4428.

Ma, W., Chen, Q., Xu, W., Yu, M., Yang, Y., Zou, B., and Yu, Z. (2021). Self-targeting visualizable hyaluronate nanogel for synchronized intracellular release of doxorubicin and cisplatin in combating multidrug-resistant breast cancer. *Nano Research, 14*, 846-857.

Machado, S., Grosso, J., Nouws, H., Albergaria, J. T., and Delerue-Matos, C. (2014). Utilization of food industry wastes for the production of zero-valent iron nanoparticles. *Science of the Total Environment, 496*, 233-240.

Manzari, M. T., Shamay, Y., Kiguchi, H., Rosen, N., Scaltriti, M., and Heller, D. A. (2021). Targeted drug delivery strategies for precision medicines. *Nature Reviews Materials, 6*(4), 351-370.

Manzoor, A. A., Lindner, L. H., Landon, C. D., Park, J.-Y., Simnick, A. J., Dreher, M. R., and Chilkoti, A. (2012). Overcoming limitations in nanoparticle drug delivery: triggered, intravascular release to improve drug penetration into tumors. *Cancer Research, 72*(21), 5566-5575.

Markwalter, C. F., Kantor, A. G., Moore, C. P., Richardson, K. A., and Wright, D. W. (2018). Inorganic complexes and metal-based nanomaterials for infectious disease diagnostics. *Chemical Reviews, 119*(2), 1456-1518.

Martinho, N., Damgé, C., and Reis, C. P. (2011). Recent advances in drug delivery systems. *Journal of Biomaterials and Nanobiotechnology, 2*(05), 510.

Mehmandoust, M., Khoshnavaz, Y., Tuzen, M., and Erk, N. (2021). Voltammetric sensor based on bimetallic nanocomposite for determination of favipiravir as an antiviral drug. *Microchimica Acta, 188*, 1-15.

Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., and Langer, R. (2021). Engineering precision nanoparticles for drug delivery. *Nature Reviews Drug Discovery, 20*(2), 101-124.

Mohammad, Z., Zeeshan, A., Faisal, S., Suhail, A., Sahar, I., Mohd, S., and Nazma, K. (2017). Vesicular drug delivery system used for liver diseases. *World Journal of Pharmaceutical Sciences*, 28-35.

Mukherjee, A., and Bhattacharyya, S. (2020). Nanotechnology in medicine. *Biotechnology Business-concept to Delivery*, 57-64.

Nakamura, Y., Mochida, A., Choyke, P. L., and Kobayashi, H. (2016). Nanodrug delivery: is the enhanced permeability and retention effect sufficient for curing cancer? *Bioconjugate Chemistry, 27*(10), 2225-2238.

Nasr, M., Najlah, M., D'Emanuele, A., and Elhissi, A. (2014). PAMAM dendrimers as aerosol drug nanocarriers for pulmonary delivery via nebulization. *International Journal of Pharmaceutics, 461*(1-2), 242-250.

Niezabitowska, E., Smith, J., Prestly, M. R., Akhtar, R., von Aulock, F. W., Lavallée, Y., and McDonald, T. O. (2018). Facile production of nanocomposites of carbon nanotubes and polycaprolactone with high aspect ratios with potential applications in drug delivery. *Rearch Advances, 8*(30), 16444-16454.

Novoselov, K. S., Geim, A. K., Morozov, S. V., Jiang, D.-e., Zhang, Y., Dubonos, S. V., and Firsov, A. A. (2004). Electric field effect in atomically thin carbon films. *Science, 306*(5696), 666-669.

Oladipo, A. O., Iku, S. I., Ntwasa, M., Nkambule, T. T., Mamba, B. B., and Msagati, T. A. (2020). Doxorubicin conjugated hydrophilic AuPt bimetallic nanoparticles fabricated from Phragmites australis: Characterization and cytotoxic activity against human cancer cells. *Journal of Drug Delivery Science and Technology, 57*, 101749.

Ortega-Oller, I., Padial-Molina, M., Galindo-Moreno, P., O'Valle, F., Jódar-Reyes, A. B., and Peula-García, J. M. (2015). Bone regeneration from PLGA micro-nanoparticles. *BioMed Research International, 2015*.

Pandit, C., Roy, A., Ghotekar, S., Khusro, A., Islam, M. N., Emran, T. B., and Bradley, D. A. (2022). Biological agents for synthesis of nanoparticles and their applications. *Journal of King Saud University-Science, 34*(3), 101869.

Park, J. S., Yi, S. W., Kim, H. J., Kim, S. M., and Park, K.-H. (2016). Regulation of cell signaling factors using PLGA nanoparticles coated/loaded with genes and proteins for osteogenesis of human mesenchymal stem cells. *ACS Applied Materials and Interfaces, 8*(44), 30387-30397.

Pearson, R. M., Sunoqrot, S., Hsu, H.-j., Bae, J. W., and Hong, S. (2012). Dendritic nanoparticles: the next generation of nanocarriers? *Therapeutic Delivery, 3*(8), 941-959.

Perry, J. L., Martin, C. R., and Stewart, J. D. (2011). Drug-Delivery Strategies by Using Template-Synthesized Nanotubes. *Chemistry–A European Journal, 17*(23), 6296-6302.

Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., and Langer, R. (2020). Nanocarriers as an emerging platform for cancer therapy. *Nano-enabled Medical Applications*, 61-91.

Qian, X., Gu, Z., and Chen, Y. (2017). Two-dimensional black phosphorus nanosheets for theranostic nanomedicine. *Materials Horizons, 4*(5), 800-816.

Ramezani, M., Rad, F. A., Ghahari, S., Ghahari, S., and Ramezani, M. (2021). Nano-bioremediation application for environment contamination by microorganism. *Microbial Rejuvenation of Polluted Environment: Volume 2*, 349-378.

Ramos, T., Villacis-Aguirre, C., López-Aguilar, K., Santiago Padilla, L., Altamirano, C., Toledo, J., and Santiago Vispo, N. (2022). The Hitchhiker's Guide to Human Therapeutic Nanoparticle Development. Pharmaceutics 2022, 14, 247: s Note: MDPI stays neutral with regard to jurisdictional claims in published

Rana, V., and Sharma, R. (2019). Recent advances in development of nano drug delivery. *Applications of Targeted Nano Drugs and Delivery Systems*, 93-131.

Ranganath, S. H., and Wang, C.-H. (2008). Biodegradable microfiber implants delivering paclitaxel for post-surgical chemotherapy against malignant glioma. *Biomaterials, 29*(20), 2996-3003.

Rizvi, S. A., and Saleh, A. M. (2018). Applications of nanoparticle systems in drug delivery technology. *Saudi Pharmaceutical Journal, 26*(1), 64-70.

Rogers-Nieman, G. M., and Dinu, C. Z. (2014). Therapeutic applications of carbon nanotubes: opportunities and challenges. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 6*(4), 327-337.

Sadauskas, E., Danscher, G., Stoltenberg, M., Vogel, U., Larsen, A., and Wallin, H. (2009). Protracted elimination of gold nanoparticles from mouse liver. *Nanomedicine: Nanotechnology, Biology and Medicine, 5*(2), 162-169.

Saeed, A., Akhtar, M., Zulfiqar, S., Hanif, F., Alsafari, I. A., Agboola, P. O., and Shakir, I. (2022). Thiamine-functionalized silver–copper bimetallic nanoparticles-based electrochemical sensor for sensitive detection of anti-inflammatory drug 4-aminoantipyrine. *Chemical Papers*, 1-11.

Safaya, M., and Rotliwala, Y. (2022). Neem oil based nano-emulsion formulation by low energy phase inversion composition method: characterization and antimicrobial activity. *Materials Today: Proceedings, 57*, 1793-1797.

Sahiner, N., Godbey, W., McPherson, G. L., and John, V. T. (2006). Microgel, nanogel and hydrogel–hydrogel semi-IPN composites for biomedical applications: synthesis and characterization. *Colloid and Polymer Science, 284*, 1121-1129.

Sahoo, S. K., and Labhasetwar, V. (2003). Nanotech approaches to drug delivery and imaging. *Drug Discovery Today, 8*(24), 1112-1120.

Saleemi, M., Kong, Y., Yong, P., and Wong, E. (2020). An overview of recent development in therapeutic drug carrier system

using carbon nanotubes. *Journal of Drug Delivery Science and Technology, 59*, 101855.

Saxena, S. K., Nyodu, R., Kumar, S., and Maurya, V. K. (2020). Current advances in nanotechnology and medicine. *NanoBioMedicine*, 3-16.

Seifi, H., Gholami, T., Seifi, S., Ghoreishi, S. M., and Salavati-Niasari, M. (2020). A review on current trends in thermal analysis and hyphenated techniques in the investigation of physical, mechanical and chemical properties of nanomaterials. *Journal of Analytical and Applied Pyrolysis, 149*, 104840.

Sendi, P., and Proctor, R. A. (2009). Staphylococcus aureus as an intracellular pathogen: the role of small colony variants. *Trends in Microbiology, 17*(2), 54-58.

Shi, J., Kantoff, P. W., Wooster, R., and Farokhzad, O. C. (2017). Cancer nanomedicine: progress, challenges and opportunities. *Nature Reviews Cancer, 17*(1), 20-37.

Shi, J., Xiao, Z., Kamaly, N., and Farokhzad, O. C. (2011). Self-assembled targeted nanoparticles: evolution of technologies and bench to bedside translation. *Accounts of Chemical Research, 44*(10), 1123-1134.

Shivaramakrishnan, B., Gurumurthy, B., and Balasubramanian, A. (2017). Potential biomedical applications of metallic nanobiomaterials: a review. *International Journal of Pharmaceutical Sciences and Research, 8*(3), 985.

Sohrabi, H., Majidi, M. R., Asadpour-Zeynali, K., Khataee, A., and Mokhtarzadeh, A. (2022). Bimetallic Fe/Mn MOFs/MβCD/AuNPs stabilized on MWCNTs for developing a label-free DNA-based genosensing bio-assay applied in the determination of Salmonella typhimurium in milk samples. *Chemosphere, 287*, 132373.

Sravani, B., Kiranmai, S., Reddy, G. R., Park, J. P., Reddy, Y. V., and Madhavi, G. (2022). Highly sensitive detection of anti-cancer drug based on bimetallic reduced graphene oxide nanocomposite. *Chemosphere, 287*, 132281.

Sugawara, E., and Nikaido, H. (2014). Properties of AdeABC and AdeIJK efflux systems of Acinetobacter baumannii compared with those of the AcrAB-TolC system of Escherichia coli. *Antimicrobial Agents and Chemotherapy, 58*(12), 7250-7257.

Tang, J., Hu, T., Li, N., Zhu, Y., Li, J., Zheng, S., and Guo, J. (2022). Ag doped Co/Ni bimetallic organic framework for determination of luteolin. *Microchemical Journal, 179*, 107461.

Tewabe, A., Abate, A., Tamrie, M., Seyfu, A., and Abdela Siraj, E. (2021). Targeted drug delivery—from magic bullet to nanomedicine: principles, challenges, and future perspectives. *Journal of Multidisciplinary Healthcare*, 1711-1724.

Thakur, A., Roy, A., Chatterjee, S., Chakraborty, P., Bhattacharya, K., and Mahata, P. P. (2015). Recent trends in targeted drug delivery. *SMGroup*.

Torrano, A. A., Herrmann, R., Strobel, C., Rennhak, M., Engelke, H., Reller, A., and Bräuchle, C. (2016). Cell membrane penetration and mitochondrial targeting by platinum-decorated ceria nanoparticles. *Nanoscale, 8*(27), 13352-13367.

Tran, S., DeGiovanni, P.-J., Piel, B., and Rai, P. (2017). Cancer nanomedicine: a review of recent success in drug delivery. *Clinical and Translational Medicine, 6*, 1-21.

Walkey, C. D., Olsen, J. B., Guo, H., Emili, A., and Chan, W. C. (2012). Nanoparticle size and surface chemistry determine serum protein adsorption and macrophage uptake. *Journal of the American Chemical Society, 134*(4), 2139-2147.

Walsh, T. J., Finberg, R. W., Arndt, C., Hiemenz, J., Schwartz, C., Bodensteiner, D., and Dummer, S. (1999). Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *New England Journal of Medicine, 340*(10), 764-771.

Wang, C., Zhao, T., Li, Y., Huang, G., White, M. A., and Gao, J. (2017). Investigation of endosome and lysosome biology by ultra pH-sensitive nanoprobes. *Advanced Drug Delivery Reviews, 113*, 87-96.

Wang, L., Hu, C., and Shao, L. (2017). The antimicrobial activity of nanoparticles: present situation and prospects for the future. *International Journal of Nanomedicine*, 1227-1249.

Wang, X., Zhang, D., Qian, H., Liang, Y., Pan, X., and Gadd, G. M. (2018). Interactions between biogenic selenium nanoparticles and goethite colloids and consequence for remediation of elemental mercury contaminated groundwater. *Science of the Total Environment, 613*, 672-678.

Warabi, S., Tachibana, Y., Kumegawa, M., and Hakeda, Y. (2001). Dexamethasone inhibits bone resorption by indirectly inducing apoptosis of the bone-resorbing osteoclasts via the action of osteoblastic cells. *Cytotechnology, 35*, 25-34.

Wei, Z., Yin, X., Cai, Y., Xu, W., Song, C., Wang, Y., and Han, W. (2018). Antitumor effect of a Pt-loaded nanocomposite based on graphene quantum dots combats hypoxia-induced chemoresistance of oral squamous cell carcinoma. *International Journal of Nanomedicine*, 1505-1524.

Weissig, V., Pettinger, T. K., and Murdock, N. (2014). Nanopharmaceuticals (part 1): products on the market. *International Journal of Nanomedicine*, 4357-4373.

Wu, K., Yang, Y., Zhang, Y., Deng, J., and Lin, C. (2015). Antimicrobial activity and cytocompatibility of silver nanoparticles coated catheters via a biomimetic surface functionalization strategy. *International Journal of Nanomedicine*, 7241-7252.

Wu, W., Luo, L., Wang, Y., Wu, Q., Dai, H.-B., Li, J.-S., and Wang, G.-X. (2018). Endogenous pH-responsive nanoparticles with programmable size changes for targeted tumor therapy and imaging applications. *Theranostics, 8*(11), 3038.

Xie, H.-Y., Xie, M., Zhang, Z.-L., Long, Y.-M., Liu, X., Tang, M.-L., and Zhou, W. (2007). Wheat germ agglutinin-modified trifunctional nanospheres for cell recognition. *Bioconjugate Chemistry, 18*(6), 1749-1755.

Yadav, H. K., Almokdad, A. A., Sumia, I., and Debe, M. S. (2019). Polymer-based nanomaterials for drug-delivery carriers *Nanocarriers for Drug Delivery* (pp. 531-556): Elsevier.

Yang, H., Zhang, X., Velu, P., Liu, X., and Vijayalakshmi, A. (2022). Enhanced green mediated synthesis of optimized Ag-Cu bimetallic nanoparticles using Leucas aspera and its application in Anti-cancer activity against alveolar cancer. *Materials Letters, 313*, 131645.

Yang, Q., Jones, S. W., Parker, C. L., Zamboni, W. C., Bear, J. E., and Lai, S. K. (2014). Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation. *Molecular Pharmaceutics, 11*(4), 1250-1258.

Yang, Y., Duan, S., Xiao, W., and Zhao, H. (2022). Silver nanowire-based stretchable strain sensors with hierarchical wrinkled structures. *Sensors and Actuators A: Physical, 343*, 113653.

Yao, Y., Zhou, Y., Liu, L., Xu, Y., Chen, Q., Wang, Y., and Shao, A. (2020). Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. *Frontiers in Molecular Biosciences, 7*, 193.

Yetisgin, A. A., Cetinel, S., Zuvin, M., Kosar, A., and Kutlu, O. (2020). Therapeutic nanoparticles and their targeted delivery applications. *Molecules, 25*(9), 2193.

Yhee, J. Y., Im, J., and Nho, R. S. (2016). Advanced therapeutic strategies for chronic lung disease using nanoparticle-based drug delivery. *Journal of Clinical Medicine, 5*(9), 82.

Yin, F., Hu, K., Chen, Y., Yu, M., Wang, D., Wang, Q., and Li, Z. (2017). SiRNA delivery with PEGylated graphene oxide nanosheets for combined photothermal and genetherapy for pancreatic cancer. *Theranostics, 7*(5), 1133.

Zazo, H., Colino, C. I., and Lanao, J. M. (2016). Current applications of nanoparticles in infectious diseases. *Journal of Controlled Release, 224*, 86-102.

Zeineldin, R., and Syoufjy, J. (2017). Cancer nanotechnology: opportunities for prevention, diagnosis, and therapy. *Cancer Nanotechnology: Methods and Protocols*, 3-12.

Zhang, D., Wen, L., Huang, R., Wang, H., Hu, X., and Xing, D. (2018). Mitochondrial specific photodynamic therapy by rare-earth nanoparticles mediated near-infrared graphene quantum dots. *Biomaterials, 153*, 14-26.

Zhang, H., Ji, Q., Huang, C., Zhang, S., Yuan, B., Yang, K., and Ma, Y.-q. (2015). Cooperative transmembrane penetration of nanoparticles. *Scientific Reports, 5*(1), 10525.

Zhang, S., Kucharski, C., Doschak, M. R., Sebald, W., and Uludağ, H. (2010). Polyethylenimine–PEG coated albumin nanoparticles for BMP-2 delivery. *Biomaterials, 31*(5), 952-963.

Zhang, W., Yuan, T., Wang, X., Cheng, Z., and Xu, J. (2022). Coal mine gases sensors with dual selectivity at variable temperatures based on a W18O49 ultra-fine nanowires/Pd@ Au bimetallic nanoparticles composite. *Sensors and Actuators B: Chemical, 354*, 131004.

Zhang, Y., Huang, Y., and Li, S. (2014). Polymeric micelles: nanocarriers for cancer-targeted drug delivery. *Aaps Pharmscitech, 15*, 862-871.

Zheng, X. T., Than, A., Ananthanaraya, A., Kim, D.-H., and Chen, P. (2013). Graphene quantum dots as universal fluorophores and their use in revealing regulated trafficking of insulin receptors in adipocytes. *ACS nano, 7*(7), 6278-6286.

Zohra, E., Ikram, M., Omar, A. A., Hussain, M., Satti, S. H., Raja, N. I., and Ehsan, M. (2021). Potential applications of biogenic selenium nanoparticles in alleviating biotic and abiotic stresses in plants: A comprehensive insight on the mechanistic approach and future perspectives. *Green Processing and Synthesis, 10*(1), 456-475.

Chapter 12

Nanomaterials Characterization

Hira Qamar[1], Amina Iqbal[1], Abdullah Saghir Ahmad[2], Sehrish Kiran[3], Salena Ahmad[4], Muhammad Usman[5], Muhammad Hamza Muneer[5], Kashif Hussain[5], Rana Muhammad Shahbakht[5], Atif Rehman[5] and Ali Haider[5]*

[1]Department of Zoology, Wildlife and Fisheries, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, 66000, Multan, Punjab, Pakistan
[2]Department of Parasitology, Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
[3]Department of Chemistry, Faculty of Science and Technology, Lahore College for Women University, Jail Road, Lahore, Pakistan
[4]Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur
[5]Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef, University of Agriculture, 66000, Multan, Punjab, Pakistan
*Corresponding author: ali.haider@mnsuam.edu.pk

ABSTRACT

Nanoparticles (NPs) are materials with size range of 1 to 100 nm. Due to their wide range of uses, nanostructures, a rapidly expanding class of materials, have drawn intense attention. Because of their small extent, NPs show increased attributes including high stability, sensitivity, strength, surface area and reactivity. These properties make them attractive candidates for a range of household and commercial uses, including as energy-based research, imaging, medicinal, catalysis, and environmental applications. Numerous methods have been used to describe the morphological, optical, structural, dimensions elemental makeup and several other physical characteristics of NPs. The main objective of NPs characterizations is to offer a summary of current understanding of that several experimental techniques accessible for NPs characterization. Numerous characterization methods that allow for accurate determination of these essential NPs characteristics are described as transmission electron microscope (TEM), scanning electron microscope (SEM), Atomic Force Microscopy (AFM), High-resolution transmission electron microscopy (HR-TEM), Energy dispersive X-ray spectroscopy (EDX), Ultraviolet-visible diffuse reflectance spectrometer (UV–Vis DRS), Ultraviolet-visible (UV) Photoluminescence Spectroscopy (PL), Fourier-transform infrared spectroscopy (FT-IR), Raman spectroscopy, Brunauer-Emmett-Teller (BET), X-ray diffractometer (XRD), and X-ray photoelectron spectroscopy (XPS).

KEYWORDS
Nanoparticles, Characterizations, SEM, TEM, XRD, XPS, FTIR

Received: 08-Jun-2024
Revised: 18-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Qamar H, Iqbal A, Ahmad AS, Kiran S, Ahmad S, Usman M, Muneer MH, Hussain K, Shahbakht RM, Rehman A and Haider A, 2024. Nanomaterials characterization. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 94-106. https://doi.org/10.47278/book.CAM/2024.233

INTRODUCTION

The word "nano" comes from Greek word "nanos," which means "a dwarf." During 14th Congress of the International Union of Pure and Applied Chemistry (IUPAC) in 1947, term "nano" was legally recognized to denote one-billionth part (10^{-9}) of a unit (Joudeh et al., 2022). Nanomaterials are defined as materials containing at least 50% of nanoparticles (NPs) having one or more external dimensions between 1 and 100 nm (Schellauf, 2019). When NPs are less than one nanometer, the phrase “atom clusters” are typically used. NPs can be crystallized or amorphous, containing either one or several crystals solids and may exist in aggregated or loose forms (Machado et al., 2015). In worldwide, nanotechnology is a concentrated field of contemporary study, endeavor for science and technology in this century. Nanotechnology is based on sophisticated production techniques and advanced nanomaterials (Wang, 2003b). Recent advancements in quickly expanding field of nanotechnology have produced wide variety of unique NPs (NP) with unique size-dependent characteristics that differ greatly from those of their bulk material (Fischer et al., 2007; Jong et al., 2008;). These materials can have general forms that are 0D, 1D, 2D, or 3D (Tiwari et al., 2012). The significance of these NPs noticed when researchers found that substance's size may have an impact on its physiochemical characteristics such as visual qualities (Khan et al., 2019). NPs are not simple molecules and are composed of three layers. (a) The surface is initial layer, and it may be modified with variety of metal ions, small molecules, polymers and surfactants (b) The shell layer, which is chemically completely different from the core; and (c) The term "core" usually refers to NPs themselves and is essentially the center of NP (Shin et al.2016). Because of these remarkable qualities, researchers in multidisciplinary fields have shown

great deal of interest in these materials (Khan et al., 2019).

More varieties and larger volumes of nanomaterials being synthesized nowadays, than they were only a decade ago. It is necessary to develop more precise and reliable techniques for NPs characterization. Meanwhile, such characterization techniques aren't always precise. This is due to inherent difficulties in precisely analyzing materials at the nanoscale in comparison to bulk materials (such as their tiny size and, in certain situations, limited quantity after manufacture on a laboratory scale) (Mourdikoudis et al. 2018). Here, we describe in detail how different techniques are used to analyze nanostructures. Sometimes various techniques are used exclusively for studying particular characteristics, and often they are combined (Kim et al. 2004). Certain microscopy-based methods (as AFM, TEM, and HR-TEM; complete titles of aforementioned technique are afterwards in the passage when describing all of them together) present details on crystal structure morphology, and size of nanomaterials. A plethora of different approaches provide further details on optical characteristics, structure, elemental composition, and various common and more specific actual aspects of NPs samples. Among these approaches are scattering techniques and X-ray spectroscopy (Mourdikoudis et al., 2018).

This chapter is divided into many sections that provide general summary of present knowledge and latest advances for different NPs characterization techniques with respect to characteristics being study. We will then discuss the practical benefits and critical review of their underlying principles of those specialized techniques currently used for NPs evaluation. Future aspects and recommendations are also included in the last part.

Characterization Techniques for NPs

Due to inherent characteristics of NPs, such as their low ligand concentration, heterogeneity, nanoscale size, surface curvature, and characterizing NPs surfaces may be challenging. Furthermore, organic ligands or capping agents are frequently present on surfaces of nanomaterial. As a result, characterizations at both material and molecular levels are required (Jayawardena et al. 2021). It is necessary to thoroughly characterize NPs properties such as size, surface morphology, crystalline nature, shape, and light absorption by utilizing relevant characterization approaches (Chanderiya et al., 2024). For analysis of various physical and chemical properties of NPs various portrayal techniques have been used as presented in Fig. 1. These techniques including infrared (IR), SEM, TEM, X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), Brunauer–Emmett–Teller (BET) and particle size analysis (Khan et al., 2019).

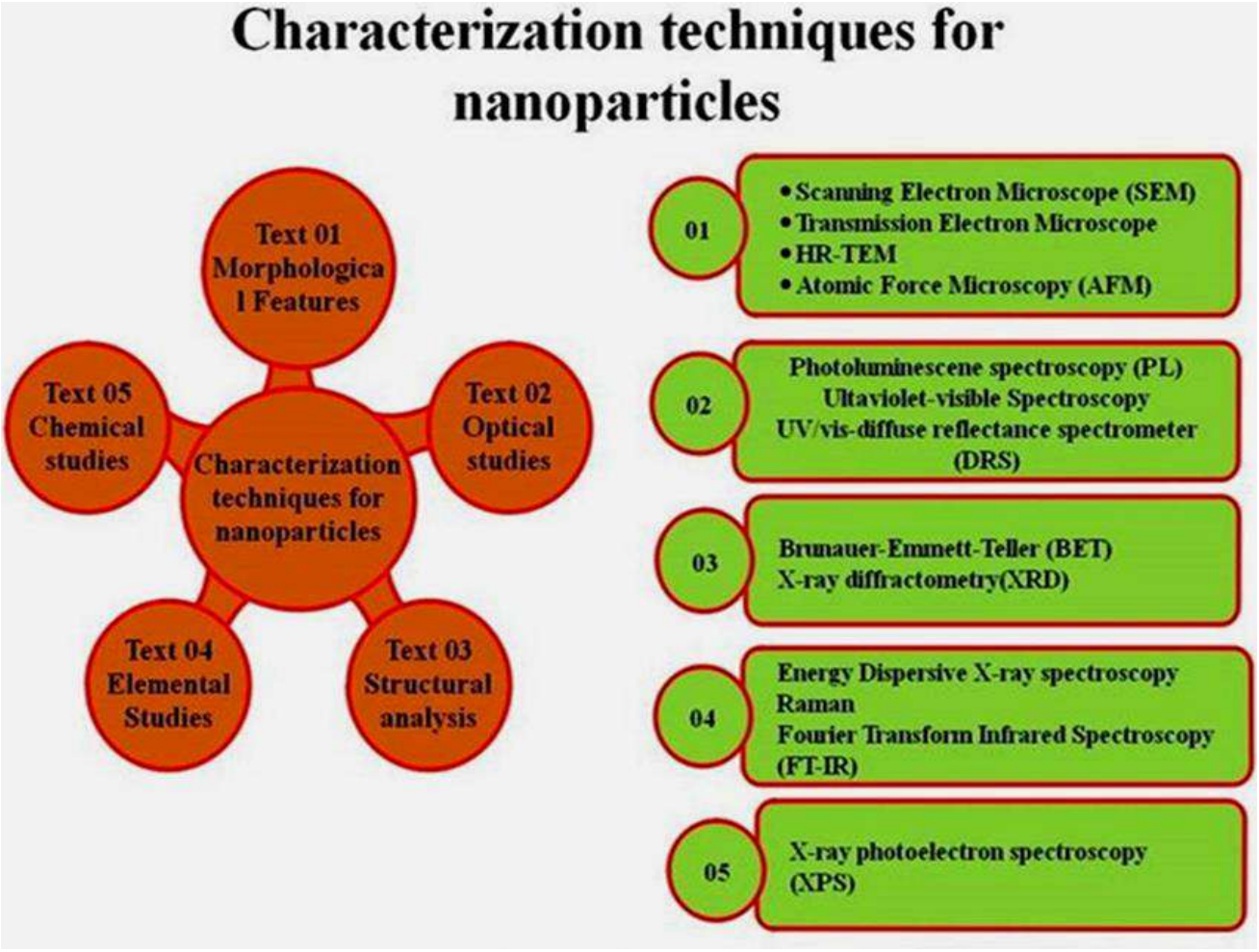


Fig. 1: Characterization techniques for nanoparticles.

Morphological Features

Scanning Electron Microscope

SEM allows revelation of details and complexity that are not visible with light microscopy. Many fields throughout the globe have used scanning electron microscopy (SEM), often classify as SEM analysis or SEM technique. SEM provides a means of glimpse to invisible world of nano and micro-space as presented in Fig. 2. The apparatus has variable pressure system that can accommodate any kind of sample, including ones that need little pretreatment or are moist. The apparatus can analyze samples up to 200 mm in diameter and 80 mm in height. The analysis will be carried out by using a high-energy electron beam with an electron voltage between 100 and 30,000 volts. For electron emission, heat source is typically utilized. It is not possible to make a crisp image with gun's spot size. The way scan coils move determines how specimen's picture is created point by point. The SEM picture that is somewhat three-dimensional is dependent on how sample's topography is visualized in terms of form, size, and surface texture (Mohammed and Abdullah 2018). On the nanometer to micrometer (µm) range, SEM may be considered as an efficient technique for analyzing both inorganic and organic nanomaterials. SEM produces extremely exact pictures of broad range of components up to 300,000x and even 1,000,000 times magnification (in certain modern versions) (Mohammed and Abdullah, 2018). SEM may offer details on crystalline structure, chemical makeup, electrical behavior, and surface topography of top 1 um or so the specimen (Vernon-Parry, 2000).

SEM's advantages of high depth of field enable for simultaneous focus on most of specimen surface, regardless of surface roughness. It is possible to obtain far greater magnification (up to 1,000,000x) while maintaining an ultimate 1 nm resolution. It is possible to obtain more knowledge beyond surface topography, i.e. electrical properties, chemical constitution, and crystal structure. Extremely brief sample preparing time (possibly only a few seconds) while the sample is fastened to a "stub" (specimen holder) (Vernon-Parry, 2000).

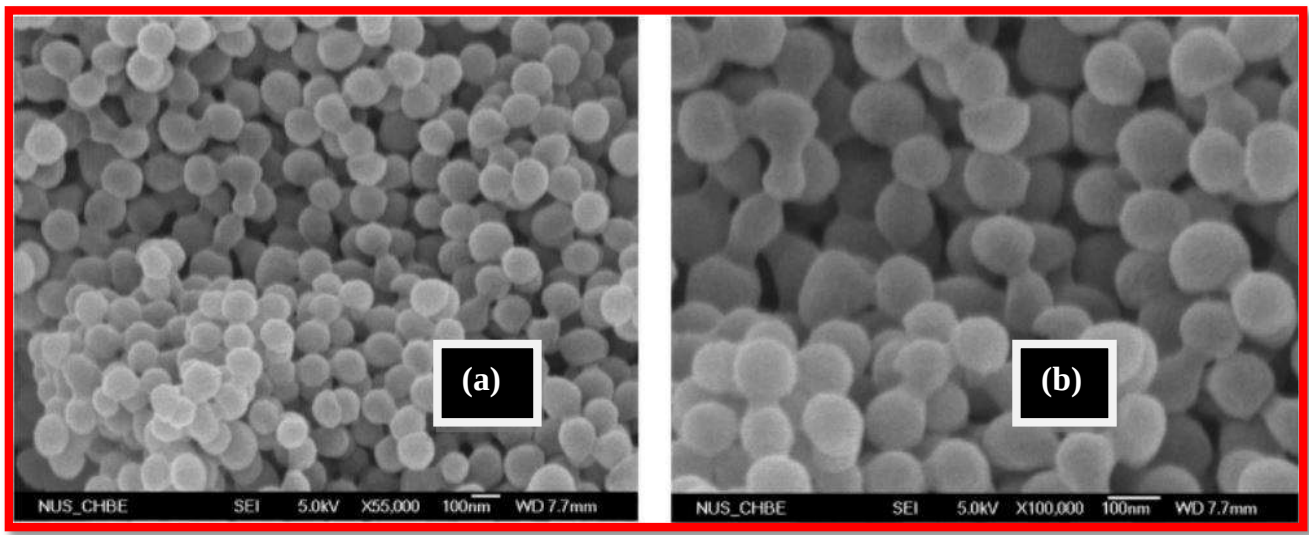


Fig. 2: (a) PLA-Tween 80-20, 55, 000 magnification; and (b) PLA-Tween 80-20, 100, 000 magnification (Zhangand Feng2006).

Transmission Electron Microscope

TEM stands for transmission electron microscope is certainly among most significant technique for NPs characterization. By concentrating an electron beam on narrow sample (often less than 200 nm), TEM produces micrographs of nanoscale materials with great lateral spatial resolution (Williams et al., 2009; Surrey et al. 2012). A portion of electrons are transferred when electron beam hits the material, while, remaining electrons are elastically or in elastically dispersed (Kohl et al., 2008). The specimens must also be prepared and handled with utmost care because they are very thin and easily bent or broken. Thinning specimens to an electron transparent thickness is a necessary step in the production of TEM specimens. After that, sample is viewed under a table light to confirm the level of polishing without taking it out of holder. After that, procedure can be continued by replacing sample holder in electrolyte. It should just take a few minutes to complete this process. After quickly turning off power supply, sample holder is removed from electrolyte and carefully immersed in a beaker of methanol. The table lamp's light may be used to examine disc's perforation. Utilizing forceps, sample is extracted from holder, cleaned with methanol, and then relocated to a new petri dish filled with methanol. This procedure will remove the sample's electrolyte layer, if any exists. Next, a filter paper is used to dry the sample. In TEM, it may be briefly inspected (Rao et al., 2010). Several parameters, including size, elemental composition, and sample density, influence the interaction's strength. The final picture is constructed by the data obtained from transmitted electrons (Mourdikoudis et al., 2018).

TEM is most widely used approach for analyzing the shape and size of NPs because it offers not only direct images of the specimen but also the most precise estimate for homogeneity of each NP (Mourdikoudis et al., 2018). TEM is a technique for examining the synthesis of different super lattice nano-composites materials, which may be iso-structural to

several systems of atomic crystals (Shevchenko et al., 2006). TEM is usually used to see a single NP because of its high resolution (Ostrowski et al., 2015). Another benefit of TEM, is the ability to evaluate alterations in sub cellular structures brought on by NPs (Mourdikoudis et al., 2018).

High-resolution Transmission Electron Microscopy

A very effective technique for analyzing nanomaterials is electron microscopy with high resolution (HR-TEM), which is essential tool of nanotechnology (Wang, 2003a). A TEM imaging mode called HR-TEM (High-resolution transmission electron microscopy) can image both transmitted and scattered electrons (Andujar et al., 2016). HR-TEM requires larger objective aperture than conventional TEM in order to exploit the scattered electrons for imaging (Mourdikoudis et al., 2018).

While traditional electron microscope may offer an analysis of statistics evaluation of NPs form, single particle crystal structure cannot be seen because of their lack of resolution. This makes HR-TEM a valuable tool for learning about structure of NPs. As a result, most effective technique for characterizing NPs internal structure is now HR-TEM. Additionally, impact of materials on characteristics of metallic NPs has also been clarified by using HR-TEM (Mourdikoudis et al., 2018). HR-TEM is able to differentiate between anisotropic polycrystalline and single crystal Au NPs with comparable optical characteristics (Pallares et al., 2016). HR-TEM has been traditionally used primarily for solid material imaging, diffraction, and chemical analysis (Wagner, 1993).

Atomic Force Microscopy

AFMs, a kind of probe microscopes which employ tiny probes instead of electrons or light beams to examine a surface. Three-dimensional views of surfaces may be obtained using this kind of microscope as depicted in Fig. 3. AFM contains a tip that can be adjusted in numerous ways to examine surface qualities; as such, it is more evolved version of STM which is capable of imaging practically any form of surfaces at micro sizes (Vahabi et al., 2013). In 1986 at IBM AFM was invented by Heinrich Rohrer and Gerard Binning (Binnig et al., 1986). The degree of closeness between sample and probe will determine, AFM may scan in 3 distinct modes: tapping mode, non-contact and contact mode (sometimes referred to as intermediate or in an oscillating form) (Clemente et al., 2008).

One benefit of AFM is that it doesn't require surface modification or coating before imaging. Therefore, AFM has been used without any specific treatment to perform topological description of tiny NPs (less than 6 nm), like ion-doped Yttrium oxide (Y_2O_3) (Patel- et al., 2007). Over last ten years, AFM has become highly effective instrument for obtaining biomechanical characteristics and nanostructural information of biological materials, such as cells and biomolecules. (Charrasand Horton, 2002; Horber et al., 2003; Pelling et al., 2004; Greenleaf et al., 2007). The primary benefit of AFM method in biology is its ability to examine biological samples in their native habitat. This is particularly useful for examining biological samples in buffer solutions *in-vitro*, *in-situ*, or even *in-vivo* a technique that used to require a lot of time to prepare (Yang et al., 1999; Sokolov, 2007;). In realm of cell biology, it can also detect live cells' surfaces down to single molecules (Hoh et al., 1994; Mathur et al., 2000; Berdyyeva et al., 2004; Rabinovich et al., 2005; Zhao et al., 2005). Researching nanoscale, *in-situ* Deoxyribonucleic acid (DNA) structures using AFM has shown interest in creation of more potent gene delivery vehicles (Vahabi et al., 2013).

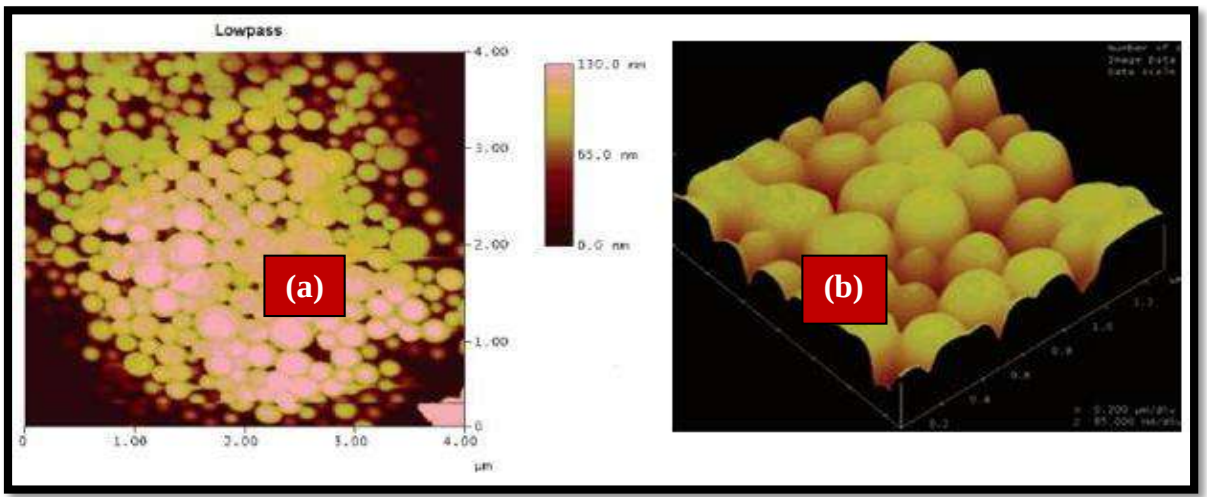


Fig. 3: AFM pictures of PLA-Tween 80-10 nanoparticles loaded with paclitaxel (a) 2D picture of 4 µm by 4 µm and (b) a 3D picture magnified (Zhang and Feng 2006).

Optical studies

Photoluminescence Spectroscopy

PL spectroscopy is an additional method for studying materials at nanoscale; it tracks light released by atoms or molecules that have taken up photons. For characterization of metal nano-clusters and fluorescent NPs like quantum dots,

PL is usually helpful. Depending on the type of study, possible PL spectrum is recorded as absorption or emission (Khan et al., 2019). Inherent PL of metallic NPs has attracted a lot of attention recently (Mourdikoudis et al., 2018).

Additionally, PL views this technique as useful for researching the visual characteristics of photosensitive NPs and different NPs. Furthermore, this method is effective in determining layer thickness (Lin et al., 2015), material doping amount (Huang et al., 2012; Gupta et al., 2013) and defects/oxygen vacancies (Torchynska et al., 2016) of NPs.

Ultraviolet–visible Spectroscopy

One rapid analytical technique to determine a light transmittance or absorbance is UV-vis spectroscopy (García et al., 2007). The feasible range for UV-vis spectroscopy is 200–800 nm range; wavelength underneath 200 nm is consider as vacuum UV while wavelength more than 800 nm is considered infrared (Rocha et al., 2018).

Chromophores are stimulated when UV-vis light strikes them; this process is known as electron-excitation. On other hand, auxochromes are electron-donating substances that may alter the color of choromophores without changing their own color. A great medium for UV-visible spectroscopy is alcohols and water generally they are transparent and they don't absorb in the UV-vis spectrum (Gürses et al., 2016). Using UV-vis spectrophotometer, light is passed through a specimen and on other side transmitted light is recorded by detector as depicted in Fig. 4. Transitions from one band to another, either longer wavelengths (red shifts) or shorter wavelengths (blue shifts), are known as bathochromic shifts and hypochromic. The terms hyperchromism and hypochromism refer to variations in the peak intensity of an absorption band (Robinson et al.,2005). The transmittance indicates amount of light absorbed at every spectrum, primarily consider greatest peak as λ_{max}. UV-visible spectroscopy is based on electronic transitions of organic molecules that excite electrons from lower energy orbital (highest occupied molecular orbital, or HOMO) to higher energy unoccupied orbital (lowest unoccupied molecular orbital, or LUMO) upon absorption of light (Rocha et al., 2018).

Applications in chemical engineering includes waste-water treatment, (Halim et al., 2016; Farias et al., 2017; Xiao et al., 2017; Quinlan et al., 2017; Zhou et al., 2017; Rocha et al., 2018) degradation of dyes, (Fan et al., 2017; Liu et al., 2017) and characterization of silver colloidal NPs, (Nogueira et al., 2016; Chen et al., 2017) copper (Das and Srivastava, 2016; Kalidhasan et al., 2017) and gold, (Haiss et al., 2007) . The semiconductor band separation is deliberate using UV-vis diffuse reflectance spectroscopy, which is very helpful in photo catalysis research (Rocha et al., 2018).

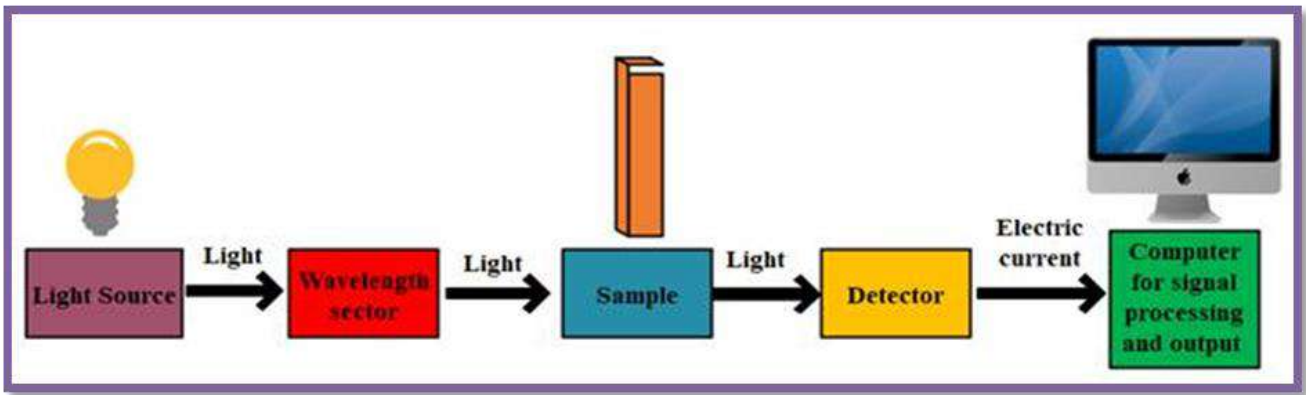


Fig. 4: Principle of Ultra visible spectroscopy

Ultraviolet-visible Diffuse Reflectance Spectrometer

UV-vis diffuse reflectance spectrometer (DRS) is a comprehensive tool for deliberate transmittance, reflectance and optical absorption (Khan et al., 2019). DRS spectroscopy is a type of spectroscopy that relies on powdered sample reflecting light in visible, near-infrared, and ultraviolet (vis) regions. The ratio of scattered light from an infinitely thick layer to scattered light from perfect non-absorbing reference sample is calculated as function of wavelength in DRS spectrum. Diffuse illumination of powdered samples is produced when incoming radiation illuminates them. Part of incident light is dispersed and partially absorbed. The sample's dispersed radiation is gathered in an integration sphere and detected (Weckhuysen and Schoonheydt, 1999). The bandgap is computed first by determining electronic state of sample by resultant diffuse reflectance spectra. The technique works incredibly well for determining out band gaps of a variety of NPs and other nanomaterials (Khan et al., 2019). Determining the bandgap is essential for evaluating conductance and photocatalytic characteristics, particularly for semiconductor NPs (Zhang et al., 2014). Comparably, this technique is also used to observe shift in absorbance when doping, composite formation, or heterostructured NPs materials are present (Zhang et al., 2014).

Structural Analysis

Brunauer-Emmett-Teller

The most efficient technique BET is used for measuring out NPs surface area. The substantial surface area of NPs provides infinite space intended for different uses. This method relies on Brunauer-Emmett-Teller (BET) theorem and

desorption and adsorption principle. For this, nitrogen gas (N_2) is often utilized (Khan et al., 2019). Since, there is little contact between the solid and gaseous phases, a partial vacuum is established during BET analysis in order to induce adsorption between sample and liquid N_2. This allows for surface to be cooled and observable levels of adsorption to be obtained.

At which point the amount of adsorption mono layers is formed the sample is taken out of N_2 environment and heated to induce the material adsorbed N_2 to be release (desorbs), after which the amount is measured. Isotherms (graphs that show how much N_2 is adsorbed function as a relative pressure on fixed heat) are used to portray gathered data. The surface area of sample is calculated using the data, which is shown in five isotherms (Naderi, 2015; Khan et al., 2019).

X-ray Diffraction

The most important characterization techniques for enlightening the structure properties of NPs are XRD. It provides sufficient information on phase and crystalline nature of NPs. Moreover, it offers a general notion size of particles via Debye-Scherer formula (Khan et al., 2017; Khanet al., 2017; Khan et al., 2017).

$$D=K\lambda / \beta Cos\theta$$

Where D is nanoparticles crystalline size, K represents Scherer constant (0.98), λ denotes wavelength (1.54), β denotes full width at half maximum (FWHM).

XRD methods are based on ability of crystals to diffract X-rays in a characteristic manner allowing precise study of the structure of crystalline phases. Recorded diffraction patterns contain additive contributions of several micro- and macro structural features of a sample as elaborated in Fig 5 (Epp, 2016). This method is well performed for identifying NPs both as solitary and multiphase processes (Emery et al. ,2016). This method is based on incident X-rays being applied to a material and then measuring the X-rays' scattering angles and intensities as they exit from substance (Epp, 2016). Based on peak intensity, information about crystal structure (atomic positions, temperature factor, or occupancy) as well as texture and quantitative phase analyses can be obtained. Finally, peak shape gives information about sample broadening contributions (micro strains and crystallite size) (Dinnebier and Billinge, 2008). However, when samples exhibit highly amorphous properties with varying inter-atomic distance or when nanomaterials are less than few hundred of atoms, resolution and accuracy of XRD may be reduced (Khan et al., 2019).

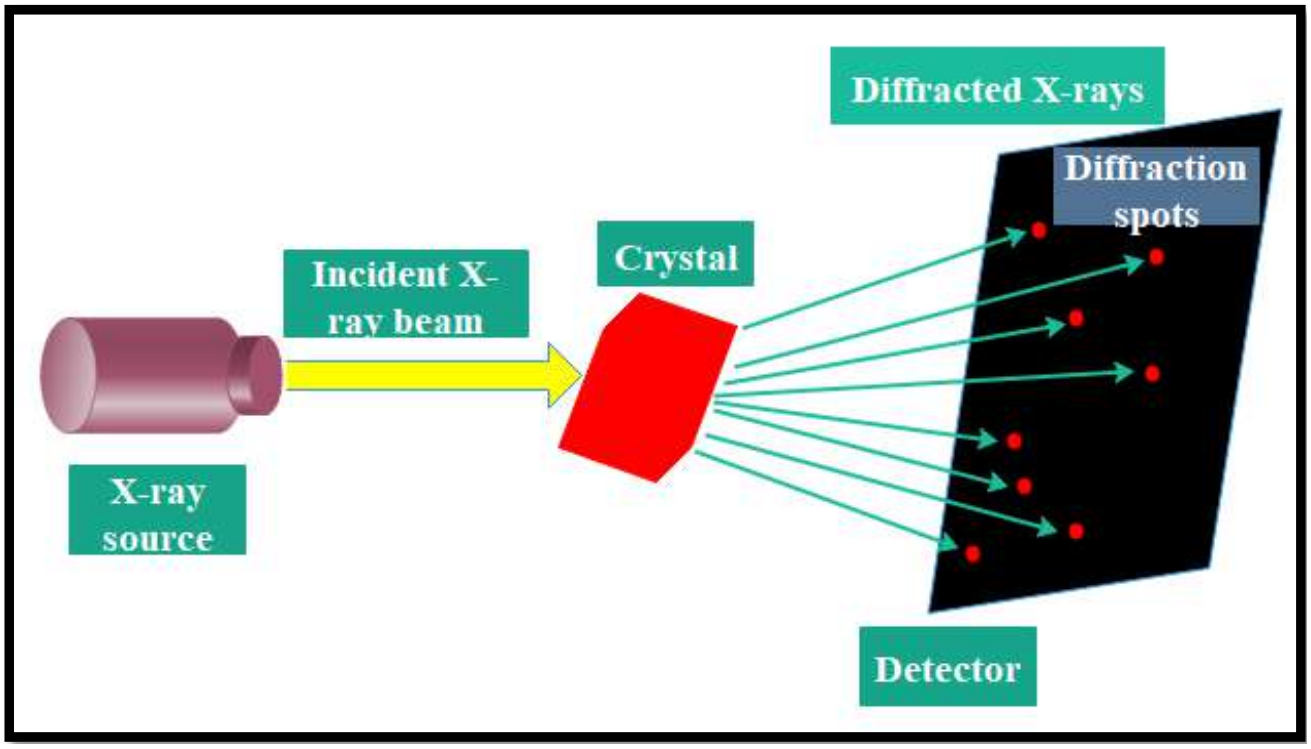


Fig. 5: An X-ray diffraction experiment's basic plan. A detector records the diffraction pattern, or "diffraction spots," created by the diffracted rays of an incoming X-ray beam entering the crystal.

Elemental Studies

Energy Dispersive X-ray Spectroscopy

Energy dispersive X-ray spectroscopy (EDX) is a non-destructive method for element classification by using scanning electron microscopy (SEM). A uniform energy of electron beam stimulates atoms in the sample, producing X-ray with distinct energy for every component which means energies of radiation released reveals elemental composition of specimen (Goldstein et al., 2017) as depicted in Fig 6. Electrons from inside shells of atoms with in specimens are removed

during contact by incoming beam of electrons, while outer shells orbits are replaced by vacancies. The energy released in the form of X-rays is a result of two shells' different energy levels. The chemical structure of sample may establish since X-ray intensity are intensities of the constituent components. Furthermore, concentration of that element in electron beams path determines the signal's strength of X-ray at any given energy intensity (Al-Fulaij et al.,2006) (Scoutaris et al., 2014).

EDX has been used in past for phase distribution and identification (Inman et al., 2007; Chen et al., 2013) enterically coated tablet dissolution (Liu et al., 2009) and composition of hydroxyapatite biomimetic coatings (Nie et al.,2000) examination of tiny size components (Doménech-Carbó et al., 2001; Iannuccelli et al., 2013; Gao et al.,2014) identification of alloys, and examination of foreign materials (Vilhelmsen et al., 2005; Chen et al.,2012). Using SEM images, EDX mapping may be utilized to evaluate the whole distribution of molecules on surfaces.

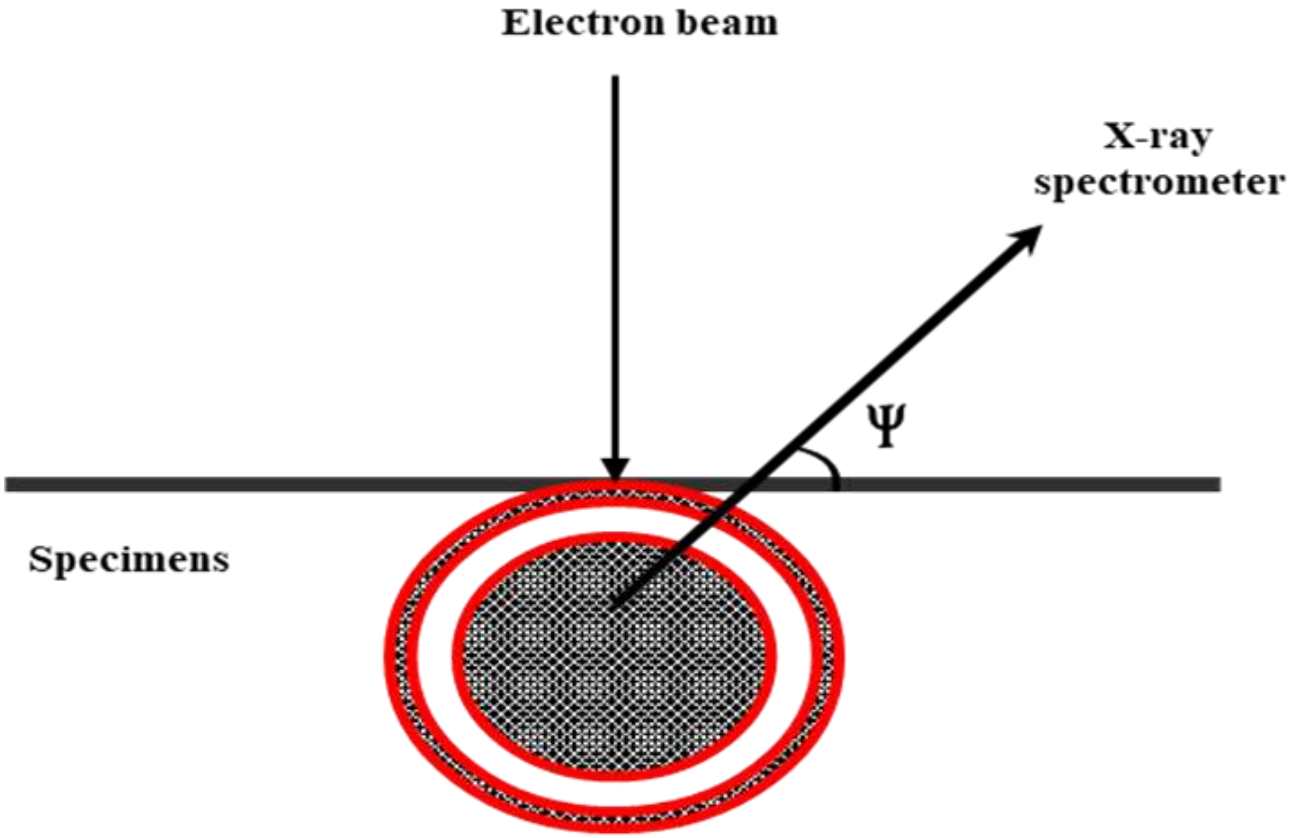


Fig. 6: X-ray source region where (X-ray path to the spectrometer, is represented by ψ being the take-off angle)

Raman Spectroscopy

The use of Raman spectroscopy has not regarded as valuable systematic technique for many years due to extremely poor competence of "typical" scattering of Raman. A normal molecule's overall Raman scattering of sample is around 10^{-29} cm^2, while an infrared and ultraviolet molecule's typical cross-sections are approximately 10^{-18} and 10^{-21} cm^2, respectively (Aroca, 2006). Cross sections Raman scattering may be significantly greater than before, for example, to 2×10^{-14} cm^2 for every element (Michaels et al., 1999) by using special resonators made of metal nano-clusters. This is approximately greater than 15 orders of magnitude rather than normal Raman scattering, and it allows for even detection of single molecule's Raman spectrum (Kneipp et al., 1997; Michaels et al., 1999; S. Nie and Emory, 1997). Analysis of sample portions not exposed at the surface can be performed when specimens is semi-transparent (or transparent) to dispersed and stimulating radiation (Matousek et al., 2005; Eliasson and Matousek, 2007; Welter et al., 2007).

Raman spectrum a useful technique that may be regarded as fingerprint of compound for identification of many compounds (Kudelski, 2008). Non-destructive Raman examination of different living specimens is very important from an operational perspective (Schrader et al., 2005; Reitzenstein et al., 2007). The Raman mapping approach may also be used to provide comprehensive information on the distribution of certain molecules, such as secondary metabolites (Baranska et al., 2004; Baranska et al., 2005; Schrader et al., 2005). Raman spectroscopy has several biological applications, including detection of precancerous cells and differentiation of malignant from normal breast tissue. Demonstrated that Raman spectroscopy may distinguish malignant tumors from healthy breast tissue, and in mouse model, it may detect early neoplastic alterations (Baranska et al., 2005). Jess et al. demonstrated the potential of Raman spectroscopy a valuable instrument for early identification of human papillomavirus (HPV)-exposed cells (Jess et al., 2007). Analytical science will employ Raman spectroscopy much more as long as technology advances spectrometers as well as lasers are smaller, less costly, more dependable, and easier to operate (Kudelski, 2008).

Fourier Transform Infrared (FTIR) Spectroscopy

The oscillatory properties of co-factors and amino acids are investigated using Fourier transform infrared (FTIR) spectroscopy that is delicate to even smallest structure alterations. With Fourier transform infrared (FTIR) spectroscopy, reducing agents that are in charge of stabilizing, reducing, and capping metal nano materials might be found as depicted in mechanistic illustration shown in Fig. 7. It is known from studying FTIR spectra that functional groups adhere the surface of biosynthetic non-metals include -C = O-, -NH_2, and -SH- groups (Huq, 2020). If molecule's dipole moment changes during typical vibration mode, mode turns on infrared activation, meaning incident infrared light absorbs by it. For this reason, symmetric vibrations are typically undetectable in infrared. Specifically, all vibrations that are symmetrical with regard to center of a molecule are infrared inactive. All molecules, on the other hand, exhibit asymmetric vibrations. Since it is less selective than other spectroscopic techniques, we are able to examine the characteristics of practically each functional groups of a single specimen, particularly those of water molecules and amino acids. Between 4,000 and 1,000 cm^{-1} in the mid-infrared, two primary vibrational type are detected: which are oscillations along chemical bond involving bond length changes is stretching vibration (m); and vibration involving change in bond angles, particularly bending vibrations (p—out of plane, d—in plane).

Applications for Fourier transform infrared (FTIR) spectroscopy or infrared (IR) are many and include examination of tiny molecules, chemical complexes, cells, and tissues (Berthomieu and Hienerwadel, 2009). Additionally, the study of proteins has made greater use of FTIR spectroscopy. During enzyme reactions, protein folding, conformation, and molecular characteristics from protein active sites are examined using reaction-induced FTIR difference spectroscopy (Siebert and Hildebrandt, 2008).

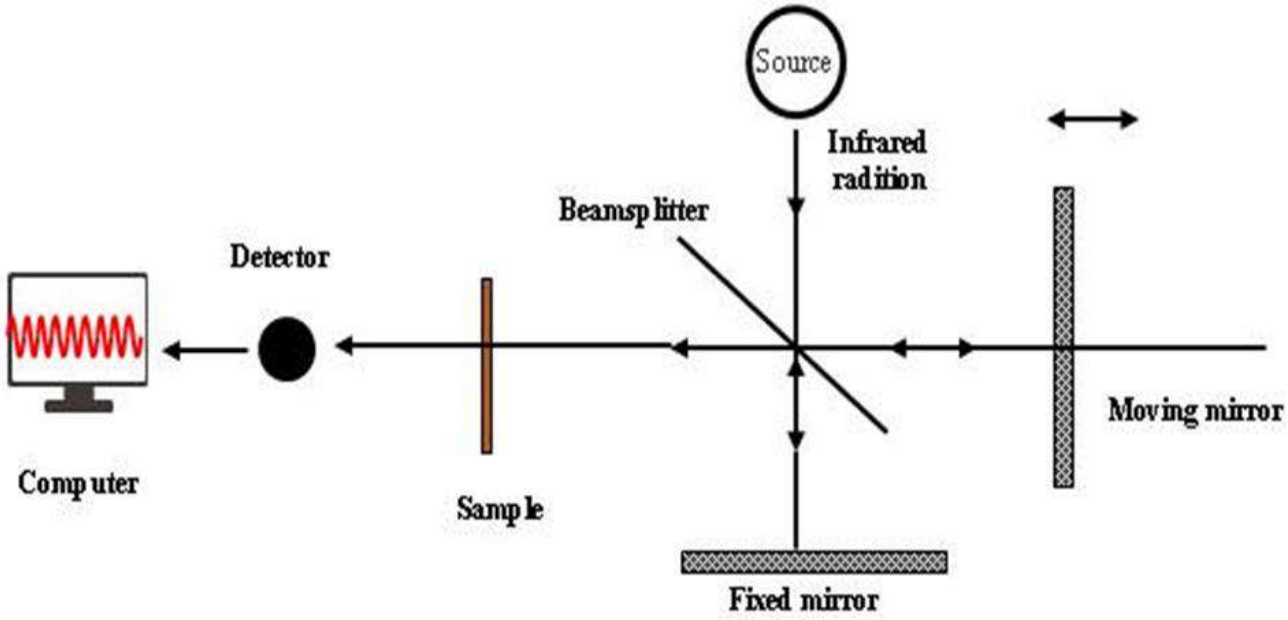


Fig. 7: Michelson interferometer's basic graphic, from Leng "Materials Characterization"

Chemical Studies

X-ray Photoelectron Spectroscopy

Among most effective methods for characterizing surface particularly assessment of corrosion, is X-ray photoelectron spectroscopy (XPS), this is capable of figuring out chemical makeup of various material surfaces within 10 nm. When examining surface reactions in vacuum, with relation to monolayer, XPS is very useful instrument. Tools for exploring nanoscale surface layers are crucial since layer on the surface involved in first surface reaction in relationship to surroundings is just a few nanometer thick as depicted in Fig. 8 (Krishna and Philip, 2022). Many different types of nanostructures are now regularly examined with XPS. The structure and shape of NPs may be crucial in accurately interpreting XPS (and relevant) information of any nanoscale-sized substance even though most XPS research is carried out under assumption that specimen has layer of uniformly smooth surface (Baer et al., 2010).

For understanding various crucial characteristics of nanostructure in natural and synthetic materials that are difficult to get through other methods, XPS is a valuable, well-established, and frequently indispensable instrument (Baer and Engelhard, 2010). Surface evaluation using XPS has recently, applied in number of domains, including mineral processing, biomedicine, electronics, corrosion, catalysis, nanomaterials, automotive, and aerospace etc (Krishna and Philip, 2022). The method is most frequently employed to determine nanomaterials' surface functionalization, element composition, coating thickness, adsorbents and in few situations, particle dimensions. For instance, core-shell structure and element composition of iron oxide NPs (Fe_3O_4 Fe_2O_3), as well as shell thickness at less than 1 nm, were effectively estimated using XPS (Anushree et al., 2020). X-ray photoelectron spectroscopy (XPS) is a tool use in material science to verify true

substance makeup as well as composition of surfaces and interfaces. In addition to these characteristics, XPS is also able to reveal the following: (i) distribution of element on shell; (ii) structure and thickness of surface layers; (iii) molecular orientation deposited on surface; (iv) coating material composition; and (v) size of NPs (1-20 nm).

In domain of organic materials and in biology, XPS offers knowledge that is comparable to that of material science. The plane chemistry of microorganisms, development of biocompatible materials, biofilms, and medicinal resources are all studied using XPS. Similar to this, in medicine, the surface characteristics of pharmacological medicines and biomaterials determine how they interact with the host body (Krishna and Philip, 2022).

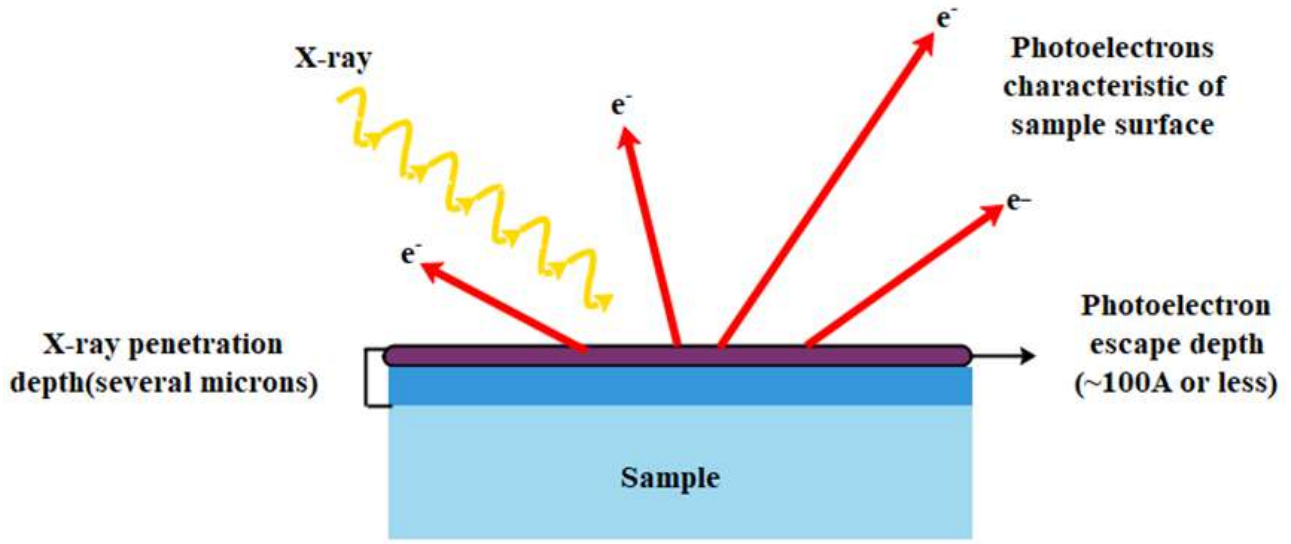


Fig. 8: X-ray photoelectron spectroscopy

Future Recommendation:

Naturally, there are barriers in scientific community that prevent accuracy and resolution of certain approaches from being further improved. As temperature, pressure, time, and pH may all have substantial impact on structure and morphology of NPs materials and produce novel products, future study should concentrate on optimizing these factors. Furthermore, certain characterization techniques have to be used for positive consequences and characteristics. It is increasingly important to think about environmental concerns before using these materials for any purpose, especially when it comes to heavy metals, which may negatively affect both environment and human health.

Conclusion

Nanotechnology, a key research area, focuses on advanced nanomaterials and manufacturing, leading to unique NPs properties. An overview of many important NPs characterization techniques is provided in this chapter. One of main areas of modern research is nanotechnology. A number of techniques for characterizing NPs are designed to help to explain their size, shape, optical, structural, elemental, and chemical characteristics. Every attribute may be obtained from various machines and through various methods. NPs characterization is carried out using different techniques, including SEM, TEM, HR-TEM, AFM, PL, UV, DRS, EDX, Raman, FTIR, BET, XPS and XRD.

REFERENCES

Al-Fulaij, O. A., Elassar, A. Z. A., and El-Dissouky, A. (2006). Synthesis, characterization, and ligating behavior of poly [N, N-p-phenylene bisacryl (methacryl) amide]. *Journal of Applied Polymer Science, 101*(4), 2412-2422.

Anushree, C., Krishna, D. N. G., Lahiri, B., and Philip, J. (2020). Enhanced thermal protection of iron oxide nanoparticle by insulating nanoporous char layer: effect of core size and char layer properties. *The Journal of Physical Chemistry C, 124*(10), 5702-5714.

Aroca, R. (2006). *Surface-enhanced vibrational spectroscopy*: John Wiley and Sons.

Baer, D. R., and Engelhard, M. H. (2010). XPS analysis of nanostructured materials and biological surfaces. *Journal of Electron Spectroscopy and Related Phenomena, 178*, 415-432.

Baer, D. R., Gaspar, D. J., Nachimuthu, P., Techane, S. D., and Castner, D. G. (2010). Application of surface chemical analysis tools for characterization of nanoparticles. *Analytical and Bioanalytical Chemistry, 396*, 983-1002.

Baranska, M., Schulz, H., Baranski, R., Nothnagel, T., and Christensen, L. P. (2005). In situ simultaneous analysis of polyacetylenes, carotenoids and polysaccharides in carrot roots. *Journal of Agricultural and Food Chemistry, 53*(17), 6565-6571.

Baranska, M., Schulz, H., Rösch, P., Strehle, M. A., and Popp, J. (2004). Identification of secondary metabolites in medicinal and spice plants by NIR-FT-Raman microspectroscopic mapping. *Analyst, 129*(10), 926-930.

Barbosa-García, O., Ramos-Ortiz, G., Maldonado, J., Pichardo-Molina, J., Meneses-Nava, M., Landgrave, J., and Cervantes-Martínez, J. (2007). UV–vis absorption spectroscopy and multivariate analysis as a method to discriminate tequila. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 66*(1), 129-134.

Berdyyeva, T. K., Woodworth, C. D., and Sokolov, I. (2004). Human epithelial cells increase their rigidity with ageing in vitro: direct measurements. *Physics in Medicine and Biology, 50*(1), 81.

Berthomieu, C., and Hienerwadel, R. (2009). Fourier transform infrared (FTIR) spectroscopy. *Photosynthesis Research, 101*, 157-170.

Binnig, G., Quate, C. F., and Gerber, C. (1986). Atomic force microscope. *Physical Review Letters, 56*(9), 930.

Blanco-Andujar, C., Walter, A., Cotin, G., Bordeianu, C., Mertz, D., Felder-Flesch, D., and Begin-Colin, S. (2016). Design of iron oxide-based nanoparticles for MRI and magnetic hyperthermia. *Nanomedicine, 11*(14), 1889-1910.

Chanderiya, A., Roy, A., and Das, R. (2024). Introduction to Advanced and Sustainable Green Nanomaterial. *Green Synthesis of Nanomaterials: Biological and Environmental Applications*, 1-21.

Charras, G. T., and Horton, M. A. (2002). Single cell mechanotransduction and its modulation analyzed by atomic force microscope indentation. *Biophysical Journal, 82*(6), 2970-2981.

Chen, H., Grassian, V. H., Saraf, L. V., and Laskin, A. (2013). Chemical imaging analysis of environmental particles using the focused ion beam/scanning electron microscopy technique: microanalysis insights into atmospheric chemistry of fly ash. *Analyst, 138*(2), 451-460.

Chen, Q., Mi, T., Chen, G., and Liu, G. (2017). Biosynthesis of silver nanoparticles applied for UV-curing conductive ink by using rice straw extract as reducing agent. *The Canadian Journal of Chemical Engineering, 95*(12), 2350-2356.

Chen, R., Zhang, Z., Lei, Z., and Sugiura, N. (2012). Preparation of iron-impregnated tablet ceramic adsorbent for arsenate removal from aqueous solutions. *Desalination, 286*, 56-62.

Das, S., and Srivastava, V. C. (2016). Synthesis and characterization of copper succinate and copper oxide nanoparticles by electrochemical treatment: Optimization by Taguchi robust analysis. *The Canadian Journal of Chemical Engineering, 94*(7), 1322-1327.

De Jong, W. H., and Borm, P. J. (2008). Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine, 3*(2), 133-149.

Dinnebier, R. E., and Billinge, S. J. (2008). *Powder diffraction: theory and practice*: Royal society of chemistry.

Doménech-Carbó, A., Doménech-Carbó, M. T., Gimeno-Adelantado, J. V., Bosch-Reig, F., Saurí-Peris, M. C., and Sánchez-Ramos, S. (2001). Electrochemistry of iron oxide pigments (earths) from pictorial microsamples attached to graphite–polyester composite electrodesElectronic supplementary information available. See http://www. rsc. org/suppdata/an/b1/b100257k. *Analyst, 126*(10), 1764-1772.

Eliasson, C., and Matousek, P. (2007). Noninvasive authentication of pharmaceutical products through packaging using spatially offset Raman spectroscopy. *Analytical Chemistry, 79*(4), 1696-1701.

Emery, A. A., Saal, J. E., Kirklin, S., Hegde, V. I., and Wolverton, C. (2016). High-throughput computational screening of perovskites for thermochemical water splitting applications. *Chemistry of Materials, 28*(16), 5621-5634.

Epp, J. (2016). X-ray diffraction (XRD) techniques for materials characterization *Materials characterization using nondestructive evaluation (NDE) methods* (pp. 81-124): Elsevier.

Fan, G., Lin, R., Su, Z., Lin, X., Xu, R., and Chen, W. (2017). Removal of Cr (VI) from aqueous solutions by titanate nanomaterials synthesized via hydrothermal method. *The Canadian Journal of Chemical Engineering, 95*(4), 717-723.

Farias, S., Mayer, D. A., de Oliveira, D., de Souza, A. A. U., and de Souza, S. M. G. U. (2017). Enzymatic reuse of simulated dyeing process effluent using horseradish peroxidase. *The Canadian Journal of Chemical Engineering, 95*(8), 1434-1441.

Fischer, H. C., and Chan, W. C. (2007). Nanotoxicity: the growing need for in vivo study. *Current Opinion in Biotechnology, 18*(6), 565-571.

Gao, W., Tjiu, W. W., Wei, J., and Liu, T. (2014). Highly sensitive nonenzymatic glucose and H2O2 sensor based on Ni (OH) 2/electroreduced graphene oxide− Multiwalled carbon nanotube film modified glass carbon electrode. *Talanta, 120*, 484-490.

Goldstein, J. I., Newbury, D. E., Michael, J. R., Ritchie, N. W., Scott, J. H. J., and Joy, D. C. (2017). *Scanning Electron Microscopy and X-ray Microanalysis*: springer.

Greenleaf, W. J., Woodside, M. T., and Block, S. M. (2007). High-resolution, single-molecule measurements of biomolecular motion. *Annual Review Biophysics Biomolecular Struct, 36*, 171-190.

Gupta, K., Singh, R., Pandey, A., and Pandey, A. (2013). Photocatalytic antibacterial performance of TiO2 and Ag-doped TiO2 against S. aureus. P. aeruginosa and E. coli. *Beilstein Journal of Nanotechnology, 4*(1), 345-351.

Gürses, A., Açıkyıldız, M., Güneş, K., Gürses, M. S., Gürses, A., Açıkyıldız, M., and Gürses, M. S. (2016). Dyes and pigments: their structure and properties. *Dyes and Pigments*, 13-29.

Haiss, W., Thanh, N. T., Aveyard, J., and Fernig, D. G. (2007). Determination of size and concentration of gold nanoparticles from UV− Vis spectra. *Analytical Chemistry, 79*(11), 4215-4221.

Halim, F. T., Guo, X., Su, G., Ngee, H. L., Zeng, X., He, N., and Danquah, M. K. (2016). Sustainable microalgae-based palm oil

mill effluent treatment process with simultaneous biomass production. *The Canadian Journal of Chemical Engineering, 94*(10), 1848-1854.

Hoh, J. H., and Schoenenberger, C.-A. (1994). Surface morphology and mechanical properties of MDCK monolayers by atomic force microscopy. *Journal of Cell Science, 107*(5), 1105-1114.

Horber, J., and Miles, M. J. (2003). Scanning probe evolution in biology. *Science, 302*(5647), 1002-1005.

Huang, C.-W., Lin, B.-J., Lin, H.-Y., Huang, C.-H., Shih, F.-Y., Wang, W.-H., and Chui, H.-C. (2012). Observation of strain effect on the suspended graphene by polarized Raman spectroscopy. *Nanoscale Research Letters, 7*, 1-6.

Huq, M. A. (2020). Biogenic silver nanoparticles synthesized by Lysinibacillus xylanilyticus MAHUQ-40 to control antibiotic-resistant human pathogens Vibrio parahaemolyticus and Salmonella Typhimurium. *Frontiers in Bioengineering and Biotechnology, 8*, 597502.

Iannuccelli, V., Coppi, G., Romagnoli, M., Sergi, S., and Leo, E. (2013). In vivo detection of lipid-based nano-and microparticles in the outermost human stratum corneum by EDX analysis. *International Journal of Pharmaceutics, 447*(1-2), 204-212.

Inman, S., Briscoe, B., and Pitt, K. (2007). Topographic characterization of cellulose bilayered tablets interfaces. *Chemical Engineering Research and Design, 85*(7), 1005-1012.

Jayawardena, H. S. N., Liyanage, S. H., Rathnayake, K., Patel, U., and Yan, M. (2021). Analytical methods for characterization of nanomaterial surfaces. *Analytical Chemistry, 93*(4), 1889-1911.

Jess, P. R., Smith, D. D., Mazilu, M., Dholakia, K., Riches, A. C., and Herrington, C. S. (2007). Early detection of cervical neoplasia by Raman spectroscopy. *International Journal of Cancer, 121*(12), 2723-2728.

Joudeh, N., and Linke, D. (2022). Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *Journal of Nanobiotechnology, 20*(1), 262.

Kalidhasan, S., Ben-Sasson, M., Dror, I., Carmieli, R., Schuster, E. M., and Berkowitz, B. (2017). Oxidation of aqueous organic pollutants using a stable copper nanoparticle suspension. *The Canadian Journal of Chemical Engineering, 95*(2), 343-352.

Khan, I., Ali, S., Mansha, M., and Qurashi, A. (2017). Sonochemical assisted hydrothermal synthesis of pseudo-flower shaped Bismuth vanadate (BiVO4) and their solar-driven water splitting application. *Ultrasonics Sonochemistry, 36*, 386-392.

Khan, I., Ibrahim, A. A., Sohail, M., and Qurashi, A. (2017). Sonochemical assisted synthesis of RGO/ZnO nanowire arrays for photoelectrochemical water splitting. *Ultrasonics Sonochemistry, 37*, 669-675.

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry, 12*(7), 908-931.

Khan, I., Yamani, Z. H., and Qurashi, A. (2017). Sonochemical-driven ultrafast facile synthesis of SnO2 nanoparticles: Growth mechanism structural electrical and hydrogen gas sensing properties. *Ultrasonics Sonochemistry, 34*, 484-490.

Kim, F., Connor, S., Song, H., Kuykendall, T., and Yang, P. (2004). Cover Picture: Platonic Gold Nanocrystals (Angew. Chem. Int. Ed. 28/2004). *Angewandte Chemie International Edition, 43*(28), 3615-3615.

Kneipp, K., Wang, Y., Kneipp, H., Perelman, L. T., Itzkan, I., Dasari, R. R., and Feld, M. S. (1997). Single molecule detection using surface-enhanced Raman scattering (SERS). *Physical Review Letters, 78*(9), 1667.

Kohl, H., and Reimer, L. (2008). Transmission Electron Microscopy. *Springer Series in Optical Sciences, 36*.

Krishna, D. N. G., and Philip, J. (2022). Review on surface-characterization applications of X-ray photoelectron spectroscopy (XPS): Recent developments and challenges. *Applied Surface Science Advances, 12*, 100332.

Kudelski, A. (2008). Analytical applications of Raman spectroscopy. *Talanta, 76*(1), 1-8.

Lin, G., Zhang, Q., Lin, X., Zhao, D., Jia, R., Gao, N., and Liu, D. (2015). Enhanced photoluminescence of gallium phosphide by surface plasmon resonances of metallic nanoparticles. *RSC Advances, 5*(60), 48275-48280.

Liu, F., Lizio, R., Schneider, U. J., Petereit, H.-U., Blakey, P., and Basit, A. W. (2009). SEM/EDX and confocal microscopy analysis of novel and conventional enteric-coated systems. *International Journal of Pharmaceutics, 369*(1-2), 72-78.

Liu, M., Liu, Y., Zhang, D., Pan, J., Liu, B., and Ouyang, S. (2017). Facile fabrication of H2BDC-NH2 modified anatase TiO2 for effective photocatalytic degradation of azo dyes. *The Canadian Journal of Chemical Engineering, 95*(5), 922-930.

Machado, S., Pacheco, J., Nouws, H., Albergaria, J. T., and Delerue-Matos, C. (2015). Characterization of green zero-valent iron nanoparticles produced with tree leaf extracts. *Science of the Total Environment, 533*, 76-81.

Mathur, A. B., Truskey, G. A., and Reichert, W. M. (2000). Atomic force and total internal reflection fluorescence microscopy for the study of force transmission in endothelial cells. *Biophysical Journal, 78*(4), 1725-1735.

Matousek, P., Morris, M., Everall, N., Clark, I., Towrie, M., Draper, E., and Parker, A. (2005). Numerical simulations of subsurface probing in diffusely scattering media using spatially offset Raman spectroscopy. *Applied Spectroscopy, 59*(12), 1485-1492.

Michaels, A. M., Nirmal, M., and Brus, L. (1999). Surface enhanced Raman spectroscopy of individual rhodamine 6G molecules on large Ag nanocrystals. *Journal of the American Chemical Society, 121*(43), 9932-9939.

Mohammed, A., and Abdullah, A. (2018). *Scanning Electron Microscopy (SEM): A review.* Paper presented at the Proceedings of the 2018 International Conference on Hydraulics and Pneumatics—HERVEX, Băile Govora, Romania.

Mourdikoudis, S., Pallares, R. M., and Thanh, N. T. (2018). Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. *Nanoscale, 10*(27), 12871-12934.

Naderi, M. (2015). Surface area: brunauer–emmett–teller (BET) *Progress in filtration and separation* (pp. 585-608): Elsevier.

Nie, S., and Emory, S. R. (1997). Probing single molecules and single nanoparticles by surface-enhanced Raman scattering. *Science, 275*(5303), 1102-1106.

Nie, X., Leyland, A., and Matthews, A. (2000). Deposition of layered bioceramic hydroxyapatite/TiO2 coatings on titanium alloys using a hybrid technique of micro-arc oxidation and electrophoresis. *Surface and Coatings Technology, 125*(1-3), 407-414.

Nogueira, A. L., Machado, R. A., de Souza, A. Z., Franco, C. V., and Dutra, G. B. (2016). Influence of process parameters and scalability of the semi-batch production of functionalized silver nanoparticles. *The Canadian Journal of Chemical Engineering, 94*(8), 1472-1485.

Ostrowski, A., Nordmeyer, D., Boreham, A., Holzhausen, C., Mundhenk, L., Graf, C., and Lademann, J. (2015). Overview about the localization of nanoparticles in tissue and cellular context by different imaging techniques. *Beilstein Journal of Nanotechnology, 6*(1), 263-280.

Pallares, R. M., Wang, Y., Lim, S. H., K Thanh, N. N. T., and Su, X. (2016). Growth of anisotropic gold nanoparticles in photoresponsive fluid for UV sensing and erythema prediction. *Nanomedicine, 11*(21), 2845-2860.

Patel, D., Perry, C., and Kennedy, S. (2007). *Spectroscopic studies and AFM analysis of Ho3+ and Tm3+ doped yttrium oxide nanoparticles*. Paper presented at the Optical Components and Materials IV.

Pelling, A. E., Sehati, S., Gralla, E. B., Valentine, J. S., and Gimzewski, J. K. (2004). Local nanomechanical motion of the cell wall of Saccharomyces cerevisiae. *Science, 305*(5687), 1147-1150.

Quinlan, P. J., Grishkewich, N., and Tam, K. C. (2017). Removal of 2-naphthoxyacetic acid from aqueous solution using quaternized chitosan beads. *The Canadian Journal of Chemical Engineering, 95*(1), 21-32.

Rabinovich, Y., Esayanur, M., Daosukho, S., Byer, K., El-Shall, H., and Khan, S. (2005). Atomic force microscopy measurement of the elastic properties of the kidney epithelial cells. *Journal of Colloid and Interface Science, 285*(1), 125-135.

Rao, D. S., Muraleedharan, K., and Humphreys, C. (2010). TEM specimen preparation techniques. *Microscopy: Science, Technology, Applications and Education, 2*, 1232.

Reitzenstein, S., Rösch, P., Strehle, M. A., Berg, D., Baranska, M., Schulz, H., and Popp, J. (2007). Nondestructive analysis of single rapeseeds by means of Raman spectroscopy. *Journal of Raman Spectroscopy: An International Journal for Original Work in all Aspects of Raman Spectroscopy, Including Higher Order Processes, and also Brillouin and Rayleigh Scattering, 38*(3), 301-308.

Robinson, J. W., Frame, E. M. S., Frame, G. M., Eileen, M., and Skelly, F. (2005). Undergraduate instrumental analysis.

Rocha, F. S., Gomes, A. J., Lunardi, C. N., Kaliaguine, S., and Patience, G. S. (2018). Experimental methods in chemical engineering: Ultraviolet visible spectroscopy—UV-Vis. *The Canadian Journal of Chemical Engineering, 96*(12), 2512-2517.

Schellauf, F. (2019). Regulation of Nanomaterials in Cosmetic Products on the EU Market. *Nanocosmetics: From Ideas to Products*, 337-346.

Schrader, B., Schulz, H., Baranska, M., Andreev, G. N., Lehner, C., and Sawatzki, J. (2005). Non-destructive Raman analyses–polyacetylenes in plants. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 61*(7), 1395-1401.

Scoutaris, N., Vithani, K., Slipper, I., Chowdhry, B., and Douroumis, D. (2014). SEM/EDX and confocal Raman microscopy as complementary tools for the characterization of pharmaceutical tablets. *International Journal of Pharmaceutics, 470*(1-2), 88-98.

Shevchenko, E. V., Talapin, D. V., Kotov, N. A., O'Brien, S., and Murray, C. B. (2006). Structural diversity in binary nanoparticle superlattices. *Nature, 439*(7072), 55-59.

Shin, W.-K., Cho, J., Kannan, A. G., Lee, Y.-S., and Kim, D.-W. (2016). Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO2 nanoparticles for lithium-ion polymer batteries. *Scientific Reports, 6*(1), 26332.

Siebert, F., and Hildebrandt, P. (2008). *Vibrational spectroscopy in life science*: John Wiley and Sons.

Sokolov, I. (2007). Atomic force microscopy in cancer cell research. *Cancer nanotechnology, 1*, 1-17.

Surrey, A., Pohl, D., Schultz, L., and Rellinghaus, B. (2012). Quantitative measurement of the surface self-diffusion on Au nanoparticles by aberration-corrected transmission electron microscopy. *Nano Letters, 12*(12), 6071-6077.

Tiwari, J. N., Tiwari, R. N., and Kim, K. S. (2012). Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. *Progress in Materials Science, 57*(4), 724-803.

Torchynska, T., El Filali, B., Ballardo Rodríguez, I. C., and Shcherbyna, L. (2016). Defect related emission of ZnO and ZnO Cu nanocrystals prepared by electrochemical method. *Physica Status Solidi (c), 13*(7-9), 594-597.

Vahabi, S., Salman, B. N., and Javanmard, A. (2013). Atomic force microscopy application in biological research: a review study. *Iranian Journal of Medical Sciences, 38*(2), 76.

Vernon-Parry, K. D. (2000). Scanning electron microscopy: an introduction. *III-Vs Review, 13*(4), 40-44.

Vilalta-Clemente, A., Gloystein, K., and Frangis, N. (2008). Principles of atomic force microscopy (AFM). *Proceedings of Physics of Advanced Materials Winter School*, 1-8.

Vilhelmsen, T., Eliasen, H., and Schæfer, T. (2005). Effect of a melt agglomeration process on agglomerates containing solid dispersions. *International Journal of Pharmaceutics, 303*(1-2), 132-142.

Wagner, G. (1993). PR Buseck, JM Cowley, L. Eyring. High-Resolution Transmission Electron Microscopy and Associated

Techniques. Oxford University Press, Inc. 1992. Price£ 27.50. ISBN 0-19-507262-6 (pbk.) and ISBN 0-19-504275-1: Wiley Online Library.

Wang, Z. L. (2003a). *Handbook of Nanophase and Nanostructured Materials; Vol. III: Materials Systems and Applications I*.

Wang, Z. L. (2003b). New developments in transmission electron microscopy for nanotechnology. *Advanced Materials, 15*(18), 1497-1514.

Weckhuysen, B. M., and Schoonheydt, R. A. (1999). Recent progress in diffuse reflectance spectroscopy of supported metal oxide catalysts. *Catalysis Today, 49*(4), 441-451.

Welter, N., Schüssler, U., and Kiefer, W. (2007). Characterisation of inorganic pigments in ancient glass beads by means of Raman microspectroscopy, microprobe analysis and X-ray diffractometry. *Journal of Raman Spectroscopy: An International Journal for Original Work in all Aspects of Raman Spectroscopy, Including Higher Order Processes, and also Brillouin and Rayleigh Scattering, 38*(1), 113-121.

Williams, D. B., Carter, C. B., Williams, D. B., and Carter, C. B. (2009). How to 'See'Electrons. *Transmission Electron Microscopy: A Textbook for Materials Science*, 115-126.

Xiao, X., Sun, Y., Sun, W., Shen, H., Zheng, H., Xu, Y., and Liu, C. (2017). Advanced treatment of actual textile dye wastewater by Fenton-flocculation process. *The Canadian Journal of Chemical Engineering, 95*(7), 1245-1252.

Yang, S. M., Sokolov, I., Coombs, N., Kresge, C. T., and Ozin, G. A. (1999). Formation of hollow helicoids in mesoporous silica: supramolecular origami. *Advanced Materials, 11*(17), 1427-1431.

Zhang, P., Hong, R., Chen, Q., and Feng, W. (2014). On the electrical conductivity and photocatalytic activity of aluminum-doped zinc oxide. *Powder Technology, 253*, 360-367.

Zhang, Z., and Feng, S.-S. (2006). In vitro Investigation on poly (lactide)− tween 80 copolymer nanoparticles fabricated by dialysis method for chemotherapy. *Biomacromolecules, 7*(4), 1139-1146.

Zhao, L., Schaefer, D., and Marten, M. R. (2005). Assessment of elasticity and topography of Aspergillus nidulans spores via atomic force microscopy. *Applied and Environmental Microbiology, 71*(2), 955-960.

Zhou, Z., Ma, Y., Liu, Y., Lu, S., and Ren, Z. (2017). Formation of hydrogen peroxide and treatment of Sunset Yellow wastewater using pulsed high-voltage discharge system. *The Canadian Journal of Chemical Engineering, 95*(2), 290-296

Chapter 13

Revolutionizing Nanoparticles in Veterinary Care: Classifications and Benefits

Muhammad Uzair[1*], Muhammad Ali[1], Muhammad Ahsan Sheraz[1], Rida Nawaz[1], Shabab Ahmad[2], Areesha Arkan[3], Khushbo Prince[4], Ali Abdullah[5], Muhammad Ali Assad[6], Habiba Shabbir[7] and Momna Mehmood[8*]

[1]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Department of Parasitology, Faculty of Veterinary Sciences, University of Veterinary and Animal Sciences, Lahore, Pakistan
[3]Department of Veterinary Surgery, Faculty of Veterinary Sciences, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Department of Clinical Medicine and Surgery, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[5]Department of Microbiology, Faculty of Veterinary Science, Cholistan University of Veterinary and Animal Science, Bahawalpur, Pakistan
[6]Department of Clinical Science (Section of Epidemiology and Public Health), University of Veterinary and Animal Science, Lahore, Pakistan
[7]Department of Zoology, Faculty of Life Sciences, Government College University, Lahore, Pakistan
[8]Department of Animal and Dairy Sciences, MNS University of Agriculture, Multan, Pakistan
*Corresponding author: 2020ag8941@uaf.edu.pk; momna.mehmood@mnsuam.edu.pk

ABSTRACT

The development of new methods for working with materials at the nanoscale has affected many medical fields. Thousands of nanomaterials exist today, and they can be categorized based on their shape, place of origin, or application. Nanotechnology offered fresh approaches to time-honored issues. They are employed in the medical sciences for either therapeutic or diagnostic objectives. They can also be used to make nano-adjuvants and nano-vaccines. Its use in cancer treatment and gene therapy ushered forth a new era in medicine. In the veterinary field, nanotechnology is now finding a lot of applications. They are quickly taking over the fields of animal nutrition, diagnostics, farm disinfectants, veterinary vaccine manufacturing, and animal breeding and reproduction. The public's health is immediately affected when they are substituted for commonly used antibiotics. These measures address the problem of residues in meat and milk and lessen drug resistance in both veterinary and human treatment. Additionally, this approach offers significant economic benefits by decreasing the quantity of milk that is wasted and reducing the number of culling of calves in dairy herds. Additionally, nanotechnology has been used in the development of sanitary products and pet care items. This chapter covers the many types of nanoparticles, the advantages of using nanomaterials over their equivalents, and the applications of nanotechnology in the field of animal care.

KEYWORDS
Nanovaccines, Nanomedicine, Nanotechnology, Nanomaterials, Nanoadjuvants

Received: 16-May-2024
Revised: 06-Jul-2024
Accepted: 10-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Uzair M, Ali M, Sheraz MA, Nawaz R, Ahmad S, Arkan A, Prince K, Abdullah A, Assad MA, Shabbir H and Mehmood M, 2024. Revolutionizing nanoparticles in veterinary care: classifications and benefits. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 107-118. https://doi.org/10.47278/book.CAM/2024.234

INTRODUCTION

The term "nanotechnology" was first coined in the year 1974 to describe technical tools used to manipulate materials at the nanoscale. Materials with dimensions between 1 and 100 nanometers are considered to be at the nanoscale. Examples of naturally occurring nanoscale biological materials include protein molecules, which are approximately 5 nanometers wide, and DNA molecules, which are about 2.5 nanometers wide. In contrast, human hair is roughly 80,000 nanometers wide. Today, "nanobiotechnology" refers to the nanotechnological use in life sciences (Troncarelli et al., 2013). "Nanomedicine" provides quick and efficient medical treatments by using nanotechnology-based techniques. This field overcomes the limitations of conventional medicine. In addition, it also enhances our understanding of various processes in living organisms. These processes may be physiological and pathological. Thus, it will be leading to innovative treatment strategies (Mohantya et al., 2014). Additionally, terms like "nanotheranostics" describe advanced formulations that serve both diagnostic and therapeutic purposes. These formulations provide critical information about drug distribution, release locations, and efficacy, aiding in the customization of treatment approaches (Chapman et al., 2013; Rizzo et al., 2013).

The recent significant advancements in nanotechnology have made it possible to conduct smart chemical delivery studies for medicinal and diagnostic purposes. They have the ability to treat damaged or malignant cells while sparing healthy ones, identify illnesses before symptoms show up, provide hormones or enzymes when required, and much more. Smart delivery systems can be designed to automatically respond to changes in temperature, acidity, or specific chemicals on their own (Scott, 2007; Manuja et al., 2012).

The recently established nanobiomaterials, which have sizes ranging from 5 to 20nm, are architecturally designed to mimic different bodily receptors, DNA, ligands, and proteins. These structural commonalities enable them to interact with tissues and cellular membranes in a range of biological situations (Venkatesan and Kim, 2014; Yi et al., 2016).

Lipid-based and biodegradable carriers of nanoparticles are among the most popular types of nanobiomaterials. The long-term toxicity and the bioaccumulation of nanoparticles in cells are avoided by using these nanobiomaterials. Macrophages can easily degrade and engulf those (Dobrovolskaia et al., 2016).

The following factors play a role in selecting the proper size of nanoparticles (NPs) (Cormode et al., 2013)

- The Nature of target cells
- The planned application
- The type and quantity of payloaded agents
- The need for rapid excretion
- The preference for tissue internalization versus a longer half lifetime in the circulation
- The method of clearance (reticuloendothelial OR renal system)
- Biodistribution
- Contrast image intensity
- The desired amount of stimulation of the immune system
- The type of the immune response

While certain nanoparticle (NP) sizes are suitable for medical applications, large NPs are typically avoided because of the risk of causing embolisms. They are also quickly phagocytized and removed from the bloodstream. Conversely, very small NPs are rapidly filtered out by the kidneys. Their tiny size increases the surface area to volume ratio, making them more toxic and reactive, leading to a noticeable rise in their chemical and biological activity. This results in an increase in the number of production of free radicals and reactive oxygen species (ROS) (Jain et al., 2011; Venkatesan and Kim, 2014; Yi et al., 2016). The release of reactive oxygen species (ROS) can lead to considerable oxidative stress and inflammation. It may also lead to damage at the cellular level. When NPs accumulate in the mitochondria, they hinder the body's defense system (Meena et al., 2018).

Nanoscale materials have different physical, chemical, and biological properties than their larger material forms. The small size of the material means it has better solubility and reactivity, thereby being more bioactive. Hence, with the increased potential, they become steadier and less susceptible to inactivation by oxidation (Troncarelli et al., 2013; Swain et al., 2015). In light of this occurrence, NPs can be modified to increase solubility, improve pharmacokinetics, reduce immunotoxicity, and minimize side effects in addition to being used as carriers. For instance, patients who are vulnerable to anaphylactic reactions may experience side effects from the cancer therapy drug Paclitaxel (Cremophor-EL); however, these reactions can be eluded by utilizing Paclitaxel (Abraxane) (Dobrovolskaia et al., 2016). Therefore, if the chemical is nano-sized, new science for nanopharmacokinetics needs to be introduced in light of the newly discovered properties of the same chemical (Casals et al., 2017).

There are many forms of nanoparticles known today. A nanoparticle basically contains a nucleus that is surrounded by a casing or capsule. The payload is planned to be delivered by NPs in two modes: either the medicinal and diagnostic compounds are attached onto the superficial surface, or they get encapsulated or trapped inside the nanoparticles. The proper encapsulation of the NPs can enhance diffusion, disintegration, drug loading, and imaging. This coating material will then protect the particles from any attack of the immune system, catalyst-induced disintegration, and harsh conditions of pH. Certain coating materials, such as PEG, protect the particles from the immune system's attack, disintegration because of catalyst, or harsh conditions of pH (Sailor and Park, 2012).

Nanoparticles Types

Nanoparticles (NPs) can be classified on the basis of their place of origin and various other factors. There are three main categories:

1. Shape: NPs can take forms such as spheres, tubes, or liquid drops.
2. Application and Type of Payload: NPs can be used for therapeutic, diagnosis, administration of vaccine, or for nutritional purposes (Thulasi et al., 2013).
3. Origin of NPs:

i. Organic NPs: These include proteins, peptides, and lipids.
ii. Inorganic NPs: These consist of materials like gold, silver, silica, iron, magnesium, or graphene.
iii. Hybrid NPs: These are a combination of organic and inorganic materials (Torres-Sangiao et al., 2016; Riley and Vermerris, 2017)

However, the major classification will be discussed in detail later in the chapter (Fig. 1)

Currently, the most commonly used taxonomy categorizes NPs as follows:

1. Polymeric NPs: According to Torres-Sangiao et al. (2016), there are 2 categories of polymers:

i) Synthetic polymers e.g. polyethylene-glycol

ii) Natural polymers, based on polysaccharides, e.g. chitosan and inulin

They are made by sticking active molecules onto the surface of the nanoparticles, which then form intricate, tree-like shapes. The shape is somewhat dendrimer-like, but the branches radiating from the center of NPs have differing numbers of branch points (Elgqvist, 2017; Mohantya et al., 2014). What distinguishes them is their substantial loading and conjugating capacity. Additionally, these polymers can be used to create hydrogel nanoparticles (NPs), which have a large surface area and high-water content (Torres-Sangiao et al., 2016).

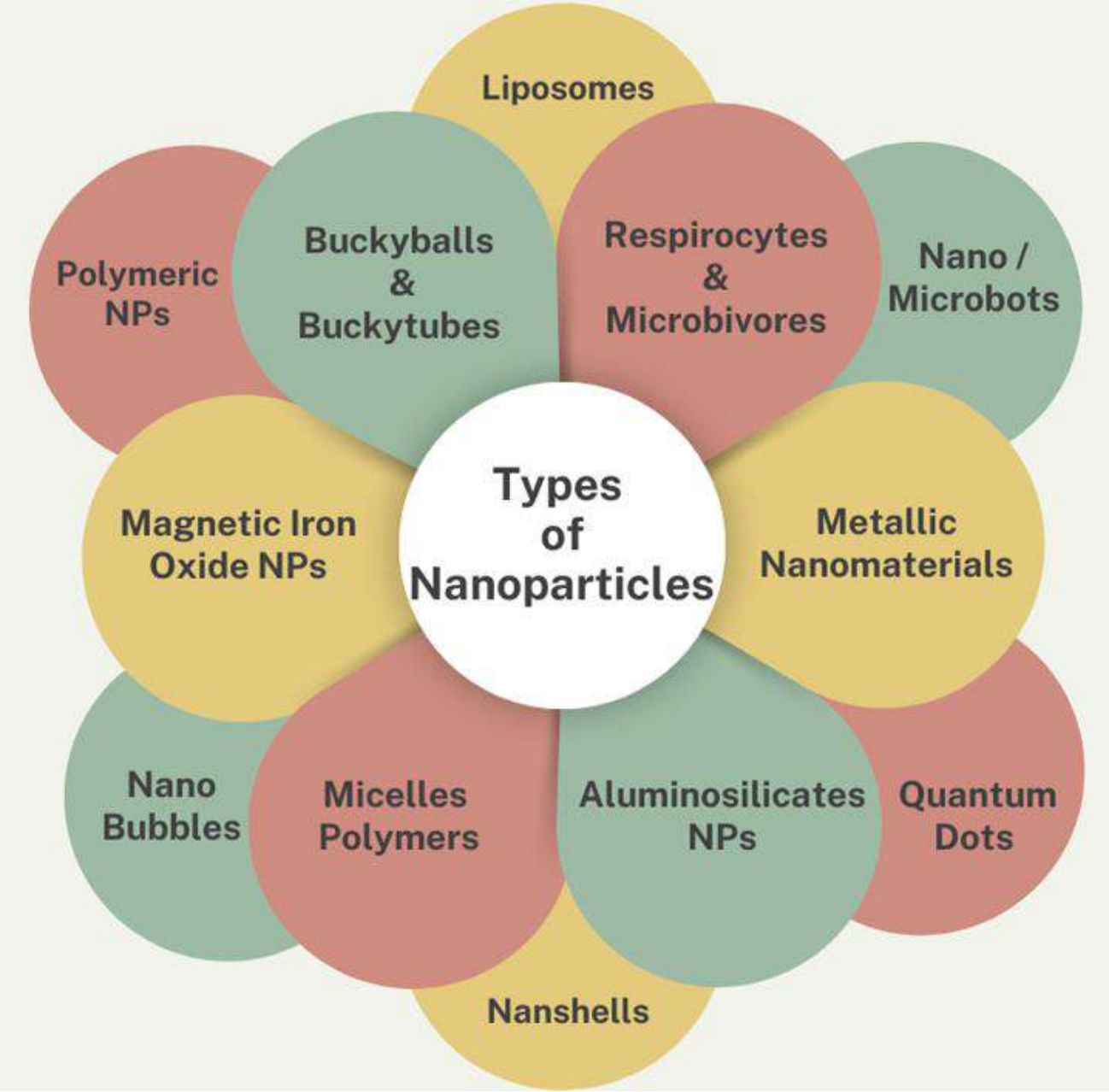


Fig. 1: Categories and Classifications of Nanoparticles.

2. Liposomes: These are the round, non-toxic, biodegradable PE glcolylated nanoparticles. Small- interference RNA (siRNA) for gene therapy, radionuclide or strings of RNA, DNA, and water-soluble drugs are transported by their aqueous core. Drugs that are fat soluble (hydrophobic) are encased in a double-layered phospholipid shell coating the particles. Various antigens, including viral envelop glycoproteins (referred to as virosomes), can be encapsulated by them (Torres-Sangiao et al., 2016). An exterior protective PEG layer covers the outside of the particle, shielding it from immune system attack. It is possible to fix chelated antibodies for imaging and targeting agents on the outside. This group's primary benefit is their capacity to administer therapeutic medicines that are both hydrophilic and hydrophobic (Elgqvist, 2017). Both hydrophobic and hydrophilic medications can be administered topically or by injection using liposomes; however,

liposomes cannot be taken orally due to the lipids' propensity to be broken down in the gastrointestinal system. Their eco-friendly structure is important in their safety. Moreover, liposomes can be attached to foreign antigens for vaccination or to antibodies known as immunoliposomes, which can bind to cancerous cells (Bakker-Woudenberg et al., 2005) (Mohantya et al., 2014). (Mohantya et al., 2014). In this regard, Torres-Sangiao et al. (2016) noted that liposome-polycation-DNA nanoparticles that can act as an adjuvant with DNA vaccines can be formulated by complexing cationic polymer-condensed DNA with cationic liposomes.

3. Fullerenes, or buckyballs, and nanotubes, or buckytubes: According to Meena et al. (2018) and Mohantya et al. (2014), buckyballs are small, spherical carbon-based nanoparticles that have a tendency to interact with proteins, cells, and pathogens. Fullerenes are typical in a number of varieties, each consisting of 20 or 60 or 100 carbon atoms. The other shape of carbon-based nanoparticles is the so-called buckytubes, which are very distinctly cylindrical and can be of one, two, or multiple walls (Elgqvist, 2017). By functionalizing these nanotubes, they can be employed as biosensors to detect immunoglobulins, glucose, ethanol, or to facilitate electrochemical DNA hybridization (Manuja et al., 2012).

4. Nanoshells: They are spherical, having an ultra-thin metal layer, usually gold, over a glass or silica core. The thickness of the gold layer can be varied to change their optical properties so that they respond to different wavelengths. Because of these properties, gold nanoparticles are mainly used for diagnosis of cancer (Mohantya et al., 2014). Infrared light can pass through blood samples. By attaching gold nanoshells with antibodies, it is possible to even detect very low levels of immunoglobulins in blood samples (Manuja et al., 2012). Because of its minute size, nanoshells can also act as therapeutic agents, as they tend to accumulate in tumor tissues. IR lasers are able to pass through healthy tissues without heating them. In tumor cells, nanoshells absorb infrared (IR) radiation and generate heat. This heat produced melts the polymer coating of the nanoshell.This releases the entrapped drug directly at the site (Freitas, 2005). Prolonged exposure to temperatures as high as 55°C can cause death to the cancerous cells. Nanoshells are chosen instead of quantum dots because gold is safe for the body and doesn't react, while quantum dots contain cadmium, which can be harmful (Hirsch et al., 2003; Krishnan and George, 2014).

5. Solid lipid Nano Particles: SLNPs are the suspensions of lipids stabilized in water. They have a hydrophobic core of lipids capable of solving lipophilic radionuclide-based pharmaceuticals used in cancer therapy, enclosed by the dehydrated tails of phosphatidylcholine lipids. An outer shell is hydrophilic that is formed to envelope the fatty core and can be coupled to many hydrophilic pharmacological drugs or antibodies. An outer hydrophilic layer improves plasma stability and, hence biodistribution of the drug, increasing its bioavailability. Solid lipid NPs (Cationic) can electrostatically associate with DNA or RNA segments, so they are suitable for gene therapy according to Elgqvist, (2017). Injections may be administered continuously over several weeks, but they may also be topically or orally applied. They get easily and quickly absorbed through mucosa because of their lipid composition and adhere to mucous membranes. Another chief advantage of solid lipid NPs is that they get efficiently delivered across the central nervous system and cross the blood-brain barrier. According to Mishra et al. (2010) and Mohantya et al. (2014), one of the main advantages of solid lipid NPs is that they can cross the blood-brain barrier. In contrast, Krishnan and George, (2014) stated that solid lipid NP formulations act as colloidal carriers, which remain in a solid state both at room temperature and inside the human body. Apart from solid lipid NPs, research into liquid lipid NP is going on at present (Elgqvist, 2017).

6. Micelles polymeric: Their hydrophobic cores allow them to carry materials that are insoluble in water, unlike solid lipid nanoparticles. They have a hydrophilic layer covering their hydrophobic core, which makes them extremely water soluble. Four types of polymeric micelles can be distinguished based on the characteristics of their shells:

i) Phospholipid
ii) Poly-amino acid
iii) Biocompatible polyester
iv) Pluronic micelles (Mohantya et al., 2014)

7. Dendrimers: Dendrimers are an artificially created polymer that is minute, even compared to human cells—thousands of times smaller. These NPs are well-known for the following properties: high biocompatibility, water solubility, and polyvalency. (Chakravarthi and Balaji, 2010, Jurj et al., 2017). Their small size and chemical properties make them unlikely to trigger unwanted immune responses upon entering the bloodstream (Chakravarthi and Balaji, 2010). Dendrimers are basically three-dimensional molecules with a branching structure, much like trees. Drugs can bind to the dendrimers at the functional groups available on their surface, or they can be encapsulated within the dendrimers' core according to Mohantya et al. 2014. In that, the dendrimers' epoxy cores can load a wide variety of hydrophobic and hydrophilic drugs through non-covalent interactions, chemical bonding or physical entrapment. The covalent conjugation of dendrimers with drugs improves the therapeutic efficiency and increases the stability of the drug as reported by Jurj et al. 2017.

8. Metallic nanomaterials: These materials consist of different metals, primarily gold. Mohantya et al. (2014) provide evidence that the main application for these materials is treating cancer. Other metals, which are occasionally used for making these materials, are manganese, silver, gadolinium, and platinum. The iron cores are contained in biocompatible

capsules, which have protective shells. The capsules may be functionalized to bind different medical or imaging agents, such as chelated radionuclides or targeted antibodies. Polyethylene glycol (PEG) coats the particles to help them avoid detection by the immune system and reduce unwanted sticking (Elgqvist, 2017). Lately, nanoparticles made from two metals, like silver-gold, silver-selenium, and gold-platinum, have been used in cancer treatment (Mittal et al., 2014; Alshatwi et al., 2015; Fakhri et al., 2017).

9. The great advantage of magnetic iron oxide NPs is the fact that they can be guided toward target cells by the help of an external magnetic field applied from outside, and due to this property, they have been proved very useful for imaging, thermal therapy, and drug delivery. However, there are fears that they might get accumulated in tissues (Manuja et al., 2012; Mohantya et al., 2014). These nanoparticles feature an iron core, either Fe_3O_4 or Fe_2O_3, surrounded by a silica shell embedded with chemotherapeutic agents. The outer polymeric shell, which is also functionalized with antibodies targeting tumor antigens, provides extra stability and must be dark to prevent intervention with fluorescence. Due to their magnetic nature, these nanoparticles are employed as multifunctional theranostic complexes in various MRI applications for diagnosis of cancer and treatment. Normally, the nanoparticles are PEGylated for preventing agglomeration and protecting them from immune attacks. However, silica is used as a coating material of choice for its application in contrast agents intended for light absorption applications in cancer imaging (Elgqvist, 2017).

10. Ceramic nanoparticles are straightforward to design and have several advantages over other types. They are also fully inert. They are easily molded into a variety of shapes, sizes, and porosities. According to (Mohantya et al., 2014), they provide protection for their burden against extreme temperatures and pH values.

11. Quantum dots are small, semiconductive nanomolecules that can be light-activated and are in the size range of 2-10 nm. Developed initially for optoelectronic applications, these semiconductor components normally comprise CdS, CdSe, CdTe, ZnS, and ZnSe materials (Patil et al., 2009; Torres-Sangiao et al., 2016). A typical quantum dot includes an inorganic nucleus and capsule (covering), with an aqueous coating that may be attached to various proteins. The size of the crystal changes the color of the light emitted. QD have been tailored to be inexpensive, simple, and durable probes, which emit light for an average of several hrs or days (Manuja et al., 2012). They can be labeled with biomarkers like DNA or proteins; hence, they are useful in screening blood samples for particular proteins, infections, and tumor markers. Thus, they find extensive applications in immunodiagnostics and diagnostics, respectively (Mohantya et al., 2014). QD physical properties make them a very suitable tool in imaging applications, and their advanced tools have been applied in pharmacological studies, medical diagnostics, and genetic tests (Meena et al., 2018). The fact that they are able to trace drugs and biomolecules in the body and image cellular pathways makes them very useful in studies (Meena et al., 2018).

12. A nano-emulsion is a type of mixture where tiny oil droplets are evenly distributed in water, and it's stabilized to keep the droplets from separating. Using co-surfactant and surfactant, a thin layer is applied to the oil droplets to stabilize them physically rather than chemically. Water-in-oil (W/O) and oil-in-water (O/W) are considered as the two varieties of nano-emulsions. Various techniques are used to prepare nano-emulsions, primarily high- or low-energy techniques. Low-energy generated nano-emulsions have greater stability over a two-month period at 4°C and 25°C (Rodríguez-Burneo et al., 2017).

13. Nanobubbles: When subjected to ultrasonic vibrations, stability is maintained by the micro-bubbles at room temperature, but they are collapsed into micro-bubbles with minimal heating. They are typically used for drug delivery and to target tumor tissues directly with the drug (Rapoport et al., 2007). Gene therapy applications also utilize the liposomal nanobubbles (Mohantya et al., 2014).

14. Respirocytes and microbivores: Respirocytes and microbivores present similar functions to red and white blood cells, respectively. Whereas respirocytes are nanorobots designed for efficient oxygen delivery to the tissues while removing the accumulated CO2 through specialized regulatory sensors for very precise control, the microbivores are circulated traps and phagocytose pathogens in the circulatory blood, functioning like macrophages. Their enzymatic digestion results in essential building blocks, such as nucleotides, fatty acids, and amino acids (Mohantya et al., 2014).

15. Micro/nano robots: Nanobots are tiny, computerized, and programmable robots capable of doing a wide variety of jobs, from scanning one's body for malignant cells to introducing nanocameras which provide real-time monitoring during surgery. Freitas remarks that the most recent research in developing cytobots and karyobots is focused on building devices that can work wirelessly inside cells (Freitas, 2005)

16. Aluminum-silicon nanoparticles (NPs), which are silica nanoparticles with a short chain of polyphosphate attached, might be used to help stop bleeding faster by speeding up the body's natural clotting process (Kudela et al., 2015).

The NPs can also be Separated into the following Categories

1. Inorganic nanoparticles (NPs): Due to their rigid structure, inorganic NPs are non-degradable. In the course of their

production, they are capable of producing different shapes. Out of these, the most well-known are silica-based NPs, which have already been proven as biocompatible (Torres-Sangiao et al., 2016; Zhao et al., 2014).

2. Immuno-stimulating complexes: Such complexes consist of antigens to be immunized, associated with supra-molecular particles of the saponin adjuvant Quil A. The presence of hydrophobic interactions renders these complexes competent to fuse antigens with viral envelope proteins. Cage-like structures can capture multiple viral antigens. (Grgacic and Anderson, 2006; Noad and Roy, 2003).
3. These particles measure between 20 and 800 nm. They have a structure similar to that of viruses but lack nucleic acids. While they are not infectious, they elicit an aggressive host immune response (Pushko et al., 2013).
4. Self-assembling systems and proteins: The role of such systems extends to generating quaternary protein complexes of higher order used in vaccinating humans and animals for immunization processes (Kanekiyo et al., 2013).
5. Polymeric nanoparticles: As it has been mentioned above, some of the natural polymeric NPs originated from polysaccharides are inulin and chitosan. They have often been utilized for production of the vaccines like DNA and Newcastle disease vaccines (Fig.2) (Zhao et al., 2014).

(Riley and Vermerris, 2017) proposed an additional classification scheme, grouping the NPs employed in gene transfer into the following categories:

We also covered carbon-based NP and natural- and synthetic-polymer-based nanomaterials, apart from organic and inorganic nanomaterials.

1. Inorganic Nanomaterials

They typically have low cytotoxicity and are biocompatible and reasonably safe. Their distinct optical and electrical characteristics are easily adjustable during the manufacturing process. According to (Erathodiyil and Ying, 2011), this group includes a variety of inorganic materials like gold, silver, iron oxide, and calcium phosphate.

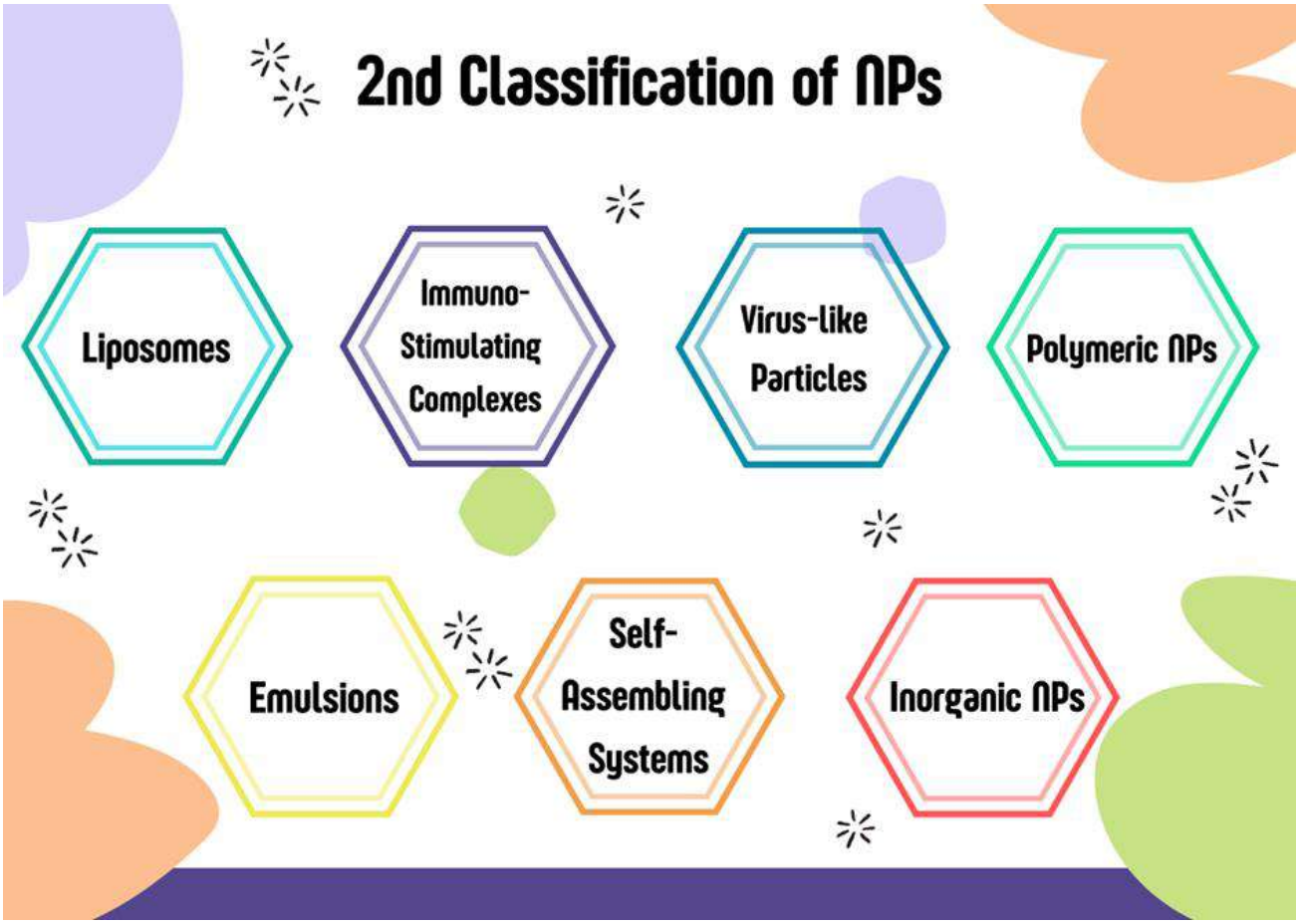


Fig. 2: Second Classification of NPs.

2. Organic Nanoparticles

A) **Proteins and peptide NPs:** They are mostly used in gene transfer experiments due to their good biodegradability, inexpensive cost of manufacture, minimal toxicity, and biocompatibility (e.g., gelatin). They can interact with a range of payloads according to their amphiphilic nature.

B) **Lipid-based nanomaterials:** It sets them apart due to their hydrophobic or amphiphilic character, making them able

to form vesicles and membranes. Catalytic lipids are more effective in delivering genetic elements than any other neutral or anionic lipids because they have the capability to attach to the cell membrane which is anionic in nature (de Ilarduya et al., 2010). Another family of small lipid molecules is lipidoids, which have recently grown further attention for their potential use as siRNA carriers. Research has been done on their possibility of siRNA transport for the therapy of HCV and cancer (Knapp et al., 2016; Moon et al., 2016).

3. **Hybrid NPs:** These include various kinds of nanoparticles; for instance, the polymer-lipid hybrid systems are developed by combining the liposomes with the polymeric NPs. In these NPs, usually the biodegradable and hydrophobic polymer core encases the water-soluble drugs to facilitate the release of drugs in a continuous manner. In order to prevent the reactions of the immune system, a coating of a hydrophilic shell covers the monolayer of lipid on the aforementioned core. This lipid layer regulates the penetration of water into the nanoparticles, thereby controlling the release of the drug contained within them. By modulating how water interacts with the nanoparticle surface, the lipid layer ensures a controlled and gradual release of the drug over time (Prabhu et al., 2015). For the administration of siRNA, further hybrid systems were also created (Bellocq et al., 2003). As with micellar hybrid nanosystems, therapeutic and diagnostic NPs can also be combined to create hybrid nanoparticles. According to (Liao et al., 2011) and (Yang et al., 2010). This approach integrates hydrophobic functional nanocrystals into the core of the nanoparticles for imaging purposes, while hydrophilic therapeutic agents are attached to the outer surface. This configuration allows for effective imaging and targeted therapy, utilizing the distinct properties of the nanocrystals and agents to enhance overall treatment efficacy. Recently, viral hybrid nanoparticles have found an application in monitoring biological functions. Such viruses exhibit a number of advantages that have been artificially redesigned as nanoparticles: uniform size and shape, specificity for delivering therapeutic nucleic acids into target tissues, improved protection of the nucleic acid payload, and the ability to encapsulate other non-nucleic acid drugs within the viral capsid itself (Steinmetz, 2010; Steinmetz et al., 2011). Attachment of magnetic nanocrystals on the capsid surface could enable MRI imaging. Very often, several functions are included in one hybrid nanosystem—for example, in cancer surgery, optical fluorescent quantum dots and superparamagnetic iron oxide NPs. Quantum dots help surgeons see the edges of tumors more clearly during surgery with special glowing images, while iron oxide nanoparticles make MRI scans more detailed, helping doctors find tumors before surgery (Sailor and Park, 2012).

Applications of Nanotechnology in Veterinary Medicine

Thanks to nanotechnology, veterinarians have access to the same range of options as physicians, including advanced disinfectants, tissue engineering, diagnostics, medications, and tissue engineering. The disciplines of animal nutrition, animal breeding and reproduction, and animal health and productivity are already using nano-applications, as Fig. 3 illustrates (Manuja et al., 2012). This technology enables the targeted delivery of drugs to specific cells, allowing for the use of very small doses. This precision means there is less leftover medicine in the animals and less time needed before they can be safely used again (Troncarelli et al., 2013).

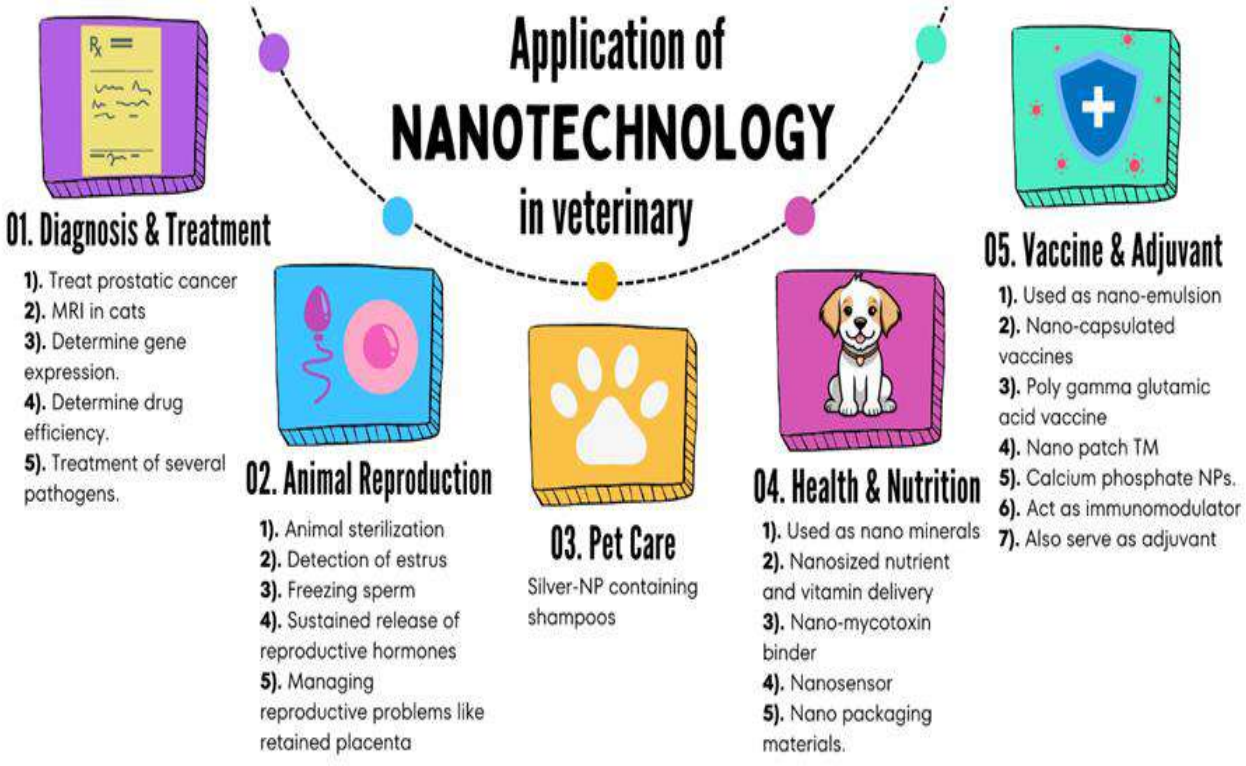


Fig. 3: Application of Nanotechnology in Veterinary Medicine

Use of Nanotechnology in the Detection and Treatment of Animal Diseases

The use of nanotechnology offers a number of innovative solutions for several problems in veterinary medicine, including treatment of infections caused by intracellular pathogens, brucellosis, FMD, and MRSA. Research is underway to exploit the potential of nanodrugs in targeting mastitic udders (Greenwood et al., 2008; Kruubi et al., 2010; Troncarelli et al., 2013). Contrary to the conventional drugs, nanodrugs can be engineered to trigger themselves in the presence of desired conditions only. For example, gentamicin attached to a hydrogel by the action of a peptide linker does not become active until the linker is cleaved by a *Pseudomonas aeruginosa* enzyme. It allows the drug to act only in the availability of *Pseudomonas aeruginosa* (Suzuki et al., 1998; Soppimath et al., 2002). Furthermore, NPs targeted against toxins of bacteria and receptors have been engineered to interact with pathogenic microorganisms in the gastrointestinal tract before they are excreted (Latour et al., 2003; Kim et al., 2010; Underwood and Van Eps, 2012). Other applications of NPs include formulations with nucleic acids or antibodies for easy, accurate, and field-based diagnosis. Nano- and biochips have been found effective in the detection of infections and genetic risk factors. High-density nano-array chips let researchers test many genes, antigens, or disease markers all at once. Protein and DNA-microarrays are used for determining drug efficiency and measuring gene expression. Using improved LOC technology, it is possible now to detect the target protein or DNA in very small sample volumes (Manuja et al., 2012). Apart from that, the NPs are used as the imaging agents in veterinary diagnostics like the MRI scan for cats (Kim et al., 2010; Underwood and Van Eps, 2012).

In the United States, gold nanoparticles replaced conventional invasive modes of treatment for canine prostate cancer. The method has the edge of not being toxic to healthy tissues and the dose it requires for treatment is comparatively much lesser than chemotherapy (Troncarelli et al., 2013).

Nanoadjuvants and Nanovaccines

Nanoparticles are now being used more and more to make vaccines for animals. They boost immune responses by helping the immune system recognize and react to invaders. Nanoparticles can also be used to slow down the release of the vaccine's ingredients, which makes the vaccine more effective (Kim et al., 2010; Underwood and Van Eps, 2012; Awate et al., 2013; Torres-Sangiao et al., 2016). Hence, targeting lymph nodes by antigen-loaded NPs can further enhance the efficacy of vaccination.

Some of the new developments in the area of veterinary nanovaccines are the following:

1. Nano-emulsion vaccines Examples include recombinant influenza viruses and Bacillus anthracis spores, which elicit mucosal immunity after intranasal administration.
2. Some of these targeted pathogens are Helicobacter pylori, Bordetella pertussis, tetanus toxoid, and rotavirus capsid, while others are bovine parainfluenza type 3 that elicited both IgG and IgA immune responses following oral administration.
3. African Horse Sickness Virus Vaccines: Vaccines for African horse sickness are made using a special virus (baculovirus) that helps produce particles similar to the virus. These particles include important proteins from the virus, which help the vaccine protect horses from the disease. These vaccines elicited only a mild immune response, indicating that better vaccine designs are required (Cher et al., 1998; Illum et al., 2001; Conway et al., 2001; He et al., 2002; Greenwood et al., 2008; Florindo et al., 2009; Fernando et al., 2010; Chen et al., 2010; Danesh-Bahreini et al., 2011; Hamouda et al., 2011)

Nanotechnology for the Feeding and Health of Animals

Nanotechnology has some valuable advantages in the animal feed industry with the use of nanominerals. Nanominerals are cost effective, used in smaller dosages, and have the eminent capability to improve immune function and to provide growth potential. They may also help in regulating rumen fermentation and control of pathogens in feed along with various problems related to reproduction in animals (Swain et al., 2015). Examples include nano-ZnO, an immunomodulator that can enhance immune response, growth rates, and reproductive health in poultry and other farm animals. It reduces the incidence of diarrhea in young pigs (Mishra et al., 2014; Yang and Sun, 2006). Studies also indicate that nano-ZnO is able to lower SCC in cows with subclinical mastitis and increase milk production in dairy herds (Rajendran, 2013).

Nanotechnology is also utilized in the production of liquid vitamins for poultry feed, where, due to the nanosize, nutrients are improved in their bioavailability as they pass through a hen's digestive tract. According to Thulasi et al., in 2013, these nano-enabled vitamins enable better nutritional dispersibility, extend the life of the feed, and reduce any undesirable flavoring with reduced use of stabilizers (Thulasi et al., 2013).

Microencapsulation helps protect food constituents from light, oxidation, and digestive enzymes. This technology enables finer dispersion and mixing of fat-soluble additives with various pH levels and temperatures, thus maintaining their stability and extending shelf life (Meena et al., 2018).

Through nanotechnology, newly effective MgO-SiO2 nanomycotoxin binders targeting the common mycotoxin, aflatoxins (normally found most in animal feeds, especially in developing countries), are being created in order to fight mycotoxicosis—a serious condition both in humans and animals (Moghaddam et al., 2010).

Besides, nanomaterials have made a foray into the field of packaging with special features like antibacterial traits—nano-zinc oxide; protection against UV and environmental exposure—nano-titanium dioxide; and high strength factor—nano-titanium nitride. Nanosensors can detect very small amounts of chemical and biological contaminants, making it

easier to find tiny traces of these substances (Manuja et al., 2012).

Animal Reproduction and Nanotechnology

Nanotechnology advances many aspects of animal reproduction, right from diagnosing and treating reproductive disorders to monitoring estrus and managing sperm sorting, freezing, etc. Nano devices can directly influence calving and address the reproductive challenge of retained placenta (Swain et al., 2015).

Moreover, some reproductive hormones are used for prolonged release purposes with nanoparticles. Nanoparticles guard the hormones and vitamins against oxidation, for example, vitamins and steroid hormones as well as hydrolysis of for instance gonadotropic hormones, hence not undergoing degradation thereby remaining effective (A Joanitti and P Silva, 2014).

High sensitivity is achieved with nanosensors that have movable probes made of biomolecules; thus, they are mainly used in medical diagnostics. These nanoscale devices can detect viral infections in the vaginal tract, estrus, and hormonal and metabolic imbalances. When inserted under the skin of cattle, these nanotubes are able to light up, thus indicating estrus (Scott, 2007; Saragusty and Arav, 2011).

Estradiol sensors check hormone levels in the blood and send live updates to a computer to keep track of livestock health. Nanocapsules with bull semen can be directed to fertilize eggs, and nanotechnology helps sort sperm and eggs. Biochips are also being created to determine the sex of the fetus, making it possible to choose the calf's gender (Patil et al., 2009).

Using Nanotechnology in Pet Care

The pet health care market is on the rise in a world where nanotechnology is playing a vital role in coming up with new products for pets. With nanotechnology, it enhances the functionality of surface deodorizers and disinfectants. In the area of pet care, one of the key products developed from this technology is shampoos containing silver nanoparticles (Troncarelli et al., 2013) (Sharif et al., 2024).

Security

While most NPs are considered safe, there are still a few risks involved in their use. For example,

1. Workers in the Pharmaceutical Industry: Prolonged exposure to carbon nanotubes, specifically through the route of inhalation, may cause reproductive abnormalities (Johansson et al., 2017).
2. Risks of injury because of the accumulation in the body of magnetic iron oxide nanoparticles or from unstable interactions between therapeutic agents and nanoparticles could occur, in which the therapeutic agent is released at times in areas of the body other than intended. This can lead to toxicity of the healthy tissue involved and also result in an insufficient therapeutic dose at the desired site.

Nanoparticle applications can also have disastrous consequences on the body and the environment. For example, the high demand for radionuclides could be hazardous or the depletion of the ozone layer by carbon nanofibers, which cannot be ruled out. The ability of nanoparticles to cross all biological barriers, such as the BBB, adds to the concerns (Manuja et al., 2012; Mohantya et al., 2014; Wu et al., 2018).

Conclusion

Recent improvements in nanoparticle design have created many options for targeted medical treatments. Nanotechnology has greatly improved veterinary medicine, making it better for diagnosing and treating animals, creating vaccines, and improving their nutrition and overall health.

REFERENCES

Joanitti, A. G., and Silva, L. P. (2014). The emerging potential of by-products as platforms for drug delivery systems. *Current Drug Targets*, *15*(5), 478-485.

Alshatwi, A. A., Athinarayanan, J., and Periasamy, V. S. (2015). Green synthesis of bimetallic Au@ Pt nanostructures and their application for proliferation inhibition and apoptosis induction in human cervical cancer cell. *Journal of Materials Science: Materials in Medicine*, *26*, 1-9.

Awate, S. (2013). Babiuk LAB, Mutwiri G. *Mechanisms of Action of Adjuvants. Frontier Immunology*, *4*, 114.

Bakker-Woudenberg, I. A., Schiffelers, R. M., Storm, G., Becker, M. J., and Guo, L. (2005). Long-circulating sterically stabilized liposomes in the treatment of infections. In *Methods in Enzymology* (Vol. 391, pp. 228-260). Academic Press.

Bellocq, N. C., Pun, S. H., Jensen, G. S., and Davis, M. E. (2003). Transferrin-containing, cyclodextrin polymer-based particles for tumor-targeted gene delivery. *Bioconjugate Chemistry*, *14*(6), 1122-1132.

Bielinska, A. U., Janczak, K. W., Landers, J. J., Makidon, P., Sower, L. E., Peterson, J. W., and Baker Jr, J. R. (2007). Mucosal immunization with a novel nanoemulsion-based recombinant anthrax protective antigen vaccine protects against Bacillus anthracis spore challenge. *Infection and Immunity*, *75*(8), 4020-4029.

Casals, E., Gusta, M. F., Cobaleda-Siles, M., Garcia-Sanz, A., and Puntes, V. F. (2017). Cancer resistance to treatment and antiresistance tools offered by multimodal multifunctional nanoparticles. *Cancer Nanotechnology*, *8*, 1-19.

Chakravarthi, V. P., and Balaji, N. (2010). Applications of nanotechnology in veterinary medicine. *Veterinary World*, *3*(10), 477.

Chapman, S., Dobrovolskaia, M., Farahani, K., Goodwin, A., Joshi, A., Lee, H., and Yang, L. (2013). Nanoparticles for cancer imaging: The good, the bad, and the promise. *Nano Today*, 8(5), 454-460.

Chen, S. C., Jones, D. H., Fynan, E. F., Farrar, G. H., Clegg, J. C. S., Greenberg, H. B., and Herrmann, J. E. (1998). Protective immunity induced by oral immunization with a rotavirus DNA vaccine encapsulated in microparticles. *Journal of Virology*, *72*(7), 5757-5761.

Chen, Y. S., Hung, Y. C., Lin, W. H., and Huang, G. S. (2010). Assessment of gold nanoparticles as a size-dependent vaccine carrier for enhancing the antibody response against synthetic foot-and-mouth disease virus peptide. *Nanotechnology*, *21*(19), 195101.

Conway, M. A., Madrigal-Estebas, L., McClean, S., Brayden, D. J., and Mills, K. H. (2001). Protection against Bordetella pertussis infection following parenteral or oral immunization with antigens entrapped in biodegradable particles: effect of formulation and route of immunization on induction of Th1 and Th2 cells. *Vaccine*, *19*(15-16), 1940-1950.

Danesh-Bahreini, M. A., Shokri, J., Samiei, A., Kamali-Sarvestani, E., Barzegar-Jalali, M., and Mohammadi-Samani, S. (2011). Nanovaccine for leishmaniasis: preparation of chitosan nanoparticles containing Leishmania superoxide dismutase and evaluation of its immunogenicity in BALB/c mice. *International Journal of Nanomedicine*, 835-842.

de Ilarduya, C. T., Sun, Y., and Düzgüneş, N. (2010). Gene delivery by lipoplexes and polyplexes. *European Journal of Pharmaceutical Sciences*, *40*(3), 159-170.

Dobrovolskaia, M. A., Shurin, M., and Shvedova, A. A. (2016). Current understanding of interactions between nanoparticles and the immune system. *Toxicology and Applied Pharmacology*, *299*, 78-89.

Elgqvist, J. (2017). Nanoparticles as theranostic vehicles in experimental and clinical applications—focus on prostate and breast cancer. *International Journal of Molecular Sciences*, *18*(5), 1102.

Erathodiyil, N., and Ying, J. Y. (2011). Functionalization of inorganic nanoparticles for bioimaging applications. *Accounts of Chemical Research*, *44*(10), 925-935.

Fakhri, A., Tahami, S., and Naji, M. (2017). Synthesis and characterization of core-shell bimetallic nanoparticles for synergistic antimicrobial effect studies in combination with doxycycline on burn specific pathogens. *Journal of Photochemistry and Photobiology B: Biology*, *169*, 21-26.

Fernando, G. J., Chen, X., Prow, T. W., Crichton, M. L., Fairmaid, E. J., Roberts, M. S., and Kendall, M. A. (2010). Potent immunity to low doses of influenza vaccine by probabilistic guided micro-targeted skin delivery in a mouse model. *PloS one*, *5*(4), e10266.

Florindo, H. F., Pandit, S., Lacerda, L., Gonçalves, L. M. D., Alpar, H. O., and Almeida, A. J. (2009). The enhancement of the immune response against S. equi antigens through the intranasal administration of poly-ε-caprolactone-based nanoparticles. *Biomaterials*, *30*(5), 879-891.

Freitas, R. A. (2005). Current status of nanomedicine and medical nanorobotics. *Journal of Computational and Theoretical Nanoscience*, *2*(1), 1-25.

Greenwood, D. L., Dynon, K., Kalkanidis, M., Xiang, S., Plebanski, M., and Scheerlinck, J. P. Y. (2008). Vaccination against foot-and-mouth disease virus using peptides conjugated to nano-beads. *Vaccine*, *26*(22), 2706-2713.

Grgacic, E. V., and Anderson, D. A. (2006). Virus-like particles: passport to immune recognition. *Methods*, *40*(1), 60-65.

Hamouda, T., Sutcliffe, J. A., Ciotti, S., and Baker Jr, J. R. (2011). Intranasal immunization of ferrets with commercial trivalent influenza vaccines formulated in a nanoemulsion-based adjuvant. *Clinical and Vaccine Immunology*, *18*(7), 1167-1175.

He, Q., Mitchell, A., Morcol, T., and Bell, S. J. (2002). Calcium phosphate nanoparticles induce mucosal immunity and protection against herpes simplex virus type 2. *Clinical and Vaccine Immunology*, *9*(5), 1021-1024.

Hirsch, L. R., Stafford, R. J., Bankson, J. A., Sershen, S. R., Rivera, B., Price, R. E., and West, J. L. (2003). Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proceedings of the National Academy of Sciences*, *100*(23), 13549-13554.

Illum, L., Jabbal-Gill, I., Hinchcliffe, M., Fisher, A. N., and Davis, S. S. (2001). Chitosan as a novel nasal delivery system for vaccines. *Advanced Drug Delivery Reviews*, *51*(1-3), 81-96.

Jain, S. K., Sahni, Y. P., Rajput, N., and Gautam, V. (2011). Nanotoxicology: An Emerging Discipline. *Veterinary World*, *4*(1).

Johansson, H. K. L., Hansen, J. S., Elfving, B., Lund, S. P., Kyjovska, Z. O., Loft, S., and Hougaard, K. S. (2017). Airway exposure to multi-walled carbon nanotubes disrupts the female reproductive cycle without affecting pregnancy outcomes in mice. *Particle and Fibre Toxicology*, *14*, 1-13.

Jurj, A., Braicu, C., Pop, L. A., Tomuleasa, C., Gherman, C. D., and Berindan-Neagoe, I. (2017). The new era of nanotechnology, an alternative to change cancer treatment. *Drug Design, Development and Therapy*, 2871-2890.

Kanekiyo, M., Wei, C. J., Yassine, H. M., McTamney, P. M., Boyington, J. C., Whittle, J. R., and Nabel, G. J. (2013). Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies. *Nature*, *499*(7456), 102-106.

Kim, B. Y., Rutka, J. T., and Chan, W. C. (2010). Nanomedicine. *New England Journal of Medicine*, *363*(25), 2434-2443.

Knapp, C. M., He, J., Lister, J., and Whitehead, K. A. (2016). Lipidoid nanoparticle mediated silencing of Mcl-1 induces apoptosis in mantle cell lymphoma. *Experimental Biology and Medicine*, *241*(9), 1007-1013.

Krishnan, S. R., and George, S. K. (2014). Nanotherapeutics in cancer prevention, diagnosis and treatment. *Pharmacology and Therapeutics*, 235-253.

Kroubi, M., Daulouede, S., Karembe, H., Jallouli, Y., Howsam, M., Mossalayi, D., and Betbeder, D. (2010). Development of a nanoparticulate formulation of diminazene to treat African trypanosomiasis. *Nanotechnology*, *21*(50), 505102.

Kudela, D., Smith, S. A., May-Masnou, A., Braun, G. B., Pallaoro, A., Nguyen, C. K., and Stucky, G. D. (2015). Clotting activity of polyphosphate-functionalized silica nanoparticles. *Angewandte Chemie International Edition*, *54*(13), 4018-4022.

Liao, C., Sun, Q., Liang, B., Shen, J., and Shuai, X. (2011). Targeting EGFR-overexpressing tumor cells using Cetuximab-immunomicelles loaded with doxorubicin and superparamagnetic iron oxide. *European Journal of Radiology*, *80*(3), 699-705.

Manuja, A., Kumar, B., and Singh, R. K. (2012). Nanotechnology developments: opportunities for animal health and production. *Nanotechnology Development*, *2*(1), e4-e4.

Meena, N. S., Sahni, Y. P., Thakur, D., and Singh, R. P. (2018). Applications of nanotechnology in veterinary therapeutics. *Journal of Entomology and Zoology Studies*, *6*(2), 167-175.

Mishra, A., Swain, R. K., Mishra, S. K., Panda, N., and Sethy, K. (2014). Growth performance and serum biochemical parameters as affected by nano zinc supplementation in layer chicks. *Indian Journal of Animal Nutrition*, *31*(4), 384-388.

Mishra, B. B. T. S., Patel, B. B., and Tiwari, S. (2010). Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. *Nanomedicine: Nanotechnology, Biology and Medicine*, *6*(1), 9-24.

Mittal, A. K., Kumar, S., and Banerjee, U. C. (2014). Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antitumor and antimicrobial potential. *Journal of Colloid and Interface Science*, *431*, 194-199.

Moghaddam, S. H., Jebali, A., and Daliri, K. (2010). The use of MgO-Sio2 nano-composite for adsorption of aflatoxin in wheat flour samples. *Proceedings of the NanoCon*, 10-15.

Mohantya, N., Palaib, T., Prustyc, B., and Mohapatrad, J. (2014). An overview of nanomedicine in veterinary science. *Veterinary Research*, 2(4), 90-5.

Patil, S. S., Kore, K. B., and Kumar, P. (2009). Nanotechnology and its applications in veterinary and animal science. *Veterinary World*, *2*(12), 475-477.

Prabhu, R. H., Patravale, V. B., and Joshi, M. D. (2015). Polymeric nanoparticles for targeted treatment in oncology: current insights. *International Journal of Nanomedicine*, 1001-1018.

Pushko, P., Pumpens, P., and Grens, E. (2013). Development of virus-like particle technology from small highly symmetric to large complex virus-like particle structures. *Intervirology*, *56*(3), 141-165.

Rajendran, D. (2013). Application of nano minerals in animal production system. *Research Journal of Biotechnology*, *8*(3), 1-3.

Rapoport, N., Gao, Z., and Kennedy, A. (2007). Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy. *Journal of the National Cancer Institute*, *99*(14), 1095-1106.

Riley, M. K., and Vermerris, W. (2017). Recent advances in nanomaterials for gene delivery—a review. *Nanomaterials*, *7*(5), 94.

Rizzo, L. Y., Theek, B., Storm, G., Kiessling, F., and Lammers, T. (2013). Recent progress in nanomedicine: therapeutic, diagnostic and theranostic applications. *Current Opinion in Biotechnology*, 24(6), 1159-1166.

Rodríguez-Burneo, N., Busquets, M. A., and Estelrich, J. (2017). Magnetic nanoemulsions: comparison between nanoemulsions formed by ultrasonication and by spontaneous emulsification. *Nanomaterials*, *7*(7), 190.

Sailor, M. J., and Park, J. H. (2012). Hybrid nanoparticles for detection and treatment of cancer. *Advanced Materials*, *24*(28), 3779-3802.

Saragusty, J., and Arav, A. (2011). Current progress in oocyte and embryo cryopreservation by slow freezing and vitrification. *Reproduction*, *141*(1), 1.

Scott, N. R. (2007). Nanoscience in veterinary medicine. *Veterinary Research Communications*, *31*, 139-144.

Sharif, M. U., Usman, M., Aslam, H. M., and Abdullah, M. (2024). Revolutionizing Animal Health: The Role of Nanoparticles in Veterinary Medicine. *Asian Journal of Research in Animal and Veterinary Sciences*, 7(3), 196-207.

Soppimath, K. S., Aminabhavi, T. M., Dave, A. M., Kumbar, S. G., and Rudzinski, W. E. (2002). Stimulus-responsive "smart" hydrogels as novel drug delivery systems. *Drug Development and Industrial Pharmacy*, *28*(8), 957-974.

Steinmetz, N. F. (2010). Viral nanoparticles as platforms for next-generation therapeutics and imaging devices. *Nanomedicine: Nanotechnology, Biology and Medicine*, *6*(5), 634-641.

Steinmetz, N. F., Ablack, A. L., Hickey, J. L., Ablack, J., Manocha, B., Mymryk, J. S., and Lewis, J. D. (2011). Intravital imaging of human prostate cancer using viral nanoparticles targeted to gastrin-releasing peptide receptors. *Small*, 7(12), 1664-1672.

Suzuki, Y., Tanihara, M., Nishimura, Y., Suzuki, K., Kakimaru, Y., and Shimizu, Y. (1998). A new drug delivery system with controlled release of antibiotic only in the presence of infection. *Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and the Australian Society for Biomaterials*, *42*(1), 112-116.

Thulasi, A., Rajendran, D., Jash, S., Selvaraju, S., Jose, V. L., Velusamy, S., and Mathivanan, S. (2013). Nanobiotechnology in animal nutrition. *Animal Nutrition and Reproductive Physiology (Recent Concepts), 1st ed.; Sampath, KT, Ghosh, J., Eds*, 499-516.

Torres-Sangiao, E., Holban, A. M., and Gestal, M. C. (2016). Advanced nanobiomaterials: vaccines, diagnosis and treatment of infectious diseases. *Molecules*, *21*(7), 867.

Troncarelli, M. Z., Brandão, H. M., Gern, J. C., Guimarães, A. S., and Langoni, H. (2013). Nanotechnology and antimicrobials in veterinary medicine Badajoz, Spain. FORMATEX available at http://www. formatex. info/microbiology4/vol1/543-556. pdf.

Underwood, C., and Van Eps, A. W. (2012). Nanomedicine and veterinary science: The reality and the practicality. *The Veterinary Journal*, *193*(1), 12-23.

Venkatesan, J., and Kim, S. K. (2014). Nano-hydroxyapatite composite biomaterials for bone tissue engineering—a review. *Journal of Biomedical Nanotechnology*, *10*(10), 3124-3140.

Wu, T. J., Chiu, H. Y., Yu, J., Cautela, M. P., Sarmento, B., das Neves, J., and Ignjatović, N. L. (2018). Nanotechnologies for early diagnosis, in situ disease monitoring, and prevention. In *Nanotechnologies in Preventive and Regenerative Medicine* (pp. 1-92). Elsevier.

Yang, X., Grailer, J. J., Rowland, I. J., Javadi, A., Hurley, S. A., Steeber, D. A., and Gong, S. (2010). Multifunctional SPIO/DOX-loaded wormlike polymer vesicles for cancer therapy and MR imaging. *Biomaterials*, *31*(34), 9065-9073.

Yang, Z. P., and Sun, L. P. (2006). Effects of nanometre ZnO on growth performance of early weaned piglets. *Journal Shanxi Agriculture Science*, *3*(024), 577-88.

Yi, H., Ur Rehman, F., Zhao, C., Liu, B., and He, N. (2016). Recent advances in nano scaffolds for bone repair. *Bone Research*, *4*(1), 1-11.

Zhao, L., Seth, A., Wibowo, N., Zhao, C. X., Mitter, N., Yu, C., and Middelberg, A. P. (2014). Nanoparticle vaccines. *Vaccine*, *32*(3), 327-337

Chapter 14

Poly Lactic-co-Glycolic Acid Nanoparticles for Drug Delivery

Sidra Altaf[1*] and Tasawar Iqbal[2]

[1]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
[2]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
*Corresponding author: sidra.altaf@uaf.edu.pk

ABSTRACT

PLGA nanoparticles are seen as very useful for delivering medicine, and they can make treatments work better. This book chapter looks at how PLGA nanoparticles are important in delivering drugs to the body. The background part explains drug delivery systems are important for making treatments work better. In this discussion, we focus on PLGA nanoparticles play a very important role in using small technology to deliver medicine. This is because they are very safe for the body and can break down naturally, which makes medicine safer and more effective. In addition, PLGA nanoparticles can release drugs in a targeted way, which makes them more flexible and effective than other ways of delivering drugs. The PLGA nanoparticles are made and different techniques can be used to change their properties for different uses. Also, the paper looks at things like the amounts of different materials, how big the molecules are, substances that help keep everything steady, and liquids can change how nanoparticles behave and can hold medicine. We use different methods to check the quality and effectiveness of PLGA nanoparticles, like measuring their size and looking at their shape. In addition, drugs are put into capsules ways to measure how much drug is in a capsule, and things that affect drugs are put into capsules. We carefully study drugs released from PLGA nanoparticles in the lab and in biological settings to understand factors that can affect the process. In general, PLGA nanoparticles are commonly used to deliver drugs for different diseases including cancer, brain diseases, vaccines, and heart problems.

KEYWORDS
Drug Delivery Systems; Biocompatibility; Controlled Release Kinetics; Targeted Drug Delivery; Therapeutic Applications

Received: 29-Jun-2024
Revised: 02-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Altaf S and Iqbal T, 2024. Poly Lactic-co-Glycolic acid nanoparticles for drug delivery. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 119-127. https://doi.org/10.47278/book.CAM/2024.376

INTRODUCTION

Drug delivery systems are methods and technology used to deliver medicine to specific parts of the body. The goal is to make the treatment work better while reducing side effects and helping patients stick to the treatment. Traditional ways of giving medicine often face problems like not being able to dissolve properly, not being available in the body, and not being able to target the right place. Scholars are researching new ways to use tiny technology in medicine to help solve the problems we mentioned earlier. Nanotechnology is about controlling tiny materials that are between 1 and 100 nanometers in size (Umair et al., 2022).

On a smaller scale, materials have special qualities that could be useful for many things, like delivering medicine. Nanoparticles are very small and have a big surface area. Nanoparticles have the potential to make strides in sedate adequacy by making strides in the power of drugs that don't promptly break down in water. These particles can be outlined to target particular cells or tissues, minimizing harm to sound cells and decreasing side impacts. In expansion, nanoparticles can be utilized to attain a moderate and controlled medicate discharge over a long period. In expansion, nanoparticles, especially those from PLGA (Poly lactic-co-glycolic corrosive), are bolstered within the field of inquiries about and improvement of medicate conveyance. PLGA is an industry-approved biodegradable fabric for sedate conveyance(Altaf et al., 2024).

Its rate of devastation and capacity to discharge drugs make it a valuable device for different treatment strategies. Nanoparticles can ensure sensitive medicate atoms amid capacity and transportation and can be altered to convey drugs or substances for helpful and investigative purposes. The flexibility of PLGA nanoparticles makes them well-suited for numerous restorative medications (Fatima et al., 2023).

Foundation for Making PLGA Nanoparticles Bigger and Better

PLGA may be a biodegradable plastic made from normal and secure fixings like lactic corrosive and glycolic corrosive. It is frequently utilized for sedate conveyance since it is moo in causing unfavorable responses within the body. This substance breaks down into safe substances that can be effectively expelled from the body, guaranteeing total disposal of

the medicate carrier without any buildup. The composition of PLGA nanoparticles gives the capacity to control the sedate discharge rate, hence empowering a customized sedate conveyance framework that can persistently discharge the medicate over a long period of time or quickly for a quick impact. By changing the structure and estimate of the polymer, researchers can control the rate of debasement of PLGA, hence empowering the creation of distinctive medicate conveyance frameworks to meet distinctive therapeutic needs(Altaf and Iqbal, 2023).

Personalized sedate conveyance frameworks are vital to maximizing helpful results in different restorative conditions. By changing the surface of PLGA nanoparticles with particular particles, drugs can be focused on particular ranges within the body, making treatment more viable and diminishing side impacts. This exact focus is vital in cancer treatment, where conveying drugs straightforwardly to cancer cells guarantees a successful and non-invasive treatment. In general, the utilization of PLGA nanoparticles for focused on medicate conveyance speaks to a promising approach to move forward cancer treatment results by specifically focusing on unhealthy cells while saving sound tissue(Humaira et al., 2023).

Making and creating PLGA Nanoparticles

PLGA may be a biodegradable polymer made by combining lactic corrosive with glycolic corrosive. By exact control of the lactic acid/glycolic corrosive proportion and polymer estimate, an assortment of PLGA forms can be delivered. PLGA corrupts within the body as water breaks the ester bonds within the polymer, coming about in the formation of lactic corrosive and glycolic corrosive (Saqib et al., 2023).

This highlight makes PLGA an appropriate fabric for sedate conveyance frameworks because it in the long run breaks down and clears out the body without causing unfavorable responses. PLGA is metabolized through the TCA cycle, an imperative pathway in living beings, and its debasement rate can be moved forward by changing the structure and estimate of the polymer. This adaptability permits exact control of the medicate discharge preparation, making PLGA a valuable fabric for pharmaceutical applications(Altaf et al., 2023).

Advantages of Drug Delivery Systems

Poly (lactic-co-glycolic acid) nanoparticles have the potential to supply supported sedate discharge over a long period. The debasement of PLGA plays an imperative part in controlling the sedate discharge, guaranteeing that it is long-lasting. This property is especially curious for drugs that require a persistent nearness within the blood or the body. PLGA nanoparticles typify an assortment of drugs, counting those that can be debased by light, warmth, or chemicals. By typifying drugs in PLGA nanoparticles, their soundness and adequacy are progressed (Saleem et al., 2023).

In expansion, PLGA nanoparticles can contain both hydrophilic and hydrophobic drugs, empowering them to convey an assortment of drugs. Due to its differing applications in medicating conveyance, PLGA is the favored choice for conveying pharmaceutical items. In expansion, the surface of PLGA nanoparticles can be altered into distinctive parts of the body, in this manner moving forward the conveyance of drugs and lessening the impacts of the work. Moreover, PLGA nanoparticles can be adjusted to join imaging operators, permitting the synchronous conveyance of drugs and imaging. Both of these administrations make strides in treatment and checking for superior understanding results. The combination of restorative and demonstrative devices is basic for personalized pharmaceuticals and the battle against cancer (Iqbal et al., 2023).

Making Nanoparticles and Getting Rid of the Emulsion Solvent

Usually, a strategy of making a blend by blending a sort of plastic called PLGA with an extraordinary fluid. The blend was mixed to advance fluid vanishing and produce small PLGA particles. The PLGA polymer has to be mixed with a certain kind of fluid called a natural dissolvable, especially within the sleek portion(Salma et al., 2023).

Mix the organic part with the water part and add a stabilizing agent, like a surfactant, to make an emulsion. Stir the mixture to help the liquid evaporate, which makes PLGA nanoparticles. We often use centrifuging or filtering to gather and clean nanoparticles. Often used and easy to understand. This process helps to enclose both water-loving and water-fearing medicines. More actions might be needed to clean the substance completely and remove any extra surfactant. This method is similar to when a liquid evaporates, as it involves making a mixture (Gulnaz et al., 2023).

The solvent diffusion method is when an organic solvent goes into the water and makes tiny particles. The PLGA polymer is mixed with a chemical in liquid form. Mix the natural part with a water part that has a stabilizer. The liquid chemical is allowed to go into the water, causing tiny particles to form. Tiny particles are usually collected and purified using a method called solvent diffusion. Adjusting diffusion parameters allows for accurate control of the size of particles. We need to find the best conditions for particles to spread out evenly (Altaf, Iqbal, et al., 2023).

Nanoprecipitation

The nanoprecipitation process quickly mixes a polymer solution with an organic solvent and another liquid to make tiny particles. PLGA is dissolved in a liquid to make a polymer solution. The polymer solution is quickly added to another liquid, usually water or some other watery solution. The fast spread of the natural solvent into the anti-solvent makes the polymer come out of the liquid and form tiny particles(Gu and Quanyin, 2019; Iqbal et al., 2023).

Nanoparticles are usually collected by spinning them fast or by using a filter to separate them from the liquid. The test was done in a simple way that can be easily done again. This technology allows putting different medicines in a protective covering. You might need to do some extra steps to clean the substance. The salting-out method uses a type of liquid that

mixes with water to help make PLGA come together and form tiny particles. The PLGA needs to be mixed with a solvent that can be dissolved in water. Use a substance like acetone to help make nanoparticles by using the salting-out process. One way to collect and purify very tiny particles is by using a spinning machine or a strainer (Salma et al., 2023).

Using Methods to Change up Nanoparticle Features

The relative proportion of lactic acid to glycolic acid within the composition of the PLGA polymer exerts a considerable influence on the properties exhibited by the resultant nanoparticles. The debasement rate of PLGA and consequent sedate discharge are affected by the composition of the fixings. A better concentration of glycolic corrosive leads to a quicker corruption of PLGA in comparison to the next concentration of lactic corrosive. The enlargement of glycolic corrosive has been watched to assist the corruption and discharge of drugs, while raised levels of lactic corrosive have been found to decelerate the degradation preparation, subsequently drawing out the nearness of the drug within the body(Salma and Iqbal 2023, Nawaz, et al., 2023).

The measurement of PLGA atoms could be a basic determinant within the behavior of nanoparticles. The expanded estimate of PLGA particles comes about within the generation of particles with a slower corruption rate, subsequently encouraging a more continuous and supported discharge of medicine. On the opposite, humble PLGA atoms display quickened corruption, driving to an assisted medicate discharge. The significant nature of PLA makes it compelling in empowering controlled and supported discharge of drugs. The utilization of decreased PLGA particle estimate may quicken medicate discharge or specifically target specific restorative conditions. The inclusion of stabilizers and surfactants within the detailing serves to preserve the solidness of the emulsion and relieve nanoparticle conglomeration. The suitable choice of stabilizers and surfactants encompasses a considerable impact on the viability and safety of PLGA nanoparticles(Iqbal et al., 2023).

Assorted surfactant variations, counting anionic, cationic, and non-ionic, serve to balance the surface charge of nanoparticles. The determination of reasonable stabilizers is pivotal in anticipating molecule conglomeration and advancing the homogeneous scattering of nanoparticles. The choice of the fluid utilized within the blend of nanoparticles may have an effect on their general execution. The need for dissolvability of PLGA in fluids contains a critical effect on the arrangement of emulsions and the properties of nanoparticles. The dissolvable ought to have the capacity to productively break up PLGA and play a part in maintaining a homogeneous blend. The rate of nucleation of diminutive particles is unexpected upon the effectiveness of fluid dissipation. Diminishing the amount of remaining chemicals within the conclusion item is basic for guaranteeing its security (Iqbal et al., 2023).

Characterization Techniques

Energetic Light Diffusing and Laser Diffraction speak to two predominant strategies utilized for the assurance of molecule measure. Different strategies are utilized to measure changes in light as a result of the arbitrary development of minute particles. The previously mentioned substances are alluded to as nanoparticles, and their movement is commonly known as the Brownian movement. The examination envelops information relating to the scattering of particles inside the fluid(Ahmad et al., 2023).

The measurements of nanoparticles have a significant impact on their versatility inside the body, cellular take-up, and natural usefulness. Guaranteeing consistency within the measure of medicate particles is pivotal for optimizing the adequacy and planning usefulness of the pharmaceutical. The assurance of zeta potential is utilized to assess the electrokinetic charge of particles scattered in a fluid medium. The zeta potential serves as a degree of the surface charge of little particles scattered in a fluid medium. This article analyzes the properties of surface charge found on nanoparticles. The comprehension and evaluation of zeta potential play a basic part in surveying the steadiness of a colloidal framework (Iqbal et al., 2023).

The accumulation propensities of nanoparticles are affected by their zeta potential, in which particles having a solid electrical charge are less vulnerable to accumulation, driving to make strides in soundness and solidness. Sifting Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are routinely utilized procedures in coherent ask to analyze small-scale structures. The sifting electron amplifying focal point (SEM) energizes the examination of an object's surface geography through the period of nitty dirty pictures, while the transmission electron amplifying instrument (TEM) licenses for the recognition of interior structures by passing electrons through the case (Iqbal et al., 2024).

The utilization of these methodologies is urgent for the examination of the estimations, morphology, and course of activity of nanoparticles, empowering the revelation of any twists such as amassing or basic anomalies by examiners. Fourier-transform infrared spectroscopy (FTIR) may be a basic informative method utilized for the characterization of PLGA nanoparticles, enabling the recognition recognition confirmation of unmistakable chemical components and utilitarian bunches interior of the iotas. This investigation is pivotal in approving the presence of both PLGA and any included pharmaceutical compounds. Furthermore, X-ray diffraction (XRD) is utilized for the examination of the precious stone structure of poly (lactic-co-glycolic corrosive) (PLGA) nanoparticles, subsequently contributing to the assessment of their geometric morphology and auxiliary keenness. It is basic to comprehend the crystallographic organization of PLGA nanoparticles in arrange to expect their mechanical properties, steadiness, and sedate discharge behavior (Margaris, 2020).

Exploring the Effectiveness of Drug Encapsulation and Methods

UV-Vis spectroscopy is utilized to degree much light an arrangement retains at certain wavelengths. Sedate atoms

have diverse crests to show how much of the sedate is ingested. Analysts can utilize these crests to degree the sum of medicatingmedication in a test. After taking the medication out of particles, we determine how much of it there is by employing a machine that checks how it retains light at certain wavelengths(Abdolkarimi-Mahabadi et al., 2021).

Numerous individuals utilize high-performance fluid chromatography (HPLC) to test drugs that retain UV-Vis light. HPLC could be a strategy that isolates and measures diverse parts in a blend by how they are associated with a stationary stage. After the pharmaceutical is isolated from the particles, it is tried utilizing HPLC. The sum of the sedate is found by comparing the estimate of the top in a chart to a standard sum. This strategy works well for finding and telling separated drugs with complicated chemical structures (Kanu, 2021).

It is exceptionally precise and particular. NMR spectroscopy makes a difference researchers learn almost the attractive properties of molecules in atoms. It is utilized to figure out the structure of particles and recognize compounds. After expelling the medicate from a substance, NMR spectroscopy can be utilized to figure out precisely how much of the sedate is displayed by looking at particular signals that speak to its atomic cosmetics. This gives critical information about the drug's cosmetics and a way to precisely degree it (Reif et al., 2021).

Mass spectrometry may be a strategy utilized to discover out huge particles are. It gives accommodates subtle elements around compounds. It makes a difference for us to find and gauge different substances. After removing the drug, we can use mass spectrometry to see how much drug is left by looking at the size of the mass spectral peaks. This method can accurately find drugs (Bauermeister et al., 2022).

Issues Disturbing Drug Encapsulation

The way PLGA is made and how much lactic acid and glycolic acid it has can affect how well it can hold medicine inside it. Changing the characteristics of polymers can affect how drugs interact with them and how much drug they can hold. The properties of a medicine, such as how well it dissolves, how stable it is, and how heavy its molecules are, can affect how well it can be put into a capsule. Studies have shown that drugs that don't mix well with water are more likely to be put inside PLGA nanoparticles (Jem and Tan, 2020).

It is important that the drug works well with the PLGA polymer in order to encapsulate the drug effectively. Improving how well something gets wrapped up can be made easier by strong interactions like hydrogen bonding. The way drugs are packaged can be changed a lot by things like how much drug there is compared to the polymer, how much drug is in the initial solution, and what solvents are used. It is very important to get the right settings in order to make sure the capsule holds a lot of the medicine. The way we make the tiny particles, like using emulsion or nanoprecipitation, can also affect how much of the medicine gets trapped inside (Lagreca et al., 2020).

The way we mix things and how long we do it for is important too. Choosing how to put medicine into tiny particles can affect how much medicine can fit inside. Different ways such as mixing, spreading, and adding drugs later can affect how well the drugs are put into the small particles. When the particles are made smaller, they have more surface area, which can affect how much drug they can hold. However, having very small particles in the drug can make it harder to load the drug and can affect how stable the drug (Ghanbari et al., 2021).

Factors Manipulating Drug Release

The way PLGA breaks down depends on how much lactic acid and glycolic acid it has big its molecules are, and what it's made of. This affects how fast the drug is released. The way the drug interacts with the PLGA polymer can affect how the drug is released from the polymer. The speed of release can be affected by how strong the molecules stick together. If they stick really well, the release might be slower, but if they stick weakly, it might be faster. Tiny particles have more surface area compared to their volume (Pardeshi et al., 2023).

This can make drugs release faster. However, tiny particles can make the formulation less stable. The amount of drug trapped in the tiny particles affects how quickly the drug is released. A higher amount of drug in the medicine is likely to make it last longer in the body when it is released. The speed at which PLGA breaks down affects how quickly drugs are released from it. The faster breaking down of plastics usually leads to drugs being released more quickly(Alonso, 2020).

The acidity, heat, and substances in the environment where the drug is released can affect how quickly the drug is released from PLGA nanoparticles. Choosing certain substances to stabilize and release drugs from PLGA nanoparticles can affect how stable the nanoparticles are and how well they release the drug. The way our body works, like blood moves, the acidity of tissues, and the presence of certain chemicals, can affect how drugs work in our body (Kashkooli et al., 2020).

Uses of PLGA Nanoparticles in Cancer Therapy and Targeted Delivery to Tumor Cells

Using tiny particles called PLGA nanoparticles can help deliver medicine to the right place in the body to fight against cancer. Changing the surfaces of tiny particles with special molecules like ligands, antibodies, or peptides can help drugs target cancer cells better. The parts on the outside of PLGA nanoparticles can attach to receptors on the outside of cancer cells and help the nanoparticles enter the tumor cells. The EPR effect helps PLGA nanoparticles gather in tumor tissues because the blood vessels are leaky and the lymphatic drainage is reduced. Targeted drug delivery systems help to protect healthy tissues from medicine, which can lower the chance of side effects. Delivering medicine directly to the tumor has been proven to make treatment work better (Narmani et al., 2023).

The research looks at how well PLGA nanoparticles with folate added can target and deliver medicine to cancer cells that have a lot of folate receptors. Giving multiple treatments at the same time using one delivery system could make the cancer treatment work better by targeting the cancer cells, stopping new blood vessels from forming, and overcoming resistance to drugs. PLGA nanoparticles have the capacity to typify and consecutively discharge different solutions, each with special instruments of activity (Jurczyk et al., 2021).

This controlled discharge highlight proposes that PLGA nanoparticles may be utilized for successive organization of distinctive treatments. Giving two drugs together makes them work way better to treat illnesses. Giving drugs at the same time or one after the other can offer assistance to diminish sedate resistance in cancer treatment. Utilizing little particles called PLGA nanoparticles to carry both chemotherapy and focused treatment drugs can offer assistance make cancer treatment work way better (Narmani et al., 2023).

Further Applications

Utilizing nanoparticles made of PLGA to provide immunizations has appeared to it can gradually discharge the antibody and offer assistance in the safe framework to work way better. These minor particles can go through the blood-brain obstruction, which implies they may well be a great way to convey pharmaceuticals to the brain. This may be accommodating for treating Alzheimer's infection and brain tumors (El-Sayed and Kamel, 2020).

Moreover, by customizing PLGA nanoparticles, ready to convey anti-inflammatory solutions specifically to where they are required, which decreases the side impacts on the entire body. Also, utilizing PLGA nanoparticles makes a difference anti-microbials remain within the body for a longer time, making them work way better in treating bacterial contaminations. Besides, PLGA nanoparticles can capture and transport hereditary fabric like siRNA or DNA for quality treatment. PLGA nanoparticles can carry medication to the heart to assist with issues like blocked courses and small blood vessels (Góra et al., 2020).

Conditions Affecting the Central Nervous System and the Infiltration of the Blood-brain Barrier

The blood brain barrier makes it intense for pharmaceuticals to go from the blood to the brain, which makes it difficult to treat clutters within the brain and spinal line. PLGA nanoparticles can be made to go through the blood-brain barrier and deliver medicine to the brain really well. Covering tiny PLGA particles with special chemicals that help them interact with cells in the brain, making it easier for the particles to pass through the cells (Tabassum et al., 2021).

Researchers are studying how to make tiny particles that can enter the brain more easily. This could help with treating brain diseases. Using tiny particles made of PLGA has shown promise in helping medicine reach the brain by passing through the blood-brain barrier. This ponder makes a difference make the treatment of brain issues superior. Researchers have been looking into ways to assist minor particles get into the brain. This may offer assistance to us discover way better ways to treat brain tumors and Alzheimer's infection (Piekut et al., 2022).

Chronic or Progressive Neurological Conditions

Maladies like Alzheimer's and Parkinson's make nerve cells within the brain gradually break down. Utilizing modest particles called PLGA can help deliver medication to the proper portion of the body, making medications work way better for distinctive illnesses. PLGA nanoparticles can hold onto defensive substances like cancer prevention agents and solutions, which can offer assistance, ensure, and repair brain cells (Annu et al., 2022).

Their specialized way of gradually discharging pharmaceuticals makes a difference to ceaselessly give the correct sum of pharmaceutical over a period of time, which is exceptionally supportive for treating long-term brain conditions. By giving the pharmaceutical specifically to the influenced parts of the brain, the chance of causing hurt to sound tissue is brought down, which decreases the probability of encountering negative impacts from the medicine (Dara et al., 2022).

Utilizing particular ways to convey drugs can make them work superior in securing the brain and treating illnesses. Researchers are examining how to form uncommon particles that hold substances that might offer assistance with the side effects of Alzheimer's infection. These minor particles might offer assistance decrease swelling, working against particular infections, or offer assistance keep the brain sound (Gombart et al., 2020).

Vaccinations and Techniques for Administering Antigens

PLGA particles are great at carrying antigens in immunizations. They make the antibodies work superior and can provide them to particular places within the body. Putting antigens into PLGA nanoparticles keeps them secure from breaking down, and lets them be discharged in a controlled way over time. This makes antibodies work superior and makes a difference in the body's resistant framework to recognize and battle off germs(Horvath and Basler, 2023).

PLGA nanoparticles ensure antigens from being broken down by chemicals and natural components, keeping them solid and compelling. The moderate discharge of antigens from PLGA nanoparticles keeps the safe framework enacted longer, making the resistant reactions more grounded. Utilizing little PLGA particles to trap antigens can offer assistance in making vaccines for ailments such as the flu or hepatitis (Iyer et al., 2022).

Immunomodulation

PLGA nanoparticles can alter the body's resistant framework to respond to antibodies and what kind of response it causes. This implies being able to form antibodies that can offer assistance to the body and fights off maladies by

making the proper safe reaction. It's truly imperative. By including substances that boost the safe framework, like Toll-like receptor stimulators, PLGA nanoparticles can make safe cells work superior. Moreover, PLGA nanoparticles can be outlined to join to particular safe cells within the body utilizing ligands or antibodies on their surface (Bhardwaj et al., 2020).

This makes a difference in coordinating the safe system's reaction. This particular strategy can make immunizations work way better by making the safe framework stronger and more centered. By changing the cosmetics and external layer of PLGA nanoparticles, we are able to alter how the resistant framework responds to them. This makes them valuable for numerous diverse sorts of antibodies. Also, including CpG oligonucleotides in PLGA nanoparticles can make the body's safe framework more grounded, and offer assistance immunizations work superior (Li et al., 2024).

Inflammatory Syndromes

PLGA nanoparticles offer assistance and provide anti-inflammatory drugs straightforwardly to the influenced region, treating aggravation without influencing the full body. Utilizing these little particles to deliver pharmaceuticals right to swollen joints may offer assistance to individuals with rheumatoid arthritis who feel superior for a longer time. In the same way, sending pharmaceuticals to particular ranges within the intestine seems to offer assistance treat maladies like Crohn's and ulcerative colitis (Ahamad et al., 2021).

Utilizing minor PLGA particles can help make beyond any doubt that pharmaceutical generally influences the debilitated tissue and not the healthy tissue. This could make the side impacts of the medicine less extreme for the whole body. In expansion, the moderate discharge of pharmaceuticals from these modest particles might cruel individuals to take their medication less frequently, which seems offer assistance they adhere to their treatment superior. Considers have found that utilizing PLGA particles with corticosteroids or NSAIDs seems to offer assistance with joint torment and stomach issues in a secure and successful way (Ding et al., 2021).

Exploring Future Perspectives and Challenges in Drug Delivery Using PLGA Nanoparticles

PLGA breaks down when it gets wet, which can make nanoparticles less stable. This breakdown can make acid that might affect how well and how long the medicine works. When tiny particles are kept, they may stick together or get bigger, which can change how they release medicine. PLGA nanoparticles become more stable when stabilizing agents are added to them. Changing the ingredients in the recipe, like the type of plastic and the amount of medicine, can make the product last longer. Making sure that each batch is the same when making a lot of something bigger can be hard because the conditions in the factory can change (Alkholief et al., 2022).

Making more PLGA nanoparticles while keeping them good quality, consistent, and cost-effective is hard. Improving how things are made so they can be made in larger quantities and done the same way each time. It is very important to have strict checks in place to make sure that the products are all the same during production. It's key to know that the body's defense system might see PLGA nanoparticles as foreign and cause worries about triggering an immune response. PLGA nanoparticles could cause inflammation in the body, which might affect how well they work and if they are safe to use. Adding biocompatible coatings to PLGA nanoparticles helps to reduce immune responses. This study wants to find out about new types of materials that can break down naturally and don't cause a strong immune response in the body (Guo et al., 2023).

Forthcoming Perspectives

The research wants to make better medicine that doesn't spoil easily, releases slowly, and can carry more medicine. Mixing smart materials that can respond to different body signals to release medicine when needed. Tailoring the PLGA nanoparticle formulations to match personalized medicine strategies based on the unique characteristics of each patient and their specific treatment needs (Ren et al., 2020).

Using biomarkers and molecular profiling to create nanoparticles that work in different ways that people's bodies process and respond to medicines. Creating tiny particles that can both diagnose and treat diseases is a big step forward in healthcare. Combining imaging substances, targeting molecules, and treatment drugs into one tiny particle system. Studying new types of biodegradable plastics to see if they are better than PLGA at breaking down and not causing immune system problems. Using natural substances or a mix of natural and synthetic materials to make medical devices safer for use in the human body (Woessner et al., 2021).

Emerging Trends and Future Directions and Multifunctional Nanoparticles

Researchers are studying tiny particles made of PLGA. These particles can carry different types of medicine at the same time, like chemotherapy and immunotherapy. This could make treating diseases easier. Adding tools to tiny particles made of PLGA to take pictures and treat problems at the same time, so we can see how well the treatment is working right away. The study is trying to make tiny particles that can react to things like pH, temperature, and enzymes in the environment. Utilizing progressed strategies to send drugs precisely where they are required can make sedate medicines more exact and successful. For illustration, utilizing atoms that respond to changes or utilizing exterior powers to assist discharge

medication can make sedate conveyance more exact (Su et al., 2021).

Improved Pharmaceuticals, Along with Innovative Genomic and Proteomic Techniques

This ponder is around utilizing hereditary and protein data to form personalized PLGA nanoparticles for each quiet. It looks at how qualities affect drugs are broken down within the body and how patients respond to treatment. Researchers are considering how to form medication that's made fair for each individual based on their well-being, restorative history, and their body responds to treatment. By utilizing biomarkers to discover certain infections and utilizing PLGA nanoparticles to convey drugs to particular regions, personalized treatment choices are getting superior (Choi and Lee, 2020).

Observing a patient's response in real-time helps doctors alter how the pharmaceutical is given, making personalized medicines more adaptable. Analysts are examining how to create PLGA nanoparticles more steady and successful for medicine. They are looking at controlling the measure and conveyance of the particles. Moreover, analysts are looking into utilizing 3D printing to form nitty gritty PLGA nanoparticles that can control how drugs are discharged within the body. Researchers are also considering if they can make a part of PLGA nanoparticles utilizing nonstop fabricating. They need to form a method of making personalized medication way better and more tried and true (Chavan et al., 2022).

Conclusion

The implementation of effective drug delivery systems is crucial for optimizing the efficacy and safety of medications. The utilization of PLGA nanoparticles in conjunction with nanotechnology represents a promising approach for delivering therapeutic agents to the human body. The particles exhibit favorable biocompatibility, undergo autonomous degradation, and enable the controlled release of pharmaceutical agents at variable kinetics within the biological system. PLGA nanoparticles demonstrate distinctive potential in their ability to encapsulate diverse pharmaceutical agents and facilitate targeted delivery to specific cellular or tissue sites. A comprehensive comprehension of the mechanisms underlying the functionality of PLGA nanoparticles may contribute to the advancement of drug delivery approaches. Researchers are constantly exploring novel applications of minuscule PLGA particles to enhance medical interventions. The utilization of PLGA nanoparticles enables the development of personalized and precise medical interventions that surpass conventional modalities.

REFERENCES

Abdolkarimi-Mahabadi, M., Bayat, A., and Mohammadi, A. (2021). Use of UV-Vis spectrophotometry for characterization of carbon nanostructures: a review. *Theoretical and Experimental Chemistry*, *57*, 191–198.

Ahamad, N., Kar, A., Mehta, S., Dewani, M., Ravichandran, V., Bhardwaj, P., Sharma, S., and Banerjee, R. (2021). Immunomodulatory nanosystems for treating inflammatory diseases. *Biomaterials*, *274*, 120875.

Ahmad, A., Iqbal, T., Altaf, S., Akram, A., and Riaz, H. (xxxx). *Botanicals Used for the Treatment of Liver Diseases*.

Alkholief, M., Kalam, M. A., Anwer, M. K., and Alshamsan, A. (2022). Effect of solvents, stabilizers and the concentration of stabilizers on the physical properties of poly (D, L-lactide-co-glycolide) nanoparticles: Encapsulation, in vitro release of indomethacin and cytotoxicity against HepG2-cell. *Pharmaceutics*, *14*(4), 870.

Alonso, M. J. (2020). Nanoparticulate drug carrier technology. In *Microparticulate systems for the delivery of proteins and vaccines* (pp. 203–242). CRC Press.

Altaf, S., and Iqbal, T. (2023). Bee Venom Used for the Treatment of Rheumatoid Arthritis. *Biomedical Journal of Scientific and Technical Research*, *53*(2), 44503–44507.

Altaf, S., Iqbal, T., Majeed, W., Farooq, M. A., Naseer, D., Saleem, M., Babar, S. U. R., and Ikram, M. (2023). Plasma membrane camouflaged nanoparticles: an emerging antibacterial approach. *One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan*, *2*, 193–200.

Altaf, S., Iqbal, T., Salma, U., Sajid, M., Basit, I., Sabir, M. Z., Riaz, K., Rasheed, R., Umair, M., and Talha, R. (2024). *Gold nanoparticles for the detection of organophosphate. Agrobiological Records 16: 11-18*.

Altaf, S., Khan, S., Iqbal, T., Farooq, M. A., and Muzaffar, H. (2023). Potential treatment of anthrax infection. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 576–588.

Annu, Sartaj, A., Qamar, Z., Md, S., Alhakamy, N. A., Baboota, S., and Ali, J. (2022). An insight to brain targeting utilizing polymeric nanoparticles: effective treatment modalities for neurological disorders and brain tumor. *Frontiers in Bioengineering and Biotechnology*, *10*, 788128.

Bauermeister, A., Mannochio-Russo, H., Costa-Lotufo, L. V, Jarmusch, A. K., and Dorrestein, P. C. (2022). Mass spectrometry-based metabolomics in microbiome investigations. *Nature Reviews Microbiology*, *20*(3), 143–160.

Bhardwaj, P., Bhatia, E., Sharma, S., Ahamad, N., and Banerjee, R. (2020). Advancements in prophylactic and therapeutic nanovaccines. *Acta Biomaterialia*, *108*, 1–21.

Chavan, Y. R., Tambe, S. M., Jain, D. D., Khairnar, S. V, and Amin, P. D. (2022). Redefining the importance of polylactide-co-glycolide acid (PLGA) in drug delivery. *Annales Pharmaceutiques Françaises*, *80*(5), 603–616.

Choi, J., and Lee, S. Y. (2020). Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. *Immune Network*, *20*(1).

Dara, S., Dhamercherla, S., Jadav, S. S., Babu, C. H. M., and Ahsan, M. J. (2022). Machine learning in drug discovery: a review.

Artificial Intelligence Review, *55*(3), 1947–1999.

Ding, Y., Li, Y., Sun, Z., Han, X., Chen, Y., Ge, Y., Mao, Z., and Wang, W. (2021). Cell-derived extracellular vesicles and membranes for tissue repair. *Journal of Nanobiotechnology*, *19*, 1–21.

El-Sayed, A., and Kamel, M. (2020). Advances in nanomedical applications: diagnostic, therapeutic, immunization, and vaccine production. *Environmental Science and Pollution Research*, *27*(16), 19200–19213.

Fatima, M., Iqbal, T., Shaheen, L., Salma, U., Siddique, R., Ali, R., Rehman, A. U., and Usman, S. (2023). Transmission dynamics of rabies virus. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 386–397.

Ghanbari, M., Davar, F., and Shalan, A. E. (2021). Effect of rosemary extract on the microstructure, phase evolution, and magnetic behavior of cobalt ferrite nanoparticles and its application on anti-cancer drug delivery. *Ceramics International*, *47*(7), 9409–9417.

Gombart, A. F., Pierre, A., and Maggini, S. (2020). A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. *Nutrients*, *12*(1), 236.

Góra, A., Tian, L., Ramakrishna, S., and Mukherjee, S. (2020). Design of novel perovskite-based polymeric poly (L-lactide-co-glycolide) nanofibers with anti-microbial properties for tissue engineering. *Nanomaterials*, *10*(6), 1127.

Gu, Z., and Quanyin, H. U. (2019). *Platelet membrane-coated drug delivery system*. Google Patents.

Gulnaz, R., Saqib, M., Saleem, M., Fatima, M., Iqbal, T., and Arif, Z. (2023). Outbreak of the ebola virus. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 359–373.

Guo, X., Zuo, X., Zhou, Z., Gu, Y., Zheng, H., Wang, X., Wang, G., Xu, C., and Wang, F. (2023). PLGA-based micro/nanoparticles: an Overview of their applications in respiratory diseases. *International Journal of Molecular Sciences*, *24*(5), 4333.

Horvath, D., and Basler, M. (2023). PLGA particles in immunotherapy. *Pharmaceutics*, *15*(2), 615.

Humaira, H. A., Iqbal, T., Habib, I., and Aman, Z. (2023). Vaccine strategies for dengue fever. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 561–575.

Iqbal, T., Ahmad, A., Naveed, M. T., Ali, A., and Ahmad, M. (2023). Potential Role of Zoonoses in Bioterrorism. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *1*, 499–512.

Iqbal, T., Altaf, S., Fatima, M., Rasheed, R., Laraib, K., Azam, M., Karamat, M., Salma, U., and Usman, S. (2024). *A narrative review on effective use of medicinal plants for the treatment of parasitic foodborne diseases. Agrobiological Records 16: 79-92*.

Iqbal, T., Altaf, S., and Iftikhar, A. (2023). *Detection of organophosphate residue in food and another agricultural commodity via gold nanoparticles*.

Iqbal, T., Altaf, S., and Iftikhar, A. (2023). *Overview of vaccination*.

Iqbal, T., Altaf, S., and Naeem, M. A. (2023). *Overview of Arthritis*.

Iqbal, T., Altaf, S., and Saleem, M. (2023). *Platelet Membrane Coated Drug Delivery System*.

Iyer, S., Yadav, R., Agarwal, S., Tripathi, S., and Agarwal, R. (2022). Bioengineering strategies for developing vaccines against respiratory viral diseases. *Clinical Microbiology Reviews*, *35*(1), e00123-21.

Jem, K. J., and Tan, B. (2020). The development and challenges of poly (lactic acid) and poly (glycolic acid). *Advanced Industrial and Engineering Polymer Research*, *3*(2), 60–70.

Jurczyk, M., Jelonek, K., Musiał-Kulik, M., Beberok, A., Wrześniok, D., and Kasperczyk, J. (2021). Single-versus dual-targeted nanoparticles with folic acid and biotin for anticancer drug delivery. *Pharmaceutics*, *13*(3), 326.

Kanu, A. B. (2021). Recent developments in sample preparation techniques combined with high-performance liquid chromatography: A critical review. *Journal of Chromatography A*, *1654*, 462444.

Kashkooli, F. M., Soltani, M., and Souri, M. (2020). Controlled anti-cancer drug release through advanced nano-drug delivery systems: Static and dynamic targeting strategies. *Journal of Controlled Release*, *327*, 316–349.

Lagreca, E., Onesto, V., Di Natale, C., La Manna, S., Netti, P. A., and Vecchione, R. (2020). Recent advances in the formulation of PLGA microparticles for controlled drug delivery. *Progress in Biomaterials*, *9*, 153–174.

Li, M., Yao, H., Yi, K., Lao, Y.-H., Shao, D., and Tao, Y. (2024). Emerging nanoparticle platforms for CpG oligonucleotide delivery. *Biomaterials Science*.

Margaris, A. V. (2020). Fourier transform infrared spectroscopy (FTIR): Applications in archaeology. In *Encyclopedia of global archaeology* (pp. 4350–4353). Springer.

Narmani, A., Jahedi, R., Bakhshian-Dehkordi, E., Ganji, S., Nemati, M., Ghahramani-Asl, R., Moloudi, K., Hosseini, S. M., Bagheri, H., and Kesharwani, P. (2023). Biomedical applications of PLGA nanoparticles in nanomedicine: advances in drug delivery systems and cancer therapy. *Expert Opinion on Drug Delivery*, *20*(7), 937–954.

Pardeshi, S. R., Nikam, A., Chandak, P., Mandale, V., Naik, J. B., and Giram, P. S. (2023). Recent advances in PLGA based nanocarriers for drug delivery system: a state of the art review. *International Journal of Polymeric Materials and Polymeric Biomaterials*, *72*(1), 49–78.

Piekut, T., Hurła, M., Banaszek, N., Szejn, P., Dorszewska, J., Kozubski, W., and Prendecki, M. (2022). Infectious agents and Alzheimer's disease. *Journal of Integrative Neuroscience*, *21*(2), 73.

Reif, B., Ashbrook, S. E., Emsley, L., and Hong, M. (2021). Solid-state NMR spectroscopy. *Nature Reviews Methods Primers*, *1*(1), 2.

Ren, L., Xu, X., Du, Y., Kalantar-Zadeh, K., and Dou, S. X. (2020). Liquid metals and their hybrids as stimulus–responsive

smart materials. *Materials Today*, *34*, 92–114.

Saleem, F., Atiq, A., Altaf, S., Habib, M., and Iqbal, T. (2023). Etiology, treatment and complications of dengue fever: a systematic analysis. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 551–560.

Salma, U., Iqbal, T., Faisal, M., Mehmood, M., and Altaf, S. (2023.). *Importance of medicinal mushrooms*.

Salma, U., Iqbal, T., Nawaz, H., Faisal, M., and Altaf, S. (2023.). *Anti-inflammatory effects of medicinal mushrooms*.

Salma, U., Nawaz, H., Farooq, M., and Iqbal, T. (2023). Management, control and treatment of monkeypox disease. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 666–675.

Saqib, M., Iqbal, K. J., Khan, S., Gulnaz, R., Iqbal, T., Mankga, L. T., and Fatima, K. (2023). Immune boosters to combat zoonotic viral diseases. *Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 344–358.

Su, Y., Zhang, B., Sun, R., Liu, W., Zhu, Q., Zhang, X., Wang, R., and Chen, C. (2021). PLGA-based biodegradable microspheres in drug delivery: recent advances in research and application. *Drug Delivery*, *28*(1), 1397–1418.

Tabassum, N., Wang, J., Ferguson, M., Herz, J., Dong, M., Louveau, A., Kipnis, J., and Acton, S. T. (2021). Image segmentation for neuroscience: lymphatics. *Journal of Physics: Photonics*, *3*(3), 35004.

Umair, M., Altaf, S., Muzaffar, H., Iftikhar, A., Ali, A., Batool, N., Iqbal, T., and Saif-ur-Rehman, B. S. R. (2022). Green nanotechnology mediated silver and iron oxide nanoparticles: Potential antimicrobials. *Agrobiological Record*, *10*, 35–41.

Woessner, M. N., Tacey, A., Levinger-Limor, A., Parker, A. G., Levinger, P., and Levinger, I. (2021). The evolution of technology and physical inactivity: the good, the bad, and the way forward. *Frontiers in Public Health*, *9*, 655491

Chapter 15

Role of Nanoparticles for the Control of Haemonchosis

Faiq Ahmad[1*], Imbasat Yousaf[2], Muhammad Usman[3], Farwa Arshad[4], Maryam Arshad[5], and Abu Bakar Yameen[6]

[1]Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad
[2]Independent researcher, Australia
[3]Animal Science Lab, University of Illinois at Urbana-Champaign, USA
[4]National institute of Food Science and Technology, University of Agriculture, Faisalabad
[5] Institute of Microbiology, University of Agriculture, Faisalabad
[6]Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad
*Corresponding author: *drfaiqahmad5@gmail.com

ABSTRACT

Particles that range in size from around 1 to 100 nanometers and are created in various shapes are called nanoparticles (NPs). Nanotechnology is a growing field of study that is expected to open up new possibilities for the control and eradication of germs since it uses substances and networks at the atomic scale. Many individuals worldwide are afflicted with parasitic infections, which are particularly prevalent in developing nations and have significant treatment limits. Some parasites have recently shown signs of medication resistance, which has heightened the demand for safer, more effective treatments to prevent parasitic infections or for pharmaceuticals to be improved. AgNPs possess distinctive physical and chemical characteristics. Multiple studies have demonstrated the advantageous biological impacts of AgNPs on a range of disorders, including antibacterial, anti-inflammatory, antioxidant, antiparasitic, and antiviral activities. AgNPs have gained recognition for their efficacy in combating multi-drug resistant bacteria, positioning them as a promising contender for antibacterial medication development. Plant-extracted AgNPs have recently demonstrated remarkable antiparasitic properties, surpassing typical antiparasitic medications in terms of shorter treatment time and superior capacity to hinder parasite reproduction. This chapter offers a thorough review of the numerous types, unique qualities, and mechanisms of action of AgNPs in the fight against parasitic diseases. The major emphasis is placed on their efficacy in treating *Haemonchus*. The objective is to offer a comprehensive guide for using AgNPs to cure and manage parasitic infections.

KEYWORDS
Nanotechnology, Nanoparticles, Control of Haemonchosis

Received: 12-Jun-2024
Revised: 13-Jul-2024
Accepted: 18-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Ahmad F, 2024. Role of nanoparticles for the control of haemonchosis. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 128-139. https://doi.org/10.47278/book.CAM/2024.132

INTRODUCTION

Parasites and parasitic diseases impact a significant number of individuals globally and are associated with numerous challenges in the field of cure and management (Norouzi, 2017; Alvi et al., 2020; Alvi et al., 2021; Alvi et al., 2022; Alvi et al., 2023). Despite the rapid and notable progress in healthcare and health advancements in various parts of the world, intestinal parasitic infections persist as a major health concern with implications for the economy, particularly in developing nations. According to WHO estimates, 3.5 billion individuals globally have parasitic infections, of which 450 million experience clinical symptoms each year. Poor hygiene contributes to the spread of these illnesses, which can lead to gastrointestinal disturbances, malnutrition, problems with nutrient absorption, and a variety of symptoms (Kousha et al., 2011). Severe consequences include cholecystitis, appendicitis, myocarditis, vaginal infections, and abdominal pain can be brought on by intestinal parasites. Intestinal parasite frequency varies from 0.5% to 62.3% across age groups, according to studies, and it is more common in densely populated areas (Momen Heravi M, 2013). Unhygienic surroundings and poor hygiene habits may contribute to the spread of these illnesses (Gamboa et al., 1998). Moreover, it has been discovered that intestinal parasites lead to malnutrition, impede the absorption of nutrients, and interfere with gastrointestinal processes. These consequences include vomiting, sickness, cholera, anemia, avitaminosis, iron deficiency, a weakened immune system, and slowed physical growth (Rehman et al., 2021). Extremely hazardous adverse effects, such as vaginal infections, stomach pain, a condition called appendicitis, myocarditis, intestinal obstruction, and extra-intestinal abscess formation can occasionally result from intestinal infections. Numerous studies have found that intestinal parasite prevalence varies from 0.5% to 62.3% in people of different ages (Tegen and Damtie, 2021). There is a notable incidence of direct and simple transmission of several parasites in the intestines from affected to uninfected people, especially in areas with high societal concentrations (Momen Heravi et al., 2013). *H. contortus* is a highly transmissible gastrointestinal parasite worm that

mostly affects ruminants and causes serious anemia, hemorrhagic gastroenteritis, diarrhea, stress, and other ailments. Additionally, it lessens the production of meat and milk, which causes a huge loss of profit for the world economy an estimated USD 120 billion is lost annually (Singh et al., 2017; Qamar et al., 2023). Many animals, including humans, can become infected with *H. contortus* through contaminated soils (Sinnathamby et al., 2018). Blood infections with *H. contortus* have also been reported in a variety of mammals, including humans, goats, sheep, rabbits, and others. These infections can alter immune responses and induce inflammation (Wang et al., 2019). Since over 30% of people globally suffer from parasitic illnesses, parasitic diseases are extremely significant. Furthermore, parasitic illnesses significantly increase the global incidence of mortality and morbidity, particularly in underdeveloped nations (Thurner et al., 2016). Though great progress has been made in recent years to investigate the pathophysiology and pharmacogenomics, causation, and cell biology of the majority of parasite-borne diseases, the condition of therapeutics is disheartening. Since most parasitic diseases do not elicit a robust immune response, there is currently no effective vaccination against any of the major parasitic infections, despite extensive research efforts. Therefore, the sole tool available to combat parasite diseases is an antiparasitic chemotherapy treatment (Sueth-Santiago et al., 2017). On the other hand, the majority of anti-parasitic medications in use today were introduced more than 50 years ago. Despite their effectiveness, the majority of these medicines do not closely resemble the contemporary definition of a "drug" in terms of patient acceptance, therapeutic regimen, duration of therapy, tolerability, or specificity (Dziduch et al., 2022). In contrast to other industries, the parasitic illness segment is not seeing as much advancement or new medication discovery as other industries do; this problem seems to be mostly caused by the lack of funding in this field. Prior to 2000, parasitic infections were considered unimportant, as demonstrated by the reality that just 0.1% of global health research money was allocated to the development of anti-parasitic medications (Norouzi, 2017). The most effective way to solve the previously described calamity associated with parasite infections is to develop innovative delivery methods to enhance the potency, specificity, tolerability, and therapeutic index of already available antiparasitic medications (Sun et al., 2019). Research on new antiparasitic compounds that are more potent, less toxic, more economical, and more active is imperative considering the side effects of antiparasitic drugs and the extent of parasitic illnesses (Mustafa et al., 2024). Because biotechnology and nanotechnology have developed so quickly, integrated them, and become widely used in pharmaceuticals, drug discovery has increased dramatically in recent years (Sarkar et al., 2017; Alfaleh et al., 2023). It is a wise decision to combine nanotechnology with conventional metal inorganic bactericides to create novel antiparasitic medications (Durak et al.,2020) and research on the insecticidal and inhibitory mechanisms of metal nanomaterials serves as a foundation for the creation of further parasite inhibitors (Rai et al., 2014). As a result, we covered an overview of all nanomaterials used to combat parasites in this chapter, with a special emphasis on silver nanoparticles. Particulate materials having more than we refer to one dimensional that is shorter than 100 nm as nanoparticles (Elhefny et al., 2021). Nanoparticles (NPs) can penetrate blood-brain obstacles, penetrate the respiratory tract, and bind to endothelial cells because of their small size and huge surface area, which also increases their colloidal strength and bioavailability (Rizvi and Salah, 2018). Metal oxide nanoparticles (MONPs) possess several advantageous properties, including straightforward preparation methods, excellent stability, and the capacity to functionalize with different molecules, the ability to be designed to precise sizes, shapes, and porosities, minimal fluctuations in swelling, and the capability to integrate into both hydrophobic and hydrophilic systems because of their negatively charged surface. These characteristics make MONPs a promising tool for biomedical properties (Sánchez-Moreno et al., 2018). Silver ions have a multilocation impact and are bactericidal to a wide spectrum of pathogens as inorganic materials (Zhang et al., 2023). Nevertheless, the use of silver-based materials is significantly restricted due to the exorbitant cost of the material, the unpredictable chemical characteristics of free silver ions, and the severe poisoning of conventional silver items (AbuDalo et al., 2019). Nanotechnology-produced sodium silver compounds possess several benefits, including superior pathogen-killing capabilities, reduced germ resistance, lower dosage requirements, and chemical stability (Ullah et al., 2018). Utilizing AgNP materials for parasite control offers the potential for developing novel substances to chemically combat clinical parasitic illnesses. By studying the inhibitory impact of AgNPs on parasites and understanding the fundamental causes of these effects, progress can be made in the creation of AgNP pesticides. The numerous forms and distinctive qualities of (AgNPs) and their usage in treating parasite diseases, especially *Haemonchus*, are the main topics of this study. We will now examine the main way in which it works: by disturbing the smoothness and structure of the parasites cell membrane. Reactive oxygen species, or ROS for short, are released as a result of this disruption, which also makes the membrane more porous and loses its internal content. This leads to inflammation and damage to biological components (Hassan et al., 2019).

History of NP's Birth

Although several techniques have been used to study the formation of nanosized particles from prehistoric times, perhaps even a century ago, the area of nanomedicine as a contemporary field of research was not formally founded until the 1990s. 21st-century research is seeing a rise in the investigation of nanomedicine (Krukemeyer et al., 2015). Nanoparticles (NPs) are artificially created and intricate molecules with precise chemical compositions. They were initially synthesized in the early 1980s. These nanoparticles consist of polymers that are extremely small in size and are constructed from smaller units called branch units. Synthetic nanomaterials possess a multitude of chain ends on their surface, which can be customized to perform specific chemical tasks. This characteristic could potentially be advantageous for catalytic applications. Nanomaterials exhibit significantly enhanced chemical and physical characteristics in comparison to

conventional polymers (Krukemeyer et al., 2015). A diverse array of applications reveals novel capabilities and properties of matter. Nanotechnology offers significant novel instruments that are anticipated to have a profound influence on various domains within the field of medical sciences. Polymer-coated functionalized metal nanoparticles have emerged as a dynamic and innovative area of advanced study. For instance, silver is a significant and easily obtainable metal, and its nanoparticles (NPs) are more effective than other nanosized metal particles in terms of their ability to combat microbial growth. Nevertheless, the stability of polar terminal groups, such as hydroxyl groups or amines, is a significant concern and is typically employed to enhance their stabilization (sufi et al., 2022). Three-dimensional nanomaterials have found extensive applications in the past few years in a variety of sectors, including medication delivery, gene therapy, ophthalmic surgery, in vitro testing for cardiac muscle injury, virulence against HIV-1, treatment for cancer, and tumor cell targeting (Chugh et al., 2021).

Categorization of Non-Precursors

Nanoparticles are divided according to their chemical composition as inorganic, organic, or carbon-based **(**Oprică and Bălășoiu, 2019).

Organic NPs

Organic compounds that are smaller than 100 nm are used to create organic nanoparticles or ONPs (Qi and Zhang, 2022). Prominent examples of this category include liposomes, micelles, dendrimers, and ferritin, which are all well-established organic nanoparticles and polymers. Micelles and liposomes are two forms of nanoparticles that exhibit sensitivity to electromagnetic radiation, including heat and light. Additionally, they possess a hollow core referred to as a nanocapsule (Esakkimuthu et al., 2014). They possess non-toxic properties and are also biodegradable. There are superior alternatives for the transportation of medicine because of their distinct attributes. The size, content, surface form, and other characteristics of drug carriers are key factors. Their efficacy and variety of uses, however, are greatly influenced by their therapeutic-carrying capability, stability, and administration methods, such as adsorption or entrapped drug systems (Illes et al., in 2017). The biomedical profession has found several uses for organic nanoparticles, especially in drug delivery systems due to their effectiveness and ability to be accurately administered in specific anatomical locations; this is known as targeted drug administration.

Carbon-based NPs

An essential factor in the growth of human civilization on Earth has been carbon. It forms connections with materials that are incredibly strong. Graphite, oxides of carbon, fullerenes, carbon nanofibers, and carbon black are among the subcategories (Ealia and Saravanakumar, 2017).

Inorganic Nanoparticles

Nanoparticles that lack carbon as a component of their structure are known as "inorganic nanoparticles". Inorganic nanoparticles (NPs) include metal and metal oxide NPs, along with their derivatives.

Metal-Based Oxide Nanoparticles

Investigators have been paying more and more attention to metal oxides in the past few years. Ionic substances known as metal oxides are made up of negatively charged oxygen ions and positively charged metallic ions. Through electrostatic attraction, the positively charged metal ions and the negative oxygen ions create strong and long-lasting ionic bonds (Devan et al., 2012). These oxide-based nanoparticles are being synthesized with the intention of altering the characteristics of their metal-based counterparts. To benefit from their improved capacity for responsiveness and performance (Nikam et al., 2018). Metal oxide nanoparticles that have been artificially produced are widespread. Some of the often-produced oxides include (SiO_2), (TiO_2), (ZnO), and (Al_2O_3) (Bulychev, 2022) (Fayad and Dhahad, 2021) (Song et al., 2021). The most commonly utilized oxide nanoparticles (NPs) for drug delivery systems are zinc oxide (ZnO) and titanium oxide.

Metal-Based NPs

Destructive or constructive methods are used to produce metal-based nanoparticles to nonmetric sizes. Nearly every metal has a synthesizable nanoparticle. Metals such as aluminum (Al) (Muzammil et al., 2020) cadmium (Cd) cobalt (Co) copper (Cu) gold (Au) silver (Ag) (Zhang et al., 2023) are regularly utilized in the creation of nanoparticles. Because of their enormous surface-to-volume ratio and quantum effects, metal nanoparticles exhibit remarkable UV-visible sensitivity as well as electrical, stimulating, heating, and antimicrobial characteristics.

Silver (Ag) NPs

Creation and Possible Uses of Silver Nanomaterials

Characteristics of Silver Nanomaterials

Small particles with widths in one or more dimensions inside a space with three dimensions that vary between 1 to 100 nanometers are called nanoparticles (Ansari et al., 2022). Applications for materials based on nanoparticles are unique and include the volume effect, interface effect, influence of small size, and enormous quantum tunneling effect. Thus,

nanomaterials considered unique compounds in the twenty-first century find application in a variety of fields, including energy, national defense, technological innovation, biology, medicine, and the chemical sector. Commercially available AgNPs are the most widely used Nano-compound on the market due to their broad potential for use in a variety of common applications as of right now, AgNPs are present in 435 out of 1814 nanoproducts, which are distributed over 32 nations or regions worldwide. This makes up about 24 percent of all nanoproducts (Vance et al., 2015). AgNP stands for "silver nanoparticles," which are tiny particles consisting of silver atoms and usually ranging in size from one to one hundred nanometers AgNPs experience oxidation on their surface, which releases free silver ions, just like bulk silver compounds do. AgNPs have unique characteristics, like area effect, quantum dimension effects, and tiny size effect, that are not found in typical materials (Naganthran et al., 2022). The greatly accelerated rate of ionized silver emission is caused by the coating and small size effects of nanoparticles. Because AgNPs function as ionized silver and increase the porousness of cell membranes, they can therefore directly harm the membranes of cells. This makes it possible for many cells to enter, which eventually leads to necrosis or apoptosis. These characteristics mean that AgNPs have a far higher bactericidal effect than silver ions. Furthermore, the negative impacts of AgNPs are associated with a range of properties, including form, concentration, chemical coating, surface charge, and others (Akter et al., 2018). AgNPs can have many different morphologies, such as triangle prism, ring, sheet, spherical, conical, disc, rod, cube, and prism (Mukherji et al., 2019). Forms that are uneven and angular increase the risk of physical injury. It was demonstrated in a study that triangular AgNPs had a stronger antibacterial impact than spherical and rod-shaped AgNPs when used to manipulate Escherichia coli (Zhang et al., 2023) or the use of both spherical and flaky AgNPs to manipulate zebrafish embryos revealed that the flaky AgNPs were more harmful (Abramenko et al., 2018). Nevertheless, because it depends on multiple variables rather than just one, the relationship between a particle's form and toxicity is not clearly defined. (Akter et al., 2018). These elements significantly affect the biotoxicity of AgNPs which include the dimension impact, redox impact, and surface stabilizers. In order to prevent aggregation, coatings are commonly placed on AgNP surfaces throughout the production process. This enhances stability and facilitates the dispersion of particles. AgNPs can be coated in a variety of ways to change their form and prevent silver ions from oxidizing. This alteration directly affects the biotoxicity of AgNPs (Zhao et al., 2021). The study discovered that AgNPs, which were altered by citrate and chitosan, exhibited more toxicity towards bacteria compared to the unmodified AgNPs. This increased toxicity is likely due to the ability of these two modifiers to expedite the release of silver ions from the AgNPs (Cavassin et al., 2015). When AgNPs are coated with citrate instead of polyvinyl pyrrolidone and poly ethyl enimine, or when there is no coating at all, their toxicity is reduced (Ivask et al.,2014). The way the coating altered the AgNPs' surface charge characteristics may have contributed to the variations in toxicity amongst the various coverings. Positively charged AgNPs are able to adhere to the negatively orientated microbial cell wall, giving them a greater bactericidal impact than negatively charged AgNPs (Zhang et al., 2023).

The Synthesis of Silver Nanoparticles

There are multiple methods for producing nanomaterials, but the two fundamental approaches currently used are: firstly, breaking down large solids into nanoparticles; and secondly, creating particles by combining individual atoms and carefully managing their growth to ensure they remain at the nanometer scale. The concept of nanoparticle preparation categorizes the ways of creating AgNPs into physical synthesis methods (Cobos et al., 2020), chemical synthesis methods (Fouda et al., 2020) and biological synthesis methods (Fig. 1) (Mohamed et al., 2019).

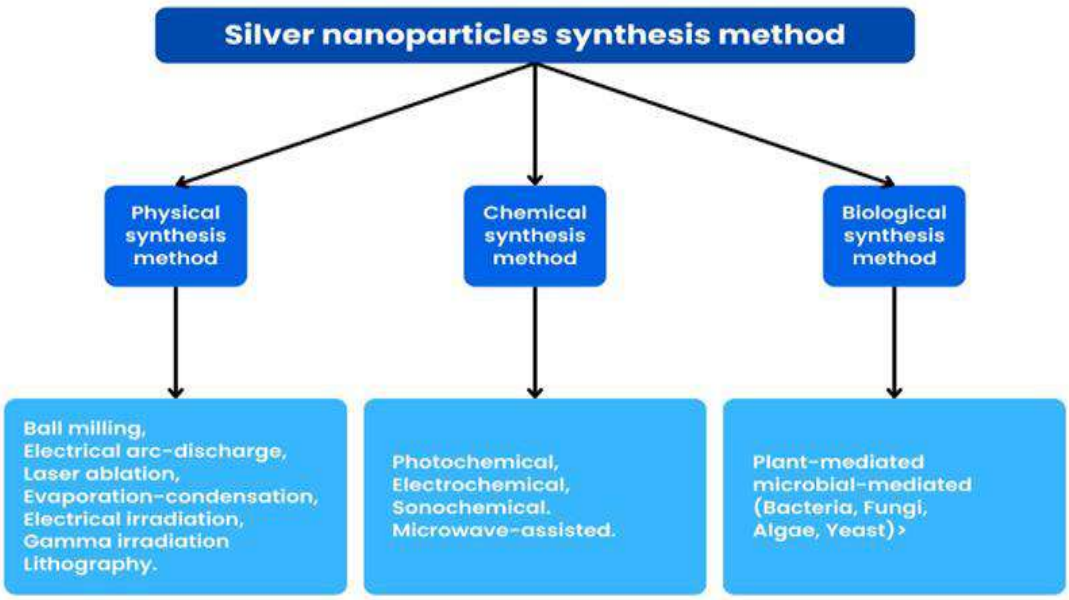


Fig. 1: Synthesis of silver nanoparticles (Mohamed et al., 2019)

A variety of techniques are used in physical synthesis, including lithography, electrical irradiation, irradiation with gamma rays, mechanical grinding, and ablation by laser, and evaporation-condensation. The metal is ground into a very fine powder using the mechanical grinding technique, which creates localized tremendous pressure through high-speed impacts. The abrasion level determines the dimension of the nanoparticles (Nguyen et al 2023). Using arc-discharge equipment, the arc-discharge process may create nanoparticles of silver in clean water without any requirement for any buffer or surfactant (El-Khatib et al., 2020). The production of nanosilver particles through evaporation and cooling plasma can be achieved by applying high voltage to silver electrodes in ionized water or by employing laser ablation in water or organic solvent (Khatami et al., 2018). In the laser elimination process, a silver block immersed in water or a synthetic solvent is quickly burned using a pulsed laser. As the plasma cools down, silver particles form and increase in size, finally resulting in the formation of nanosilver (Sharma and Bharti, 2023). The action of evaporation and later condensation turns metallic silver into particles in the evaporation-condensation technique. These nanoparticles can then further condense into atomic clusters or nano-silver particles (Mandal et al., 2016). Gamma rays have the ability to cause a radioactive breakdown of solvents, resulting in the production of dissolved electrons. These electrons can then react with metal ions, such as Ag+, in a solution to create nanoparticles (Bekhit et al., 2020).

Although the physical synthesis process looks simple, it requires exact machinery and is costly to prepare, thus it is not appropriate for large-scale manufacture (Nguyen et al 2023). This method enables the degradation of silver ions to basic silver or silver nanoparticles by electron transfer under certain conditions. Nanosilver preparation can be expedited by chemical techniques that use external energy sources, including photochemical, electrochemical, microwave-assisted, and sonic approaches (Jara et al., 2021). In photochemical processes, light—typically ultraviolet (UV) light is employed to cause silver ions to reduce and become silver nanoparticles. (Jara et al., 2021). Excitation of silver ions and the promotion of the reduction reaction can occur due to photon energy produced by light (dos Santos et al., 2019In order to cause the decrease of silver ions to silver nanoparticles, the electrochemical technique applies an electromotive force. typically, a silver electrode electrochemical cell is used for this. Silver atoms are created when electrons from the applied potential are transferred to silver ions, causing them to congregate into nanoparticles. (Kuntyi et al., 2021In order to facilitate the conversion of silver ions to nanoparticles, microwave energy is used in the process of microwave-assisted synthesis to warm the reaction mixture (Naganthran et al., 2022). Using ultrasonics, bubbles from cavitation in liquids can be produced for the purpose of synthesizing nanoparticles. When these bubbles burst, a great deal of pressure and heat is generated locally, which can turn silver ions into nanoparticles (Bhangu et al., 2020).

Through the application of reducing reagents, metallic colloidal silver particles are created by reducing oligomeric complexes formed when silver atoms and silver ions come together (Mofidfar et al., 2019). Reducing agents that are often utilized include Tollens reagent, ethylene glycol, sodium borohydride, and hydrazine (Suriati et al., 2014). In addition to lowering agents, polymers must be added as moderators during the chemical synthesis of AgNPs in order to increase their durability and keep them from clumping together. Decanethiol, polyvinyl ether, and polyvinylpyrrolidone are a few examples of these polymers. Unfortunately, one major barrier to the chemical production of AgNPs is the harmful effects of chemical reagents. Moreover, the selected stabilizers and decreasing agents have particular harmful qualities to the organism, making the chemically generated AgNPs biotoxic. Consequently, this limits the possible uses for them (Liu et al., 2016). The biological approach includes the use of plant and microbial methods which use carbohydrates, proteins, and antioxidants obtained from organic creatures like microorganisms, yeast, and herbs (including seaweed, mustard, and tea) as a substitute for agents that reduce hazardous compounds and maintain substances (Alves et al., 2022). The synthesis of these substances is potentially achieved through enzymatic and non-enzymatic reductions.

Plant strategy involves using different plant extracts to decrease silver ions into silver nanoparticles. Plant extracts include bioactive chemicals, including phenolic compounds, flavonoids, and terpenoids, which have the ability to function as stabilizing agents and lowering agents typically, the procedure is easy to follow, reasonably priced, and ecologically friendly. With this technique, a large range of plant sources, such as mustard, seaweed, tea leaves, and others, can be used (Xu et al., 2020). Utilizing microorganisms like yeast, fungi, and bacteria to create silver nanoparticles is known as the microbiological technique. It is possible for microorganisms to produce the enzymes needed to conduct the conversion of silver ions to elemental silver. To increase their stability, the nanoparticles in this process are usually coated with a coating of protein. The ability of some bacterial and fungal strains to reduce metal ions and generate nanoparticles has been investigated (Ibrahim et al., 2022). This product is distinguished by its environmentally friendly and sustainable nature, as well as its homogeneous and extremely fine particle size. It exhibits excellent dispersion and is resistant to precipitation (Adnan et al., 2022), however, when the particle size decreases, the number of surface atoms rises, resulting in the agglomeration of nanoparticles (Li et al., 2022). Because AgNPs have tendency to joint together when used alone as an antimicrobial solution, which limits their effectiveness. As a result, AgNPs are frequently mixed with other substances to create AgNPs-hydroxyapatite composites. (Bee et al., 2021), Poly (vinyl alcohol)- AgNP (PVA-AgNP) (Yang et al., 2023), AgNP-TiO2 composites, Ag/ZnO nanocomposites, etc (Kavaliūnas et al., 2022). The incorporation of AgNPs with other materials enhances compatibility for certain applications, hence expanding the range of unique qualities shown by AgNPs. AgNP-TiO2 composites have excellent biocompatibility and demonstrate significant antibacterial activity, as evidenced by a study conducted by researchers (Wang et al., 2018), and The Ag/ZnO nanocomposites, consisting of silver nanoparticles attached to the surface of ZnO, had a suppressive impact on Streptococcus mutans. Furthermore, these nanocomposites show superior antibacterial efficacy compared to ZnO nanorods (Wang et al., 2017).

Prospective Uses for AgNPs

Research into silver nanoparticles, or AgNPs, has shown promising results for application in living things. AgNPs have been shown to possess antibacterial and anticancer effects through in vivo studies. According to studies, AgNPs on Bermuda grass may be able to successfully fight off root-knot nematodes (Khan et al., 2021) as well as the plant-parasitic nematode Meloidogyne graminicola (Baronia et al., 2020). Subsequent research has unequivocally shown that (AgNPs) are effective at eradicating incognita Meloidogyne infestations on aubergine, tomato, and okra plants (Abdellatif et al., 2016). Investigations on animals have shown that AgNPs are effective in treating a variety of diseases, including those that impact the skin, respiratory system, and urinary tract, and are parasite-related (De Silva et al., 2021). Furthermore, studies have demonstrated that AgNPs can impede the development of tumors and enhance the survival rates in animal cancer models (Ansar et al., 2020). AgNPs have different uses in the medical field for curing human ailments, such as bioimaging, cancer therapy, medicine delivery, and dental technology. The unique physicochemical properties of silver nanoparticles (AgNPs) have attracted a lot of interest in the treatment of cancer (Xu et al., 2020). Instead of using conventional anticancer methods, using metal nanoparticles entails mixing therapeutic drugs and treatment candidates with drug carriers. This tactic enables targeted techniques to lessen negative consequences (Andleeb et al., 2021). In research aimed at human cervical carcinoma cells, Nepeta deflersiana (ND) was used to extract AgNPs. The AgNPs that were collected showed face-centered cubic structures that measured 33 nm on averageHeLa, a model organism of human cervical cancer cells, was to be used to assess its anticancer ability. The generation of reactive oxygen compounds (ROS), structural alterations, toxic concentrations on oxidative stress indicators, and mitochondrial membrane potential were among the parameters used to evaluate the cytotoxic reaction. The amount of AgNPs present affected the reported cytotoxicity in various ways. According to the study, ND-AgNPs can potentially cause a reduction in glutathione levels and the mitochondrial membrane, which will ultimately cause cervical carcinoma cells to die. This implies that ND-AgNPs may be useful as a cervical cancer anticancer treatment (Al-Sheddi et al., 2018). Because of their optical characteristics, which enable them to create the best contrast in cellular imaging and other therapeutic applications, nanoparticles are also used in cell biological imaging or cell sensitivity (Pratiwi et al., 2019). Silver nanoparticles (AgNPs) are extensively utilized in dentistry to enhance dental biomaterials by minimizing the formation of biofilm through their antibacterial properties. Additionally, AgNPs are integrated into root canal fillings to decrease the presence of Staphylococcus aureus and Streptococcus mutans (Yin et al., 2020).

Use of AgNPs for Control of Haemonchosis

Globally, G.I.T. parasitic nematodes represent the most economically consequential infectious illnesses (Szewc et al., 2021). They significantly impact babies and preschoolers, who are most vulnerable and are more common in tropical areas. Worm infestations can be fatal in certain age ranges (Stracke et al., 2021). The gastrointestinal tract can become infected with the highly contagious parasitic worm *H. contortus,* which can cause hemorrhagic enteritis, diarrhea, and severe anemia. If these indications are present, cattle may produce less dairy and meat, which could result in financial losses (Singh et al., 2017). *H. contortus* is spread by contaminated soil of different species and has the potential to cause human illness (Salle et al., 2019). Prior therapies for helminths have only utilized a limited number of medicines, including benzimidazole, imidazothiazole, and ivermectin (Dixit et al., 2017). A new medicine needs to be created immediately to fill the vacuum left by the increasing prevalence of parasitic infections, the scarcity of current drugs, and the evolution of drug resistance. Carvacrol-coated chitosan nanoparticles are utilized (Fernandes et al., 2020) for anthelminthic activity against the adult stage of *Haemonchus contortus* (Fernandes et al., 2020). *Lansium parasiticum* is a common plant used for food and timber production in both Bangladesh and India. Indian researchers exploited this plant to manufacture silver nanoparticles (LAgNPs). The use of LAgNPs made from this plant, a unique anthelminthic medication, could lead to new developments in the field of contemporary medicine. The study discovered that all of the males and 80% of the females in the samples passed away after 12 hours of starting LAgNP treatment. In contrast, just 26% of the males and 11.3% of the females in the citric acid-coated AgNPs sample perished after 12 hours, and none of the males or females in the sample became paralyzed after one hour. Consequently, LAgNPs exhibited elevated toxicity and demonstrated greater efficacy against the parasite. When LAgNPs were given to *Haemonchus contortus*, the stress caused by nitric oxide synthase (NOS) and reactive oxygen species (ROS) increased more quickly, which inhibited the growth of the parasite (Goel et al., 2020).

Anti-Parasitic Mechanism of AgNPs

Because of their huge surface area, capacity to release silver ions (Ag+), and generation of reactive oxygen species (ROS), which possess substantial antibacterial and antifungal capabilities, AgNPs have the potential to be extremely successful in battling infections. (Flores-López et al., 2019) The entry of silver ions and the production of reactive oxygen species (ROS) are associated with the effects of AgNPs on parasites. The tiny-sized silver particles have the ability to penetrate the Cryptosporidium oocyst and kill the sporozoites, whilst the released silver ions have the potential to engage with the cell wall and induce leakage (Cameron et al., 2016) Metallic silver can negatively affect a cell by interfering with its membrane or by chemically attaching to and accumulating on its surface. Plasmodium and other parasitic protozoa are among the parasites that are harmful to silver ions released by silver nanoparticles (AgNPs) (Al-Quraishy et al., 2020). The mobility and stability of the parasite's cell membrane may be compromised by the binding of these silver ions. The disturbance ultimately results in the malfunction and demise of the parasite's cells by increasing the membrane's permeability and causing the loss of vital intracellular components (Cameron et al., 2016). Silver nanoparticles (AgNPs)

cause cell death and primarily eliminate parasites by producing reactive oxygen species (ROS) (Ahmed et al., 2018). The majority of stress reactions that occur within cells are a result of the harmful effects generated by reactive oxygen species (ROS). Among these responses, oxidative stress is believed to be the primary mechanism responsible for the cytotoxicity induced by silver nanoparticles (AgNPs). The release of silver ions has the potential to cause the parasite to produce reactive oxygen species, which can lead to oxygen consumption and damage to its cellular components. This can ultimately lead to the demise of the parasite cells and the eradication of the parasite (Ullah et al., 2018). Every normal cell has some ROS, but the immune system balances it out. After cells are exposed to AgNP stress, they quickly produce large amounts of reactive oxygen species (ROS). The proteins that eliminate excess reactive oxygen species (ROS) include glutathione (GSH), catalase, or superoxide dismutase (SOD), thioredoxin, vitamin E, and others. Glutathione has the ability to bind to and neutralize reactive oxygen species (ROS). Therefore, it is acknowledged that the glutathione-regulated antioxidant system is an essential defense mechanism for cellular survival (Docea et al., 2020). AgNPs decrease the amounts of GSH by blocking GSH synthase, which results in the cells being unable to efficiently remove intracellular ROS (Zorraquín-Peña et al., 2020). When there is an imbalance between the production of oxygen species that are reactive (ROS) and the antioxidant system's ability to break them down, oxidative stress may result. This imbalance may result in catastrophic events such as lipid and protein peroxidation, mitochondrial damage, DNA damage, and ultimately apoptosis-induced cell death (Flores-López et al., 2019). When cells produce too much reactive oxygen species (ROS), the p53, protein kinase B (AKT), and mitogen-activated protein kinase (MAPK) signaling pathways become active, initiating the apoptotic process. AKT expression is first downregulated when cells are subjected to AgNP stress, which causes them to produce a significant amount of reactive oxygen species (ROS). Pro-apoptotic kinase p38 expression is subsequently elevated as a result of this reduction. Simultaneously, there is a decline in the expression of the DNA repair enzyme PARP, which significantly amplifies the expression of p53. Consequently, the increased p53 expression induces apoptosis (Li et al., 2016)

Moreover, by upsetting the proton transport chain, silver ions can impede metabolism and interfere with the synthesis of ATP. Silver ions have the ability to disrupt the functioning of important enzymes and metabolic pathways in the parasite, resulting in cellular malfunction and ultimately causing its demise (Hamad et al., 2020). The precise mechanism by which AgNPs operate against the parasite is currently being studied, and there might be alternative methods that are equally effective. AgNPs possess the capability to serve as a valuable instrument in combating parasitic illnesses (Ghorbani et al., 2019).

Conclusion

AgNPs have a promising future due to their unique features, which are in high demand for many applications. It is anticipated that they will significantly influence industries like electronics, energy, environmental cleanup, medical applications, and antimicrobial applications. This article has given a succinct summary of the most recent developments in understanding AgNPs' antiprotozoal properties. AgNPs have an antiparasitic effect through a variety of mechanisms, including breaking down the parasite's cellular membranes, lowering metabolism, and preventing proper development. Silver nanoparticles (AgNPs) pose practical challenges. Primarily, when silver is discharged into the environment, it poses a significant risk to human health and environmental safety due to its detrimental effects on humans, animals, and the ecosystem. Silver nanoparticles (AgNPs) may potentially have possible adverse effects on animal health, including hepatotoxicity and nephrotoxicity. Furthermore, the issue of AgNP stability poses an additional hurdle. The effectiveness of AgNPs may diminish over time due to degradation and interactions with other chemicals in the environment. This can result in the development of parasite resistance and a decrease in their ability to effectively combat parasites when used extensively over a long period. Therefore, further research and development are needed to address the concerns regarding the stability, safety, and drug resistance of AgNPs, as well as to ensure the safe and long-lasting use of these materials.

REFERENCES

Abdellatif, K.F., Abdelfattah, R.H., and El-Ansary, M.S.M. (2016). Green Nanoparticles Engineering on Root-knot Nematode Infecting Eggplants and Their Effect on Plant DNA Modification. *Iranian Journal Biotechnology*, Vol,14, p 250–259.

Abramenko, N.B., Demidova, T.B., Abkhalimov capital Ie, C., Ershov, B.G., Krysanov, E.Y., and Kustov, L.M. (2018). Ecotoxicity of different shaped silver nanoparticles: Case of zebrafish embryos. *Journal Hazard. Mater*, Vol, 347, p89–94.

AbuDalo, M.A., Al-Mheidat, I.R., Al-Shurafat, A.W., Grinham, C. and Oyanedel-Craver, V., (2019). Synthesis of silver nanoparticles using a modified Tollens' method in conjunction with phytochemicals and assessment of their antimicrobial activity. *PeerJournal*, vol*7*, p.e 6413

Adnan, M., Akbar, A., Mussarat, S., Murad, W., Hameed, I., Begum, S., Nazir, R., Ali, N., Ali, E.A., and Bari, A. (2022). Phyto-Extract Mediated Synthesis of Silver Nanoparticles (AgNPs) and Their Biological Activities. *Biology Research International*, 9845022.

Ahmed, B., Hashmi, A., Khan, M.S. and Musarrat, J., (2018). ROS mediated destruction of cell membrane, growth and biofilms of human bacterial pathogens by stable metallic AgNPs functionalized from bell pepper extract and quercetin. *Advance Powder Technology,* Vol *29*(7), pp.1601-1616.

Akter, M., Sikder, M.T., Rahman, M.M., Ullah, A., Hossain, K.F.B., Banik, S., Hosokawa, T., Saito, T., and Kurasaki, M. A. (2018). systematic review on silver nanoparticles-induced cytotoxicity: Physicochemical properties and perspectives. *Journal Advance,* Vol, 9, pp1–16

AlFaleh, F. A., Ismael, S. S., Aguilar-Marcelino, L., Silva, F. E. M., Ashraf, T., Abbas, R. Z., and Qamar, W. (2023). Use of nanoparticles, a modern means of drug delivery, against cryptosporidiosis. *Journal of Advanced Veterinary and Animal Research*, *10*(4), 704**.**

Al-Quraishy, S., Murshed, M., Delic, D., Al-Shaebi, E.M., Qasem, M.A.A., Mares, M.M., Dkhil, M.A. (2020). Plasmodium chabaudiinfected mice spleen response to synthesized silver nanoparticles from Indigofera oblongifolia extract. *Letter Applied Microbiology*, Vo, 71, p542–549.

Al-Sheddi, E.S., Farshori, N.N., Al-Oqail, M.M., Al-Massarani, S.M., Saquib, Q., Wahab, R., Musarrat, J., Al-Khedhairy, A.A., and Siddiqui, M.A. (2018). Anticancer Potential of Green Synthesized Silver Nanoparticles Using Extract of Nepeta deflersiana against Human Cervical Cancer Cells (HeLA). *Bioinorg Chemistry Applied*, 9390784

Alves, M.F., and Murray, P.G. (2020). Biological Synthesis of Monodisperse Uniform-Size Silver Nanoparticles (AgNPs) by Fungal Cell-Free Extracts at Elevated Temperature and pH. *Journal Fungi,* vol 8, p439.

Alvi, M. A., Alshammari, A., Ali, R. M. A., Ul Haq, S., Bashir, R., Li, L., and Jia, W. Z. (2023). Revealing novel cytb and nad5 genes-based population diversity and benzimidazole resistance in Echinococcus granulosus of bovine origin. *Frontiers in Veterinary Science*, *10*, 1191271.

Alvi, M. A., Khan, S., Ali, R. M. A., Qamar, W., Saqib, M., Faridi, N. Y., and Jia, W. Z. (2022). Herbal medicines against hydatid disease: A systematic review (2000–2021). *Life*, *12*(5), 676.

Alvi, M. A., Li, L., Bahadur, K., Ullah, S., Saqib, M., Ohiolei, J. A., and Jia, W. Z. (2022). First Comparative Biochemical Profile Analysis of Cystic Fluids of Taenia hydatigena and Echinococcus granulosus Obtained from Slaughtered Sheep and Goats. *Pakistan Veterinary Journal*, *42*(2).

Alvi, M. A., Ohiolei, J. A., Saqib, M., Li, L., Tayyab, M. H., Alvi, A. A., and Jia, W. Z. (2020). Echinococcus granulosus (sensu stricto)(G1, G3) and E. ortleppi (G5) in Pakistan: phylogeny, genetic diversity and population structural analysis based on mitochondrial DNA. *Parasites and Vectors*, *13*, 1-10.

Andleeb, A., Andleeb, A., Asghar, S., Zaman, G., Tariq, M., Mehmood, A., Nadeem, M., Hano, C., Lorenzo, J.M. and Abbasi, B.H., (2021). A systematic review of biosynthesized metallic nanoparticles as a promising anti-cancer-strategy. *Cancers*, vol. *13*(11), p.2818.

Ansar, S., Tabassum, H., Aladwan, N.S.M., Naiman Ali, M., Almaarik, B., AlMahrouqi, S., Abudawood, M., Banu, N., and Alsubki, R. (2020). Eco friendly silver nanoparticles synthesis by Brassica oleracea and its antibacterial, anticancer and antioxidant properties. *Science Rep*, vol.10, p18564

Ansari, M.J., Kadhim, M.M., Hussein, B.A., Lafta, H.A. and Kianfar, E., (2022). Synthesis and stability of magnetic nanoparticles. *Bio Nano Science*, vol. *12*(2), pp.627-638.

Baronia, R., Kumar, P., Singh, S.P., and Walia, R.K. (2020). Silver nanoparticles as a potential nematicide against Meloidogyne graminicola. *Journal Nematology*, Vol. 52, p1–9

Bee, S.L., Bustami, Y., Ul-Hamid, A., Lim, K. and Abdul Hamid, Z.A. (2021). Synthesis of silver nanoparticle-decorated hydroxyapatite nanocomposite with combined bioactivity and antibacterial properties. *Journal Mater Science Mater Medicine*, vol. *32*(9), p.106.

Bekhit, M., Abu el-naga, M.N., Sokary, R., Fahim, R.A. and El-Sawy, N.M. (2020). Radiation-induced synthesis of tween 80 stabilized silver nanoparticles for antibacterial applications. *Journal Environment Science Health A*, vol. *55*(10), pp.1210-1217

Bhangu, S.K., Ashokkumar, M. and Cavalieri, F. (2020). Synthesis of bio-functional nanoparticles from sono-responsive amino acids using high frequency ultrasound. *Ultrason Sonochem*, vol. *63*, p.104967

Bulychev, N. (2022). Synthesis of gaseous hydrogen and nanoparticles of silicon and silicon oxide by pyrolysis of tetraethoxysilane in an electric discharge under the action of ultrasound. *International Journal Hydrogen Energy*, *vol. 47*(84), p35581-35587

Cameron, P., Gaiser, B.K., Bhandari, B., Bartley, P.M., Katzer, F., and Bridle, H. (2016). Silver

Cavassin, E.D., de Figueiredo, L.F., Otoch, J.P., Seckler, M.M., de Oliveira, R.A., Franco, F.F. Marangoni, V.S., Zucolotto, V., Levin, A.S., and Costa, S.F. (2015). Comparison of methods to detect the in vitro activity of silver nanoparticles (AgNP) against multidrug resistant bacteria. *Journal Nanobiotechnology*, Vol. 13, p64.

Chugh, D., Viswamalya, V.S., and Das, B. (2021). Green synthesis of silver nanoparticles with algae and the importance of capping agents in the process. *Journal Genetic Eng Biotechnology*, vol. 19(1), p.126

Cobos, M., De-La-Pinta, I., Quindos, G., Fernandez, M.J., and Fernandez, M.D. (2020). Synthesis, Physical, Mechanical and Antibacterial Properties of Nanocomposites Based on Poly (vinyl alcohol)/Graphene Oxide-Silver Nanoparticles. *Polymers*, vol. 12, p723.

De Silva, C., Nawawi, N.M., Abd Karim, M.M., Abd Gani, S., Masarudin, M.J., Gunasekaran, B. and Ahmad, S.A., (2021). The mechanistic action of biosynthesised silver nanoparticles and its application in aquaculture and livestock industries. *Animals*, vol.*11*(7), p.2097

Devan, R. S., Patil, R. A., Lin, J. H., and Ma, Y. R. (2012). One-dimensional metal-oxide nanostructures: recent developments in synthesis, characterization, and applications. *Advance Function Mater*, vol. *22*(16), p3326-3370.

Din, M. I., and Rehan, R. (2017). Synthesis, characterization, and applications of copper nanoparticles. *Analytical Letters*, *50*(1), 50-62.

Dixit, A. K., Das, G., Dixit, P., Singh, A.P., Kumbhakar, N.K., and Sankar, M. (2017). An assessment of benzimidazole resistance against caprine nematodes in Central India. *Tropical Animal Health Prod*, Vol. 49 p1471

Docea, A.O., Calina, D., Buga, A.M., Zlatian, O., Paoliello, M.M.B., Mogosanu, G.D., Streba, C.T., Popescu, E.L., Stoica, A.E., Bîrcă, A.C. and Vasile, B.Ș. (2020). The effect of silver nanoparticles on antioxidant/pro-oxidant balance in a murine model. *International Journal Molecular Science*, vol. *21*(4), p.1233.

dos Santos, M. A., Paterno, L. G., Moreira, S. G. C. and Sales, M. J. A. (2019). Original

Durak, S., Arasoglu, T., Ates, S.C. and Derman, S. (2020). Enhanced antibacterial and antiparasitic activity of multifunctional polymeric nanoparticles. *Nanotechnology*, vol. *31*(17), p.175705.

Dziduch, K., Greniuk, D. and Wujec, M. (2022). The current directions of searching for antiparasitic drugs. *Molecules*, vol. *27*(5), p.1534

Ealia, S. A. M., and Saravanakumar, M.P. (2017). A review on the classification, characterisation, synthesis of nanoparticles and their application. *Mater Science Eng*, Vol. 263, No. 3, p. 032019.

Elhefny, M.T., Mostafa, N.E., Mohamed, E.A., Abdelhameed, R.M., Sarhan, M.H. and Moawad, H.S.F. (2021). Role of nanoparticles in diagnosis and management of parasitic diseases. *Egypt Journal Hosp Medicine* vol. *86*(1), pp.85-89.

El-Khatib, A.M., Doma, A.S., Abo-Zaid, G.A., Badawi, M.S., Mohamed, M.M. and Mohamed, A.S. (2020). Antibacterial activity of some nanoparticles prepared by double arc discharge method. *Nano-Structures and Nano-Objects*, vol. *23*, p.100473.

Esakkimuthu, T., Sivakumar, D., and Akila, S. (2014). Application of nanoparticles in wastewater treatment. *Pollution Research*, vol 33(03), p567-571.

Fayad, M. A., and Dhahad, H. A. (2021). Effects of adding aluminum oxide nanoparticles to butanol-diesel blends on performance, particulate matter, and emission characteristics of diesel engine. *Fuel*, vol. 286, p119363.

Fernandes, B., Matama, T., Andreia, C.G., Cavaco-Paulo, A. (2020). Cyclosporin A-loaded poly (d,l-lactide) nanoparticles: A promising tool for treating alopecia. *Nanomedicine*, vol. 15, p1459–1469

Flores-López, L.Z., Espinoza-Gómez, H. and Somanathan, R., (2019). Silver nanoparticles: Electron transfer, reactive oxygen species, oxidative stress, beneficial and toxicological effects. Mini review. *Journal Applied Toxicology*, *39*(1), pp.16-26.

formation by multidrug resistant Acinetobacter baumannii. Biofouling. vol. *36*(4), p.492-504.

Fouda, M.M.G., Abdelsalam, N.R., Gohar, I.M.A., Hanfy, A.E.M., Othman, S.I., Zaitoun, A.F., Allam, A.A., Morsy, O.M., and El-Naggar, M. (2020). Utilization of High throughput microcrystalline cellulose decorated silver nanoparticles as an eco-nematicide on root-knot nematodes. *Colloids Surf. B Biointerfaces*. Vol. 188, p110805

Gamboa, M.I., Basualdo, J.A., Kozubsky, L., Costas, E., Cueto Rua, E. and Lahitte, H.B., (1998). Prevalence of intestinal parasitosis within three population groups in La Plata, Argentina. *Europe Journal Epidemiology*, vol. *14*, pp.55-61

Gholamali, I., Asnaashariisfahani, M. and Alipour, E., (2020). Silver nanoparticles incorporated in pH-sensitive nanocomposite hydrogels based on carboxymethyl chitosan-poly (vinyl alcohol) for use in a drug delivery system. *Regen Eng Transl Medicine*, vol. *6*, pp.138-153.

Ghorbani, M., Fekrvand, S., Shahkarami, S., Yazdani, R., Sohani, M., Shaghaghi, M., Hassanpour, G., Mohammadi, J., Negahdari, B., and Abolhassani, H. (2019). The evaluation of neutropenia in common variable immune deficiency patients. *Expert Review Clinical Immunology,* Vol. 15, p1225–1233

Goel, V., Kaur, P., Singla, L.D., and Choudhury, D. (2020). Biomedical Evaluation of Lansium parasiticum Extract-Protected Silver Nanoparticles Against Haemonchus contortus, a Parasitic Worm. *Frontier Molecular Bioscience,* Vol. 7, p595646

Hamad, A., Khashan, K.S. and Hadi, A. (2020). Silver nanoparticles and silver ions as potential antibacterial agents. *Journal Inorg Organomet Polym Mater*, Vol. *30*(12), pp.4811-4828.

Hassan, D., Farghali, M., Eldeek, H., Gaber, M., Elossily, N. and Ismail, T. (2019). Antiprotozoal activity of silver nanoparticles against Cryptosporidium parvum oocysts: New insights on their feasibility as a water disinfectant. *Journal Microbiology Methods,* Vol. *165*, p.105698

Hayat, S. (2020). Aluminium oxide nanoparticles inhibit EPS production, adhesion and biofilm

Ibrahim, S., Ahmad, Z., Manzoor, M.Z., Mujahid, M., Faheem, Z., and Adnan, A. (2021). Optimization for biogenic microbial synthesis of silver nanoparticles through response surface methodology, characterization, their antimicrobial, antioxidant, and catalytic potential. *Science Rep*, vol. 11, p770

Illes, B., Hirschle, P., Barnert, S., Cauda, V., Wuttke, S. and Engelke, H. (2017). Exosome-coated metal–organic framework nanoparticles: an efficient drug delivery platform. *Chemistry of Materials*, vol. 29(19), pp.8042-8046

Ivask, A., Elbadawy, A., Kaweeteerawat, C., Boren, D., Fischer, H., Ji, Z., Chang, C.H., Liu, R. Tolaymat, T., and Telesca, D. (2014). Toxicity mechanisms in Escherichia coli vary for silver nanoparticles and differ from ionic silver. *ACS Nano*, Vol. 8, p374–386.

Jamkhande, P. G., Ghule, N. W., Bamer, A. H., and Kalaskar, M. G. (2019). Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. *Journal Drug Deliv Science Technology*, vol. *53*, p101174.

Jara, N., Milán, N.S., Rahman, A., Mouheb, L., Boffito, D.C., Jeffryes, C. and Dahoumane, S.A., (2021). Photochemical synthesis of gold and silver nanoparticles—A review. *Molecules*, vol. *26*(15), p.4585.

Kavaliūnas, V., Čeplikas, P., Sriubas, M. and Laukaitis, G. (2022). The sensitization of TiO2 thin film by Ag nanoparticles for the improvement of photocatalytic efficiency. *Applied Science*, vol. *12*(11), p.5725.

Khan, F., Ansari, T., Shariq, M. and Siddiqui, M.A., (2021). Nanotechnology: a new beginning to mitigate the effect of plant-parasitic nematodes. In Innovative Approaches in Diagnosis and Management of Crop Diseases, pp. 19-43.

Khatami, M., Sharifi, I., Nobre, M.A.L., Zafarnia, N., and Aflatoonian, M.R. (2018). Waste-grass-mediated green synthesis of silver nanoparticles and evaluation of their anticancer, antifungal and antibacterial activity. *Green Chemistry Letter Review,* vol. *11*, p125–134.

Kousha, A., Hakimi, S., Fallah, E., Nokhahi, I., Sarafraz, S., and Shahnami, A. (2015). Prevalence of intestinal parasites among symptomless primary school children attending urban health centers, Tabriz.

Krukemeyer, M.G., Krenn, V., Huebner, F., Wagner, W. and Resch, R., (2015). History and possible uses of nanomedicine based on nanoparticles and nanotechnological progress. *Journal Nanomedicine Nanotechnology*, vol. *6*(6), p.336

Kuntyi, O.I., Kytsya, A.R., Bondarenko, A.B., Mazur, A.S., Mertsalo, I.P. and Bazylyak, L.I., (2021). Microplasma synthesis of silver nanoparticles in PVP solutions using sacrificial silver anodes. *Colloid Polym Sci*ence, vol. *299*, pp.855-863.

Li, Y., Guo, M., Lin, Z., Zhao, M., Xiao, M., Wang, C., Xu, T., Chen, T., and Zhu, B. (2016). Polyethylenimine-functionalized silver nanoparticlebased co-delivery of paclitaxel to induce HepG2 cell apoptosis. *International Journal Nanomedicine*, Vol. 11, p6693–6702.

Li, Y., Qin, T., Ingle, T., Yan, J., He, W., Yin, J.J., and Chen, T. (2017). Differential genotoxicity mechanisms of silver nanoparticles and silver ions. *Archive Toxicology,* Vol. 91, 509–519.

Liu, M., Fang, F., Song, X., Yu, F., Li, F., Shi, X., Xue, C., Chen, T., and Wang, X. (2016). The first visually observable three-mode antibiotic switch and its relative 3D printing assisted applications. *Journal Mater. Chemistey, B*. vol. 4, 2544–2547

Mandal, D., Kumar Dash, S., Das, B., Chattopadhyay, S., Ghosh, T., Das, D., and Roy, S. (2016). Bio-fabricated silver nanoparticles preferentially target Gram positive depending on cell surface charge. *Biomedicine Pharmacother,* Vol. *83*, p548–558.

Mofidfar, M., Kim, E.S., Larkin, E.L., Long, L., Jennings, W.D., Ahadian, S., Ghannoum, M.A., and Wnek, G.E. (2019). Antimicrobial Activity of Silver Containing Crosslinked Poly (Acrylic Acid) Fibers. *Micromachines*, vol. 10, p829

Mohamed, N.H., Ismail, M.A., Abdel-Mageed, W.M., and Mohamed Shoreit, A.A. (2019). Antimicrobial activity of green silver nanoparticles from endophytic fungi isolated from Calotropis procera (Ait) latex. *Microbiology*, vol.165, 967–975.

Momen Heravi, M., Rasti, S., Vakili, Z., Moraveji, A. and Hosseini, F. (2013). Prevalence of intestinal parasites infections among Afghan children of primary and junior high schools residing Kashan city, Iran, 2009-2010. *Iran Journal Microbiology,* Vol. *7*(1), pp.46-52.

Mukherji, S., Bharti, S., Shukla, G. and Mukherji, S., (2019). Synthesis and characterization of size-and shape-controlled silver nanoparticles. *Physics Science Review*, vol. *4*(1), p.20170082.

Mustafa, S., Alharbi, L. M., Abdelraheem, M. Z., Mobashar, M., Qamar, W., A. Al-Doaiss, A., and Abbas, R. Z. (2024). Role of Silver Nanoparticles for the Control of Anthelmintic Resistance in Small and Large Ruminants. *Biological Trace Element Research*, 1-20.

Naganthran, A., Verasoundarapandian, G., Khalid, F.E., Masarudin, M.J., Zulkharnain, A., Nawawi, N.M., Karim, M., Che Abdullah, C.A., Ahmad, S.A. (2022). Synthesis, Characterization and Biomedical Application of Silver Nanoparticles. Materials. Vol. 15, p427.

Nguyen, N.P.U., Dang, N.T., Doan, L. and Nguyen, T.T.H., 2023. Synthesis of silver nanoparticles: from conventional to 'modern'methods—a review. *Processes*, vol. *11*(9), p.2617.

Nikam, A.V., Prasad, B.L.V. and Kulkarni, A.A. (2018). Wet chemical synthesis of metal oxide nanoparticles: a review. *Cryst Eng Comm*, vol. *20*(35), pp.5091-5107.

Norouzi, R. (2017). A review on most nanoparticles applied against parasitic infections. *J Biol Today's World*, vol. *6*(10), pp.196-203.

Oprică, L. and Bălășoiu, M. (2019). Nanoparticles: an overview about their clasifications, synthesis, properties, characterization and applications. *Journal Expriment Molecular Biology*, Vol. *20*(4), pp.43-60

Pratiwi, F.W., Kuo, C.W., Chen, B.C. and Chen, P. (2019). Recent advances in the use of fluorescent nanoparticles for bioimaging. *Nanomedicine*, vol. *14*(13), pp.1759-1769.

Qamar, W., and Alkheraije, K. A. (2023). Anthelmintic Resistance in Haemonchus contortus of Sheep and Goats from Asia--A Review of In Vitro and In Vivo Studies. *Pakistan Veterinary Journal*, *43*(3).

Qi, H. and Zhang, C. (2022). Organic nanoparticles for electrogenerated chemiluminescence assay. *Current Opin Electrochemistry*, Vol. *34*, p.101023

Rai, M., Kon, K., Ingle, A., Duran, N., Galdiero, S., Galdiero, M. (2014). Broad-spectrum bioactivities of silver nanoparticles: the emerging trends and future prospects. *Applied Microbiology Biotechnology*, Vol. 98(5). p1951-61

Rehman, T., Iqbal, K. J., Anwer, A., Abbas, R. Z., Babar, W. and Ali, A. (2021). In vitro anthelmintic efficacy of Citrullus colocynthis (L.) Schrad on Haemonchus contortus. *Veterinary Archive,* Vol. 91. p309-318

Rizvi, S.A. and Saleh, A.M. (2018). Applications of nanoparticle systems in drug delivery technology. *Saudi Pharm Journal,* vol. *26*(1), pp.64-70.

Salle, G., Doyle, S.R., Cortet, J., Cabaret, J., Berriman, M., Holroyd, N. and Cotton, J.A. (2019). The global diversity of Haemonchus contortus is shaped by human intervention and climate. *Nature Communication*, Vol. *10*(1), p.4811

Sanchez-Moreno, P., Ortega-Vinuesa, J., Peula-Garcia, J. (2018). Smart drug-delivery systems for cancer nanotherapy. *Current Drug Targets*, Vol. 19(4). p339-359.

Sarkar, S., Osama, K., Mohammad Sajid Jamal, Q., Amjad Kamal, M., Sayeed, U., Khan, K.A., Siddiqui, H. and Akhtar, S. (2017). Advances and implications in nanotechnology for lung cancer management. *Current Drug Metabolism*, Vol. *18*(1), pp.30-38

Sharma, R. and Bharti, R. (2023). A Review on the Synthesis and Photocatalytic Application of Silver Nano Particles. In *IOP Conference Series: Earth and Environmental Science,* Vol. 1110. No. 1, p. 012021

Shnoudeh, A.J., Hamad, I., Abdo, R.W., Qadumii, L., Jaber, A.Y., Surchi, H.S. and Alkelany, S.Z. (2019). Synthesis, characterization, and applications of metal nanoparticles. *In Biomaterials and Bionanotechnology*, pp. 527-612.

Singh, R., Bal, M.S., Singla, L.D. and Kaur, P. (2017). Detection of anthelmintic resistance in sheep and goat against fenbendazole by faecal egg count reduction test. *Journal Parasitology Disease*, Vol. *41*, pp.463-466.

Sinnathamby, G., Henderson, G., Umair, S., Janssen, P., Bland, R., and Simpson, H. (2018). The bacterial community associated with the sheep gastrointestinal nematode parasite Haemonchus contortus. *PLoS ONE,* 13e0192164. doi: 10.1371/journal.pone.0192164.

Skheel, A.Z., Jaduaa, M.H. and Abd, A.N. (2021). Green synthesis of cadmium oxide nanoparticles for biomedical applications (antibacterial, and anticancer activities). *Mater Today Proc*, Vol. *45*, pp.5793-5799

Sofi, M.A., Sunitha, S., Sofi, M.A., Pasha, S.K. and Choi, D. (2022). An overview of antimicrobial and anticancer potential of silver nanoparticles. *Journal King Saud University Science*, vol.*34*(2), p.101791

Song, G., Cheng, N., Zhang, J., Huang, H., Yuan, Y., He, X., Luo, Y., and Huang, K. (2021). Nanoscale cerium oxide: Synthesis, biocatalytic mechanism, and applications. *Catalysts*, *vol. 11*(9). p1123.

Stracke, K., Adisakwattana, P., Phuanukoonnon, S., Yoonuan, T., Poodeepiyasawat, A., Dekumyoy, P., Chaisiri, K., Roth Schulze, A., Wilcox, S., Karunajeewa, H. and Traub, R.J. (2021). Field evaluation of the gut microbiome composition of pre-school and school-aged children in Tha Song Yang, Thailand, following oral MDA for STH infections. *PLoS Neg Tropical Disease*, Vol. *15*(7), p.e0009597

Sueth-Santiago, V., Decote-Ricardo, D., Morrot, A., Freire-de-Lima, C.G. and Lima, M.E.F. (2017). Challenges in the chemotherapy of Chagas disease: Looking for possibilities related to the differences and similarities between the parasite and host. *World Journal Biology Chemistry,* Vol. *8*(1), p.57.

Sun, Y., Chen, D., Pan, Y., Qu, W., Hao, H., Wang, X., Liu, Z. and Xie, S. (2019). Nanoparticles for antiparasitic drug delivery. *Drug Delivery*, *26*(1), pp.1206-1221.

Suriati, G., Mariatti, M., and Azizan, A. (2014). Synthesis of silver nanoparticles by chemical reduction method: Effect of reducing agent and surfactant concentration. *International Journal Automot Mech Eng,* Vol. *10*, p1920–1927

Szewc, M., De Waal, T. and Zintl, A. (2021). Biological methods for the control of gastrointestinal nematodes. *Journal Veterinary*, Vol. *268*, p.105602

Tegen, D. and Damtie, D. (2021). Prevalence and risk factors associated with intestinal parasitic infection among primary school children in Dera district, northwest Ethiopia. *Can Joural Infect Disease Medicine Microbiology*.

Thurner, G.C., Chabicovsky, M., Abdelmoez, A. and Debbage, P. (2016). Targeted drugs and nanomedicine: present and future. *Frontier Medicine Chemistry*, pp.182-233.

Ullah, A., Sun, H., Hakim, Yang, X., Zhang, X. (2018). A novel cotton WRKY gene, GhWRKY6-like, improves salt tolerance by activating the ABA signaling pathway and scavenging of reactive oxygen species. *Physiology Plant*, Vol. 162, p439–454

Ullah, I., Cosar, G., Abamor, E.S., Bagirova, M., Shinwari, Z.K. and Allahverdiyev, A.M. (2018). Comparative study on the antileishmanial activities of chemically and biologically synthesized silver nanoparticles (AgNPs). *Biotechnology*, vol. *8*, pp.1-8.

Vance, M.E., Kuiken, T., Vejerano, E.P., McGinnis, S.P., Hochella, M.F., Rejeski, D., and Hull, M.S. (2015). Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory. *Beilstein Journal Nanotechnology,* Vol. 6, p1769–1780

Vinosha, P.A., Manikandan, A., Ceicilia, A.S.J., Dinesh, A., Nirmala, G.F., Preetha, A.C., Slimani, Y., Almessiere, M.A., Baykal, A. and Xavier, B. (2021). Review on recent advances of zinc substituted cobalt ferrite nanoparticles: Synthesis characterization and diverse applications. *Ceram International*, vol. *47*(8), pp.10512-10535

Wang, S., Wu, J., Yang, H., Liu, X., Huang, Q., and Lu, Z. (2017). Antibacterial activity and mechanism of Ag/ZnO nanocomposite against anaerobic oral pathogen Streptococcus mutans. *Journal Mater. Science Mater Medicine,* Vol. 28, p23.

Wang, Y., Yan, C., Li, C., Lu, Z., Ma, C., Yan, Y., and Zhang, Y. (2018). Charge Transfer Tuned by the Surrounding Dielectrics in TiO(2)-Ag Composite Arrays. *Nanomaterials*. Vol. 8, p1019.

Xu, L., Wang, Y. Y., Huang, J., Chen, C. Y., Wang, Z. X., and Xie, H. (2020). Silver nanoparticles: Synthesis, medical applications and biosafety. *Theranostics*, Vol. 10, p8996–9031.

Yang, D., Liu, Q., Gao, Y., Wan, S., Meng, F., Weng, W. and Zhang, Y. (2023). Characterization of silver nanoparticles loaded chitosan/polyvinyl alcohol antibacterial films for food packaging. *Food Hydrocoll*, vol. *136*, p.108305

Yin, I.X., Zhang, J., Zhao, I.S., Mei, M.L., Li, Q. and Chu, C.H. (2020). The antibacterial mechanism of silver nanoparticles and its application in dentistry. *International Journal Nanomedicine* pp.2555-2562

Zhang, P., Gong, J., Jiang, Y., Long, Y., Lei, W., Gao, X. and Guo, D. (2023). Application of silver nanoparticles in parasite treatment. *Pharmaceutics*, vol. 15(7), p.1783.

Zhao, J., Wang, X., Hoang, S.A., Bolan, N.S., Kirkham, M.B., Liu, J., Xia, X. and Li, Y. (2021). Silver nanoparticles in aquatic sediments: Occurrence, chemical transformations, toxicity, and analytical methods. *Journal Hazard Mater*, vol. *418*, p.126368.

Zorraquín-Peña, I., Cueva, C., González de Llano, D., Bartolomé, B. and Moreno-Arribas, M.V. (2020). Glutathione-stabilized silver nanoparticles: antibacterial activity against periodontal bacteria, and cytotoxicity and inflammatory response in oral cells. *Biomedicines*, vol. *8*(10), p.375.

Chapter 16

Role of Silver Nanoparticles in Poultry Health

Syed Muhammad Faizan[1], Zain ul Abadeen[2], Amalash Shakoor[3], Noman Yousaf Fridi[3], Tayyab Zafar[4] and Muhammad Asif Javed[1]

[1]Department of Pathology, Faculty of Veterinary Science, University of Agriculture, Faisalabad
[2]Department of Pathobiology, Riphah College of Veterinary Science, Riphah International University-Lahore Campus Raiwind Road, Lahore
[3]Directorate of Poultry Research Institute, Livestock and Dairy Development, Punjab Pakistan
[4]Department of Clinical Medicine and Surgery, Faculty of Veterinary Science, University of Agriculture Faisalabad.
*Corresponding author: syedfaizan3506@gmail.com

ABSTRACT

Poultry sector is one of the vibrant sectors all around the world and plays significant role in countries GDP. Pakistan is the 11th largest poultry meat-producing country and plays a significant role in countries GDP. Despite of this flourishing status and discriminatory position poultry sector suffers a lot due to certain challenges. Infectious disease such as viral bacterial and fungal diseases is the major concern for poultry industry. Among these infectious diseases, bacterial infection is the major problem that causes heavy economic losses due decrease in productivity. Furthermore, poultry sector suffers a lot in terms of high mortality and morbidity. To overcome the problem of bacterial infection antimicrobial agents are used commonly. Under dose, Excessive and absurd antibiotic usage in the poultry industry leads to antibiotic resistance. Due to ban on usage of the antimicrobial agents in some countries there is need to develop some alternative to antibiotics which can help to tackle the issue of antimicrobial resistance. Nanotechnology also helps to overcome the problem of multi drug resistance in the field of veterinary medicine particularly in poultry. Nanotechnology also considers as a novel tool to improve animal production and health status. Among metallic nanoparticles, silver nanoparticles are more suitable nanoparticles that can be used to overcome the challenge of antimicrobial resistance. Silver nanoparticles are less toxic and can be used against a variety of pathogenic organisms which have a harmful impact on the poultry industry.

KEYWORDS	Received: 29-May-2024	A Publication of
Silver nanoparticles, poultry	Revised: 25-Jul-2024	Unique Scientific
	Accepted: 03-Aug-2024	Publishers

Cite this Article as: Faizan SM, Abadeen ZU, Shakoor A, Fridi NY, Zafar T and Javed MA, 2024. Role of silver nanoparticles in poultry health. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 140-145. https://doi.org/10.47278/book.CAM/2024.133

INTRODUCTION

The poultry sector is powerful all around the world. Along with that plays a vital role in the economy. The poultry industry is huge and can offer employment directly and indirectly to millions of people all over the world. In Pakistan, the current status of the industry indicates that the poultry industry produces more than 700 billion rupees. The poultry sector generated 177.9 billion rupees compared with in 2019 in which this industry generated about 99.9 billion rupees. In Pakistan, the annual production of broiler meat is around 2160 tonnes. The total contribution of broiler meat in the country is 35.5%. More than 15000 environmentally controlled poultry houses have been developed all over the country with capacities ranging from 5000 to 500,000 broilers. The per capita broiler meat consumption in Pakistan is about 51 kilograms (Pakistan Economic Survey, 2022-23). Regardless of this progressive status, the poultry sector suffers a lot due to various challenges. Infectious diseases are the foremost factors that cause mammoth monetary damage to the poultry industry due to morbidity and mortality. As a result of these problems, the cost of the treatment to tackle these infectious diseases problems has also been increased. Several viral and bacterial diseases are the main problems in the poultry industry (Logue et al., 2017). Antimicrobials are the agents are widely used in poultry industry for growth promotion, treatment and for disease control. Poor selection, overuse, and misuse of antimicrobial agents may lead to development of the antimicrobial resistance (Logue *et al.*, 2017). Antimicrobial resistance has been considered extensively in human, livestock and poultry products. Recently antimicrobial resistance is a global health challenge when the bacterial pathogen no longer responds to medicine, making infection tough for treatment. (Logue et al., 2017).

Nano medicine is the use of medical science in combination with nanotechnology. Nanotechnology is an advanced progress in the world of medical science that has various advantageous aspects. Nanotechnology is the branch that deals with particles of less than 100 nm. The word Nano is a Greek word that means dwarf. Nanotechnology is an important tool

of molecular biology and medicine because the process of life is maintained by a series of biological events at the molecular level in the cell machinery (Pinnada et al., 2012). Nanotechnology proves to be beneficial in the field of animal and human medicine practices. Nanotechnology is a revolutionary invention in the world of medicinal science. Nanotechnology has been used in the fields of diagnosis, DNA sequencing, gene therapy, and tissue engineering. Nanotechnology also helps to overcome the problem of multi-drug resistance in the field of veterinary medicine particularly in poultry (Daud et al., 2022). Nanotechnology also considered as a novel tool to improve animal production and health status (Bai et al., 2018). Along with that through nanotechnology, medical science found another way to overcome the challenge of multidrug resistance due to their broad-spectrum antimicrobial activity against bacteria and considered as an alternative strategy to combat with multidrug resistance problem.

Multidrug Resistance Problem in Poultry

Antimicrobial resistance is the resistance of the antimicrobial drug particularly used in poultry farming against dreadful microorganisms. Antibiotics are regularly used to control the propagation of the microorganism. Under dose, excessive and absurd antibiotic usage in the poultry industry leads to antibiotic resistance. Various pathogenic microorganisms showed resistance against antibiotics which are also used regularly in human beings on a large scale. Since 2006, the use of antimicrobial agents has been banned due to antimicrobial resistance problems by the European Union (EU) implemented Regulation (EC) No. 1831/2003, and legislation was implemented by food drug authority called Veterinary Feed Directive (VFD) drugs (Van et al., 2012; Chand et al., 2016). This results in the re-emergence of severe poultry diseases in European countries like Norway (Gangadoo et al., 2016). It was also noted that increased intestinal disorders was seen associated with removal of these feed additives and alternative strategies should be adopted (Sharma et al., 2021).

How Antimicrobial Resistance Problem Developed in Poultry

Antimicrobial agents usually used in poultry inhibit the propagation of the different bacterial populations by bactericidal substances (e.g. beta-lactams) or by killing the bacteria by bacteriostatic substances (e.g. macrolides). Antimicrobial resistance can be produced through chromosomal gene variation and can also be produced by acquiring resistant genes from different organisms. Treatment through antibiotics results interchanging of resistant elements both within and across bacterial growth that leads to formation, survival and proliferation of the bacteria (Kazemnia et al., 2014).

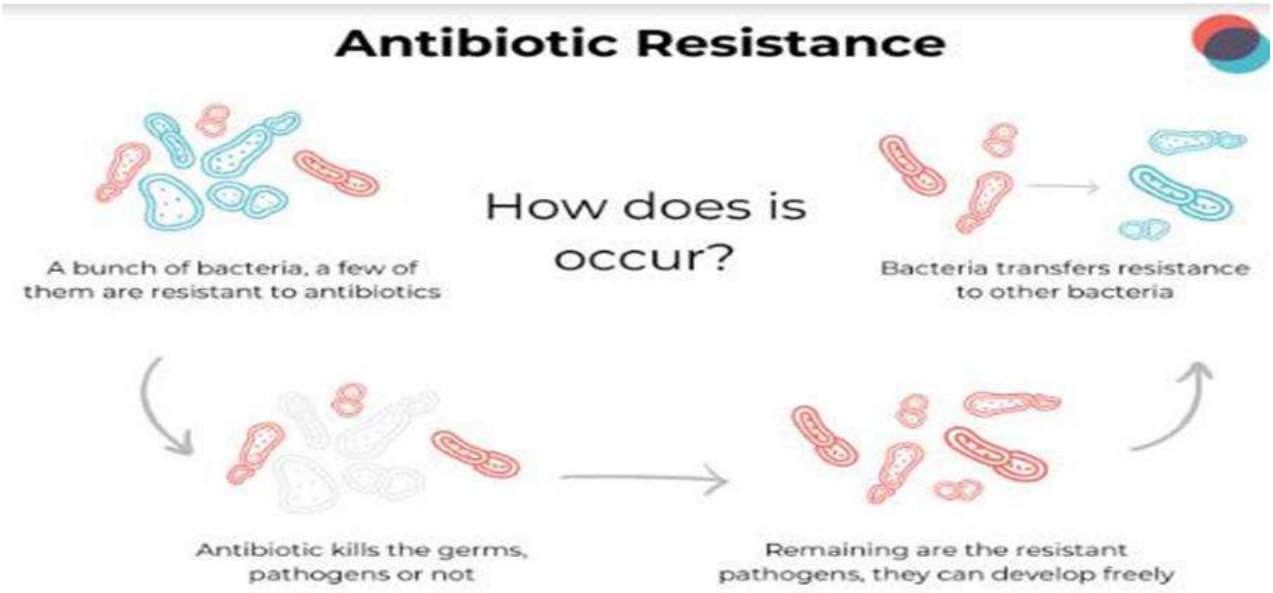


Fig. 1: The mechanism of development of the antibacterial resistance (https://www.labtoo.com/en/blog/antibiotic-resistance)

Use of Metal Nanoparticles as Antimicrobial agents in poultry

The usage of Metallic nanoparticles as an alternative to antimicrobial agents is a latest advancement in poultry farming to overcome the challenge of antimicrobial resistance. Metal nanoparticles are an important tool and possess antimicrobial abilities biosensing, cancer therapy, and bioimaging (Ge et al., 2014). Nanoparticles prepared from essential minerals are minor in dimension and have different physical and chemical properties. Due to their small size these nanoparticles are usually absorbed in an abundant amount in the gastrointestinal tract and produce their biological effect in the targeted tissues in animals. Metallic nanoparticles such as zinc oxide, copper oxide, and silver nitrate own durable antimicrobial properties and dreadful organisms that cause severe disease in poultry. Metal oxide nanoparticles produced strong antibacterial effects against lethal organisms such as *Salmonella,* and *Escherichia coli* which causes the problem in poultry (Sirelkhatim et al., 2015).

Silver Nanoparticles

Silver Nanoparticles are very Fine Particles of Silver

These particles are ten to a hundred nanometers outsized and vary from the silver as they have different colors such as yellow, as opposed to the silver. This is due to Plasmon absorbance. Incident light rays create oscillation in free electrons on the surface of nanoparticles, causing them to absorb electromagnetic radiation, creating different colors reflected (Daud et al., 2022).

Properties of Silver Nanoparticles

Silver (Ag) nanoparticles have enhanced physico-chemical properties. Ag nanoparticles are non-toxic compared to other metallic components. Along with that have high electrical and thermal conductivity. Highly stable and less cost-effective compared to gold and platinum. Chemically Ag nanoparticles are more stable and have enhanced catalytic activity. Ag nanoparticles displays strong antimicrobial and antifungal properties which attract the scientific community to develop silver nanoparticles based disinfectant products (Rashid et al., 2013).

Properties of Silver Nanoparticles in Poultry Production

In the field of poultry production, Ag Nanoparticles may function as a substitute for antimicrobial agents. Along with that Ag nanoparticles can also be used as a growth promoter in poultry (Ravikumar et al., 2012). Silver nanoparticles similar to other metal composites such as zinc and copper that are used as growth promoters in poultry nutrition, modify the gastrointestinal tract. The silver nanoparticles can affect the microbial population in the intestinal tract and as a result, can improve the immune status of the broiler birds. The silver nanoparticles can also help to increase the growth performance of the broiler birds. Currently, the effect of Ag nanoparticles is seen in chicken embryos on oxidative stress parameters, growth, and development (Sawosz et al., 2009). Ag nanoparticles can be used as carriers available to oxygen and might be considered as a modulator of the mechanism. Silver nanoparticles display exceptional biological properties. Nanoparticles possess' broad-spectrum bactericidal activity against gram-negative and gram-positive bacteria (Sawosz et al., 2009). Due to these exceptional properties, Ag nanoparticles possess discriminatory status in the world `of pharmaceutical and medical devices (Monteiro et al., 2009; Rai et al., 2009)

Silver Nanoparticles as Antimicrobial Agent

Elemental silver occurs naturally and it is considered as non-toxic, non-invasive and non-allergic. One of the most suitable properties of this component is that silver does not accumulate in the tissue of the body (Singh et al., 2008). The metallic silver nanoparticles are below 200 nm in for greater microbial effect than silver salts (Yun et al., 2017). Much experimental analysis showed that silver nanoparticles can be effectively used as an antimicrobial agent against various organisms (Roth et al., 2009). Currently, there has been transformed attention in the use of silver nanoparticles as an antimicrobial agent. Metallic silver components and its ions have long been recognized to have exceptional antibacterial properties. The presentation of nanotechnology has empowered silver to be caused to Nano size (1-100nm) and have enormous functional service area (Rena et al., 2009).

Synthesis of Silver Nanoparticles

Silver nanoparticles can be synthesized by physical, chemical and biological methods. Physical methods involve electrochemical, Ultra sonication, laser ablation, irradiation, evaporation and condensation. Chemical reduction method was used to prepare silver nanoparticles by chemical process. Biologically silver nanoparticles can be prepared by fungi, yeast and plant extracts. (Manyasree et al., 2018)

Mechanism of Action of Ag Nanoparticles as an Antibacterial Agent

The antibacterial activity of silver nanoparticles depends upon the size of the nanoparticles. As far as the size of the nanoparticles decreases the activity of the silver nanoparticles increases. Silver nanoparticles with a diameter of less than 10 nm directly interact with bacteria. Ag nanoparticles increase the permeability of the membrane. After that, silver nanoparticles attach with the thiol groups in the respiratory enzymes and lead to the deactivation of the enzyme. The interaction of the Ag nanoparticles with the respiratory enzymes generates reactive oxygen species which tends to produce oxidative stress (Pinnada et al., 2012). As a result of the oxidative stress, destruction of bacteria occurs. Another mode of action of Ag nanoparticles is the interaction of the Ag nanoparticles with deoxyribose nucleic acid which inhibits the replication of the bacteria. Along with that silver nanoparticles can destroy peptidoglycan layer in the cell wall, can cause structural alteration in the cell wall and nuclear membrane, can affect ribosomes and constrains protein synthesis (Khalil et al., 2020).

Routes through which Silver Nanoparticles given

Silver Nanoparticles can be administered in the broilers through various routes such as oral route and respiratory route by Inhalation. Along with that can be given by injection and In-ovo inoculation can also be done (Mayer et al., 2009). After the up taking of the nanoparticles through different route like inhalation, ingestion, and skin contact silver nanoparticles are diffused into the bloodstream and distributed to various organs and tissues (Mohanraj et al., 2007).

Role of silver Nanoparticles in Poultry

Silver Nanoparticles as Feed Supplement in Poultry

Silver nanoparticles are the most suitable feed supplement in the poultry industry. The current status of the poultry industry showed that silver nanoparticles appeared as a modern tool to increase health status and feed conversion ratio. Silver nanoparticles not only destroy harmful bacteria in gastro-intestinal tract but also help in proliferation of the beneficial bacteria (Mahmoud. 2012).

Silver Nanoparticles as Antibacterial agents against different Poultry Diseases

Silver nanoparticles are repeatedly used in the poultry industry as the colloidal solution in poultry due to their antimicrobial property. Silver nanoparticles are attached with cellular structure and purpose in straight ways to remove bacteria from the body (Mahmoud, 2012). Silver nanoparticles can be used as antimicrobial agents against multi-drug-resistant bacteria (Ali et al., 2020). Metal nanoparticles such as Ag nanoparticles have potential to exhibits powerful antimicrobial role against variety of dreadful microorganism like *Escherichia coli* and *Staphylococcus aureus*. Acceptable antibacterial activity against these bacteria was seen (Kumar et al., 2020). Nanoparticles prepared with metallic components always prove to be potential antimicrobial agents against *Salmonella typhimurium* and *Staphylococcus aureus*. It was also analyzed from the study that silver nanoparticles can be replaced with antimicrobial agents as a suitable alternative (Akbar et al., 2019). In-vitro analysis also discovered use of silver nanoparticles can induce strong antibacterial effects against *Escherichia coli* and *Klebsiella*. Use of silver nanoparticles can produce significant to stop the proliferation of microorganisms (Khalil et al., 2020). Silver nanoparticles own durable antimicrobial properties against deadly pathogens linked to poultry. Use Nanoparticles against poultry pathogens like *Escherichia coli, Salmonella,* and *Campylobacter* helps control this problem. (Duffy et al., 2018). Silver nanoparticles had an outstanding antibacterial outcome against *B.subtilis* and *E. coli*. Various observations from the study presented that the antibacterial action of silver nanoparticle solution had a durable effect against these organisms. (Arifin et al., 2020). The antimicrobial action of silver nitrate nanoparticles can be used as antimicrobial agents against gram-positive and gram-negative bacteria. Gram-negative bacteria are more vulnerable to nanoparticles as compared to the gram-positive. Furthermore, Silver nanoparticles are more time-dependent and the capacity of these nanoparticles gets lowered by increasing the size and lessening the concentration of nanoparticles (Karvani et al., 2011).

Silver nanoparticles are also seen as valuable against organisms like bacteria and fungi. The development of antibacterial resistance against numerous pathogenic organisms due to the irrational use of antibiotics in the poultry industry has convinced the world to control the microbial population through alternative modes. To overcome this problem silver nanoparticles are considered as a more suitable antimicrobial agent against against *Salmonella* and *Escherichia coli* isolated from chickens (Mohamed et al., 2018). Silver nanoparticles can be used separately or in combination with other metal nanoparticles. The combination of zinc and silver nanoparticles can increase the antibacterial effects manifold as compare to use them alone (Fardin et al., 2016). Silver nanoparticles proved to be sensitive to bacteria that were highly resistant to standard antibiotics (Roy et al., 2020). Silver nanoparticles also help to improve the growth health, immunological and hematological status of the broiler birds challenged with microorganism. Along with that Ag Nanoparticles can help to modulate TNF alpha and NF-KB levels which are expressively increased in broiler birds that received silver nanoparticles (Vadalasetty et al., 2018). Use of silver nanoparticles at different levels can induce pathological impact on the intestine and liver of the broiler birds. The height of the intestinal brush border remarkably increased after treatment with Ag nanoparticles (Ahmadi et al., 2009). These nanoparticles can affect the immune response and antioxidant activity in poultry (Hafeez et al., 2020). Long-term use of silver nanoparticles helps in tackling issues related to antimicrobial resistance and the use of silver and zinc oxide nanoparticles as effective antimicrobial agents and lack of resistance issues (Saleem et al., 2015).

Role of Silver Nanoparticles as Growth Promoting Supplements

Along with antimicrobial properties Silver nanoparticles can be used as growth-promoting agent in broiler chickens. Silver nanoparticles supplementation in broilers can modulate growth performance and energy metabolism in broilers (Pineda et al., 2012). Silver nanoparticles as feed supplements for poultry can also be used for biomedical applications. The silver nanoparticles have minimal risk of toxicity in humans and animals (Mahmmadi et al., 2015).

Role of Silver Nanoparticles as Meat Quality Enhancer

Silver nanoparticles can also improve meat production and the quality of broiler birds infected with microorganisms. Along with that with the help of Ag nanoparticles the meat quality indices of broilers like live weight carcass quality, dressing percentage, carcass quality dry matter crude protein can be enhanced (Mahmoud et al., 2012). Silver nanoparticles can notably increase the weight of broiler birds (Ahmadi, 2009).

Silver nanoparticles and Immune Status of Broiler Birds

Silver nanoparticles in broilers can modulate the overall adaptive and innate immunity (Bhanja et al., 2015). Silver nanoparticles can be used at different levels which can improve the overall body status of the broilers like increased body weight, total serum protein, and anti-oxidative status decreased in the cholesterol (Elkloub et al., 2015).

In-ovo administration of silver nanoparticles improved the structure of the chicken embryo pectoral muscle (Sawosz et

al., 2009). Silver nanoparticles have also the ability to increase the gene expression of fibroblast growth factor 2, and vascular endothelium growth factors. Along with that, some other metallic nanoparticles such as selenium can help to improve the daily feed intake of the broiler birds. Significantly improved growth performance was also seen in broilers in which selenium NPs were given. NPs nowadays are used as a new tool for targeted drug delivery and nutritional improvement (Sawosz et al., 2007).

Impact of Silver Nanoparticles on Hematological Parameter in Poultry

The use of silver nanoparticles helps to improve the hematological indicators. Significant improvement was seen on lymphocyte count in broiler birds in which nanoparticle treatment was given challenged with bacterial infection. Along with that these nanoparticles also to improve the erythrocyte indices in broilers treated with silver nanoparticles as reported by

Conclusion

Antimicrobial resistance is a significant problem related to the poultry industry to overcome the challenge of antimicrobial resistance. Nano-medicine is the most suitable alternative mode which can help to control the problem of antimicrobial resistance in the poultry industry. Metallic nanoparticles particles silver nanoparticles have a significant role in controlling the problem of the poultry industry and possess significant properties to overcome the challenge of antibiotic resistance in poultry.

REFERENCES

Ahmadi, J. (2009). Application of different levels of silver nanoparticles in food on the performance and some blood parameters of broiler chickens. *World Applied Sciences Journal*, *7*(1), 24-27.

Arifin, D. C. V., Saragih, D. I., and Santosa, S. J. (2020). Antibacterial Activity of Silver Nanoparticles Synthesized Using Tyrosine as Capping and Reducing Agent. *International Journal of Emerging Trends in Engineering Research*, 8(6), 2414-2421.

Akbar, A., Sadiq, M. B., Ali, I., Muhammad, N., Rehma, Z., Khan, M. N., Muhammad, J., Khan, S. A., Rehmana F.U., and Anal, A. K. (2019).Synthesis and antimicrobial activity of zinc oxide nanoparticles against foodborne pathogens *Salmonella typhimuriu*m and Staphylococcus aureus. *Biocatalysis and Agricultural Biotechnology*, 7, 36-42.

Bhanja, S.K., Hotowy, A., Mmehra, M., Sawosz, E., Pineda, L., Vadalasetty, K.P., Kurontowicz N., and Chawalibog, A. (2015). *I*n Ovo Administration of Silver Nanoparticles and/or Amino Acids Influence Metabolism and Immune Gene Expression in Chicken Embryos. *International Journal of Molecular Sciences*, 16, 9484-9503

Chand, N., Faheem, H., Khan, R.U., Qureshi, M.S., Alhidary, I.A., and Abudabos, A.M. (2016). Anticoccidial effect of mannan oligosaccharide against experimentally induced coccidiosis in broiler. *Environmental Science Pollution Research*, 23: 14414-14421.

Duffy, L.L., Osmond-McLeod, M.J., Judy, J., and King, T. (2018). Investigation into the antibacterial activity of silver, zinc oxide, and copper oxide nanoparticles against poultry-relevant isolates of Salmonella and Campylobacter. *Food Control*, 92:293-300.

Elkloub, K., Moustafa, M. El., Ghazalah, A.A., and Rehan, A.A.A. (2015). Effect of Dietary Nanosilver on Broiler Performance. *International Journal of Poultry Science*, 14 (3), 177-182.

Fardin, M., Jafari1, A., Arastoo, S., and Safarkar, R. (2016). Synthesis andAntibacterial Effect of Metallic Oxide Nanoparticle against of *Escherichia coli* Isolated of Tabriz Aviculture. *International Journal of Molecular and Clinical Microbiology*, 6(1), 618-628.

Gangadoo, S., Stanley, D., Hughes, R.J., Moore, R.J., and Chapman, J. (2016). Nanoparticles in feed: Progress and prospects in poultry research. *Trends in Food Science and Technology*, 58:115-126.

Ge, L., Li, Q., Wang, L., Wang, M., Ouyang, J., Li, X., and Xing, M.M.Q. (2014). Nanosilver particles in medical applications: synthesis, performance, and toxicity. *International Journal of Nanomedicine*, 9.

Hafeez, M., Zeb, M., Khan, A., Akram, B., Abdin, Z.U., Haq, S., Zaheer M., and Ali, S. (2020). *Populus ciliata* mediated synthesis of silver nanoparticles and their antibacterial activity. *Microscopy Research and Techniques*, 84,480-488.

Khan, D., Chand, N., Saeed, M., Tahir, M., Zeb, A., and Khan, R. U. (2023). Effects of Silver Nitrate as Alternative to Antibiotic on Production Performance, Bacterial Count and Intestinal Histological Features of Broiler under Escherichia coli Challenge. *Pakistan Journal of Zoology*, 55(4).

Khan, D., Naila, C., Muhammad, S., Muhammad, T., Alam, Z., and Riffat, U.K. (2022). Effects of Silver Nitrate as Alternative to Antibiotic on Production Performance, Bacterial Count and Intestinal Histological Features of Broiler under Escherichia coli Challenge. *Pakistan Journal of Zoology*, 1-8.

Karvani, Z. E., and Chehrazi, P. (2011). Antibacterial activity of ZnO nanoparticle on grampositive and gram-negative bacteria. African Journal of Microbiology Research. Antibacterial activity of ZnO nanoparticle on gram-positive and gram-negative bacteria. *African Journal of Microbiology Research*, 5(12), 1368-1373.

Khalil, O.A., Enbaawy, M. I., Salah, T., Mahmoud H., and Ragab, E. (2020). In Vitro Investigation of the Antibacterial Effect of Silver Nanoparticles on ESBL-producing *E. coli* and *Klebsiella* spp. Isolated from Pet Animals. *World Veterinary Journal*, 10(4), 514-524.

Kazemnia, A., Ahmadi, M., and Dilmaghani, M. (2014). Antibiotic resistance pattern of different *Escherichia coli* phylogenetic groups isolated from human urinary tract infection and avian colibacillosis. *Iran Journal of Biomedical*, 18:219-224.

Kumar, J., Bhattacharya, J., and Das, B.K. (2020). Dispersion, availability and antimicrobial activity of silver nanoparticles during application to drinking water of the poultry. *Environmental Nanotechnology Monitoring and Management*, 14, 100368.

Logue, C.M., Annemuehler, Y.W., Nicholson, B.A., Doekott, C., Barbieri N.L., andNolan L.K. (2017). Comparative analysis of phylogenetic assignment of human and avian ExPEC and fecal commensal *Escherichia coli* using the Clermont phylogenetic typing method and its impact on avian pathogenic *Escherichia coli* (APEC) classification. *Frontiers in Microbiology*, 8, 283.

Manyasree, D., Kiranmayi, P., and Venkata, R.K. (2018). Characterization and antibacterial activityof ZnO nanoparticles synthesized by the co-precipitation method. *International Journal of Applied Pharmacology*, 10:224-228.

Mohammed, A.E., Qahtani, A.A., Mutahiri, A.A., Shamiri B.A., and Aabed, K. (2018). Antibacterial and Cytotoxic Potential of Biosynthesized Silver Nanoparticles by SomePlant Extracts. *Nanoomaterial*, *8*(6):382.

Mohammadi, F., Ahmadi, F., and Andi, M.A. (2015). Effect of zinc oxide nanoparticles on carcass parameters, relative weight of digestive and lymphoid organs of broiler fed wet diet during the starter period. *International Journal of Bioscience*, 6, 389-394.

Mayer, A., Rinner, M. V. B., Novak, A., Wintersteiger, R., and Fröhlich, E. (2009). The role of nanoparticle size in hemocompatibility. *Toxicology*, 258(3),139-147.

Pakistan-Economic-Survey (2022-23). Pakistan Economic Survey. Government of Pakistan, 16-19.

Pineda, L.E., Charlotte, S., Ricarda, L., Engberg, M., Elnif, J., Hotowy, A., Sawosz, F., and Chawlibog, A. (2012). Influence of the In-ovo injection and subsequent provision of silver Nanoparticles on growth performance and microbial profile, and immune status of broiler chicken. *Animal Physiology*, 4, 1-8.

Rashid., U.R. Bhuiyan, M.D.H., and Quayum, M.E. (2013). Synthesis of Silver Nano Particles (Ag-NPs) and their uses for Quantitative Analysis of Vitamin C Tablets. Journal of *Pharmacology Science*, 12(1):29-33.

Ravikumar, S., and Gokulalkrishna, R. (2012). Inhibitory effects of metal oxide nanoparticles against poultry pathogens. *International Journals of Pharmaceutical sciences and Drug Research*, 4(2):157-159.

Rena, G., Hub, D., Cheng, E.W.C., Vargas, M.A., Reipd, R. P., and Allaker, R.P. (2009). Characterization of copper oxide nanoparticles for antimicrobial applications. International *Journal of Antimicrobial Agent*, 33:587.

Roy, S., Hai, L. V., Kim, H. C., Zhai, L., and Kim, J. (2020). Preparation and characterization of synthetic melanin-like nanoparticles reinforced chitosan nanocomposite films. *Carbohydrate Polymers*, 231,115729.

Roth, N., Kasbohrer, A., Mayrhofer, S., Zitz, U., Hofacre, C., and Domig, K.J. (2019). The application of antibiotics in broiler production and the resulting antibiotic resistance in *Escherichia coli*: A global overview. *Poultry Science*, 98:1791-1804.

Sawosz, E., Marta, G., Marlena, Z., Pawel, S., Maciej, S., and Andre, T. N. (2007). Influence of the hydrocolloidal silver nanoparticles on gastrointestinal microflora of enterocytes of quails. *Archives of Animal Nutrition*, 61,444-451.

Singh, D., Rathod, V., Shivaraj, N., Hiremath, J., Singh A.K., and Methew, J. (2014). Optimization and characterization of silver nanoparticles by endophytic fungi Penicillium sp. isolated from Curcuma longa (turmeric) and application studies against MDR *E.coli* and *S. aureus*. *Bioinorganic Chemistry Applied*, 8, 408021.

Sirelkhatim, A., Mahmud, S., Seeni, A., Kaus, N.H.M., Ann, L.C., Bakhori, S.K.M., Hasan, H., and Mohamad, D. (2015).Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism. *Nano Micro Letters*, 7(3):219-242.

Sawosz, E., Marta, G., Marlena, Z., Niemwc, Z., Boena, T.O., and Chawlibog, A. (2009). Nanoparticles of silver do not effect growth development and DNA oxidative damage in chicken embryos. *Archive Future Geflugel Kunde*, 73, 208-213.

Sawosz, E., Marta, G., Marlena, Z., Pawel, S., Maciej, S., and Andre, T. N. C. (2007). Influence of the hydrocolloidal silver nanoparticles on gastrointestinal microflora of enterocytes of quails. *Archives of Animal Nutrition*, 61, 444-451.

Salem, W., Leitner, D.R., Zingl, F.G., Schratter, G., Prassl, R., Goessler, W., Reidl, J., and S. Schild. (2015). Antibacterial activity of silver and zinc nanoparticles against *Vibrio cholerae* and enterotoxin *Escherichia coli*. *International Journal of Medical Microbiology*, 305, 85-95.

Sharma, S., Kumar K., and Thakur, N. (2021). Green synthesis of silver nanoparticles and evaluation of their anti-bacterial activities: use of *Aloe barbadensis miller* and *Ocimum tenuiflorum* leaf extracts. *Nanofabrication*, 6:52-67.

Singh, M., Shinjini, S., Prasad, S., and Gambhir, I. S. (2008). Nanotechnology in medicine and antibacterial effect of silver nanoparticles. *Digest Journal of Nanomaterials and Biostructures*, 3:157-159.

Vadalasetty, K.P., Lauridsen, C., Engberg, R. M., Vadalasetty, R., Kutwin, M., Chwalibog, A., and Sawosz E. (2018). Influence of silver nanoparticles on growth and health of broiler chickens after infection with *Campylobacter jejuni*. *BMC Veterinary Research*, 14(1), 4384.

Van, D. Z., Vandebriel R.J., Van, D.E., Kramer, E., Haerreira, R. Z., Rojero C. S., Hollman P.C., and Handriekson, P.J. (2012). Distribution, elimination and toxicity of silver nanoparticles and silver ions in rats after 28 days oral exposure. *ACS Nano*, 6.

Yun, J.E., and Lee, D.G. (2017). Silver Nanoparticles: A Novel Antimicrobial Agent. Antimicrobial Nanoarchitectonics, 139-166

Chapter 17

Overview of Nanoparticles and their Role in Management of Parasitic Diseases

Abu Baker Yameen[1], Hafiz Aamir Ali Kharl[2], Abdul Aleem[1], Kashif Isamail[1], Junaid Ahmad[6], Faiq Ahmad[1], Khadija Iqbal[4], and Maryam Arshad[5]

[1]Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad
[2]Department of Pharmacy, University of Agriculture, Faisalabad
[3]Department of Theriogenology, University of Agriculture, Faisalabad
[4]Department of Zoology, University of Okara
[5] Institute of microbiology, University of Agriculture, Faisalabad
[6] Independent researchers, Pakistan
*Corresponding author: abubakaryameen153@gmail.com

ABSTRACT

Nanoparticles (NPs) belong to a huge group of materials that consist of microscopic compounds with an approximate dimension of 100 nanometers. It's because of their huge circumference and tiny dimensions, which enable them to pass over endothelial cells, enter the circulatory system, and cross the blood-brain barrier. Investigators are constantly looking into ways to improve the long-term absorption, intracellular penetrability, and accessibility of nanoparticles utilized in drug administration due to increasing achievements in nanomedicine. Millions of people worldwide, especially in developing countries, suffer from parasitic infections, for which there are few effective treatments. Drug-resistant parasites have become more common, which emphasizes the need for more effective and safer options for treatment. Parasitic infection or better drug delivery. Since there is currently no vaccine available to prevent the majority of parasite infections, chemotherapy is the main technique for controlling these infections. In the observation and treatment of parasitic infections, nanoparticles have been shown to be valuable instruments that provide novel approaches to address issues such as drug susceptibility and the limited efficacy of traditional treatments. In this review, we look into the potential application of nanomaterials to the diagnosis and cure of parasitic infestations.

KEYWORDS
Nanoparticle's, Drug resistance parasites, chemotherapy, Drug susceptibility, traditional treatment.

Received: 16-Jun-2024
Revised: 18-Jul-2024
Accepted: 20-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Yameen AB, Kharl HAA, Aleem A, Ismail K, Ahmad J, Ahmad F, Iqbal K, Arshad M, 2024. Overview of nanoparticles and their role in management of parasitic diseases. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 146-154. https://doi.org/10.47278/book.CAM/2024.135

INTRODUCTION

Any substance with a narrowest dimension of hundred nanometers (nm) is known as a nanoparticle (NP). Due to their dimensions being close to those of biological components and molecules, nanotechnology, and nanomaterials are being used more and more in medical research, particularly in oncology and antiparasitic applications, where they may one day be used as disease treatments (Quadir et al., 2017). Due to their narrow dimension and huge surface area, they can be absorbed by endothelial cells and pass across the tight junctions to enter the circulatory system. Regarding nanomedicine, current research on nanoparticles for drug delivery aims to enhance long-term release, intracellular penetration, and bioavailability (Laurent et al., 2008). NPs huge surface area and tiny dimensions allow them to adhere to endothelial cells, enter the circulatory system, and pass across blood-brain barriers, enhancing their colloidal stability and bioavailability. (Rizvi et al., 2018).

Specifically, due to their many beneficial properties, simple preparation, exceptional durability, simplicity in design to the necessary size, shape, and permeability, lack of inflammation variation, simplicity of integration by different molecules, and simplicity of formation into both water-resistance and waterproof systems due to their negative surface charge on metal oxide nanoparticles, or MONPs, they are primarily a useful tool for biological applications (Sanchez-Moreno et al., 2018). Parasites are of great economic importance as they lead to severe economic losses by reducing the health and production of humans and animals (Alvi et al., 2020; Alvi et al., 2021; Alvi et al., 2022; Alvi et al., 2023). Parasitic infections caused by resistant strains of protozoa such as *Plasmodium*, *Leishmania*, *Toxoplasma,* and *Trypanosoma* have become a global health concern, with malaria being a leading cause of illness and death (McCoy et al., 2013; Qamar et al., 2023).The

purpose of the present book chapter was to summarize how useful nanoparticles might be in the detection and management of parasitic diseases.

Classification of NPs

NPs are categorized as organic, inorganic, or carbon-based on the basis of their chemical makeup as shown in Fig.1.

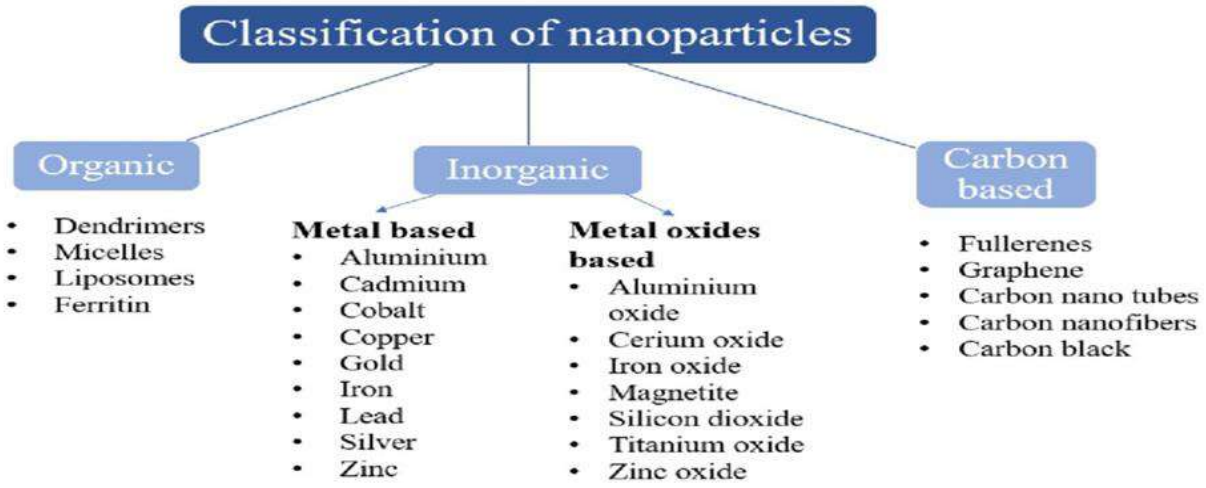


Fig. 1: Classification of Nanoparticles. (Mehta et al., 2023).

Organic NPs

This class of nanoparticles, called organic nanoparticles, is made up of biological molecules that are 100 nanometer or less. (Qi and Zhang, 2022). Recognized nanoparticles and polysaccharides in this class include iron, microorganisms, liposomes, and dendrimers. Two kinds of nanoparticles with hollow interiors known as Nanocapsules include micellar and liposomes. Both of them have sensitivity to electromagnetic radiation, which includes warmth and luminosity (Esakkimuthu et al., 2014). These are safe to use and washable as well. They are better options for medicine delivery due to their unique characteristics. The size, composition, surface shape, and other features are important, but overall pharmaceutical-carrying capacity, strength, and application methods an absorbed medication complex or an entrapped drug system affect their efficiency and range of uses (Hamidi et al., 2008). Since organic nanoparticles are effective and may be administered into specific body sections, they are widely used in the biomedical industry, including in the medicine delivery system (Gholamali et al., 2020).

Carbon-based NPs

Carbon has been a vital component in the development of humanity's culture on the planet. It forms connections with other materials that are unparalleled in strength. Because of their unique physicochemical properties, biocompatibility, and changeable surface science, carbon-based nanoparticles (NPs) represent a different class of nanomaterials with significant properties that stand out sufficiently to be noted in numerous sectors, including medication (Xin et al., 2019). Grapheme, oxides of carbon, fullerenes, carbon microfibers, and carbon black are some of the subcategories (Saravanakumar2017**).**

Inorganic Nanoparticles

"Inorganic NPs" are frequently referred to as NPs whose structure does not contain any carbon. Metals and oxide-based NPs, as well as their byproducts, are classified as inorganic NPs.

Metal-Based Nanoparticles

Metal-based nanoparticles can be obtained from Metals such as aluminum (Al)(Ghanta and Muralidharan, 2013), cadmium (Cd) (Prakash et al., 2010), cobalt (Co)(Mondal et al., 2015), copper (Cu) (Din and Rehan, 2017), and gold (Au) (Jamkhande et al., 2019) are often used in the creation of nanoparticles. Metal nanoparticles have exceptional UV-visible sensitivity as well as electrical, beneficial, heating, and antimicrobial abilities because of their huge volume-to-volume-to-surface relations and quantum impacts (Wang, 2000).

Metal Oxide-Based Nanoparticles

Examiners have been paying increasing attention to metal oxides in the last several years. Ionic compositions consisting of a mixture of negative oxygen ions and positive metallic ions are called metal oxides. The electrostatic interactions among the charged metal ions and the adverse oxygen ions produce powerful and long-lasting ionic bonds (Devan et al., 2012). The goal of creating these oxide-based particles is to change the characteristics of their metal-based equivalents. To profit from their increased reactivity or efficacy. (Tai et al., 2007). Synthesized metal oxide nanoparticles are common. SiO_2, TiO_2, ZnO, and Al_2O_3 are among the oxides that are most frequently manufactured (Bulychev, 2022; Fayad

and Dhahad, 2021; Song et al., 2021). Zinc oxide (ZnO) and titanium oxide are the oxide nanoparticles (NPs) that are most commonly utilized as drug delivery methods.

Zinc Oxide NPs

Although a number of zinc oxide (ZnO) nanoparticles (NPs) are proving to be effective in a variety of technical areas ZnO NPs have gained a lot of attention lately. This is because of its remarkable and enticing qualities, which include excellent resistance to chemicals, high sunlight absorption, a high electrochemical coupling coefficient, and a broad range of photon intake (Kołodziejczak-Radzimska and Jesionowski, 2014). ZnONPs are mostly used as photosynthetic catalysts for biological sensors, energy sources, antibacterial, antiparasitic, anti-cancer, and vaccine systems, as well as biological imaging resources (Talebian et al., 2013; Al Faleh et al., 2023).

Techniques for Preparing ZnONPs

There are three main methods:

Chemical Processes

Zinc nanocomposites can be produced in three different phases: liquid (by wet chemical processes), vapor phase, and solid. A gas phase synthesis provides advantages, but wet chemical techniques are more widely applied and have shown successful in the commercial world. (Kursawe M et al.2005). A few advantages are the use of controllable, reasonably priced chemicals, the use of basic apparatus, and the least amount of energy needed for chemical reactions involving water. Therefore, the composition, shape, and size of nanomaterials may be precisely controlled by adjusting the synthesis variables during the process (Van den Rul, 2006). We can designate microemulsions as one of the wet-chemical techniques. (Elen et al., 2011) sol-gel synthesis (Ristić et al., 2005) precipitation (Sepulveda-Guzman et al., 2009) and hydrothermal Technique (Xu L et al. 2009).

Physical Processes

Two examples of physical approaches are laser ablation and ultrasonic ablation, as well as the thermal evaporation method (Zou C et al., 2015).

Biological Processes

Natural sources such as lower plants, products of higher angiosperm plants, yeasts, bacteria, and fungi can all create NPs. Considering all of its limitations, using biological systems is a compelling substitute for traditional chemical synthesis. Because this approach does not require the use of expensive or dangerous organic solvents, it has the advantage of being more environmentally friendly (Yuvakkumar et al., 2014).

Biomedical Application of zinc Oxide NPs

Zinc Oxide's Antibacterial Properties

The in vitro antibacterial activity of nanomaterials can be assessed using a variety of methods, including the medium diluting technique accompanied by population measures, the gel dilution approach, the disc diffusion test, the microtiter plate-based approach, the flow cytometry survival test kits, and the conductometric tests (Espitia et al.2012). The anti-microbial activity of ZnO NPs has been evaluated against a variety of bacteria, including *P. aeruginosa, E. coli, B. subtilis*, and *S. aureus*, as well as monoderm and diderm bacteria. The exterior membranes of diderm bacteria are covered with a fine sheet of peptidoglycan and lipopolysaccharide. This layer blocks the entry of negatively charged molecules into ROS (Russell et al. 2003). Both monoderm and diderm bacteria are susceptible to the potent antibacterial properties of zinc oxide. Nevertheless, particle size has a remarkable impact on ZnO antimicrobial effectiveness. It has been found that ZnO antimicrobial activity is high when the atom size is reduced. (Czyżowska and Barbasz, 2022).

Anti-Inflammatory Activity of ZnO

Nanoparticles have been more and more well-liked as anti-inflammatory medicines in recent decades. Their huge surface area to volume ratio gives them significant surface reactive properties that enhance their physical transit and contact with the biological membrane. ZnO NPs are easily absorbed across biological membranes due to their nanoscale size. Previous studies have demonstrated a considerable anti-inflammatory impact of zinc oxide nanoparticles. (M. Ilves, et al. 2014). Common antibacterial strategies for zinc oxide nanoparticles include preventing the expression of the enzyme that produces nitric oxide. (Cortese-Krott et al., 2014). inhibition of myeloperoxidase and pro-inflammatory cytokine release along with the corresponding protein expressions.

Immunostimulant Activity of ZnO

Zinc oxide (ZnO) immunomodulatory activity is its capacity to regulate or influence the body's immune response. Research suggests that ZnO nanoparticles may possess immunomodulatory properties that impact various immune cells and processes (Mehessen et al., 2023). Zinc oxide (ZnO) nanoparticles have been found to affect the activity of T cells, B cells, dendritic cells, and macrophage function, among other immune cells. They exhibit the capacity to regulate

phagocytosis, antigen presentation, and the production of cytokines, among other immune response modulation mechanisms. These nanoparticles are often found in nutritious foods and drinks. Their capacity to modulate immunity was discovered. ZnO NPs enhanced mice's immune responses specific to antigens. Serum levels of antibodies specific to antigens, namely IgE and IgG, were higher. It was also found that ZnO NPs improved the Th2 response by raising the body's activation and synthesis of cytokines (Roy et al., 2014).

Beneficial Effects of zno-nps in Different Animal Species

Because of their remarkable biocompatibility, affordability, and low toxicity, zinc oxide nanoparticles are among the most frequently used metal oxide nanoparticles in a variety of animal species (Table 1) for biological, medicinal, and industrial applications.

species	Benefits of ZNO NP in Different Animal Species
Mice	Shown antibacterial and antidiabetic properties, increased spermatogenesis, lipid profile, and neurotransmitter stability (Pati et al., 2014).
Rats	Exhibited signs of antidiabetic activity, analgesic efficacy via nociception inhibition, and improved lipid profile (El-Maddawy and Abd El Naby, 2019).
Pigs	Increase in body weight, increased the duodenal villi's length, enhanced gut morphology, and heightened immunological response (Wang et al., 2017).
Rabbits	Demonstrated the ability to repair tendon damage and liver protection against aflatoxicosis by the use of free radicals (Atef et al., 2016).
Equine	Increased gas generation, better gut health, and decreased mineral release in the feces, increased wound healing, and higher feed digestibility (Adegbeye et al., 2019).
Poultry	Gain in body weight, better lipid profile, enhanced dite adaptation, and elevated antioxidant activity (Zahra et al., 2017).
Fish	Provide antibacterial properties against fish infections, enhance fish zinc bioavailability and intestine absorption, and raise MCHC and RBC values.
Cattle	Shown antimicrobial properties, enhanced the state, enhanced mastitis, enhanced milk output, and enhanced rumen fermentation (Bai et al., 2018).

Toxicity of zno-np in Animals

It is thought that the release of Zn+ ions from the nanoparticles is what gives ZnO-NPs their poisonous characteristics. Consequently, even for brief periods of time, a high concentration of ZnO-NPs in food can make animals poisonous to zinc. (Underwood and Van Eps, 2012). Moreover, ZnO-NPs resulted in hemolysis, lowering erythrocyte parameters, platelet count, serum haptoglobin content, and many liver histological abnormalities (Ibrahim et al., 2017). Evidence that these nanoparticles have detrimental effects in a range of animal models has stimulated research on the potential dangers and toxicity mechanisms of these particles. Studies have shown that exposure to ZnO-NP might result in harmful physiological responses like oxidative harm, irritation, DNA damage, and harm to organs (Shahzad et al., 2019).

Function of Nanomaterials in the Identification of Parasitic Illnesses

Malaria

The identification of malaria antigens was demonstrated to be effective when various parasite heat shock proteins 70 (HSP 70) were combined to metallic nanoparticles modified with monoclonal antibodies; and polyester NPs coupled to polyclonal anti-*P. Falciparum* IgG antibodies produced highly precise outcomes. Improved resonance for the detection of β-hematin or hemozoin Raman spectroscopy and atomic force microscopy were used to successfully screen blood films. Utilizing a magnetic field to gather information allows for the prior identification of malaria. (Yuen C et al.2013**).** A new method of diagnosing malaria was developed using nanotechnology. Using a quantum-magnetic droplet test, serum or urine carrying *P. falciparum* (PF) protein 2 (HRP2 protein 2; high in histidine) can be recognized. Anti-HRP2 antibodies and magnetic beads can be used to capture the target protein. Following that, it can be purified and identified using quantum dot technology (Castro-Sesquen et al., 2016).

Leishmaniasis

Agents significantly increased the isothermally of Leishmaniasis DNA in blood tests from sick dogs by using gold nanoparticles, specific Leishmania spp. markers, and a sticky cushion. The nanoparticles' electrocatalytic response was reliable for the speedy detection of amplified DNA. This method of diagnosing visceral leishmaniasis (VL) has been shown to be more accurate and cautious than traditional PCR methods. (de la Escosura-Muñiz et al., 2016).

Toxoplasmosis

When antigen-coated gold nanoparticles are used in the reducing agent differentiation verification procedure, the results of an ELISA correlate. To improve the reliability of extracting circulating surface antigens, the examiner used an

immunomagnetic tablet coated with a polyclonal counteracting agent for *T. gondii* IgG that was wrapped in sticky nanoparticles (Wang et al., 2004). Further, *T. gondii* clinical techniques that make use of nanomaterials include modern detection strategies, such as measuring assays of DNA with nanoparticles (Sousa et al., 2021). Considerable improvement has been made in terms of affectability, specificity, and adequateness with the addition of intriguing and luminous nickel nanoparticles (CdTE/Ni mQD) nanodot assays to diagnostic frameworks for the detection of *T. gondii* DNA. (Assolini et al., 2017).

Amebiasis

The research has shown that luminous nanoparticles based on artificial antiparasitic silica, *Entamoeba histolytica* IgG1, have a significant perceptivity to identify amebiasis with no interaction with other protozoa (Hemadi et al., 2015).

Cryptosporidiosis

The mRNA of *C. parvum* oocytes, was combined with gold nanoparticles. When stool samples are analyzed, oocyst nucleic acids from *C. parvum* can be identified using two gold NP probes functionalized with oligonucleotides that match the 18S rRNA sequences of the bacterium (Weigum et al., 2013).

Schistosomiasis

The majority of research has relied on the identification of *Schistosoma* antigens. An example is an enzyme affinity test known as the magnetic affinity enzyme-linked immunoassay. The MEIA test is carried out depend on the production of specific antibodies in response to the aspect of larval antigens. Magnetic beads with functional polymer components and superparamagnetic nanoparticles are used in the MEIA test. Furthermore, distinctive functional groups were added to magnetic beads to enable them to form bonds with charged molecules. Molecular targets were placed on magnetic beams and then the reactive system was exposed to the magnetic field thus, via magnetic separation, an immunological complex was obtained. A distinct type of metallic nanoparticle was employed in colloidal gold, an additional diagnostic technique. Because Ig-bonded colloidal gold can connect with biological macromolecules like immunoglobulins, it is a useful tool for important clinical diagnostic research. Schistosomal antigen creates an immunological combination with IgG–colloidal gold during the diagnostic procedure (Wu et al., 2018).

Trypanosomiasis (Chagas' disease)

Nanomaterials, like metallic nanoparticles, have been used in recent years to diagnose Chagas disease. These identification instruments should be used in an integrated microflow system connected to an electrode pull with carbon screens (Quijia Quezada et al., 2019). Its purpose is to measure certain IgG antibodies present in serum. It employs *Trypanosome cruzi* proteins that have been isolated from epimastigotes and functionalized on AuNPs. 3.065 ng/mL was determined to be the test's lower detection limit, and the coefficients of variation between tests were lower than 6.95% (Quijia Quezada et al., 2019). The Chunap test, also known as the Chagas' urine nanoparticles test, is used to diagnose congenital Chagas disease early. Its foundation is the identification of antigens released by trypomastigote forms using Western blot analysis (Choudhury, 2021). Because tryptan blue and polyunsaturated N-isopropylacrylamide are used to functionalize nanoparticles that can collect and concentrate *T. cruzi*, the sensitivity and specificity of a urine-based test are roughly 95% (Quijia Quezada et al., 2019).

Nanoparticles in Parasitic Diseases

Kinds of NPs that are Susceptible to Parasites

Type of nanoparticle	Parasite	Results
Silver, chitosan, and curcumin NPs	*Giardia lamblia*	When the three nanoforms were combined, the fighting effect was maximized. It was discovered that the parasite had disappeared from the intestine and stool (Said et al., 2012).
Ag-NPs	*Leishmania Tropica*	Ag-NPs significantly reduced promastigotes' metabolic activity and rate of proliferation, exhibiting antileishmanial effects (Ponarulselvam et al., 2012).
LCu(CH3COO)2 and LCuCl2	*P.falciparum*	Significant antimalarial activity against the parasites was demonstrated by the two substances (Tripathy et al., 2012).
Gold NPs	*Leishmania major*	Compared to MW alone, when promastigotes and amastigotes were exposed to microwave radiation, the presence of GNPs was more lethal (Alshamiri et al., 2021)
Chitosan and silver	*T. gondii*	The results show that using AgNPs either by themselves or in conjunction with chitosan has shown promising anti-Toxoplasma capacity.
Nano-Nitazoxanide (NTZ)	*Cryptosporidium parvum*	On day six, nano nitazoxanide showed efficacy against parasites.
Silver NPs	*Plasmodium falciparum*	When applied to P. falciparum, the AgNPs exhibited antiplasmodial action (Mohapatra et al., 2010).

NPs' Function in Treating Parasitic Illnesses

As a Sole Method Therapy

NPs that specifically target infected macrophages can enhance the treatment of VL. AgNPs, and curcumin NPs were used to treat giardiasis-infected animals. Curcumin NPs provided the most effective and comprehensive treatment. Experimental animals with toxoplasmosis were treated with silver alone, and used in combination. The combined treatment dramatically decreased the parasite load in the spleen and liver. Microscopic research revealed that tachyzoites were deformed in shape and unable to move (Said et al., 2012).

As a Drug Delivery System

Treatment was administered to VL strains resistant to the wild type using gold nanoparticle quercetin-conjugated strains. Comparing drugs with amphotericin B and rifampicin, two treatments for VL, demonstrated a substantial level of effectiveness. *L. major* ulcers in mice treated with glucantime liposomes were successfully healed with topical application of glucantime. It drops the number of parasites and the extent of the splenic lesion. *Trichoderma harzianum,* a soil fungus, was conjugated with silver nanoparticles to increase the effectiveness of triclabendazole in treating fascioliasis. (Gaafar et al., 2014). Liposomal praziquantel (300 mg/kg) decreased the parasite load, the number of worms and eggs in the feces, and the number of liver tumors when cure *Schistosom mansoni*. In *S. mansoni*-infected mice, the effectiveness of miltefosine, an anticancer medication, was compared to that of praziquantel at an oral dosage of 20 mg/kg. The outcomes indicated the potential of *S. mansoni* and the effectiveness of nanomedicine in drug delivery (Gaafar et al., 2014).

Immunization and Vaccination

It's crucial to remember that adding NPs can increase the antigenicity of conjugated or adsorbed antigens. NPs have the ability to trigger both innate and adaptive immune responses. Aside from that, they are perfect for usage as antigen bearers to enhance antigen processing and display due to their enormous specific surface area and activity. Because NPs release antigens in a regulated manner, most vaccinations have longer half-lives. They can also act as independent immunological potentiators (Kheirollahpour et al., 2020).

REFERENCES

AlFaleh, F. A., Ismael, S. S., Aguilar-Marcelino, L., Silva, F. E. M., Ashraf, T., Abbas, R. Z., and Qamar, W. (2023). Use of nanoparticles, a modern means of drug delivery, against cryptosporidiosis. *Journal of Advanced Veterinary and Animal Research*, *10*(4), 704.

Alvi, M. A., Alshammari, A., Ali, R. M. A., Ul Haq, S., Bashir, R., Li, L., and Jia, W. Z. (2023). Revealing novel cytb and nad5 genes-based population diversity and benzimidazole resistance in Echinococcus granulosus of bovine origin. *Frontiers in Veterinary Science*, *10*, 1191271.

Alvi, M. A., Ohiolei, J. A., Saqib, M., Li, L., Tayyab, M. H., Alvi, A. A., and Jia, W. Z. (2020). Echinococcus granulosus (sensu stricto)(G1, G3) and E. ortleppi (G5) in Pakistan: phylogeny, genetic diversity and population structural analysis based on mitochondrial DNA. *Parasites and Vectors*, *13*, 1-10.

Alvi, M. A., Li, L., Bahadur, K., Ullah, S., Saqib, M., Ohiolei, J. A., and Jia, W. Z. (2022). First Comparative Biochemical Profile Analysis of Cystic Fluids of Taenia hydatigena and Echinococcus granulosus Obtained from Slaughtered Sheep and Goats. *Pakistan Veterinary Journal*, *42*(2).

Alvi, M. A., Khan, S., Ali, R. M. A., Qamar, W., Saqib, M., Faridi, N. Y., and Jia, W. Z. (2022). Herbal medicines against hydatid disease: A systematic review (2000–2021). *Life*, *12*(5), 676.

Assolini, J. P., Concato, V. M., Gonçalves, M. D., Carloto, A. C. M., Conchon-Costa, I., Pavanelli, W. R., Melanda, F. N., and Costa, I. N. (2017). Nanomedicine advances in toxoplasmosis: diagnostic, treatment, and vaccine applications. *Parasitology Research*, *116*, 1603-1615.

Bulychev, N. (2022). Synthesis of gaseous hydrogen and nanoparticles of silicon and silicon oxide by pyrolysis of tetraethoxysilane in an electric discharge under the action of ultrasound. *International Journal of Hydrogen Energy*, *47*(84), 35581-35587.

Cortese-Krott, M. M., Kulakov, L., Opländer, C., Kolb-Bachofen, V., Kröncke, K. D., and Suschek, C. V. (2014). Zinc regulates iNOS-derived nitric oxide formation in endothelial cells. *Redox Biology*, *2*, 945-954.

Adegbeye, M. J., Elghandour, M. M., Barbabosa-Pliego, A., Monroy, J. C., Mellado, M., Reddy, P. R. K., and Salem, A. Z. (2019). Nanoparticles in equine nutrition: Mechanism of action and application as feed additives. *Journal of Equine Veterinary Science*, *78*, 29-37.

Alshamiri, M. M. A., Ali, S. A. M., Abdalla, H. O., and Ahmed, H. B. (2021). The effect of supplementing different levels of phytase enzyme on performance, some carcass properties and economics of broiler chickens. *Agrobiol Records*, *4*(1), 14-22.

Assolini, J. P., Concato, V. M., Gonçalves, M. D., Carloto, A. C. M., Conchon-Costa, I., Pavanelli, W. R., Melanda, F. N., and Costa, I. N. (2017). Nanomedicine advances in toxoplasmosis: diagnostic, treatment, and vaccine applications. *Parasitology research*, *116*, 1603-1615.

Atef, H. A., Mansour, M. K., Ibrahim, E. M., Sayed El-Ahl, R. M., Al-Kalamawey, N. M., El Kattan, Y., and Ali, M. (2016). Efficacy

of zinc oxide nanoparticles and curcumin in amelioration the toxic effects in aflatoxicated rabbits. *International Journal Current Microbiology Applied Science*, *5*(12), 795-818.

Bai, D.-P., Lin, X.-Y., Huang, Y.-F., and Zhang, X.-F. (2018). Theranostics aspects of various nanoparticles in veterinary medicine. *International Journal of Molecular Sciences*, *19*(11), 3299.

Bulychev, N. (2022). Synthesis of gaseous hydrogen and nanoparticles of silicon and silicon oxide by pyrolysis of tetraethoxysilane in an electric discharge under the action of ultrasound. *International Journal of Hydrogen Energy*, *47*(84), 35581-35587.

Castro-Sesquen, Y. E., Kim, C., Gilman, R. H., Sullivan, D. J., and Searson, P. C. (2016). Nanoparticle-based histidine-rich protein-2 assay for the detection of the malaria parasite Plasmodium falciparum. *The American Journal of Tropical Medicine and Hygiene*, *95*(2), 354.

Choudhury, S. D. (2021). Nano-medicines a hope for Chagas disease! *Frontiers in Molecular Biosciences*, *8*, 655435.

Czyżowska, A., and Barbasz, A. (2022). A review: zinc oxide nanoparticles–friends or enemies? *International journal of environmental health research*, *32*(4), 885-901.

Devan, R. S., Patil, R. A., Lin, J. H., and Ma, Y. R. (2012). One-dimensional metal-oxide nanostructures: recent developments in synthesis, characterization, and applications. *Advanced Functional Materials*, *22*(16), 3326-3370.

Din, M. I., and Rehan, R. (2017). Synthesis, characterization, and applications of copper nanoparticles. *Analytical Letters*, *50*(1), 50-62.

El-Maddawy, Z. K., and Abd El Naby, W. S. H. (2019). Protective effects of zinc oxide nanoparticles against doxorubicin induced testicular toxicity and DNA damage in male rats. *Toxicology Research*, *8*(5), 654-662.

Esakkimuthu, T., Sivakumar, D., and Akila, S. (2014). Application of nanoparticles in wastewater treatment. *Pollutution Research*, *33*(03), 567-571.

Fayad, M. A., and Dhahad, H. A. (2021). Effects of adding aluminum oxide nanoparticles to butanol-diesel blends on performance, particulate matter, and emission characteristics of diesel engine. *Fuel*, *286*, 119363.

Gaafar, M., Mady, R., Diab, R., and Shalaby, T. I. (2014). Chitosan and silver nanoparticles: promising anti-toxoplasma agents. *Experimental Parasitology*, *143*, 30-38.

Ghanta, S. R., and Muralidharan, K. (2013). Chemical synthesis of aluminum nanoparticles. *Journal of Nanoparticle Research*, *15*, 1-10.

Gholamali, I., Asnaashariisfahani, M., and Alipour, E. (2020). Silver nanoparticles incorporated in pH-sensitive nanocomposite hydrogels based on carboxymethyl chitosan-poly (vinyl alcohol) for use in a drug delivery system. *Regenerative Engineering and Translational Medicine*, *6*, 138-153.

Hamidi, M., Azadi, A., and Rafiei, P. (2008). Hydrogel nanoparticles in drug delivery. *Advanced Drug Delivery Reviews*, *60*(15), 1638-1649.

Hemadi, A., Ekrami, A., Oormazdi, H., Meamar, A. R., Akhlaghi, L., Samarbaf-Zadeh, A. R., and Razmjou, E. (2015). Bioconjugated fluorescent silica nanoparticles for the rapid detection of Entamoeba histolytica. *Acta Tropica*, *145*, 26-30.

Ibrahim, D., Ali, H. A., and El-Mandrawy, S. A. (2017). Effects of different zinc sources on performance, bio distribution of minerals and expression of genes related to metabolism of broiler chickens. *Zagazig Veterinary Journal*, *45*(3), 292-304.

Jamkhande, P. G., Ghule, N. W., Bamer, A. H., and Kalaskar, M. G. (2019). Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. *Journal of Drug Delivery Science and Technology*, *53*, 101174.

Kheirollahpour, M., Mehrabi, M., Dounighi, N. M., Mohammadi, M., and Masoudi, A. (2020). Nanoparticles and vaccine development. *Pharmaceutical Nanotechnology*, *8*(1), 6-21.

Kołodziejczak-Radzimska, A., and Jesionowski, T. (2014). Zinc oxide—from synthesis to application: a review. *Materials*, *7*(4), 2833-2881.

McCoy, M. E., Golden, H. E., Doll, T. A., Yang, Y., Kaba, S. A., Burkhard, P., and Lanar, D. E. (2013). Mechanisms of protective immune responses induced by the Plasmodium falciparum circumsporozoite protein-based, self-assembling protein nanoparticle vaccine. *Malaria Journal*, *12*(1), 1-12.

Mehessen, N., Khalil, W. F., Aly, A.-F. M. M., and Eldemerdash, E. A. (2023). The antibacterial and immunomodulatory effect of Zinc-oxide nanoparticles on .water fish-aeruginosa infected fresh pseudomonas *Suez Canal Veterinary Medical Journal. SCVMJ*.

Mohapatra, S. C., Tiwari, H. K., Singla, M., Rathi, B., Sharma, A., Mahiya, K., Kumar, M., Sinha, S., and Chauhan, S. S. (2010). Antimalarial evaluation of copper (II) nanohybrid solids: inhibition of plasmepsin II, a hemoglobin-degrading malarial aspartic protease from Plasmodium falciparum. *JBIC Journal of Biological Inorganic Chemistry*, *15*, 373-385.

Mondal, A., Adhikary, B., and Mukherjee, D. (2015). Room-temperature synthesis of air stable cobalt nanoparticles and their use as catalyst for methyl orange dye degradation. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *482*, 248-257.

Pati, R., Mehta, R. K., Mohanty, S., Padhi, A., Sengupta, M., Vaseeharan, B., Goswami, C., and Sonawane, A. (2014). Topical application of zinc oxide nanoparticles reduces bacterial skin infection in mice and exhibits antibacterial activity by inducing oxidative stress response and cell membrane disintegration in macrophages. *Nanomedicine: Nanotechnology,*

Biology and Medicine, *10*(6), 1195-1208.

Ponarulselvam, S., Panneerselvam, C., Murugan, K., Aarthi, N., Kalimuthu, K., and Thangamani, S. (2012). Synthesis of silver nanoparticles using leaves of Catharanthus roseus Linn. G. Don and their antiplasmodial activities. *Asian Pacific Journal of Tropical Biomedicine*, *2*(7), 574-580.

Prakash, A., Sharma, S., Ahmad, N., Ghosh, A., and Sinha, P. (2010). Bacteria mediated extracellular synthesis of metallic nanoparticles. *International Research Journal Biotechnology*, *1*(5), 071-079.

Qi, H., and Zhang, C. (2022). Organic nanoparticles for electrogenerated chemiluminescence assay. *Current Opinion in Electrochemistry*, *34*, 101023.

Quadir, M. A., Morton, S. W., Mensah, L. B., Shopsowitz, K., Dobbelaar, J., Effenberger, N., and Hammond, P. T. (2017). Ligand-decorated click polypeptide derived nanoparticles for targeted drug delivery applications. *Nanomedicine: Nanotechnology, Biology and Medicine*, *13*(5), 1797-1808.

Quijia Quezada, C., Azevedo, C. S., Charneau, S., Santana, J. M., Chorilli, M., Carneiro, M. B., and Bastos, I. M. D. (2019). Advances in nanocarriers as drug delivery systems in Chagas disease. *International Journal of Nanomedicine*, 6407-6424.

Ristić, M., Musić, S., Ivanda, M., and Popović, S. (2005). Sol–gel synthesis and characterization of nanocrystalline ZnO powders. *Journal of Alloys and Compounds*, *397*(1-2), L1-L4.

Roy, R., Kumar, S., Verma, A. K., Sharma, A., Chaudhari, B. P., Tripathi, A., Das, M., and Dwivedi, P. D. (2014). Zinc oxide nanoparticles provide an adjuvant effect to ovalbumin via a Th2 response in Balb/c mice. *International Immunology*, *26*(3), 159-172.

Said, D., Elsamad, L., and Gohar, Y. (2012). Validity of silver, chitosan, and curcumin nanoparticles as anti-Giardia agents. *Parasitology Research*, *111*, 545-554.

Sepulveda-Guzman, S., Reeja-Jayan, B., de La Rosa, E., Torres-Castro, A., Gonzalez-Gonzalez, V., and Jose-Yacaman, M. (2009). Synthesis of assembled ZnO structures by precipitation method in aqueous media. *Materials Chemistry and Physics*, *115*(1), 172-178.

Shahzad, K., Khan, M. N., Jabeen, F., Kosour, N., Chaudhry, A. S., Sohail, M., and Ahmad, N. (2019). Toxicity of zinc oxide nanoparticles (ZnO-NPs) in tilapia (Oreochromis mossambicus): tissue accumulation, oxidative stress, histopathology and genotoxicity. *International Journal of Environmental Science and Technology*, *16*, 1973-1984.

Song, G., Cheng, N., Zhang, J., Huang, H., Yuan, Y., He, X., Luo, Y., and Huang, K. (2021). Nanoscale cerium oxide: Synthesis, biocatalytic mechanism, and applications. *Catalysts*, *11*(9), 1123.

Sousa, S., Castro, A., Correia da Costa, J. M., and Pereira, E. (2021). Biosensor based immunoassay: A new approach for serotyping of Toxoplasma gondii. *Nanomaterials*, *11*(8), 2065.

Tai, C. Y., Tai, C.-T., Chang, M.-H., and Liu, H.-S. (2007). Synthesis of magnesium hydroxide and oxide nanoparticles using a spinning disk reactor. *Industrial and Engineering Chemistry Research*, *46*(17), 5536-5541.

Talebian, N., Amininezhad, S. M., and Doudi, M. (2013). Controllable synthesis of ZnO nanoparticles and their morphology-dependent antibacterial and optical properties. *Journal of Photochemistry and Photobiology B: Biology*, *120*, 66-73.

Tripathy, S., Das, S., Chakraborty, S. P., Sahu, S. K., Pramanik, P., and Roy, S. (2012). Synthesis, characterization of chitosan–tripolyphosphate conjugated chloroquine nanoparticle and its in vivo anti-malarial efficacy against rodent parasite: A dose and duration dependent approach. *International Journal of Pharmaceutics*, *434*(1-2), 292-305.

Underwood, C., and Van Eps, A. (2012). Nanomedicine and veterinary science: The reality and the practicality. *The Veterinary Journal*, *193*(1), 12-23.

Wang, C., Zhang, L., Su, W., Ying, Z., He, J., Zhang, L., Zhong, X., and Wang, T. (2017). Zinc oxide nanoparticles as a substitute for zinc oxide or colistin sulfate: effects on growth, serum enzymes, zinc deposition, intestinal morphology and epithelial barrier in weaned piglets. *PloS one*, *12*(7), e0181136.

Wang, H., Lei, C., Li, J., Wu, Z., Shen, G., and Yu, R. (2004). A piezoelectric immunoagglutination assay for Toxoplasma gondii antibodies using gold nanoparticles. *Biosensors and Bioelectronics*, *19*(7), 701-709.

Wang, Z. L. (2000). Characterizing the structure and properties of individual wire-like nanoentities. *Advanced Materials*, *12*(17), 1295-1298.

Weigum, S., Castellanos-Gonzalez, A., White Jr, A., and Richards-Kortum, R. (2013). Amplification-free detection of Cryptosporidium parvum nucleic acids with the use of DNA/RNA-directed gold nanoparticle assemblies. *The Journal of Parasitology*, *99*(5), 923-926.

Wu, Y., Liu, J., Lin, Y., Weng, R., Chen, R., Li, J., and Lv, Z. (2018). Diagnosis, monitoring, and control of schistosomiasis—an update. *Journal of Biomedical Nanotechnology*, *14*(3), 430-455.

Xin, Q., Shah, H., Nawaz, A., Xie, W., Akram, M. Z., Batool, A., Tian, L., Jan, S. U., Boddula, R., and Guo, B. (2019). Antibacterial carbon-based nanomaterials. *Advanced Materials*, *31*(45), 1804838.

Zahra, J., Iqbal, S., Zahra, K., Javed, Z., Shad, M. A., Akbar, A., Ashiq, M. N., and Iqbal, F. (2017). Effect of variable doses of zinc oxide nanoparticles on male albino mice behavior. *Neurochemical Research*, *42*, 439-445.

Wang, Z.L. (2000). Characterizing the structure and properties of individual wire-like nanoentities. *Advanced Materials*, 12(17):1295-8.

Xu, L., Hu, Y., Pelligra, C. et al. (2009). ZnO with different morphologies synthesized by solvothermal methods for enhanced photocatalytic activity. *Chemistry of Materials*, 21(13): 2875-2885

Yuvakkumar, R., Suresh, J., Nathanael, A, et al. (2014): Novel green synthetic strategy to prepare ZnO nanocrystals using rambutan (Nephelium lappaceum L.) peel extract and its antibacterial applications. *Materials Science and Engineering*, 41: 17-27.

Yuen, C., and Liu, Q. (2013). Optimization of Fe 3 O 4@ Ag nanoshells in magnetic field-enriched surface-enhanced resonance Raman scattering for malaria diagnosis. *Analyst*, 138(21): 6494-6500.

Zou, C., Liang, F., and Xue, S. (2015). Synthesis and oxygen vacancy-related photocatalytic properties of ZnO nanotubes grown by thermal evaporation. *Research on Chemical Intermediates,* 41:5167-76.

Chapter 18

Nanomedicines Utilizing Trace Elements as Targeted Intervention to Revolutionize Diabetes Treatment

Muhammad Sajid[1], Muqader Shah[5] Muhammad Azam[2], Wazir Muhammad Ikhlaq[3], Sajawal Ali[1], Abdul Mateen[2], Hussain Abbas[1], Faiza Bibi[2], Sara Khan[2] and Shahna Jabeen[2], and Ghulam Murtaza[4*]

[1]Faculty of Veterinary Sciences, University of Agriculture Faisalabad, Pakistan
[2]Department of Allied Health Professionals, Faculty of Life Sciences, Government College University Faisalabad
[3]Department of Chemistry, Faculty of Physical Science, Government College University Faisalabad
[4]Department of Anatomy, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad, Pakistan
[5]College of Veterinary Sciences, The University of Agriculture, Peshawar, KPK, Pakistan
*Corresponding author: murtazakhanarman516@gmail.com

ABSTRACT

Diabetes mellitus (DM), a metabolic disease, has been rising annually all across the world based on epidemiology. An effective treatment is essential for diabetic patients to improve their quality of life and to prevent the development of chronic diseases. Microelements, also known as trace elements or nanoparticles, are small amounts of chemicals that are present in human body, and are essential for the growth, and development of the body. Over the last several years, there has been a lot of interest in nanoparticles as a novel class of nanomedicines for antidiabetic application. The nanomedicines are based on trace elements or nanoparticles that have the potential to significantly enhance the care and treatment of diabetes by controlling glucose metabolism. According to several researches, nanoparticles can prevent diabetes in various ways, including lowering blood sugar, promoting insulin secretion, reducing glucose intolerance, enhancing insulin sensitivity, modifying lipid profiles, and reducing inflammation and antioxidant stress. This chapter includes a detailed analysis of the physiological functions of nanoparticles, the pathophysiology of diabetes, the current status of diabetes therapy, and many emerging nanoparticles particularly for diabetes. To conclude, nanoparticles can be used as dietary supplements or as nanomedicines to effectively treat diabetes.

KEYWORDS
Diabetes Mellitus Pathophysiology, ZnNPs, CuNPs, MgNPs, CrNPs, FeNPs.

Received: 29-Jun-2024
Revised: 02-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Sajid M, Murtaza G, Azam M, Ikhlaq WM, Ali S, Mateen A, Abbas H, Bibi F, Khan S and Jabeen S, 2024. Nanomedicines utilizing trace elements as targeted intervention to revolutionize diabetes treatment. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 155-162. https://doi.org/10.47278/book.CAM/2024.485

INTRODUCTION

DM is a metabolic disorder characterized by hyperglycemia (High blood sugar), polydipsia (excessive thirst), hyperphagia, and polyuria (excessive urination volume) (Mukhtar et al., 2020). Chronic hyperglycemia leads to the destruction and dysfunction of several organs and tissues, including the kidneys, heart, blood vessels, nerves, and eyes. Although these conditions are a substantial cause of morbidity and mortality, but these are unrelated to the disorder's direct effects. Instead, they are linked to the long-term effects of diabetes, which include neurological problems, retinal and diabetic nephropathy, coronary heart disease, peripheral artery disease (macroangiopathy), and diabetic nephropathy. Although there is no effective technique for treating DM completely, even though glycemic control drugs can impede its advancement (Teck, 2022). Trace elements are chemical elements that are required for one or more of the vital processes carried out by human bodies. Even though these microelements are just somewhat needed by the body, but their absence can seriously impair an organism's ability to survive and function (Skalnaya and Skalny, 2018). There is an evidence to support a link between the variations in the blood/serum level of trace elements, and the onset of pathoglycemia and diabetes. In an individual with diabetes, serum microelements including zinc (Zn), selenium (Se), magnesium (Mg), copper (Cu), etc. are frequently found in aberrant concentrations, or in vivo, these microelements are usually lost or reduced pathologically. Glucose homeostasis depends on the preservation of ideal trace nutrient levels. The ultimate objective of treating diabetes is believed to be modifying the way pancreatic cells function and restoring glucose homeostasis, however this is still challenging because of variations in the glucose metabolic rate but supplementation of food with microelements, particularly in the form of nanoparticles, is an emerging novel therapeutic approach for control of diabetes (Kravchenko et al., 2023). This chapter included an appropriate summary of the pathophysiology of diabetes and the

present state of therapy. It is discussed how diabetes and the physiological effect of micro elements relate to each other and also figure out the therapeutic potential of micro element nanoparticles and their underlying mechanism of action on diabetes and its complications. It is also relied to a conclusion with an overview and recommendations for the use of trace element nanoparticles for the cure and treatment of diabetes and its complications.

Diabetes Mellitus Pathophysiology

DM is a disorder of glucose metabolism that results due to inadequate production of insulin and/or a malfunction in the body's ability to produce or react to insulin, leading to an inability to maintain appropriate blood glucose level (Balaji et al., 2019). There are two main factors that contribute to the etiology and pathophysiology of DM such as genetics and environmental variables. There is an evidence of significant genetic variability for type 1 diabetes (T1DM) and type 2 diabetes (T2DM). DM is a heritable condition that affects 1/4 to 1/2 of people, and is linked to approximately 60 different genetic disorders (Cole and Florez, 2020). The pathophysiology of T1DM is linked to several DNA loci present across the whole human nucleic acid sequence, with diversiforms in the HLA genes that encode DQ and DR. Additionally, several distinct genetic mutations related to T2DM have been discovered such as abnormalities in the genes for glucokinase, insulin, insulin receptor, and mitochondria. The pathophysiology of DM is significantly influenced by environmental variables as well. One of the primary environmental factor contributing to T2DM is obesity, which is the result of overindulging and inadequate physical activity that will increases the risk of T2DM in people who are genetically predisposed to the disease.(Yasmin et al., 2021). On another hand, when a T1DM-susceptible population is infected with particular viruses, such as the parotid, rubella, or coxsackie viruses, that induced an autoimmune reaction and destroy the islet β cells (cells that release insulin) causing diabetes. About 5–10% of clinical instances of diabetes are caused by T1DM and it is mostly occurred in youngsters or teenagers. The autoimmune loss of the pancreatic islets is the primary cause of T1DM which is detected by the presence of antibodies against insulin and other islet components in the serum of patients. The existence of the antibodies is associated with a reduction in insulin secretion and typically manifests several years prior to the onset of diabetes. Approximately 90% of cases are T2DM, which is significantly more frequent than T1DM (Carey et al., 2018).

T2DM is particularly occurred in older ones, while younger patients can also be affected. Obesity due to insulin insufficiency or resistance is closely associated with T2DM because insulin resistance is a prevalent feature of T2DM in obese individuals, and their serum insulin levels are neither below nor above normal. This leads to hyperglycemia because these obese people are unable to respond to elevated blood glucose levels by producing an adequate quantity of insulin (Czech, 2017). In order to help in the metabolism of carbohydrates, healthy individuals may secrete more insulin than fat individuals. The body might produce insulin but not use it efficiently, which also results in insulin resistance. Oxidative stress in cells typically arises from overeating and inactivity. Human cells produce reactive oxidative species (ROS) during the oxygen-driven metabolism of nutrients to generate energy (Yun et al., 2022).

These free radicals emerge as excess oxygen byproducts accumulate. When these radicals interact with other biomolecules, they induce oxidative stress, which is detrimental to cellular health. Such stress can alter specific glucose transporters like GLUT4, potentially leading to insulin resistance due to enzymatic changes affecting glucose absorption in response to insulin. A mounting body of research highlights a beneficial correlation between heightened inflammation and hyperglycemia. Hyperglycemia not only escalates ROS production but also boosts the expression of inflammatory mediators. Consequently, cellular stressors such as mitochondrial oxidative stress and endoplasmic reticulum stress intertwine with metabolic inflammation. The autoimmune reaction to chronic inflammation and oxidative stress, triggered by genetic and environmental mutagenesis, underlies the physiopathology of diabetes (Lima et al., 2022). Pathophysiology of T2DM is shown in Fig. 1.

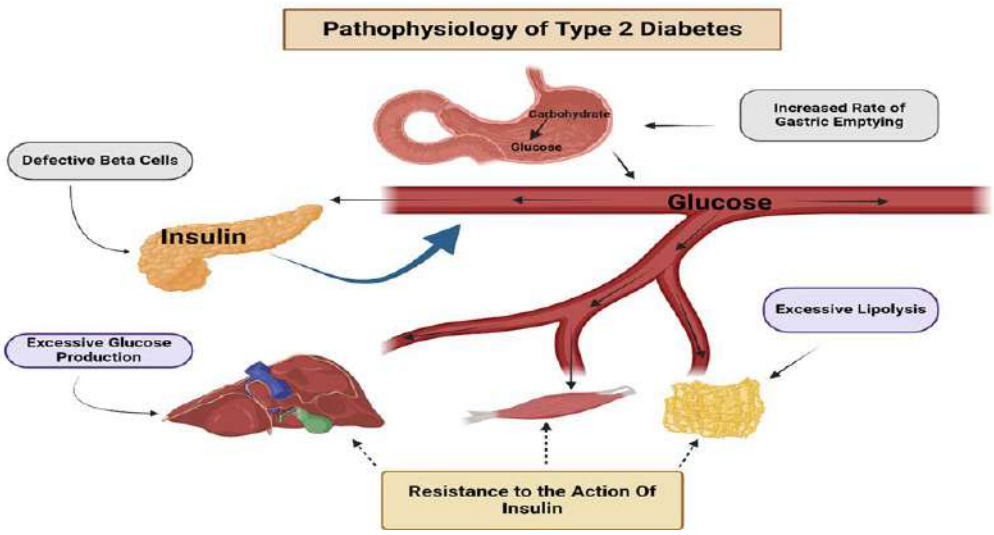


Fig. 1: Physiopathology of Type 2 DM.

Contemporary Approaches in Diabetes Management

DM is diagnosed, when blood glucose levels exceed 7 mmol/L after an overnight fast or 11.1 mmol/L during any meal period (Turner, 2023). Many individuals remain unacquainted of their diabetes until the appearance of typical symptoms like excessive urination, hyperphagia, and high blood sugar levels. Ketoacidosis, characterized by an accumulation of acids and ketones (fat-metabolizing enzymes) in the bloodstream, can result from untreated diabetes. Nausea, vomiting, and diabetic coma may occur due to the in-vivo accumulation of metabolites from lipids and saccharides. Current DM treatment focuses on maintaining nearly normal blood glucose levels, thereby enhancing diabetic patient quality of life and potentially slowing the progression of disease (Aguiar et al,, 2019).

On another hand, active therapies, including nonclinical and clinical interventions such as exercise, nutrition, insulin supplements, oral hypoglycemic medications, and insulin therapy, aim to improve the glucose utilization within the body. Diabetic patients are recommended to take high protein and low carbohydrates and lipids diet. An estimated 34% of calories are attributed to lipids, 12–16% to proteins, and the remaining portion to carbohydrate (Ludwig and Ebbeling, 2018). DM or obesity patients, are recommended to manage their daily calorie intake with 5 to 6 small meals instead of 3 large ones. Calorie restriction combined with moderate hunger can dramatically reduce hyperglycemia. Beside this, exercise in conjunction with diets can help the body to actively mobilize glucose consumption, enhancing insulin sensitivity and possibly restoring glucose homeostasis. Insulin intervention therapy is necessary for diabetic patients whose bodies are unable to produce insulin. T1DM and T2DM patients are not satisfied with oral hypoglycemic medications are the target spectators for insulin treatment (Chan et al., 2021).

Insulin therapy is known as regular subcutaneous injection of the hormone in accordance with the real state of blood glucose level. Because of significant advancements in genetically recombinant DNA technology, recombinant human insulin now fully exchanges pig and cow insulin for clinical usage. Insulin for injections, can be made from human tissue. The optimal insulin secretion schedule is most closely resembling to the standard profile, which is defined by a stimulus-responsive insulin secretion following meals but a steady amount of secretion throughout the non-eating state. A once-daily dose of both a fast-acting insulin preparation and a long-acting insulin preparation can be used to achieve target. Insulin administered subcutaneously can swiftly lower the blood sugar levels, but unlike endogenous insulin produced by pancreas, this external administered insulin does not act directly in the liver (Bolli et al., 2021). Insulin therapy has poor injectable compliance and is costly for a lifelong prescription. On the other hand, a lot of diabetic patient's favor taking oral hypoglycemic medications. Oral medications for blood glucose control fall into multiple forms, such as thiazolidinediones, and sulfonylureas. Conversely, these hypoglycemic agents bring some side effects, e.g., lower glucose level in blood, edema and nausea. The treatment for DM available today is an after-the-fact intervention that aims to reduce sign and symptoms of disease for short period of time rather than completely eradicate the disease. Dapagliflozin and empagliflozin are highly preferred as new-type hypoglycemic agents (Holtzclaw et al., 2018). They are classified as sodium-glucose co-transporter 2 (SGLT2) inhibitors, that can lower blood sugar level by preventing glucose from being reabsorbed through the tubules and reducing the insulin threshold in the kidneys, which increases glucose excretion through the urine. These medications exhibit pharmacological activities beyond the impact of hypoglycemia, such as reducing blood pressure, promoting weight loss, and lowering uric acid levels. Consequently, they may offer cardiovascular protection in addition to blood glucose control.

In recent years, new treatments for diabetes have also emerged, including implanted insulin infusion, β cell transplantation, and pancreas transplantation (Paez-Mayorga et al., 2022). Due to their complete lack of insulin secretion, patients with T1DM typically seek active intervention with novel therapeutic alternatives. The practical application of pancreas or islet transplantation is hindered by the scarcity of pancreatic tissue donors, the necessity of immunosuppressive medication, and the risk of tissue rejection. Ongoing projects involve the development of mechanical islets and the use of cell engineering to improve transplantation outcomes. Reconstructing the body's physiological processes and restoring glucose homeostasis are essential for curing DM. The current objective of DM treatment, although insufficient to meet the initial aspiration, is to control blood glucose level and help prevent long lasting problems. In reality, greater attention should be directed toward modifications in the metabolic profiles associated with diabetes, including alterations in metabolic paths and enzymes, tissue and organ damage, and loss of micro elements (Korac et al., 2021). The main physiological function of nanoparticles for human health are shown in Fig. 2.

Nanoparticles Used for DM Treatment

The types of micro element based nanoparticles utilized in DM research can be categorized into the following sections.

Zinc (ZN) Nanoparticles

Zn is present in body fluids, and almost every tissues of the human body. Zn is vital element for optimum growth of the human body, and it is an essential for approximately 300 enzymes that are necessary for various metabolic pathways. The secretory vesicles of islet β cells contain insulin crystals that assemble into hexamers, with two Zn^{2+} ions coordinating the movement of six insulin monomers. Zn influences the production, storage, secretion, structural integrity, and extending hypoglycemic potential of insulin (Pizzo et al., 2022). It is also a cofactor for enzymes that break down lipids, proteins and also used in glucose metabolism. Zn is directly involved in the energy supply system of glucose oxidation, and activates lactate dehydrogenase, glycerol 3-phosphate dehydrogenase and malate dehydrogenase. Additionally, it controls the glucose homeostasis by activating carboxypeptidase, and facilitating the proinsulin conversion into insulin. Low Zn levels decrease proinsulin conversion, lowering blood insulin levels and glucose consumption by fat and muscle cells, leading to high level of glucose in blood (Bjørklund et al., 2020).

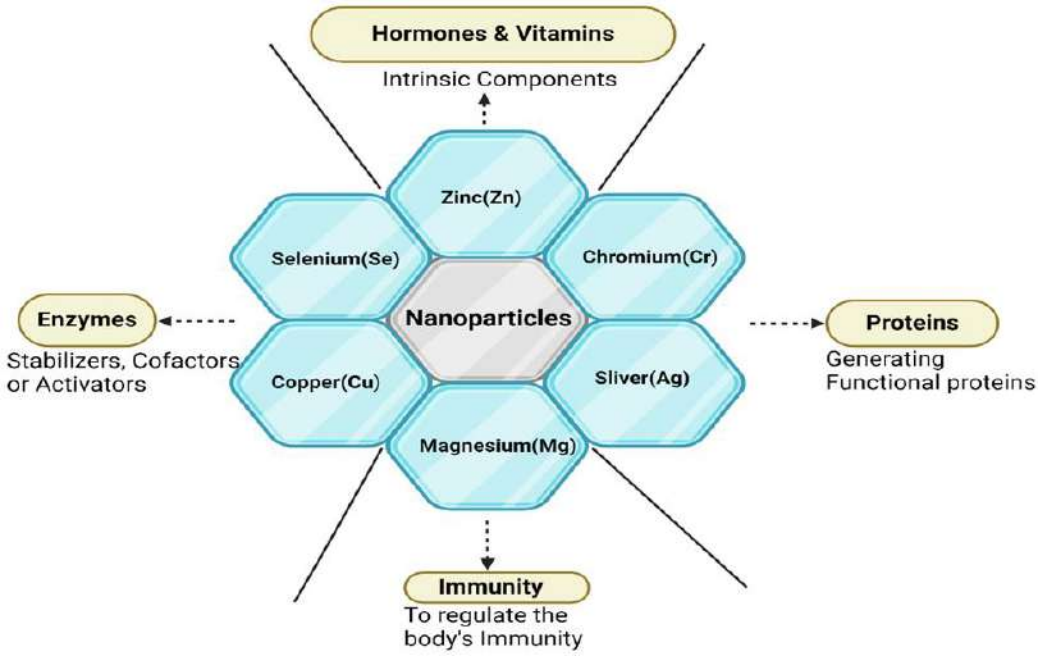


Fig. 2: The Physiological Function of Nanoparticles for Human Health

It also aids in glucose metabolism and endosomal insulin receptor trafficking, exhibiting insulin-mimetic properties and reducing insulin requirements when it is present in sufficient level. Researches reveal the prevalance of Zn shortage in diabetics, linked to reduced cellular Zn and Zn-dependent antioxidant enzymes. Zn loss through urine and decreased serum Zn concentrations are observed in hypoglycemic T2DM, suggesting major role of Zn in diabetes etiology, insulin and glucose metabolism. The growing interest in Zn supplementation or medications for diabetes treatment stems from significant Zn benefits. Zinc oxide nanoparticles (ZnONPs), discovered in 2013, notably reduce diabetes risk in both T1DM and T2DM rats. Oral ZnONPs decrease triglycerides and non-esterified fatty acids, increase serum insulin, and lower blood glucose, leading to increased Zn levels in pancreatic, liver, and adipose tissues (Jeevanandam et al., 2015). The synthesized ZnONPs exhibit outstanding anti-diabetic properties, potentially enhanced by loading docosahexaenoic acid (DHA) to boost the insulin signaling pathway. ZnONPs significantly lower blood glucose levels and prevent advanced glycated end products (AGEs) formation, showing promise in managing DM. Further research is warranted to explore therapeutic potential of ZnNPs in diabetes management.

Magnesium Nanoparticles (MgNPS)

MgNPs functions as a vital trace element necessary for numerous metabolic processes, controlling blood sugar levels, blood pressure, muscle and nerve activity (Jomova et al., 2022). The patients with T2DM often experience clinical hypomagnesemia or chronic magnesium deficit, particularly with poorly managed glycemic profiles. MgNPs is essential for control of vascular tone, insulin-mediated glucose absorption, and insulin action. The deficiency of magnesium can lead to insulin resistance, impairing glucose delivery into cells, resulting in high blood glucose levels, fatigue, increased thirst and urination, impaired vision, and other symptoms. The chronic hyperglycemia can cause severe complications over time, including cardiovascular disease, renal damage, and nerve damage (Porri et al., 2021). As a treatment for DM and its consequences, MgNPs show promising effects, and studies on animals and cells indicate that MgNPs increase insulin sensitivity, enhancing cellular response to insulin, lowering glucose level in blood, and decreasing the risk of T2DM.

In a specific investigation, diabetic rats administered naturally synthesized magnesium hydroxide nanoparticles from *Monodora myristica* showed improvements in fasting blood glucose, hepatic hexokinase activity, serum insulin, and LDH action, potentially alleviating hyperglycemia by protecting β-cells and restoring glycolytic enzyme activity. Another substance developed for anti-diabetic purposes is Magnesium oxide (MgO). Manganese oxide (MnO) and Magnesium oxide (MgO) nanoparticles were produced, and their antidiabetic and antioxidant properties were assessed. The comparing high-dose MgO (300 mg/kg/day) with the positive control group (diabetic rats) demonstrated a substantial declined in blood glucose and an increment in insulin, along with elevated serum paraoxonase levels (Shaukat et al., 2021). Subsequent investigations found that magnesium supplementation greatly improved parameters related to DM and thyroid profile, while MgO nanoparticles protected against pancreatic cell loss, maintaining pancreatic islet size and β-cell quantity. In contrast, synthesized MgO nanoparticles using *Pterocarpus marsupium* heartwood aqueous extracts, demonstrating antioxidant, antidiabetic, and anti-inflammatory properties. These studies suggest that MgNPs may serve as supplemental and alternative therapy to control diabetes.

Chromium Nanoparticles

Chromium (Cr) is an important trace mineral involved in numerous biological processes, including glucose metabolism. The insufficient Cr intake has been linked to the progression and development of DM (Lewicki et al., 2014). Cr significantly

improve insulin function, promoting cellular glucose absorption, and reducing glucose levels in blood which influences glucose metabolism. The individuals susceptible to DM often consume insufficient Cr amounts, and in diabetic's patient, supplementing with Cr can progress glycemic control and insulin sensitivity. Additionally, Cr can lower blood pressure and cholesterol levels, safeguarding diabetics from cardiovascular diseases. (Abdali et al., 2015). Micro particles, can be engineered to possess particular characteristics like enhanced bioavailability and oral absorption. According to certain studies, Cr nanoparticles outperform conventional chromium molecules improving insulin sensitivity and reducing glucose level in blood. For illustration, two-month study evaluated the effect of Cr(III) micro particles on immunological reactions and hormones in heat-stressed rats. The serological analyses revealed higher serum levels of insulin-like growth factor and immunoglobulin G in heat-stressed rats, while the control group exhibited lower insulin concentration (Ghasemi and Nari, 2020).

Subsequent investigations indicated that chromium nanoparticles might decrease serum insulin levels. Another study, suggested that chromium's physiological effect on enhancing hormone internalization into cells and increasing membrane fluidity could underlie the decrease in peripheral insulin levels. In a recent study, oral administration of Cr_2O_3 nanoparticles at a dose rate of 1 mg/kg b.w.t reestablished all genetic and biochemical factors, including hepatic and renal functions restored blood insulin, serum glucose, lipid profile, IL-6, glutathione peroxidase (GSH-Px), serum superoxide dismutase activity, γ-peroxisome proliferator-activated receptor (γ-PPAR), insulin receptor substrate-1 (IRS-1), and serum insulin to normal levels in diabetic rats. It was believed that reducing cellular DNA damage would mitigate diabetes's negative effects and protect the liver and pancreas from oxidative damage. Additionally, Cr nanoparticles may beneficial for diabetics patient through anti-inflammatory, antioxidatory, and as regulator for fat metabolism (Javanshir et al., 2020). In conclusion, Cr nanoparticles grip capacity as a potential diabetic cure, however, further study is necessary to conclude their safety and efficacy before recommending human use.

Copper Nanoparticles

Copper (Cu) is also a necessary trace element that plays an important role in human well-being. It contributes to the production of RBCs, the preservation of strong bones, and the appropriate operation of the immune system. Cu also aids in the synthesis of collagen, an essential protein for the development of connective tissues like ligaments, and skin. While the central nervous system (CNS) regulates insulin secretion from pancreatic β cells, so Cu plays a crucial role in both regular hematopoiesis and the health of the CNS. Cu is also believed to be beneficial for the production and release of insulin by the pancreas (Rajeswari and Swaminathan, 2014). So, a number of studies have linked Cu deficiency to glucose intolerance and impaired insulin secretion. The antidiabetic potential of Cu in diabetes intervention has been investigated in numerous studies that revealed a strong connection between mutative glycemic management and serum Cu level. So improving the control of diabetes, there has been requires a physiological balance level of Cu in the body. A study discovered that Cu nanoparticles (CuNPs) could suppress the activity of α-amylase, indicating possible anti-diabetic property. CuNPs have been shown in other studies to reduce inflammation and oxidative stress and to potentially enhance blood glucose regulation by blocking the actions of α-amylase and α-glucosidase (Ramasubbu et al., 2023).

Rats with Streptozotocin-induced diabetes was treated with low-dose CuNPs (1 mg/kg, p.o.). The levels of glucose in the serum of the diabetic rats were considerably lower after 4 weeks of treatment. Similarly, in Streptozotocin -induced diabetic mice, strong hypoglycemic effects of copper oxide nanoparticles (CuONPs) biosynthesized with *Bacopa monnieri* leaf extracts were noted. The resulting CuONPs, which have an usual size of 34.4 nm, were administered orally for fourteen days at a dose rate of 14 mg/kg, and this caused a 35.74% decrease in blood glucose levels (Faisal et al., 2022). According to these research findings, at the right concentrations, CuNPs have a good antidiabetic potential.

Iron Nanoparticles

Iron **(**Fe), the prevalent micro element in the human body, is involved in many physiological processes, including growth, and development of the body. Diabetes and Fe are typically perceived as two distinct illnesses that are unrelated to one another. Nonetheless, some data points to a possible connection between the onset of T2DM and iron metabolism (Backe et al., 2016). Health risks arise from both increased body iron deposition and iron deficiency. Iron overload, or excessive iron accumulation in the body, has been linked to a higher chance of developing T2DM. Conversely, low iron levels have been associated to decreased insulin sensitivity, poor glucose tolerance, and a higher chance of T2DM. When iron deficiency is identified as a contributing factor to diabetes, intervention in iron metabolism may be beneficial for managing the disease and its complications (Abbaspour et al., 2014).

For example, diabetic rats were treated through various dosages of superparamagnetic iron oxide microparticles (SPIONs) once a week for 28 days. When compared to the untreated group, SPIONs properly balanced the insulin and fasting blood glucose levels in diabetic rats. The improvement of $C_6H_{12}O_6$ detecting and active elements in the insulin nodding pathway were linked to SPIONs' antidiabetic property. Additionally, it was shown that iron micro particles might suppress the function of alpha-amylase, a protein that is essential for the breakdown of starch, glycogen, and carbohydrates. Fe2O3 nanoparticles with stem extracts from *Securidaca longipedunculata*, utilizing a green synthesis approach, and assessed their potential for antidiabetic effects. The resulting spheroidal nanoparticles had a crystallite size of 4.07 nm and a size range of 25 to 45 nm. The level of glucose in the blood of diabetic rats was reduced by 409.50 ± 5.50–199.16 ± 9.33 mg/dL by the green-synthesized iron nanoparticles (Ruan et al., 2023). According to the aforementioned research, iron nanoparticles may help to treat diabetes and prevent hyperglycemia. Table 1 shows the characteristics and anti-diabetic effects of nanoparticles that are used to treat Diabetes Mellites.

Table. 1: The Characteristics and Anti-Diabetic Effects of Nanoparticles Used to Treat DM

Type of Nanoparticles	Characteristics	Anti-Diabetic Effects	Reference
Selenium Nanoparticles	Antioxidant	Reduces blood glucose levels, enhances insulin secretion	Ruan et al., 2023
Zinc Nanoparticles	Insulin Regulator	Improves insulin function, lowers blood glucose levels	Pizzo et al., 2022
Magnesium Nanoparticles	Insulin Sensitizer	Increases insulin sensitivity, lowers blood glucose levels	Porri et al., 2021
Chromium Nanoparticles	Glucose Regulator	Enhances insulin sensitivity, reduces blood glucose levels	Ghasemi and Nari, 2020
Copper Nanoparticles	Enzyme Inhibitor	Suppresses α-amylase activity, lowers blood glucose levels	Ramasubbu et al., 2023
Iron Nanoparticles	Insulin Stabilizer	Balances insulin and blood glucose levels	Backe et al., 2016

Other Microelement Nanoparticles

A wide range of additional nanoparticles have been investigated for DM interference, in addition to the trace element nanoparticles covered above. Insulin sensitivity and glucose metabolism are enhanced in diabetic animal or cell models by these trace element nanoparticles, which include titanium (Ti), cerium (Ce), and vanadium (V). These specifically engineered microelement nanoparticles have demonstrated strong antioxidant and anti-inflammatory properties, in addition to their ability to regulate blood sugar, which may help against issues related to diabetes (Singh et al., 2021).

Prospects and Recommendations

Nanomedicine is a microscale medical way that combines biomaterial, micro technology, and medicinal molecules to treat complex and long-term illnesses. Because of their programmable features and nanoscale effect, medications based on nanoparticles offer more therapeutic options, targeted distribution, and sustained/controlled release than conventional pharmaceuticals. Because of their good intestinal absorption, micro elements in the formula of nanoparticles have superior oral bioavailability. They also have decreased systemic toxicity because of their minimal surge experience to the body and long-lasting regulatory effects because of their constant trace element release. These qualities make micro element nanoparticles very useful for diabetic treatments. (Zhu et al., 2021). The determination of trace element levels in the serum and the correlation between diabetes and an element deficiency are prerequisites for the utilization of nanoparticles in the treatment of diabetes. The quantity of nanoparticles given, in vivo buildup, and long-term harmfulness are further clinical considerations. Nanomedicine may herald a new era in diabetes treatment once these concerns are resolved. To completely comprehend the functions of nanoparticles in the cause of DM, more study is necessary (Collins et al., 2016).

It is crucial to remember that consuming too many trace elements can be hazardous and poisonous. It has been demonstrated that the release of dissolved ions and the dosage of trace element nanoparticles are related to their toxicity. High doses and ionization often result in increased production of reactive oxygen species, which stresses cells and tissues oxidatively. Because of their zero-valence condition, trace elements that are formed into nanomedicines show less toxicity than other chemical modalities because they are more stable in vivo. However, more research in superior populations is warranted to determine the efficacy of using trace element nanoparticles for diabetes treatments. Consuming microelements like Zn and Se through diet may help prevent the development of T2DM and insulin resistance. No doubt, it is essential to complement the trace element in the correct form (such as nanoparticles) when the pathophysiology of diabetes points to a micronutrient abnormality. Eating a nutritious diet is always the best method to ensure that your intake of microelements is balanced (Godswill et al., 2020). Additionally, before beginning any new supplement regimen or making big dietary adjustments, people with diabetes should get advice from their healthcare providers. Some of the nanoparticles used for various useful application in the body are shown in Fig. 3.

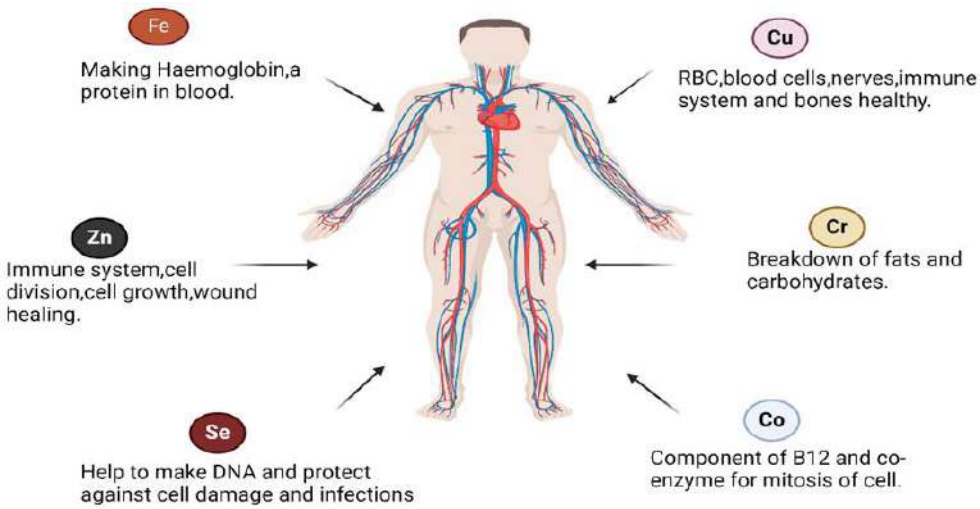


Fig. 3: Application of Nanoparticles for Various Useful Application in the Body

Conclusions

This retrospective study indicates that trace elements play a crucial role in various biological processes, particularly in glucose homeostasis. Among these elements, Se, Zn, and Mg stand out as outstanding microelements for the development of diabetes-combatting nanomedicines. These trace element nanoparticles may possess anti-diabetic properties through direct or indirect reduction of blood glucose levels, enhanced insulin tolerance, and augmented insulin secretion, improved activity of saccharide metabolism enzymes, increased glucose utilization, and restoration of islet β cell function. Moreover, it has been observed that microelement-based nanoparticles can mitigate diabetes-induced chronic microangiopathy, including diabetic nephropathy and retinopathy, by modulating immune responses, reducing inflammation, and ameliorating oxidative stress. In summary, trace element nanoparticles demonstrate promising anti-diabetic characteristics as nanomedicines.

REFERENCES

Abbaspour, N., Hurrell, R., and Kelishadi, R. (2014). Review on iron and its importance for human health. *Journal of research in medical sciences: the official Journal of Isfahan University of Medical Sciences, 19*(2), 164.

Abdali, D., Samson, S. E., and Grover, A. K. (2015). How effective are antioxidant supplements in obesity and diabetes? *Medical Principles and Practice, 24*(3), 201-215.

Aguiar, C., Duarte, R., and Carvalho, D. (2019). New approach to diabetes care: from blood glucose to cardiovascular disease. *Revista Portuguesa de Cardiologia (English Edition), 38*(1), 53-63.

Backe, M. B., Moen, I. W., Ellervik, C., Hansen, J. B., and Mandrup-Poulsen, T. (2016). Iron regulation of pancreatic beta-cell functions and oxidative stress. *Annual Review of Nutrition, 36*, 241-273.

Balaji, R., Duraisamy, R., and Kumar, M. P. (2019). Complications of diabetes mellitus: A review. *Drug Invention Today, 12*(1).

Bjørklund, G., Dadar, M., Pivina, L., Doşa, M. D., Semenova, Y., and Aaseth, J. (2020). The role of zinc and copper in insulin resistance and diabetes mellitus. *Current Medicinal Chemistry, 27*(39), 6643-6657.

Bolli, G. B., Porcellati, F., Lucidi, P., and Fanelli, C. G. (2021). The physiological basis of insulin therapy in people with diabetes mellitus. *Diabetes Research and Clinical Practice, 175*, 108839.

Carey, I. M., Critchley, J. A., DeWilde, S., Harris, T., Hosking, F. J., and Cook, D. G. (2018). Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. *Diabetes care, 41*(3), 513-521.

Chan, J. C. N., Gagliardino, J. J., Ilkova, H., Lavalle, F., Ramachandran, A., Mbanya, J. C., and Aschner, P. (2021). One in seven insulin-treated patients in developing countries reported poor persistence with insulin therapy: Real world evidence from the cross-sectional International Diabetes Management Practices Study (IDMPS). *Advances in Therapy, 38*(6), 3281-3298.

Cole, J. B., and Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature Reviews Nephrology, 16*(7), 377-390.

Collins, K. G., Fitzgerald, G. F., Stanton, C., and Ross, R. P. (2016). Looking beyond the terrestrial: The potential of seaweed derived bioactives to treat non-communicable diseases. *Marine Drugs, 14*(3), 60.

Czech, M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature Medicine, 23*(7), 804-814.

Faisal, S., Jan, H., Abdullah, Alam, I., Rizwan, M., Hussain, Z., and Uddin, M. N. (2022). In vivo analgesic, anti-inflammatory, and anti-diabetic screening of Bacopa monnieri-synthesized copper oxide nanoparticles. *ACS Omega, 7*(5), 4071-4082.

Ghasemi, H. A., and Nari, N. (2020). Effect of supplementary betaine on growth performance, blood biochemical profile, and immune response in heat-stressed broilers fed different dietary protein levels. *Journal of Applied Poultry Research, 29*(2), 301-313.

Godswill, A. G., Somtochukwu, I. V., Ikechukwu, A. O., and Kate, E. C. (2020). Health benefits of micronutrients (vitamins and minerals) and their associated deficiency diseases: A systematic review. *International Journal of Food Sciences, 3*(1), 1-32.

Holtzclaw, B., Kenner, C., and Walden, M. (2018). *Grant writing handbook for nurses and health professionals*: Springer Publishing Company.

Javanshir, R., Honarmand, M., Hosseini, M., and Hemmati, M. (2020). Anti-dyslipidemic properties of green gold nanoparticle: Improvement in oxidative antioxidative balance and associated atherogenicity and insulin resistance. *Clinical Phytoscience, 6*, 1-10.

Jeevanandam, J., K Danquah, M., Debnath, S., S Meka, V., and S Chan, Y. (2015). Opportunities for nano-formulations in type 2 diabetes mellitus treatments. *Current Pharmaceutical Biotechnology, 16*(10), 853-870.

Jomova, K., Makova, M., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., and Valko, M. (2022). Essential metals in health and disease. *Chemico-biological Interactions*, 110173.

Korac, B., Kalezic, A., Pekovic-Vaughan, V., Korac, A., and Jankovic, A. (2021). Redox changes in obesity, metabolic syndrome, and diabetes. *Redox Biology, 42*, 101887.

Kravchenko, V., Ivaskiva, K. Y., Andrusyshyna, I. M., Pankiv, V. I., Khalangot, M. D., Orlenko, V. L., and Vasiuk, V. L. (2023). Assessment of serum calcium, magnesium and zinc levels in patients with type 2 diabetes mellitus in the Ukrainian population. *International Journal of Endocrinology (Ukraine), 19*(7), 505-509.

Lewicki, S., Zdanowski, R., Krzyzowska, M., Lewicka, A., Debski, B., Niemcewicz, M., and Goniewicz, M. (2014). The role of

Chromium III in the organism and its possible use in diabetes and obesity treatment. *Annals of Agricultural and Environmental Medicine, 21*(2).

Lima, J. E. B. F., Moreira, N. C. S., and Sakamoto-Hojo, E. T. (2022). Mechanisms underlying the pathophysiology of type 2 diabetes: From risk factors to oxidative stress, metabolic dysfunction, and hyperglycemia. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 874*, 503437.

Ludwig, D. S., and Ebbeling, C. B. (2018). The carbohydrate-insulin model of obesity: beyond "calories in, calories out". *Jama Internal Medicine, 178*(8), 1098-1103.

Mukhtar, Y., Galalain, A., and Yunusa, U. (2020). A modern overview on diabetes mellitus: a chronic endocrine disorder. *European Journal of Biology, 5*(2), 1-14.

Paez-Mayorga, J., Lukin, I., Emerich, D., de Vos, P., Orive, G., and Grattoni, A. (2022). Emerging strategies for beta cell transplantation to treat diabetes. *Trends in Pharmacological Sciences, 43*(3), 221-233.

Pizzo, F., Mangione, M. R., Librizzi, F., Manno, M., Martorana, V., Noto, R., and Vilasi, S. (2022). The Possible Role of the Type I Chaperonins in Human Insulin Self-Association. *Life, 12*(3), 448.

Porri, D., Biesalski, H. K., Limitone, A., Bertuzzo, L., and Cena, H. (2021). Effect of magnesium supplementation on women's health and well-being. *NFS Journal, 23*, 30-36.

Rajeswari, S., and Swaminathan, S. (2014). Role of copper in health and diseases. *Internationa Journal Current Science, 10*, 94-107.

Ramasubbu, K., Padmanabhan, S., Al-Ghanim, K. A., Nicoletti, M., Govindarajan, M., Sachivkina, N., and Rajeswari, V. D. (2023). Green Synthesis of Copper Oxide Nanoparticles Using Sesbania grandiflora Leaf Extract and Their Evaluation of Anti-Diabetic, Cytotoxic, Anti-Microbial, and Anti-Inflammatory Properties in an In-Vitro Approach. *Fermentation, 9*(4), 332.

Ruan, S., Guo, X., Ren, Y., Cao, G., Xing, H., and Zhang, X. (2023). Nanomedicines based on trace elements for intervention of diabetes mellitus. *Biomedicine and Pharmacotherapy, 168*, 115684.

Shaukat, A., Anwar, H., Mahmood, A., Hussain, G., Rasul, A., Ijaz, M. U., and Ali, A. (2021). Synthesis cum characterization of MgO and MnO nanoparticles and their assessment as antidiabetic and antioxidative agents in diabetic rat model. *Physica B: Condensed Matter, 602*, 412570.

Singh, K. R. B., Nayak, V., Singh, J., Singh, A. K., and Singh, R. P. (2021). Potentialities of bioinspired metal and metal oxide nanoparticles in biomedical sciences. *RSC Advances, 11*(40), 24722-24746.

Skalnaya, M. G., and Skalny, A. V. (2018). Essential trace elements in human health: a physician's view. *Tomsk: Publishing House of Tomsk State University, 224*, 1-222.

Teck, J. (2022). Diabetes-associated comorbidities. *Primary Care: Clinics in Office Practice, 49*(2), 275-286.

Turner, L. V. (2023). The Timing of Walking and Post-Meal Blood Sugar Levels in Adults with Type 1 Diabetes.

Yasmin, I., Khan, W. A., Naz, S., Iqbal, M. W., Awuchi, C. G., Egbuna, C., and Uche, C. Z. (2021). Etiology of obesity, cancer, and diabetes. *Dietary Phytochemicals: A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer and Diabetes*, 1-27.

Yun, B., King, M., Draz, M. S., Kline, T., and Rodriguez-Palacios, A. (2022). Oxidative reactivity across kingdoms in the gut: Host immunity, stressed microbiota and oxidized foods. *Free Radical Biology and Medicine, 178*, 97-110.

Zhu, W., Wei, Z., Han, C., and Weng, X. (2021). Nanomaterials as promising theranostic tools in nanomedicine and their applications in clinical disease diagnosis and treatment. *Nanomaterials, 11*(12), 3346.

Chapter 19

Nano-biotics: An Advanced Approach to Control Biofilm of Antibiotic Resistant ESKAPE Pathogens

Kaleem Ullah[1]*, Rimsha Kanwal[2], Izza[3], Rabia Kanwar[2]*, Muhammad Usman Qaiser[2], Hadia Bilal[4], Abid Ahmad[5], Mushtaq Ahmad[6], Usama Saleem[1] and Sajjad Ahmad[2]

[1]Directorate General (Research) Livestock and Dairy development Department Peshawar, 25000, Khyber Pukhtunkhwa (KPK), Pakistan
[2]Institute of Microbiology, University of Agriculture Faisalabad, 38000, Punjab, Pakistan
[3]University of Veterinary and Animal Sciences Lahore, 52254, Punjab, Pakistan
[4]Department of Plant Breeding and Genetics, University of Agriculture Faisalabad, 38000, Punjab, Pakistan
[5]Department of Animal Nutrition, the University of Agriculture Peshawar, 25000, Khyber Pukhtunkhwa (KPK), Pakistan
[6]Livestock and Dairy Development Department (Extension), Peshawar, Khyber Pakhtunkhwa, Pakistan
*Corresponding author: rabiakanwar98@gmail.com; kaleemaup@gmail.com

ABSTRACT

The rise of anti-microbial resistance in *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* species (ESKAPE) microorganisms present a significant worldwide general well-being risk. The development of biofilms, which is a pivotal component adding to the severity of numerous microbes, deteriorates the trouble of treating infections. Common antibiotics now and again demonstrate inadequate in wiping out biofilms because of their natural components of obstruction. Nano-biotics offer a confident way to deal with tending to infections connected with biofilms in this specific circumstance. Nano-biotics use nanotechnology to make innovative antibacterial substances that can successfully combat biofilm resistance mechanisms. Nano-biotics can enter the biofilm lattice, disrupt bacterial communication, and improve the transport of the antimicrobial medications to bacterial cells. This results in the viable anticipation of biofilm improvement and the elimination of previously existing biofilms. This Chapter features the most current improvements in nano-biotics for controlling the development of biofilms brought about by ESKAPE infections that are resistant to anti-microbials. It additionally discusses different nano-biotic approaches. Moreover, the review makes sense of how the combination of nano-biotics with conventional antibiotics or other therapeutic agents could help antimicrobial effectiveness and lessen the risk of resistance. Also, this chapter talks about the possible difficulties and future paths in the advancement and use of nano-biotics to treat diseases associated with biofilms.

KEYWORDS
Nano-biotics, Biofilm, Antibiotic resistant, ESKAPE, Pathogens

Received: 12-Jun-2024
Revised: 18-Jul-2024
Accepted: 13-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Ullah K, Kanwal R, Izza, Kanwar R, Qaiser MU, Bilal H, Ahmad A, Ahmad M, Saleem U and Ahmad S, 2024. Nano-biotics: An advanced approach to control biofilm of antibiotic resistant ESKAPE pathogens. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 163-171. https://doi.org/10.47278/book.CAM/2024.145

INTRODUCTION

The term "nano biotics" refers to the administration of antibiotics, which are either wrapped in fabricated nanoparticles or that are chemically made and with 100-nm or smaller dimensions. These nano-biotics are designed to deliver modern antimicrobial medication directly to the microorganisms (Lei et al., 2018). The techniques can also be used in treating problems linked to planktonic and multiresistant biofilms (Batalha et al., 2019). Nano biotics is a revolutionary and thrilling way to administer antibiotics. Particles with a minimum diameter of 100 nm may be synthesized as pure antibiotics or in a mix of antibiotics and little particle (Saidykhan et al., 2016; Zhu et al., 2022). Antibacterial compounds are attached to particles. NPs may be chemically pure and have native properties; pure NPs covered with diverse groups of substances synthetically, such as polymers, citrates, and carboxylates (Mamun et al., 2021). Due to an inherent ability to target particular sites, nano-biotics penetrate more exactly and permanently through bacterial defense mechanisms than free antibiotic molecules (Lei et al., 2018). Nature cures might be developed with zinc oxide NPs, nickel, copper (Cu) NPs, titanium dioxide and silver NPs, and selenium lifetimes. However, nanoparticles with antimicrobial characteristics, referred to as "nano-biotics," can also be used to carry antimicrobial medications. In the form of liposomes and dendrimers and polymeric NPs, nano-biotics can be utilized to drug antimicrobials carriers. Nano-biotics become a tool to get drugs to patients through a precisely controlled spatial and temporal drug regimen. It increases the quantity of drugs that reach targeted tissue and pharmaceutical resistance. While nano-biotics also lessen drugstocks are on a downward path, they

sustained hazardous outcomes (Sánchez-López et al., 2020).

Nanoparticles may be a successful transporter for increasing and assisting to enhance the activity of antibiotics. Owing to their small dimensions and a greater source area to weight rate, nanomaterials are distinctive. This offers enhanced touch with germs and application that is controlled and shifts due to their condensed size and greater exterior area to mass rate. The survivability of nanoparticles NPs may be enhanced by altering its sizes, contours, and chemical constitution. By incorporating modified metallic, organic, biomolecular, radioactive, or antibody parts, nanoparticles NPs can efficiently destroy bacteria by a diverse range of approaches (Fig. 1) By including additional traits such as light, ionizing radiation, magnetic fields, and ultrasound, it might be further enhanced (Chakraborty et al., 2022).

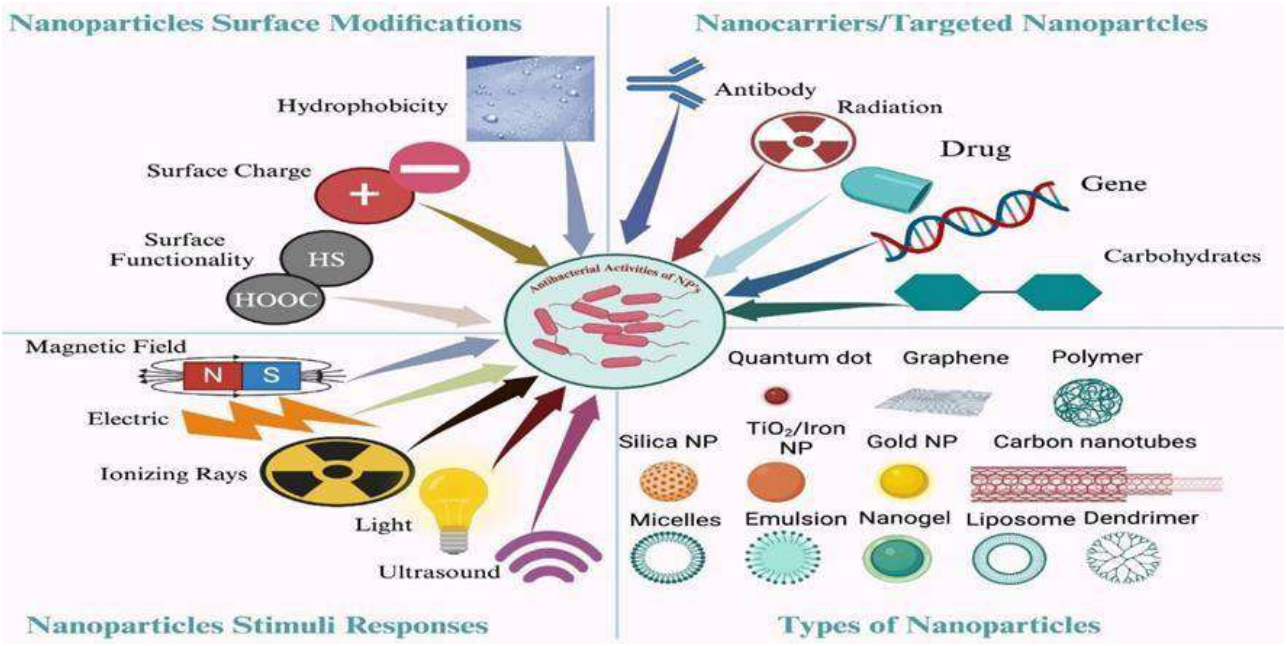


Fig. 1: Nano-biotics against AMR.

ESKAPE Pathogens

Another hurdle to achieving and paying for socialized health care is the challenge of the sustainable development goals. To address the issue of antibiotic resistance, the World Health Organization in 2017 worked out scripts for new therapies and produced a full worldwide list of artificially resistant small organisms (Slavcovici et al., 2015). The usage of reserve preparations to treat illnesses with first-line resistance will be necessary. These medications have a better economic performance and a reduced level of security (Santajit and Indrawattana, 2016). ESKAPE germs is an abbreviation for six multidrug-resistant bacteria that have a substantial impact on hospital-acquired infections/various illness in immunosuppressants. These bacteria have developed ways to evade the germicidal action of pharmaceuticals (Gheorghe et al., 2017). This abbreviation is gotten from *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species belong in the gram -positive and gram-negative bacterial category (Rice, 2010). Based on the results of the multicriteria assessments, the list was divided into groups, medium, high, and critical (Denissen et al., 2022). Critical include *Acinetobacter baumannii* carbapenem-resistant, *Pseudomonas aeruginosa* carbapenem-safe, *Klebsiella pneumoniae* third generation cephalosporin-resistant, *Enterobacter spp*. third-generation cephalosporin-resistant. High classification include *Enterococcus faecium* vancomycin-resistant, *Staphylococcus aureus* methicillin-resistant, vancomycin intermediate and resistant (Pendleton et al., 2013).

Antimicrobial Resistance Mechanisms of ESKAPE Pathogens

The bacterial chromosome, transposon and plasmid act as a carrier of antimicrobial resistance gene (Giedraitiene, et al., 2011). The main causes of antimicrobial resistance are the binding sites of drug modified, inactivation of the drug, formation of biofilm, drug efflux (Wright, 2005).

Vancomycin-Resistant *Enterococci Faecium*

It is deeply troubling that enterococci, and notably vancomycin-resistant *Enterococcus*, are showing alarming rates of antibiotic resistance. (Cencič and Langerholc, 2010), which is primarily concomitant with *E. faecium* (Hope et al., 2008). VRE has a six types (Van A-E, Van-G). Van-A is the most common and has the highest degree of resistance to all glycopeptide antibiotics (Smith, 2004). In 2011, Scientists provided evidence of two distinct clades (A, B) of *E. faecium* that exhibit genetic differences. Both clades exhibit the presence of low-affinity binding proteins for penicillin (referred to as PBP5) that

have a weak binding capacity to β-lactam medicines. Furthermore, clade B has a gene that encodes ampicillin-sensitive PBP5 (pbp5S), whereas clade A possesses numerous resistance genes and virulence determinants due to IS16 and a gene that encodes ampicillin-resistant PBP5 (pbp5R) (Arias and Murray, 2012).

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus infections were effectively treated with penicillin previously. However, the overuse of these antibiotics in 1948 resulted in the appearance of *Staphylococcus* isolates that produce β-lactamase. Penicillin G resistance investigated in 65–85% Staphylococcus clinical isolates (Bush and Bradford, 2013). The primary antibiotics used to treat MRSA infections are glycopeptide antibiotics, such as teicoplanin and vancomycin. (Hryniewicz and Garbacz, 2017).

Klebsiella pneumonia

The β-lactamase enzymes evolved from the Klebsiella pneumoniae strains degrade the β-lactam antibiotics chemical composition such as carbapenems, cephalosporins, penicillins. The rising frequency of *K. pneumoniae* resistant to carbapenem poses substantial issue for clinicians due to the typical use of carbapenems for the treatment of infections (Queenan and Bush, 2007).The *K. pneumoniae* super enzyme, NDM-1 led to a higher number of *K. pneumoniae* isolates that are resistant to carbapenem antibiotics. This might potentially endanger the effectiveness of other antibiotics such fluoroquinolones, aminoglycosides, and β-lactams (Yong et al., 2009). *Acinetobacter baumannii*

There have been recent reports of the appearance of *A. baumannii* strains that produce carbapenemase and contain imipenem metallo-β-lactamases, which are carried by certain genes and blaOXA gene carry oxacillinase serine β-lactamases. Both colistin and imipenem are not effective against these germs, and they are able to resist most conventional antibiotics due to combination of resistance genes.(Vila et al., 2007).

Pseudomonas aeruginosa

Multiple strains of *P. aeruginosa* have inherent reduced susceptibility to various antibacterial drugs, together with a tendency to acquire resistance while undergoing treatment, particularly in strains that are resistant to carbapenems, namely imipenem. *P. aeruginosa* changes the porin structure and synthesize the chromosomal *AmpC* to combat imipenem drug. The lower amount of AmpC enzyme alone do not cause resistance to carbapenem drugs because they have limited ability to break down these drugs. However, when there is an overproduction of *AmpC* enzymes, combined with reduced permeability of the outer membrane porin and/or overexpression of efflux pumps, it contributes to high-level resistance to carbapenem drugs in this pathogen (Elsner et al., 2000). *P. aruginosa* can produce extended-spectrum beta-lactamases (ESBLs), carbapenemases and imipenem metallo-β-lactamases to resist antibiotic mechanisms. The presence of these enzymes results in a significant increase in carbapenem resistance in *P. aeruginosa* isolates. Additionally, it may lead to the development of strains that are resistant to fluoroquinolones, since the same plasmid may carry the mechanisms of resistance for both types of antibiotics (Livermore, 2002).

***Enterobacter spp*.**

Enterobacter microbes species have carbapenemases, like OXA,VIM, KPC, metallo-β-lactamase-1 and Expanded Range Beta-Lactamases (ESBLs) (Castanheira et al., 2011). Besides, it is critical to accomplish steady concealment of *AmpC* β-lactamases and upregulated by genetic mutation in this group of microrganisms. The MDR strains display resistance ta practically all current antimicrobial drugs except colistin and tigecycline (Boucher et al., 2009).

Nanotechnology Applications in Medicine and Antimicrobial Therapy

The area of nanotechnology and the discoveries connected with nanomedicines are broad and envelop a wide range of applications. Nanomedicine has encountered amazing advancement, raised the efficacy of medications, and prompted significant enhancements in healthcare results. It is important to analyze the striking limits of nanotechnology in the field of healthcare (Keskinbora and Jameel, 2018). Because of their small size, nanoparticles have a high surface-to-volume ratio, which permits them to rapidly absorb a lot of drugs as they circulate through the circulation system. Their extraordinary properties originate from their increased surface area, which improves their mechanical, magnetic, optical, and catalytic properties and makes them more reasonable for use in pharmaceutical applications (Huang et al., 2018; Ren et al., 2021). Nanomedicines have been used in gene therapy too. Multiple inquiries have concentrated on the use of viral vectors as potential mechanisms for delivering medicine (Quader et al., 2021).

Nanomedicine is used in many different fields, such as drug delivery, diagnostic and imaging tools, high-performance screening platforms, antimicrobials, vaccine research, wearable technology (Wang et al., 2021). The primary and most significant antibacterial mechanisms of nanoparticles involve the generation of reactive oxygen by photocatalysis. The mechanisms by which reactive oxygen species (Hope et al. 2008) exert their effects include the breakdown of bacterial and cell membranes, disruption of energy transfer, reduction of enzyme activity, and suppression of DNA synthesis (Fig. 2) (Kianfar and Kianfar, 2019).

Mechanism of Action of Nanobiotics against Biofilms

Multiple studies have documented nanoparticles (NPs) ability to reduce biofilms formation caused by various

bacterial pathogens (Ahmed et al., 2016). NPs have an anti-biofilm effect because they can penetrate bacterial cell walls and membranes, interfere with the biofilm's EPS matrix, and disrupt the quorum sensing system (Gupta and Chhibber, 2019) (Sánchez-López et al., 2020). Reactive oxygen species activity of NPs cause membrane damage in the pathogen (Li et al., 2012). Hydrogen peroxide, hydroxyl radicals, and superoxide radicals are produced by ROS mediated oxidative stress. These radicals cause protein degradation and DNA damage leading to cell death of bacteria (Fig. 3) (Chhibber et al., 2017).

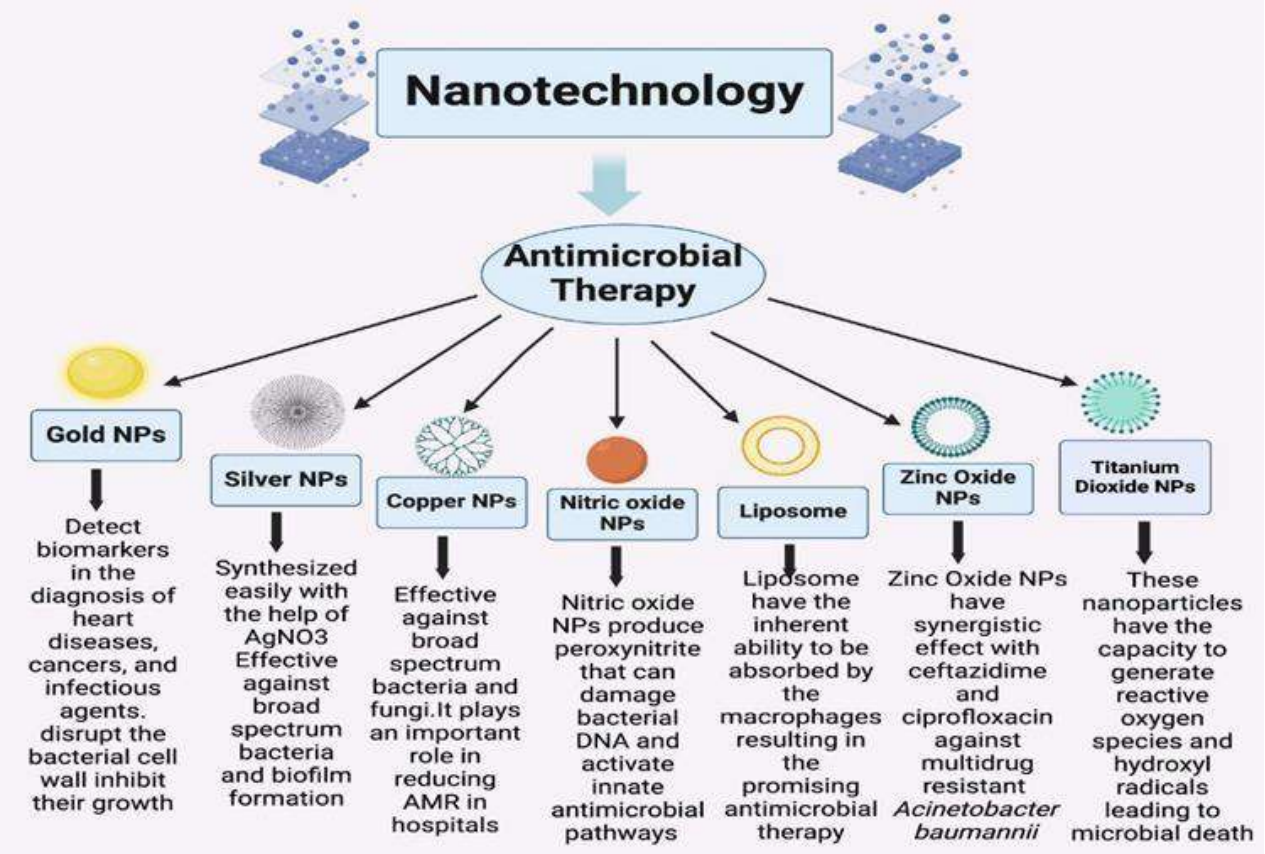


Fig. 2: Applications of Nanotechnology in healthcare

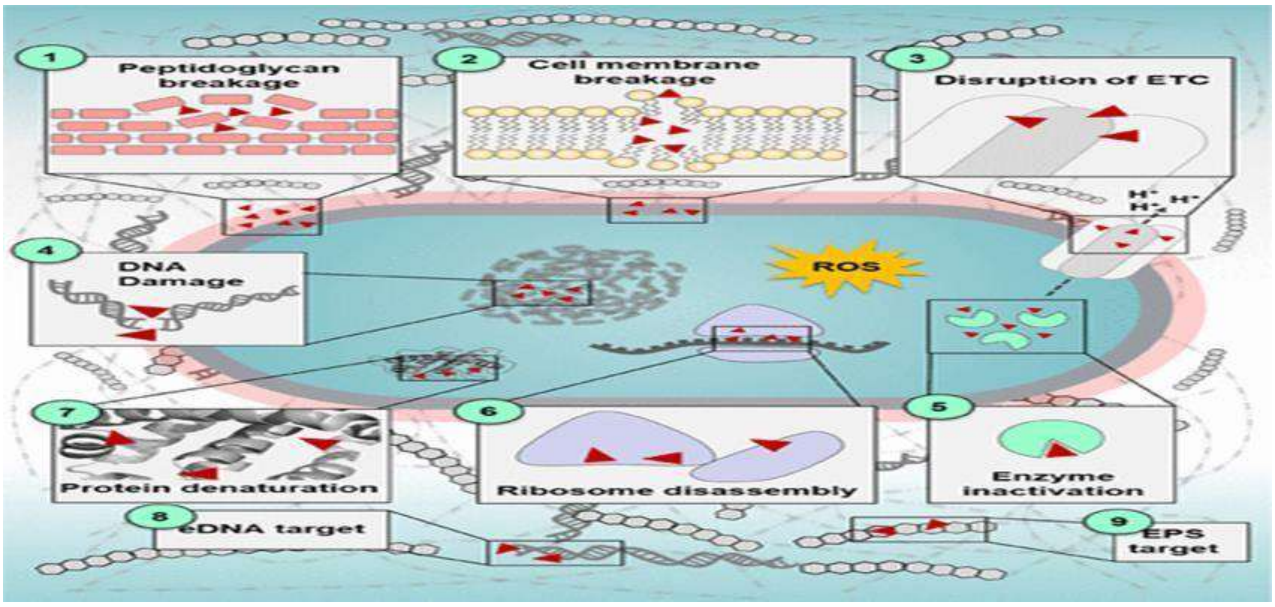


Fig. 3: Antibiofilm Mechanism of Nanoparticles

Synergistic Approaches with Conventional Antibiotics

In recent years, nanotechnology has become a significant area of study with diverse applications across several

sectors. The chemical and physical properties of nanoparticles are influenced by high surface area to volume ratio at nanoscale, resulting in distinct properties compared to bulk matter (Amendola, 2008). The unique characteristics of nanoparticles make them appealing choices for a variety of applications. Silver nanoparticles have been widely studied for their antibacterial ability in very recent times. The growth of bacilli resistance and the dissemination of numerous resistant strains demonstrate an urgent need for such compounds. Given the global resistance of antimicrobial drugs, the utilization of silver nanoparticles as new antimicrobial agents for fighting infections is of particular relevance (Yuan et al., 2017). Recent scientific investigations have shown that combining silver and appropriate antibiotics can improve the antimicrobial properties of the drug against some pathogenic bacteria (Nishanthi et al., 2019). Comprehensive and in-depth studies on the impact of SACs on multidrug-resistant bacteria, particularly ESKAPE pathogens, are lacking The study conducted by (Mishra et al., 2024) explored how SACs combat bacteria like ESKAPE strains found in food sources, like chicken, beef, fish, and sprouts. The research also aimed to know about the antibacterial mechanisms of these SACs. The study examined the use of anti-microbial (SACs) and silver nanoparticles in combination to fight ESKAPE germs using a two-dimensional checkerboard method. The combination of AgNPs and antibiotics kills the multidrug-resistant ESKAPE bacteria more effectively. In both the log stage and the biofilm development stages, the SACs demonstrated antibacterial activity against cells.

Table 1: Nanoparticles characteristics, activity, and mechanism of action against multidrug-resistant (MDR) bacteria

Nanoparticles	Size	Targeted bacteria and antibiotic resistance	Mechanism of action	Factors affecting antimicrobial activity	References
Magnesium Oxide (MgO)	15-100nm	*E. coli, S. aureus*	Alkaline effect, ROS production, lipid peroxidation	Concentration, pH, particle size	(Rudramurthy, et al., 2016)
Titanium Dioxide (TiO_2)	35-45nm	*P. aeruginosa, S. aureus, E. coli, E. faecium*	Surface adsorption, ROS production	Shape, crystal structure, Size	(Hemeg 2017), (Rudramurthy, et al., 2016)
Zinc Oxide (ZnO)	10-100nm	*E. coli, K. pneumoniae, K oxytoca E. aerogenes ,*	Disruption of membrane, ROS production,protein damage, surface adsorption	Concentration and particle size	(Hemeg 2017), (Rudramurthy, et al., 2016)
Iron Oxide	1-100nm	MRSA, *E. coli, K. pneumoniae*	ROS mediated oxidative stress: hydrogn peroxide, hydroxyl, and superoxid radicals	Loss of dispersity and magnetism due to air oxidation, high chemical activity	(Rudramurthy, et al., 2016), (Zaidi et al.,2017)
Aluminium (Al)	10-100nm	*E. coli*	ROS causes disruption in cell wall		(Rudramurthy, et al., 2016)
Silica (Si)	20-400nm	MRSA	ROS cause disruption in cell wall	Shape, stability particle, size	(Zaidi et al.,2017)
Copper (Cu)	2-350nm	*A. baumannii, E. coli*	ROS generation, DNA damage, protein oxidation, lipid peroxidation,	Concentration, particle size	(Zaidi et al.,2017), (Hemeg 2017)
Gold (Au)	1-100nm	MRSA	Membrane damage, ATPase activity reduced, respiratory chain disruption, membrane potential loss	Particle size, roughness,	(Zaidi et al.,2017), (Hemeg 2017)
Silver (Ag)	1-100nm	ESKAPE pathogens	ROS production, DNA, and protein damage, respiratory chain disruption, lipid peroxidation	Shape and size	(Hemeg 2017), (Rudramurthy, et al., 2016)

Several theories have been put out to explain how AgNPs exert their effects (Zhao et al., 2023). AgNPs cause a continuous and persistent ion release when they penetrate bacterial cells, which leads to the consumption of ATP, condensation of DNA, generation of ROS, and eventual death. While the specific process via which the antibacterial effectiveness of SACs is enhanced remains unclear, earlier studies indicate that the presence of silver nanoparticles in SACs results in a more confined release of Ag+ ions, which leads to the destruction of bacterial cells. Silver ions produced are harmful since they interact with and damage cell wall proteins of bacteriaa and DNA, resulting in cell death (Deng et al., 2016). A different investigation on the pharmacodynamic interaction between AgNPs and antibiotics suggested that the combinations impair the bacterial membrane, enhance K+ ion release, and prevent biofilm formation (Thirumurugan et al., 2016). Similarly, further research revealed that antibiotics and AgNPs together have been shown to have combined effects against *P. aeruginosa, S. aureus,* and *E. coli.* (Saha et al., 2007). Furthermore, at doses much below the minimum inhibitory concentration (MIC) of either the nanoparticle or antibiotic component of the combination, AgNPs coupled with antibiotics demonstrated increased antibacterial efficacy against multi resistant, β-lactamase and carbapenemase-producing Enterobacteriaceae (Panáček et al., 2015). Saha et al. describe on the direct attachment of ampicillin, streptomycin, and kanamycin to gold nanoparticles (Saha et al., 2007). The complexes obtained exhibited a reduced minimum inhibitory concentration (MIC) compared to the free drug equivalents when tested against both Gram-negative and Gram-positive

bacteria. The authors of the study did not provide a detailed explanation of the mechanism behind these effects. However, Fayaz et al. conducted research to understand how their gold nanoparticles functionalized with vancomycin showed activity against strains that are typically resistant to vancomycin due to either mutations (vancomycin resistant *S. aureus*) or membrane structure (*E. coli*) (Fayaz et al., 2011). The proposal suggests that the antibiotic can only lead to nonspecific, multivalent contacts and attachment of the carrier to the cell wall synthesis proteins when it is complexed with the NPs. The scientists deduced that the weakened integrity of the cell membrane and the resulting cell death were the consequences of non-specific binding, as detected using transmission electron microscopy, due to the existence of pits in the cells (Gao et al., 2018). Gold nanoparticles (NPs) have been shown to exhibit synergistic effects when used in conjunction with several antibiotics against susceptible bacteria, including both Gram-negative and Gram-positive bacteria. An example of notable synergy is shown when gold nanoparticles are used with meropenem to combat Acinetobacter baumannii (Shaker and Shaaban, 2017) while amoxicillin and streptomycin show similar effects against Staphylococcus aureus and Escherichia coli. These effects were seen at concentrations of gold ranging from 1 to 16 mg L−1. For bismuth nanoparticles (NPs), the assessment of synergistic effects has been evaluated using antibiotics that hinder the production of nucleic acids, namely fluoroquinolones. Only the combination of ciprofloxacin and bismuth NPs demonstrated an increase in antibacterial efficacy against Klebsiella pneumoniae (Tarjoman et al., 2015). Zinc oxide nanoparticles (NPs) at concentrations ranging from 30 to 80 mg L−1 have been synergistically combined with fluoroquinolones (norfloxacin, ofloxacin) (Namasivayam et al., 2015) or β-lactams (cephalexin, ceftriaxone, cefotaxime) (Bhande et al., 2013) to significantly augment their efficacy against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria. Research has investigated the use of Titanium dioxide nanoparticles (NPs) as an antibacterial agent in conjunction with streptomycin. The results have shown enhanced antibacterial effects against *Klebsiella pneumoniae, Salmonella typhimurium, Escherichia coli, and Staphylococcus aureus.*

Novel Nanomaterials and their Applications

Nanomaterials have been developed and examined to inhibit biofilm formation. There are two main categories into which they fall:

(i) Natural NPs encompass various types, such as solid lipid NPs, cyclodextrins, dendrimers, liposomes, and polymeric NPs.

(ii) Inorganic NPs such as quantum dots, fullerene, organic-inorganic hybrid, metallic (gold, silver, silica, copper, and iron) and their oxides (aluminium and iron oxides).

The bactericidal activity can be attributed to the characteristics of the nanomaterial or nanocarrier. Some enable the encapsulation of a medicine, shielding it from enzymatic inactivation, unfavorable environmental conditions (low pH or oxygen), bacterial defense mechanisms (Prateeksha et al., 2019; Singh et al., 2021).

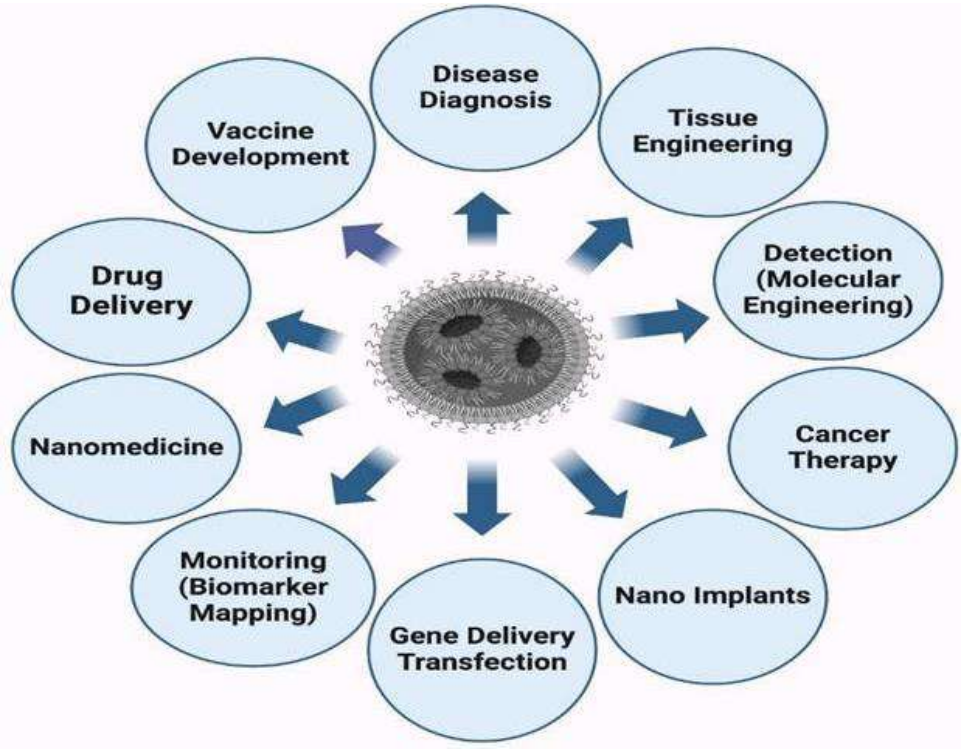


Fig. 4: Antibiofilm activity of nanomaterials

To investigate the capability of gold nanoparticles (AuNPs) to prevent the formation of biofilms, gold nanorods (AuNRs) were modified with a polymer called polymethacrylate. This polymer has carboxyl betaine groups and can vary its surface charge in response to near-infrared (Mamun et al.) Light and changes in pH. The reversible addition-fragmentation chain transfer polymerization (RAFT) reaction was used for the modification of the AuNRs. All the planktonic cells were killed off due to the charge fluctuations of pH responsive. Photothermal near-infrared (Mamun et al.) Irradiation induces localized overheating, resulting in the demise of *S. aureus* bacteria and subsequent disintegration of biofilm (Qiao et al.,

2020). The scientist examined a developed formulation of solid-lipid nanoparticles loaded with silver sulfadiazine (SSD-SLNs) which enhanced its efficacy in treating burn wounds associated with *P. aeruginosa* biofilm by incorporating DNase-I and chitosan gel. The vulnerability of *P. aeruginosa* biofilms to antibiotics enhanced due to DNase- I which breaking down the extracellular DNA (eDNA), resulting in the eradication of the biofilm. After 72 hours, Pure SSD and SSD-SLN could eliminate only 58.1% and 78.7% of the biofilm, respectively. The incorporation of DNase I into SSD-SLN inhibited 96.8% biofilm formation of *P. aeruginosa*. The SSD-SLNs and DNase-I synergism healed the wound completely within 21 days according to in-vivo study (Patel et al., 2019).

The silver NPs synthesis functionalized with α-Amylase (biofilm-disrupting enzyme) and polydopamine (DA) for inhibiting the growth of *S. aureus* biofilms on titanium surfaces (Tran, et al., 2021). A1 (Serpin), an elastase inhibitor, and LL37 (the endogenous host defense peptide) are administered topically by nanomedicine to treat chronic wounds by regulating their sustained release. The co-administration of A1 and LL37 successfully healed the injury in BJ fibroblast cells and keratinocytes, eliminated microbial contamination, suppressed E. coli and *S. aureus* biofilm development, and improved anti-inflammatory action (Fumakia, et al., 2016). The researchers developed a formulation of ofloxacin-loaded solid lipid nanoparticles (SLN) to treat *S. aureus* and *P. aeruginosa* biofilm related-pulmonary infections. This formulation exhibited selectivity and supported the arrival of the medication at the targeted spot, and increased effectiveness. The nano composite diminished threefold minimum inhibitory concentration (MIC) when compared with free antibiotics (Rodenak-Kladniew et al., 2019). As indicated by another study, oxacillin-loaded nanostructured lipid carriers (NLC) formulation upgrades the adequacy of oxacillin against MRSA (Alalaiwe et al., 2018).

Challenges and Future Perspectives

The formation of biofilms by ESKAPE infections has become challenging to treat because of the ineffectiveness of traditional treatments. The limited effectiveness of antimicrobials in biofilms is mostly attributed to their low penetration, enzymatic inactivation, and destruction inside the biofilm microenvironment. Nanotechnology become new and successful approach for treating bacterial biofilms with precision. Nanomaterials may effectively penetrate biofilm EPS matrix becauseof their minute size. This allows them to eradicate the sessile and persister cells due to their inherent antimicrobial properties and/or by administering therapeutic agents. Nanoparticles impede and disrupt the development of biofilms by compelling with the quorum sensing (QS) pathway and degrading extracellular polymeric substances and extracellular DNA (eDNA). Despite many benefits of nanotechnology, it is not without limitations. These include cytotoxicity, impacts on metabolism, inadequate renal clearance, and aggregation in the blood and protein cells, which might affect human health. The metal ions from waste nanoparticles also develop harmful effects in the body. Moreover, overcoming biological obstacles and evading immunity to accomplish precise delivery pose major challenges. It is necessary to identify and address the unknown adverse effects and costly clinical studies. To develop suitable antimicrobial nanomaterials, it is essential to have accurate in vivo and in vitro models that specifically address biocompatibility, antibiofouling, antibacterial, and nanotoxicology properties. To advance the clinical development of nanomaterials, it is mandatory to conduct a comprehensive investigation on basic, pharmacological, and biological characteristics of nanoparticles, as well astheir interactions with pathogens. Future work has the potential to solve all these limitations of nanomaterials. Thus, we conclude that Nano biotics offer a promising solution for addressing ESKAPE pathogens. This is achieved through the administration of therapeutics at sub-inhibitory doses and employing multiple bactericidal pathways to eliminate bacteria.

REFERENCES

Ahmed, K. B. A., Raman, T., and Veerappan, A. (2016). Future prospects of antibacterial metal nanoparticles as enzyme inhibitor. *Materials Science and Engineering: C*, *68*, 939-947.

Alalaiwe, A., Wang, P.-W., Lu, P.-L., Chen, Y.-P., Fang, J.-Y., & Yang, S.-C. (2018). Synergistic anti-MRSA activity of cationic nanostructured lipid carriers in combination with oxacillin for cutaneous application. *Frontiers in microbiology*, *9*, 1493.

Arias, C. A., and Murray, B. E. (2012). The rise of the Enterococcus: beyond vancomycin resistance. *Nature Reviews Microbiology*, *10*(4), 266-278.

Amendola, V. (2008). Synthesis of gold and silver nanoparticles for photonic applications.

Batalha, I. L., Bernut, A., Schiebler, M., Ouberai, M. M., Passemar, C., Klapholz, C., Kinna, S., Michel, S., Sader, K., and Castro-Hartmann, P. (2019). Polymeric nanobiotics as a novel treatment for mycobacterial infections. *Journal of Controlled Release*, *314*, 116-124.

Bhande, R. M., Khobragade, C., Mane, R., and Bhande, S. (2013). Enhanced synergism of antibiotics with zinc oxide nanoparticles against extended spectrum β-lactamase producers implicated in urinary tract infections. *Journal of Nanoparticle Research*, *15*, 1-13.

Bush, K., and Bradford, P.A., (2013). Epidemiology of β-Lactamase-Producing Pathogens. *Clin Microbiology Review* Feb 26;33(2):e00047-19.

Boucher, H. W., Talbot, G. H., Bradley, J. S., Edwards, J. E., Gilbert, D., Rice, L. B., Scheld, M., Spellberg, B., and Bartlett, J. (2009). Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *48*(1), 1-12.

Castanheira, M., Deshpande, L. M., Mathai, D., Bell, J. M., Jones, R. N., and Mendes, R. E. (2011). Early dissemination of NDM-1-and OXA-181-producing Enterobacteriaceae in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006-2007. *Antimicrobial Agents and Chemotherapy*, *55*(3), 1274-1278.

Cencič, A., and Langerholc, T. (2010). Functional cell models of the gut and their applications in food microbiology—a review. *International Journal of Food Microbiology*, *141*, S4-S14.

Chakraborty, N., Jha, D., Roy, I., Kumar, P., Gaurav, S. S., Marimuthu, K., Ng, O.-T., Lakshminarayanan, R., Verma, N. K., and Gautam, H. K. (2022). Nanobiotics against antimicrobial resistance: harnessing the power of nanoscale materials and technologies. *Journal of Nanobiotechnology*, *20*(1), 375.

Chhibber, S., Gondil, V. S., and Wangoo, N. (2017). A novel approach for combating Klebsiella pneumoniae biofilm using histidine functionalized silver nanoparticles. *Frontiers in Microbiology*, *8*, 261401.

Deng, H., McShan, D., Zhang, Y., Sinha, S. S., Arslan, Z., Ray, P. C., and Yu, H. (2016). Mechanistic study of the synergistic antibacterial activity of combined silver nanoparticles and common antibiotics. *Environmental Science and Technology*, *50*(16), 8840-8848.

Denissen, J., Reyneke, B., Waso-Reyneke, M., Havenga, B., Barnard, T., Khan, S., and Khan, W. (2022). Prevalence of ESKAPE pathogens in the environment: Antibiotic resistance status, community-acquired infection and risk to human health. *International Journal of Hygiene and Environmental Health*, *244*, 114006.

Fumakia, M., & Ho, E. A. (2016). Nanoparticles encapsulated with LL37 and serpin A1 promotes wound healing and synergistically enhances antibacterial activity. *Molecular Pharmaceutics*, *13*(7), 2318-2331.

Elsner, H.-A., Sobottka, I., Mack, D., Laufs, R., Claussen, M., and Wirth, R. (2000). Virulence factors of Enterococcus faecalis and Enterococcus faecium blood culture isolates. *European Journal of Clinical Microbiology and Infectious Diseases*, *19*, 39-42.

Fayaz, A. M., Girilal, M., Mahdy, S. A., Somsundar, S., Venkatesan, R., and Kalaichelvan, P. (2011). Vancomycin bound biogenic gold nanoparticles: a different perspective for development of anti VRSA agents. *Process Biochemistry*, *46*(3), 636-641.

Gao, W., Chen, Y., Zhang, Y., Zhang, Q., and Zhang, L. (2018). Nanoparticle-based local antimicrobial drug delivery.
Advanced Drug Delivery Reviews, *127*, 46-57.

Gheorghe, I., Tatu, A. L., Lupu, I., Thamer, O., Cotar, A. I., Pircalabioru, G. G., Popa, M., Cristea, V. C., Lazar, V., and Chifiriuc,
M. C. (2017). Molecular characterization of virulence and resistance features in Staphylococcus aureus clinical strains isolated from cutaneous lesions in patients with drug adverse reactions. *Rom Biotechnology Letter*, *22*(1), 12321-12327.

Gupta, K., and Chhibber, S. (2019). Biofunctionalization of silver nanoparticles with lactonase leads to altered antimicrobial and cytotoxic properties. *Frontiers in Molecular Biosciences*, *6*, 63.

Giedraitienė, A., Vitkauskienė, A., Naginienė, R., & Pavilonis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina*, *47*(3), 19.

Hope, R., Livermore, D. M., Brick, G., Lillie, M., and Reynolds, R. (2008). Non-susceptibility trends among staphylococci from bacteraemias in the UK and Ireland, 2001–06. *Journal of Antimicrobial Chemotherapy*, *62*(suppl_2), ii65-ii74.

Hryniewicz, M. M., and Garbacz, K. (2017). Borderline oxacillin-resistant Staphylococcus aureus (BORSA)–a more common problem than expected? *Journal of Medical Microbiology*, *66*(10), 1367-1373.

Hemeg, H. A. (2017). Nanomaterials for alternative antibacterial therapy. *International Journal of Nanomedicine*, 8211-8225.

Huang, B., Chen, F., Shen, Y., Qian, K., Wang, Y., Sun, C., Zhao, X., Cui, B., Gao, F., and Zeng, Z. (2018). Advances in targeted pesticides with environmentally responsive controlled release by nanotechnology. *Nanomaterials*, *8*(2), 102.

Keskinbora, K., and Jameel, M. A. (2018). Nanotechnology applications and approaches in medicine: a review. *Journal Nanoscience Nanotechnology Research*, *2*(2), 6.

Kianfar, F., and Kianfar, E. (2019). Synthesis of isophthalic acid/aluminum nitrate thin film nanocomposite membrane for hard water softening. *Journal of Inorganic and Organometallic Polymers and Materials*, *29*, 2176-2185.

Lei, R., Hou, J., Chen, Q., Yuan, W., Cheng, B., Sun, Y., Jin, Y., Ge, L., Ben-Sasson, S. A., and Chen, J. (2018). Self-assembling myristoylated human α-defensin 5 as a next-generation nanobiotics potentiates therapeutic efficacy in bacterial infection. *ACS nano*, *12*(6), 5284-5296.

Li, Y., Zhang, W., Niu, J., and Chen, Y. (2012). Mechanism of photogenerated reactive oxygen species and correlation with the antibacterial properties of engineered metal-oxide nanoparticles. *ACS nano*, *6*(6), 5164-5173.

Livermore, D. M. (2002). Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: our worst nightmare? *Clinical Infectious Diseases*, *34*(5), 634-640.

Mamun, M. M., Sorinolu, A. J., Munir, M., and Vejerano, E. P. (2021). Nanoantibiotics: Functions and properties at the nanoscale to combat antibiotic resistance. *Frontiers in Chemistry*, *9*, 687660.

Mishra, M., Ballal, A., Rath, D., and Rath, A. (2024). Novel Silver Nanoparticle-Antibiotic Combinations as Promising Antibacterial and Anti-biofilm Candidates against Multiple-Antibiotic Resistant ESKAPE Microorganisms. *Colloids and Surfaces B: Biointerfaces*, 113826.

Namasivayam, S. K. R., Prasanna, M., and Subathra, S. (2015). Synergistic antibacterial activity of zinc oxide nanoparticles with antibiotics against the human pathogenic bacteria. *Journal of Chemical and Pharmaceutical Research*, *7*(3), 133-138.

Nishanthi, R., Malathi, S., and Palani, P. (2019). Green synthesis and characterization of bioinspired silver, gold and platinum nanoparticles and evaluation of their synergistic antibacterial activity after combining with different classes of antibiotics. *Materials Science and Engineering: C*, *96*, 693-707.

Panáček, A., Smékalová, M., Kilianová, M., Prucek, R., Bogdanová, K., Večeřová, R., Kolář, M., Havrdová, M., Płaza, G. A., and Chojniak, J. (2015). Strong and nonspecific synergistic antibacterial efficiency of antibiotics combined with silver nanoparticles at very low concentrations showing no cytotoxic effect. *Molecules*, *21*(1), 26.

Patel, M., Mazumder, R., Mishra, R., & Kant Kaushik, K. (2022). Potential of Nanotechnology-based Formulations in Combating Pulmonary Infectious Diseases: A Current Scenario. *Curr Pharm Des*, *28*(42), 3413-3427.

Pendleton, J. N., Gorman, S. P., and Gilmore, B. F. (2013). Clinical relevance of the ESKAPE pathogens. *Expert Review of Anti-infective Therapy*, *11*(3), 297-308.

Prateeksha, Barik, S. K., and Singh, B. N. (2019). Nanoemulsion-loaded hydrogel coatings for inhibition of bacterial virulence and biofilm formation on solid surfaces. *Scientific Reports*, *9*(1), 6520.

Quader, S., Liu, X., Toh, K., Su, Y.-L., Maity, A. R., Tao, A., Paraiso, W. K. D., Mochida, Y., Kinoh, H., and Cabral, H. (2021). Supramolecularly enabled pH-triggered drug action at tumor microenvironment potentiates nanomedicine efficacy against glioblastoma. *Biomaterials*, *267*, 120463.

Qiao, J., Zheng, L., Lu, Z., Meng, F., & Bie, X. (2021). Research on the biofilm formation of Staphylococcus aureus after cold stress. *Microorganisms*, *9*(7), 1534.

Queenan, A. M., and Bush, K. (2007). Carbapenemases: the versatile β-lactamases. *Clinical Microbiology Reviews*, *20*(3), 440-458.

Rudramurthy, G. R., Swamy, M. K., Sinniah, U. R., & Ghasemzadeh, A. (2016). Nanoparticles: alternatives against drug-resistant pathogenic microbes. *Molecules*, *21*(7), 836.

Ren, C., Wang, Z., Zhang, X., Gao, J., Gao, Y., Zhang, Y., Liu, J., Yang, C., and Liu, J. (2021). Construction of all-in-one peptide nanomedicine with photoacoustic imaging guided mild hyperthermia for enhanced cancer chemotherapy. *Chemical Engineering Journal*, *405*, 127008.

Rice, L. B. (2010). Progress and challenges in implementing the research on ESKAPE pathogens. *Infection Control and Hospital Epidemiology*, *31*(S1), S7-S10.

Rodenak-Kladniew, B., Montoto, S. S., Sbaraglini, M. L., Di Ianni, M., Ruiz, M. E., Talevi, A., Alvarez, V. A., Durán, N., Castro, G. R., & Islan, G. A. (2019). Hybrid Ofloxacin/eugenol co-loaded solid lipid nanoparticles with enhanced and targetable antimicrobial properties. *International journal of pharmaceutics*, *569*, 118575.

Saha, B., Bhattacharya, J., Mukherjee, A., Ghosh, A., Santra, C., Dasgupta, A. K., and Karmakar, P. (2007). In vitro structural and functional evaluation of gold nanoparticles conjugated antibiotics. *Nanoscale Research Letters*, *2*, 614-622.

Saidykhan, L., Abu Bakar, M. Z. B., Rukayadi, Y., Kura, A. U., and Latifah, S. Y. (2016). Development of nanoantibiotic delivery system using cockle shell-derived aragonite nanoparticles for treatment of osteomyelitis. *International Journal of Nanomedicine*, 661-673.

Sánchez-López, E., Gomes, D., Esteruelas, G., Bonilla, L., Lopez-Machado, A. L., Galindo, R., Cano, A., Espina, M., Ettcheto, M., and Camins, A. (2020). Metal-based nanoparticles as antimicrobial agents: an overview. *Nanomaterials*, *10*(2), 292.

Santajit, S., and Indrawattana, N. (2016). Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed Research International*, *2016*.

Shaker, M. A., and Shaaban, M. I. (2017). Formulation of carbapenems loaded gold nanoparticles to combat multi-antibiotic bacterial resistance: In vitro antibacterial study. *International Journal of Pharmaceutics*, *525*(1), 71-84.

Singh, P., Pandit, S., Jers, C., Joshi, A. S., Garnæs, J., and Mijakovic, I. (2021). Silver nanoparticles produced from Cedecea sp. exhibit antibiofilm activity and remarkable stability. *Scientific Reports*, *11*(1), 12619.

Slavcovici, A., Maier, C., and Radulescu, A. (2015). Antimicrobial resistance of ESKAPE-pathogens in culture-positive pneumonia. *Farmacia*, *63*(2), 201-205.

Smith, A. (2004). Bacterial resistance to antibiotics. *Hugo and Russell's Pharmaceutical Microbiology*, 220-232.

Tarjoman, Z., Ganji, S. M., and Mehrabian, S. (2015). Synergistic effects of the bismuth nanoparticles along with antibiotics on PKS positive Klebsiella pneumoniae isolates from colorectal cancer patients; comparison with quinolone antibiotics. *Research Journal Medicine Medicine Science*, *3*, 387-393.

Tran, M.-T., Nguyen, L.-P., Nguyen, D.-T., Le Cam-Huong, T., Dang, C.-H., Chi, T. T. K., & Nguyen, T.-D. (2021). A novel approach using plant embryos for green synthesis of silver nanoparticles as antibacterial and catalytic agent. *Research on Chemical Intermediates*, *47*, 4613-4633.

Thirumurugan, G., Seshagiri Rao, J., and Dhanaraju, M. (2016). Elucidating pharmacodynamic interaction of silver nanoparticle-topical deliverable antibiotics. *Scientific Reports*, *6*(1), 29982.

Vila, J., Martí, S., and Sanchez-Céspedes, J. (2007). Porins, efflux pumps and multidrug resistance in Acinetobacter baumannii. *Journal of Antimicrobial Chemotherapy*, *59*(6), 1210-1215.

Wang, W., Jin, Y., Liu, X., Chen, F., Zheng, X., Liu, T., Yang, Y., and Yu, H. (2021). Endogenous stimuli-activatable nanomedicine for immune theranostics for cancer. *Advanced Functional Materials*, *31*(26), 2100386.

Wright, G. D. (2005). Bacterial resistance to antibiotics: enzymatic degradation and modification. *Advanced Drug Delivery Reviews*, *57*(10), 1451-1470.

Yong, D., Toleman, M. A., Giske, C. G., Cho, H. S., Sundman, K., Lee, K., and Walsh, T. R. (2009). Characterization of a new metallo-β-lactamase gene, bla NDM-1, and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. *Antimicrobial Agents and Chemotherapy*, *53*(12), 5046-5054.

Yuan, Y.-G., Peng, Q.-L., and Gurunathan, S. (2017). Effects of silver nanoparticles on multiple drug-resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa from mastitis-infected goats: an alternative approach for antimicrobial therapy. *International Journal of Molecular Sciences*, *18*(3), 569.

Zaidi, A. A., RuiZhe, F., Shi, Y., Khan, S. Z., & Mushtaq, K. (2018). Nanoparticles augmentation on biogas yield from microalgal biomass anaerobic digestion. *International Journal of Hydrogen Energy*, *43*(31), 14202-14213.

Zhao, X., Qiu, H., Shao, Y., Wang, P., Yu, S., Li, H., Zhou, Y., Zhou, Z., Ma, L., and Tan, C. (2023). Silver nanoparticle-modified 2D MOF nanosheets for photothermally enhanced silver ion release antibacterial treatment. *Acta phys.-chim. Sin*, *39*(7), 221104.

Zhu, H., Wen, Q., Bhangu, S. K., Ashokkumar, M., and Cavalieri, F. (2022). Sonosynthesis of nanobiotics with antimicrobial and antioxidant properties. *Ultrasonics Sonochemistry*, *86*, 106029.

Chapter 20

Low Molecular Weight Hyaluronic Acid Fe_3O_4 Nanoparticles: Biological Assessment of Their Ability to Target Breast Cancer Cells

Zainab Shahid*[1], Zaib un-Nisa[1], Muhammad Zafran[1], Tanziha Zualfiqar[2], Orba Maan[2], Muqadas Fatima[1], Baby Hooria Azam[1], Aneela Nazir[2], Noor ul Huda[3] and Dilshad Fatima[1].

[1]Department of Zoology, Faculty of Life Sciences, Government College University, Faisalabad, Pakistan
[2]Department of Zoology Faculty of Sciences, University of Agriculture, Faisalabad, Pakistan
[3]Department of Chemistry, Faculty of Physical Sciences, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: Zainabsha58@gmail.com

ABSTRACT

This study involved superparamagnetic Fe_3O_4 nanoparticles (Fe_3O_4 NPs) with low-molecular-weight hyaluronic acid (LMWHA). A comprehensive analysis was conducted on the size distribution, zeta potential, viscosity, thermogravimetric, and paramagnetic characteristics of LMWHA-Fe_3O_4 nanoparticles. The MCF7 breast cancer cell line was used for cellular experiments. In addition, the researchers employed the thiocyanate method and time-of-flight secondary ion mass spectrometry (TOF-SIMS) to analyze the properties and ability of LMWHA-Fe_3O_4 NPs to target MCF7 breast cancer cells. The experiment revealed that the LMWHA-Fe_3O_4 NPs had a prominent superparamagnetic property and may be easily injected due to their low viscosity. Furthermore, the outcomes of the in vitro experiment revealed that the nanoparticles exhibited a strong capacity to specifically target cancer cells while exhibiting minimal damage. The results suggest that LMWHA-Fe_3O_4 nanoparticles show potential as an injectable drug for enhancing magnetic resonance imaging (MRI) and treatment of hyperthermia in breast cancer.

KEYWORDS
Iron Oxide, Nanoparticles, Hyaluronic Acid, Alternatives, Breast Cancer

Received: 05-Jun-2024
Revised: 11-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Shahid Z, Nisa ZU, Zafran M, Zualfiqar T, Maan O, Fatima M, Azam BH, Nazir A, Huda NU and Fatima D, 2024. Low molecular weight hyaluronic acid fe3o4 nanoparticles: biological assessment of their ability to target breast cancer cells. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 172-179. https://doi.org/10.47278/book.CAM/2024.298

INTRODUCTION

Cancer comprises a group of diseases described by uncontrolled cell proliferation, with the capacity for these aberrant cells to infiltrate and spread to other body regions. Classification of cancer is based on tumor cells that is classified that include, carcinoma, sarcoma, lymphoma, and germ cell tumors. Carcinoma specifically refers to malignancies that originate from epithelial cells and include a wide range of tumors such as breast, prostate, lung, pancreatic, and colon cancers (Varricho, 2004). Cancer is a hereditary illness linked to unchecked cell division and inhibition of cell death (Yahya and Alqadhi, 2021).

Around 9.6 million deaths worldwide are attributed to cancer, which is still the leading cause of mortality due to cancer, due to a lack of efficient early detection techniques (Miranda et al., 2020). In 2018, 2 million new cases of breast cancer (BC) were identified, making it the most common invasive malignancy diagnosed in women worldwide (Mirza et al., 2021). However, it is thought to be curable if detected early, particularly before metastasis (Liyanage et al., 2019).

In consideration of the adverse effects that different types of cancer cause, skin, and lung cancer rank as the most prevalent cancers globally. Furthermore, BC is the most frequent type of cancer in women, making up over 30% of all cancer occurrences (Liyanage et al., 2019). On the contrary, BC in men constitutes merely 1% of all malignant breast neoplasms (Fentiman et al., 2006). Additionally, in comparison to women, men typically receive a diagnosis of BC at a more advanced age, around 67 years (Medeira et al., 2011). Despite being the most prevalent type of cancer in women, if detected early enough, it is thought to be curable (Keivit et al., 2015; Seigel et al., 2017).

Like other cancers, breast cancer is traditionally treated with surgery, chemotherapy, and radiation. These treatments' main objective is to remove tumors while extending the patients' lives. However, advanced and metastatic cancers pose a challenge to these standard approaches in terms of medication resistance and tumor recurrence. For example, when a tumor recurs and spreads to other organs such as the liver, lung, and bone, surgery is ineffective. In contrast,

chemotherapy aims to utilize cytotoxic chemotherapeutic drugs, administered either after or independently of surgery, to impede the division and growth of tumor cells. Radiotherapy, on the other hand, entails the delivery of potent energy waves to disrupt tumor cell division, leading to the reduction or elimination of tumors. While both chemotherapy and radiotherapy are potent cancer treatment methods designed to enhance survival rates, they may also result in acute and long-term adverse effects on the healthy organs of patients (Thati et al., 2010; Dao et al., 2012). For example, a drug known as a monoclonal antibody used in cancer treatment has demonstrated toxicity assistance with cardiac dysfunction when administered over a long period (Zeglinski et al., 2011).

Breast cancer is usually a result of malignant breast cells spreading out of control (Barzaman et al., 2020). The most common cancer in women, breast cancer requires special care because it does not respond well to standard treatment (Miller et al., 2019). Breast cancer can be treated in a variety of ways, with several side effects, such as surgery, chemotherapy, radiation, and hormone treatment (Valencia et al., 2017; Waks and Winer, 2019). Limiting the toxicity of medications to normal cells by specifically targeting them is the optimum approach to treating cancer (Klochkov et al., 2021).

Furthermore, it is difficult to deal with the overexpression of certain proteins in tumor cells that leads to multidrug resistance. In this situation, the impact of chemotherapy is frequently significantly diminished. Radiation therapy is a type of local therapy that solely targets the tumor's exact site. However, because of the harm done to the nearby healthy tissues, adverse consequences might happen. Given the negative effects of traditional cancer treatment methods, it is imperative to look for new and effective alternatives.

Nanoparticles

According to the International Union of Pure and Applied Chemistry, nanoparticles (NPs) are tiny particles with dimensions between 1 to 100 nm (Batista et al., 2015; Kantoff et al., 2017). These particles are suitable for materials science and biology because of their unique physical characteristics, which include conductivity, stability, and optical qualities. Nanoparticles exhibit effectiveness across various fields, including medicine, pharmacy, and many others like environmental science, energy, electronics, and biomolecules (Kausar et al., 2023). This is attributed to their versatile applications in optical, biological, and electronic domains, showcasing their wide-ranging impact. They are categorized into many groups according to their characteristics, dimensions, and forms (Khan et al., 2019).

Targeted therapies stand out as the most efficient treatments for common cancers, surpassing other modalities like conventional chemotherapy. They offer advantages such as reduced side effects, enhanced viability, lower dosage needs, fewer adverse reactions, improved therapeutic indicators, and more precise, specific treatment goals (Senapati et al., 2018). Recent studies indicate that nanoparticles provide numerous advantages in tumor diagnosis and therapy. These benefits extend beyond medications and include applications in imaging agents and genes (Farokhzad et al., 2009).

Over the past 20 years, the properties of NPs have led to the development of numerous NP-based therapy approaches in clinical trials. In this ongoing study, we assessed the efficacy of nanoparticles in treating cancer, comparing their effectiveness with alternative drug delivery strategies (Khan et al., 2023).

Utilizing NPs (Nanoparticles) for Drug Delivery in the Field of Anticancer Treatment

NPs have recently been acknowledge as potential carriers for medications. Drugs' pharmacokinetic features are changed by using nanocarriers to increase their effectiveness and decrease their negative effects (Karra et al., 2012). These systems release the medications at precise locations and timings, thereby influencing the body's pharmacokinetics and the processes of drug distribution (Tiwari et al., 2012).

The special features of their structure can make therapeutic drugs work better. Drugs are released in the body, defending drug molecules, being smaller than cells, moving through biological barriers to reach specific targets, keeping drug active in bloodstream for longer, helping deliver drug to specific places, and being safe for the body (De Jong and Borm, 2008).

Over the past fifty years, there has been a substantial evolution in the diversity of nanocarriers due to various developments in the disciplines of chemistry, biology, mechanics, polymers, and physics. As a result, a variety of carriers with distinct qualities have been brought into the medical sciences (Khan et al., 2017).

Drug distribution is a method of delivering medication to the human body in the most effective manner (Shreyash et al., 2021). To produce a desired impact on the body, it entails a range of formulations, methods, and techniques, including but not limited to nanoparticles. The major goal is to get right amount of medication to the right location in the body without reducing quality in order to have a greatest possible benefit and avoid any negative side effects. The goal of methods including site-targeting and systematic toxicology is same (Blugarten, 1915). Although the available nanohybrids, particularly the ones used to treat malignancies, have prolonged bloodstream residence periods, extravasation (leakage) of nanoparticles is favored (Wang et al., 2018). The ability of nanoparticles to split into different fine sized inorganic particles is another advantage of using them as shown in Fig. 1.1.

When a nanomedicine come in contact with white blood cells (WBCs), namely leucocytes, they determine whether the medicine will be absorbed or whether an immune reaction will be triggered against it (Diaz et al., 2008). Before they may be examined with TEM (transmission electron microscope) imaging, the observation necessitates several treatments which may change the organelles (Gupta et al., 2005).

Different outcomes are elicited by nanoparticles of varying sizes. Mesoporous silica nanoparticles (MSNs) with round

shape and size of 100nm could not considerably break the membrane of red blood cells (RBCs), while bigger particles, measuring 600nm, induced a considerable disruption that might potentially result in hemolysis (Zhao et al., 2011).

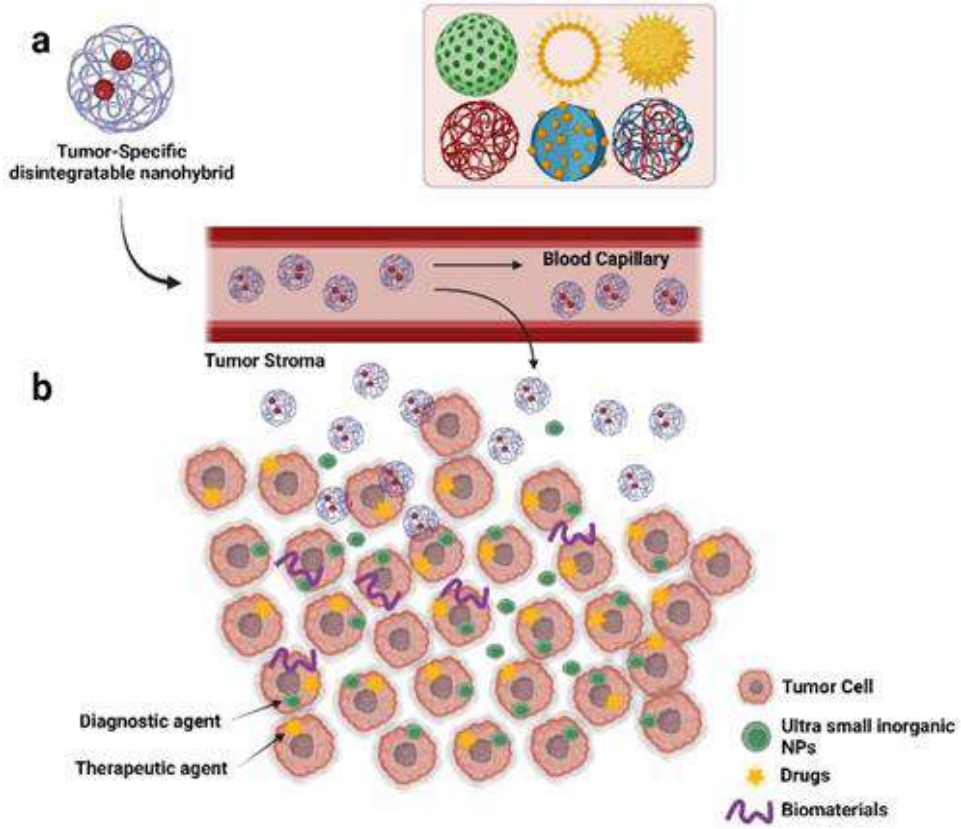


Fig. 1.1: (a) Nano hybrids, which are made of tiny inorganic nanoparticles, are used for effective cancer treatment. (b) Nano hybrids are utilized in cancer therapy

The goal of using nanoparticles for medication distribution is to make sure that the pharmaceuticals are absorbed more by cancer cells that are targeted and less by healthy cells. To achieve this, targeting agents are used. Functionalization of nanoparticles has an impact on how they interact with cell membranes. Individual nanoparticles cross the membrane more easily than when they are clumped together. Over time, methods for assessing the efficiency of nanoparticles in cancer treatment have greatly improved. One study introduced the enhanced permeability and retention (EPR) effect. This concept came from research evaluating how well a protein polymer conjugate worked in preventing cancer (Matsumura et al., 1986). This investigation revealed that the conjugate accumulates more in tumor tissues compared to free proteins. The EPR effect (Fang et al., 2011) leads to a major increase in number of tumor cells. Figure 1.2 shows how the EPR effect helps nanoparticles enter the tumor environment and enhances their therapeutic impact.

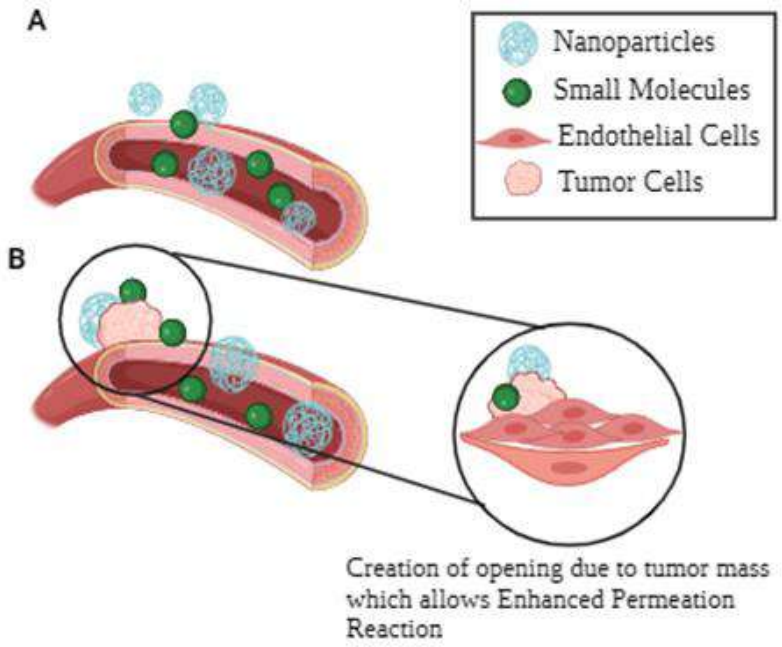


Fig. 1.2: Drug loading mechanism in a tumor cell (A) Cells in normal state. (B) Cells that have tumors develop openings that let nanoparticles move out of the blood vessels. Hyaluronic Acid

Hyaluronic acid, often known as hyaluronan or HA, is a glycosaminoglycan that is not sulfated and constitutes a significant component of the extracellular matrix. It is made up of β-N-acetylglucosamine (GIcNAc)-(1-3)-β-glucoronic acid (GlcA)-(1-4) repeating units. An increasing number of studies suggest that HA is involved in a number of biological processes, including cell adhesion, migration, and proliferation (Viola et al., 2015; Liang et al., 2016).

HA- mediated motility receptors (RHAMM), toll-like receptors (TLRs), lymphatic vessel endothelial hyaluronan receptors (LYVE1), and cluster of differentiation 44 (CD44) are cell surface receptors that have been found to intact with HA (Hardwick et al., 1992; Banerji et al., 1999; Calikoglu et al., 2003; Tesar et al., 2006). Recent studies has shown that HA plays a vital role in the formation, dissemination, metastasis, and progression of cancer (Bharadwaj et al., 2007; Kothapalli et al., 2008; Weigel et al., 2017).

Breast cancer is the most frequent type of cancer among women worldwide, accounting for 25% of all cases (Nave et al., 2006; Seigel et al., 2018). Because the cancer cells in triple-negative breast cancer (TNBC) do not express HER2, progesterone receptors, or estrogen receptors, it is a high-grade, aggressive form of breast cancer that frequently has a high patient death rate (Heldin et al., 2013). Numerous investigations have shown that HA controls the development and invasions of tumor cells both in vivo and in vitro (Bourguignon et al., 2010; Tolg et al., 2014; Yang et al., 2015).

The naturally occurring polysaccharide HA binds attractively to CD44 receptors that are overexpressed on a variety of malignant cells. An increasing body of studies suggests that HA oligosaccharides (HAOs) demonstrate unique biological effects not found in native hyaluronic acid. Additionally, research indicates that the bioactivity of HAOs differs from that of HA, particularly in the context of cancer advancements. It has been observed that HA oligomers prevent tumor growth in vivo (Zeng et al., 1998).

Hyaluronic acid (HA) is a glycosaminoglycan biopolymer that is mostly found in biological creatures' connective, epidermal, neural, and joint tissues (Fraser et al., 1997). Additionally, it acts as the primary constituent of the extracellular matrix (Toole and B.P., 2009). In medical contexts, HA finds frequent application in addressing osteoarthritis and healing skin wounds. Moreover, due to its ability to readily attach to the CD44 receptors found on tumor cells (Holmes et al., 1988; Mattheolabakis et al., 2015), HA is employed as a material for targeting tumors (Kahmann et al., 2000; Toole and B.P., 2009).

HA maintains exceptional viscoelasticity even after absorbing water, making it valuable for retaining skin moisture and managing osteoarthritis (Kablik et al., 2009). Nevertheless, natural HA has a high viscosity and a molecular weight of about 2000 kDa, which makes it difficult to inject into blood arteries in humans. As a result, numerous research teams have examined the physiological characteristics of low-molecular-weight-hyaluronic acid (ranging from 80 to 800kDa) (Cowman et al., 1996; Sun et al., 2011). Research indicates that low-molecular-weight hyaluronic acid (LMWHA) may have beneficial impacts on the wound healing process, immune system function, and formation of new blood vessels (Huang et al., 2019).

Hyaluronic acid (HA) and magnetic nanoparticles combined have demonstrated potential as a contrast agent for tumor magnetic resonance imaging (MRI), with a focus on CD44 receptors on tumor cell surfaces (Zhang et al., 2014). Although progress in understanding the targeting efficiency and functionality of low-molecular-weight hyaluronic acid nanoparticles (LMWHA-NPs) through in vitro and in vivo experiments, their physical properties, particularly dynamic viscoelasticity, remain unexplored. To fully harness LMWHA-NPs as an injectable MRI contrast medium, it is essential to synthesize and characterize LMWHA with precise molecular weights and reduced viscosity. Current methods for producing LMWHA involve either physical techniques (e.g., ultrasonic, ozone) or chemical approaches (e.g., enzymatic and acid degradation) to break down high-molecular-weight hyaluronic acid (HMWHA) (Zhong et al., 2019).

Fe_3O_4 Nanoparticles

Recently, significant advancements have been made in the use of Fe_3O_4 nanoparticle (Fe_3O_4 NPs) in medical sectors, including magnetic resonance imaging (MRI) (Guo et al., 2018), medication or gene administration (Cazares et al., 2017), treatment for magnetic hyperthermia (MHT) (Albarqi et al., 2019), and bimolecular separation and cleansing (Das et al., 2010). Studies have investigated how well Fe_3O_4 NPs work in magnetic hyperthermia treatment for various cancer types, including neck, head, brain and liver cancers (Jordan et al., 2006; Wang et al., 2012; Attaluri et al 2015). The underlying principle of this technique is that, when there is elevated to between 42 and 45C, malignant cells exhibit greater sensitivity to temperature rise than normal cells.

Magnetic hyperthermia therapy (MHT) involves delivering magnetic nanoparticle (MNPs) as heat bases to tumor tissue through systemic injection. Exposing the tumor tissue to high-frequency magnetic fields subsequently induces heat generation by MNPs through hysteresis losses. This thermal effect has the potential to cause damage to or eliminate cancer cells.

Iron Oxide nanoparticles ($Fe3O_4$ NPs) are highly promising due to their exceptional superparamagnetic and biocompatible properties. Importantly, NPs exhibit the phenomena of superparamagnetic, in which they become fully magnetized and do not retain any residual magnetic interaction once the external magnetic field is removed (Mahmoudi et al., 2011). Numerous biomedical applications, including drug administration, magnetofection, and hyperthermia, hold promise for these magnetic iron oxide nanoparticles. These NPs have also been demonstrated to have cytotoxicity against cancer cells in addition to these characteristics (Calero et al., 2015; Vinardell et al., 2015). On normal cells, however, Fe_3O_4 NPs exhibited little to no effect, consistent with earlier research (Sato et al., 2013).

While the mentioned research utilized experiments with cells in a lab (in vitro) and live animals (in vivo) to evaluate

how well LMWHA-NPs targeted and performed, they didn't focus on physical properties of the particles, especially their dynamic viscoelastic features. As a result, it is extremely important to synthesize and characterize LMWHA with a specific molecular weight and low viscosity for use as an injectable contrast agent for MR imaging. The primary bonds of HMWHA are broken by two main processes used in the current manufacturing of LMWHA: physical methods (such as heat treatment, gamma rays, ozone, electron beams, and ultra-sonication) and chemical procedures (such as enzymatic and acid degradation) (Hokputsa et al., 2003; Choi et al., 2010; Chen et al., 2019).

Among these techniques, γ-ray irradiation demonstrates Newtonian liquid behavior and notably decreases the dynamic viscosity of generated LMWHA when subjected to an applied share rate (Zhang et al., 2014; Huang et al., 2019). This greatly increases the viability of LMWHA as an injectable tumor-targeting therapy.

Conclusions

The synthesis of LMWHA was achieved through the utilization of gamma ray technique in this work. Scientists performed a comprehensive examination of biological and characteristics of LMWHA-Fe_3O_4 nanoparticles after merging superparamagnetic Fe_3O_4 nanoparticles with LMWHA. Various techniques were employed, such as superconducting quantum interference devices, electrophoretic light scattering, X-ray diffraction (XRD) and viscosity testing. Additionally, the capacity of LMWHA-Fe_3O_4 NPs to specifically target MCF7 breast cancer cells was assessed through the use of the thiocynate method and time-of-flight secondary ion mass spectrometry (TOF-SIMS).

REFERENCES

Albarqi, H. A., Wong, L. H., Schumann, C., Sabei, F. Y., Korzun, T., Li, X., and Taratula, O. (2019). Biocompatible nanoclusters with high heating efficiency for systemically delivered magnetic hyperthermia. *ACS Nano*, *13*(6), 6383-6395. https://doi.org/10.1021/acsnano.8b06542

Attaluri, A., Kandala, S. K., Wabler, M., Zhou, H., Cornejo, C., Armour, M., and Ivkov, R. (2015). Magnetic nanoparticle hyperthermia enhances radiation therapy: A study in mouse models of human prostate cancer. *International Journal of Hyperthermia*, *31*(4), 359-374. https://doi.org/10.3109/02656736.2015.1005178

Baeza, A., Castillo, R. R., Torres-Pardo, A., González-Calbet, J. M., and Vallet-Regí, M. (2017). Electron microscopy for inorganic-type drug delivery nanocarriers for antitumoral applications: what does it reveal?. *Journal of Materials Chemistry B*, *5*(15), 2714-2725.https://doi.org/10.1039/C6TB03062A

Banerji, S., Ni, J., Wang, S. X., Clasper, S., Su, J., Tammi, R., and Jackson, D. G. (1999). LYVE-1, a new homologue of the CD44 glycoprotein, is a lymph-specific receptor for hyaluronan. *The Journal of Cell Biology*, *144*(4), 789-801.https://doi.org/10.1083/jcb.144.4.789

Barzaman, K., Karami, J., Zarei, Z., Hosseinzadeh, A., Kazemi, M. H., Moradi-Kalbolandi, S., and Farahmand, L. (2020). Breast cancer: Biology, biomarkers, and treatments. *International Immunopharmacology*, *84*, 106535.https://doi.org/10.1016/j.intimp.2020.106535

Bharadwaj, A. G., Rector, K., and Simpson, M. A. (2007). Inducible hyaluronan production reveals differential effects on prostate tumor cell growth and tumor angiogenesis. *Journal of Biological Chemistry*, *282*(28), 20561-20572.https://doi.org/10.1074/jbc.M702964200

Blumgarten, A. S. (1915). The Administration of Medicines. *AJN the American Journal of Nursing*, *15*(7), 565-572.

Bourguignon, L. Y., Wong, G., Earle, C., Krueger, K., and Spevak, C. C. (2010). Hyaluronan-CD44 interaction promotes c-Src-mediated twist signaling, microRNA-10b expression, and RhoA/RhoC up-regulation, leading to Rho-kinase-associated cytoskeleton activation and breast tumor cell invasion. *Journal of Biological Chemistry*, *285*(47), 36721-36735.https://doi.org/10.1074/jbc.M110.162305

Bozzuto, G., and Molinari, A. (2015). Liposomes as nanomedical devices. *International Journal of Nanomedici* 975-999.*ne*, https://doi.org/10.2147/IJN.S68861

Bulbake, U., Doppalapudi, S., Kommineni, N., and Khan, W. (2017). Liposomal formulations in clinical use: an updated review. *Pharmaceutics*, *9*(2), 12.https://doi.org/10.3390/pharmaceutics9020012

Cai, S., Thati, S., Bagby, T. R., Diab, H. M., Davies, N. M., Cohen, M. S., and Forrest, M. L. (2010). Localized doxorubicin chemotherapy with a biopolymeric nanocarrier improves survival and reduces toxicity in xenografts of human breast cancer. *Journal of Controlled Release*, *146*(2), 212-218.https://doi.org/10.1016/j.jconrel.2010.04.006

Calero, M., Chiappi, M., Lazaro-Carrillo, A., Rodríguez, M. J., Chichón, F. J., Crosbie-Staunton, K., and Carrascosa, J. L. (2015). Characterization of interaction of magnetic nanoparticles with breast cancer cells. *Journal of Nanobiotechnology*, *13*, 1-15.https://doi.org/10.1186/s12951-015-0073-9

Calikoglu, E., Augsburger, E., Chavaz, P., Saurat, J. H., and Kaya, G. (2003). CD44 and hyaluronate in the differential diagnosis of dermatofibroma and dermatofibrosarcoma protuberans. *Journal of Cutaneous Pathology*, *30*(3), 185-189.https://doi.org/10.1034/j.1600-0560.2003.300304.x

Cazares-Cortes, E., Espinosa, A., Guigner, J. M., Michel, A., Griffete, N., Wilhelm, C., and Ménager, C. (2017). Doxorubicin intracellular remote release from biocompatible oligo (ethylene glycol) methyl ether methacrylate-based magnetic nanogels triggered by magnetic hyperthermia. *ACS Applied Materials and Interfaces*, *9*(31), 25775-25788.https://doi.org/10.1021/acsami.7b06553

Chen, H., Qin, J., and Hu, Y. (2019). Efficient degradation of high-molecular-weight hyaluronic acid by a combination of ultrasound, hydrogen peroxide, and copper ion. *Molecules*, *24*(3), 617.https://doi.org/10.3390/molecules24030617

Choi, J. I., Kim, J. K., Kim, J. H., Kweon, D. K., and Lee, J. W. (2010). Degradation of hyaluronic acid powder by electron beam irradiation, gamma ray irradiation, microwave irradiation and thermal treatment: A comparative study. *Carbohydrate Polymers*, *79*(4), 1080-1085.https://doi.org/10.1016/j.carbpol.2009.10.041

Cowman, M. K., Hittner, D. M., and Feder-Davis, J. (1996). 13C-NMR studies of hyaluronan: conformational sensitivity to varied environments. *Macromolecules*, *29*(8), 2894-2902.https://doi.org/10.1021/ma951701x

Dao, K. L., and Hanson, R. N. (2012). Targeting the estrogen receptor using steroid–therapeutic drug conjugates (hybrids). *Bioconjugate Chemistry*, *23*(11), 2139-2158.https://doi.org/10.1021/bc300378e

Das, M., Dhak, P., Gupta, S., Mishra, D., Maiti, T. K., Basak, A., and Pramanik, P. (2010). Highly biocompatible and water-dispersible, amine functionalized magnetite nanoparticles, prepared by a low temperature, air-assisted polyol process: a new platform for bio-separation and diagnostics. *Nanotechnology*, *21*(12), 125103. DOI 10.1088/0957-4484/21/12/125103

De Jong, W. H., and Borm, P. J. (2008). Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine*, *3*(2), 133-149.https://doi.org/10.2147/ijn.s596

Diaz, B., Sánchez-Espinel, C., Arruebo, M., Faro, J., de Miguel, E., Magadán, S., and González-Fernández, Á. (2008). Assessing methods for blood cell cytotoxic responses to inorganic nanoparticles and nanoparticle aggregates. *Small*, *4*(11), 2025-2034. https://doi.org/10.1002/smll.200800199

Fang, J., Nakamura, H., and Maeda, H. (2011). The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced Drug Delivery Reviews*, *63*(3), 136-151.https://doi.org/10.1016/j.addr.2010.04.009

Farokhzad, O. C., and Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano*, *3*(1), 16-20. https://doi.org/10.1021/nn900002m

Fentiman, I. S., Fourquet, A., and Hortobagyi, G. N. (2006). Male breast cancer. *The Lancet*, *367*(9510), 595-604. https://doi.org/10.1016/S0140-6736(06)68226-3

Fraser, J. R. E., Laurent, T. C., and Laurent, U. B. G. (1997). Hyaluronan: its nature, distribution, functions and turnover. *Journal of Internal Medicine*, *242*(1), 27-33. https://doi.org/10.1046/j.1365-2796.1997.00170.x

Guo, H., Sun, H., Zhu, H., Guo, H., and Sun, H. (2018). Synthesis of Gd-functionalized Fe 3 O 4@ polydopamine nanocomposites for T 1/T 2 dual-modal magnetic resonance imaging-guided photothermal therapy. *New Journal of Chemistry*, *42*(9), 7119-7124.https://doi.org/10.1039/C8NJ00454D

Gupta, A. K., and Gupta, M. (2005). Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials*, *26*(18), 3995-4021. https://doi.org/10.1016/j.biomaterials.2004.10.012

Hardwick, C., Hoare, K., Owens, R., Hohn, H. P., Hook, M., Moore, D., and Turley, E. A. (1992). Molecular cloning of a novel hyaluronan receptor that mediates tumor cell motility. *The Journal of Cell Biology*, *117*(6), 1343-1350. https://doi.org/10.1083/jcb.117.6.1343

Heldin, P., Basu, K., Olofsson, B., Porsch, H., Kozlova, I., and Kahata, K. (2013). Deregulation of hyaluronan synthesis, degradation and binding promotes breast cancer. *The Journal of Biochemistry*, *154*(5), 395-408. https://doi.org/10.1093/jb/mvt085

Hokputsa, S., Jumel, K., Alexander, C., and Harding, S. E. (2003). A comparison of molecular mass determination of hyaluronic acid using SEC/MALLS and sedimentation equilibrium. *European Biophysics Journal*, *32*, 450-456. https://doi.org/10.1007/s00249-003-0299-6

Holmes, M. W. A., Bayliss, M. T., and Muir, H. (1988). Hyaluronic acid in human articular cartilage. Age-related changes in content and size. *Biochemical Journal*, *250*(2), 435-441. https://doi.org/10.1042/bj2500435

Huang, Y. C., Huang, K. Y., Lew, W. Z., Fan, K. H., Chang, W. J., and Huang, H. M. (2019). Gamma-irradiation-prepared low molecular weight hyaluronic acid promotes skin wound healing. *Polymers*, *11*(7), 1214. https://doi.org/10.3390/polym11071214

Jordan, A., Scholz, R., Maier-Hauff, K., van Landeghem, F. K., Waldoefner, N., Teichgraeber, U., and Felix, R. (2006). The effect of thermotherapy using magnetic nanoparticles on rat malignant glioma. *Journal of Neuro-oncology*, *78*, 7-14. https://doi.org/10.1007/s11060-005-9059-z

Kablik, J., Monheit, G. D., Yu, L., Chang, G., and Gershkovich, J. (2009). Comparative physical properties of hyaluronic acid dermal fillers. *Dermatologic Surgery*, *35*, 302-312. https://doi.org/10.1111/j.1524-4725.2008.01046.x

Kahmann, J. D., O'Brien, R., Werner, J. M., Heinegård, D., Ladbury, J. E., Campbell, I. D., and Day, A. J. (2000). Localization and characterization of the hyaluronan-binding site on the link module from human TSG-6. *Structure*, *8*(7), 763-774. https://doi.org/10.1016/S0969-2126(00)00163-5

Karra, N., and Benita, S. (2012). The ligand nanoparticle conjugation approach for targeted cancer therapy. *Current Drug Metabolism*, *13*(1), 22-41. https://doi.org/10.2174/138920012798356899

Kausar, M., Saleem, Z., Azhar, R., Rukhsar, G., Ali, M., Fan, C., and Khan, A. M. A. (2023). Role Of Nanoparticles In Covid-19 Management. https://Doi.Org/10.61748/Cam.2023/010

Khan, A. M. A., Wei, C. R., Fatima, K., Ali, A., Akram, M. S., Saeed, Z., and Ullah, H. (2017). Use of Nanoparticles As Antioxidant Agents To Combat Bacterial Infections And Its Benefits To Intestinal Microbiota And Immune Response.

https://Doi.Org/10.61748/Cam.2023/001

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931. https://doi.org/10.1016/j.arabjc.2017.05.011

Klochkov, S. G., Neganova, M. E., Nikolenko, V. N., Chen, K., Somasundaram, S. G., Kirkland, C. E., and Aliev, G. (2021, February). Implications of nanotechnology for the treatment of cancer: Recent advances. In *Seminars in cancer Biology* (Vol. 69, pp. 190-199). Academic Press. https://doi.org/10.1016/j.semcancer.2019.08.028

Liang, J., Jiang, D., and Noble, P. W. (2016). Hyaluronan as a therapeutic target in human diseases. *Advanced Drug Delivery Reviews*, *97*, 186-203. https://doi.org/10.1016/j.addr.2015.10.017

Liyanage, P. Y., Hettiarachchi, S. D., Zhou, Y., Ouhtit, A., Seven, E. S., Oztan, C. Y., and Leblanc, R. M. (2019). Nanoparticle-mediated targeted drug delivery for breast cancer treatment. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1871*(2), 419-433. https://doi.org/10.1016/j.bbcan.2019.04.006

Liyanage, P. Y., Hettiarachchi, S. D., Zhou, Y., Ouhtit, A., Seven, E. S., Oztan, C. Y., and Leblanc, R. M. (2019). Nanoparticle-mediated targeted drug delivery for breast cancer treatment. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1871*(2), 419-433. https://doi.org/10.1016/j.bbcan.2019.04.006

Madeira, M., Mattar, A., Passos, R. J. B., Mora, C. D., Mamede, L. H. B. V., Kishino, V. H., and Gebrim, L. H. (2011). A case report of male breast cancer in a very young patient: What is changing?. *World Journal of Surgical Oncology*, *9*(1), 1-5. https://doi.org/10.1186/1477-7819-9-16

Mahmoudi, M., Sant, S., Wang, B., Laurent, S., and Sen, T. (2011). Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy. *Advanced Drug Delivery Reviews*, *63*(1-2), 24-46. https://doi.org/10.1016/j.addr.2010.05.006

Matsumura, Y. (1986). A new concept for macromolecular therapies in cancer chemotherapy: mechanisms of tumor tropic accumulation of proteins and the antitumor agents smancs. *Cancer Research*, *6*, 6397-6392.

Mattheolabakis, G., Milane, L., Singh, A., and Amiji, M. M. (2015). Hyaluronic acid targeting of CD44 for cancer therapy: from receptor biology to nanomedicine. *Journal of Drug Targeting*, *23*(7-8), 605-618. https://doi.org/10.3109/1061186X.2015.1052072

Miller, K. D., Nogueira, L., Mariotto, A. B., Rowland, J. H., Yabroff, K. R., Alfano, C. M., and Siegel, R. L. (2019). Cancer treatment and survivorship statistics, 2019. *CA: A Cancer Journal for Clinicians*, *69*(5), 363-385. https://doi.org/10.3322/caac.21565

Miranda-Filho, A., Bray, F., Charvat, H., Rajaraman, S., and Soerjomataram, I. (2020). The world cancer patient population (WCPP): An updated standard for international comparisons of population-based survival. *Cancer Epidemiology*, *69*, 101802. https://doi.org/10.1016/j.canep.2020.101802

Mirza, Z., and Karim, S. (2021, February). Nanoparticles-based drug delivery and gene therapy for breast cancer: Recent advancements and future challenges. In *Seminars in Cancer Biology* (Vol. 69, pp. 226-237). Academic Press. https://doi.org/10.1016/j.semcancer.2019.10.020

Mu, Q., Kievit, F. M., Kant, R. J., Lin, G., Jeon, M., and Zhang, M. (2015). Anti-HER2/neu peptide-conjugated iron oxide nanoparticles for targeted delivery of paclitaxel to breast cancer cells. *Nanoscale*, *7*(43), 18010-18014. https://doi.org/10.1039/C5NR04867B

Neve, R. M., Chin, K., Fridlyand, J., Yeh, J., Baehner, F. L., Fevr, T., and Gray, J. W. (2006). A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. *Cancer Cell*, *10*(6), 515-527. https://doi.org/10.1016/j.ccr.2006.10.008

Sato, A., Itcho, N., Ishiguro, H., Okamoto, D., Kobayashi, N., Kawai, K., and Watanabe, M. (2013). Magnetic nanoparticles of Fe3O4 enhance docetaxel-induced prostate cancer cell death. *International Journal of Nanomedicine*, 3151-3160. https://doi.org/10.2147/IJN.S40766

Senapati, S., Mahanta, A. K., Kumar, S., and Maiti, P. (2018). Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduction and Targeted Therapy*, *3*(1), 7. https://doi.org/10.1038/s41392-017-0004-3

Shi, J., Kantoff, P. W., Wooster, R., and Farokhzad, O. C. (2017). Cancer nanomedicine: progress, challenges and opportunities. *Nature Reviews Cancer*, *17*(1), 20-37. https://doi.org/10.1038/nrc.2016.108

Shreyash, N., Sonker, M., Bajpai, S., and Tiwary, S. K. (2021). Review of the mechanism of nanocarriers and technological developments in the field of nanoparticles for applications in cancer theragnostics. *ACS Applied Bio Materials*, *4*(3), 2307-2334. https://doi.org/10.1021/acsabm.1c00020

Siegel, R. L., Miller, K. D., and Jemal, A. (2018). Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, *68*(1), 7-30. https://doi.org/10.3322/caac.21442

Siegel, R. L., Miller, K. D., Fedewa, S. A., Ahnen, D. J., Meester, R. G., Barzi, A., and Jemal, A. (2017). Colorectal cancer statistics, 2017. *CA: A Cancer Journal for Clinicians*, *67*(3), 177-193. https://doi.org/10.3322/caac.21442

Silvera Batista, C. A., Larson, R. G., and Kotov, N. A. (2015). Nonadditivity of nanoparticle interactions. *Science*, *350*(6257), 1242477. https://doi.org/10.1126/science.1242477

Tesar, B. M., Jiang, D., Liang, J., Palmer, S. M., Noble, P. W., and Goldstein, D. R. (2006). The role of hyaluronan degradation products as innate alloimmune agonists. *American Journal of Transplantation*, *6*(11), 2622-2635. https://doi.org/10.1111/j.1600-6143.2006.01537.x

Tiwari, G., Tiwari, R., Sriwastawa, B., Bhati, L., Pandey, S., Pandey, P., and Bannerjee, S. K. (2012). Drug delivery systems: An

updated review. *International journal of pharmaceutical Investigation*, *2*(1), 2. doi: 10.4103/2230-973X.96920

Tolg, C., McCarthy, J. B., Yazdani, A., and Turley, E. A. (2014). Hyaluronan and RHAMM in wound repair and the "cancerization" of stromal tissues. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/103923

Toole, B. P. (2009). Hyaluronan-CD44 interactions in cancer: paradoxes and possibilities. *Clinical Cancer Research*, *15*(24), 7462-7468. https://doi.org/10.1158/1078-0432.CCR-09-0479

Valencia, O. M., Samuel, S. E., Viscusi, R. K., Riall, T. S., Neumayer, L. A., and Aziz, H. (2017). The role of genetic testing in patients with breast cancer: a review. *JAMA Surgery*, *152*(6), 589-594. doi:10.1001/jamasurg.2017.0552

Varricchio, C. G. (2004). *A cancer source book for nurses*. Jones and Bartlett Learning.

Vinardell, M. P., and Mitjans, M. (2015). Antitumor activities of metal oxide nanoparticles. *Nanomaterials*, *5*(2), 1004-1021. https://doi.org/10.3390/nano5021004

Viola, M., Vigetti, D., Karousou, E., D'Angelo, M. L., Caon, I., Moretto, P., and Passi, A. (2015). Biology and biotechnology of hyaluronan. *Glycoconjugate Journal*, *32*, 93-103. https://doi.org/10.1007/s10719-015-9586-6

Waks, A. G., and Winer, E. P. (2019). Breast cancer treatment: a review. *Jama*, *321*(3), 288-300. doi:10.1001/jama.2018.19323

Wang, L., Dong, J., Ouyang, W., Wang, X., and Tang, J. (2012). Anticancer effect and feasibility study of hyperthermia treatment of pancreatic cancer using magnetic nanoparticles. *Oncology Reports*, *27*(3), 719-726. https://doi.org/10.3892/or.2011.1567

Wang, Y., Wang, F., Shen, Y., He, Q., and Guo, S. (2018). Tumor-specific disintegratable nanohybrids containing ultrasmall inorganic nanoparticles: from design and improved properties to cancer applications. *Materials Horizons*, *5*(2), 184-205. DOI

https://doi.org/10.1039/C7MH01071K

Weigel, P. H. (2017). Planning, evaluating and vetting receptor signaling studies to assess hyaluronan size-dependence and specificity. *Glycobiology*, *27*(9), 796-799. https://doi.org/10.1093/glycob/cwx056

Wu, M., Cao, M., He, Y., Liu, Y., Yang, C., Du, Y., and Gao, F. (2015). A novel role of low molecular weight hyaluronan in breast cancer metastasis. *The FASEB Journal*, *29*(4), 1290-1298. https://doi.org/10.1096/fj.14-259978

Yahya, E. B., and Alqadhi, A. M. (2021). Recent trends in cancer therapy: A review on the current state of gene delivery. *Life Sciences*, *269*, 119087. https://doi.org/10.1016/j.lfs.2021.119087

Zeglinski, M., Ludke, A., Jassal, D. S., and Singal, P. K. (2011). Trastuzumab-induced cardiac dysfunction: a 'dual-hit'. *Experimental and Clinical Cardiology*, *16*(3), 70.

Zeng, C., Toole, B. P., Kinney, S. D., Kuo, J. W., and Stamenkovic, I. (1998). Inhibition of tumor growth in vivo by hyaluronan oligomers. *International Journal of Cancer*, *77*(3), 396-401. https://doi.org/10.1002/(SICI)1097-0215(19980729)77:3%3C396::AID-IJC15%3E3.0.CO;2-6

Zhang, H., Li, J., Sun, W., Hu, Y., Zhang, G., Shen, M., and Shi, X. (2014). Hyaluronic acid-modified magnetic iron oxide nanoparticles for MR imaging of surgically induced endometriosis model in rats. *PLoS One*, *9*(4), e94718. https://doi.org/10.1371/journal.pone.0094718

Zhao, Y., Sun, X., Zhang, G., Trewyn, B. G., Slowing, I. I., and Lin, V. S. Y. (2011). Interaction of mesoporous silica nanoparticles with human red blood cell membranes: size and surface effects. *ACS Nano*, *5*(2), 1366-1375. https://doi.org/10.1021/nn103077k

Zhong, L., Liu, Y., Xu, L., Li, Q., Zhao, D., Li, Z., and He, Z. (2019). Exploring the relationship of hyaluronic acid molecular weight and active targeting efficiency for designing hyaluronic acid-modified nanoparticles. *Asian Journal of Pharmaceutical Sciences*, *14*(5), 521-530. https://doi.org/10.1016/j.ajps.2018.11.002

Chapter 21

Overview of Nanoparticles and their Biomedical Applications

Moazama Batool[1], Qurat ul Ain[1], Sheeza Bano[1], Mamoona Mahmood[1], Hafsa Sultan[1] and Fatima Talib[1]

[1]Department of Zoology, Government College Women University, Sialkot 51310, Pakistan
*Corresponding author: moazama.batool@gcwus.edu.pk

ABSTRACT

The development and implications of nanoparticles synthesis is an emerging field that covers a wide range of applications. It plays a major role in the development of innovative methods to produce new products to suitable existing production equipment and to reformulate new material and chemicals. The nanoparticles are classified usually into organic, inorganic and carbon based on their nature. They can also be classified on the basis of dimension into zero, one, two and three-dimensional nanoparticles. Nanotechnology has been efficiently and successfully used in the field of biomedical sciences. Currently, hundreds of nanoparticles are known and have found their applications in cancer therapy, gene delivery, treatment of cardiovascular diseases, dentistry, drug delivery, molecular imaging, biosensors, orthopedic infection regenerative medicine and infectious diseases, etc. The following chapter deliberates on nanoparticles, their classification, their applications in the biomedical science, and future perspectives are also briefed.

KEYWORDS
Nanotechnology, Nanoparticles, Biomedical science, Therapeutic effect, Cancer therapy

Received: 08-June-2024
Revised: 18-July-2024
Accepted: 04-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Batool M, Ain QU, Bano S, Mahmood M, Sultan H and Talib F, 2024. Overview of nanoparticles and their biomedical applications. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 180-188. https://doi.org/10.47278/book.CAM/2024.244

INTRODUCTION

The current progression in the biomedical field is the result of the progress of the synthesis and application of nanoparticles. Nanoparticles also refer to as "zero-dimensional" nanomaterials, can be easily synthesized and modified so that they have new electronic, optical, magnetic, medical, catalytic, and mechanical properties. Such a powerful modification results in a high surface-to-volume ratio and quantum size effect, which depend greatly on their structure, size and shape (Khursheed et al., 2022). Nanoparticles are referred to as solid particles having a size within in the range of 10-100 nm. The nanocapsules and nanoparticles can be produced by using different preparation methods. The drugs are usually encapsulated, dissolved, entrapped, or attached to a nanoparticle matrix (Langer, 2000). Nanotechnology referred to the technology that is involved in the development and study of nanoscale-level matter their function and organization (Boulaiz et al., 2011; Jeevanandam et al., 2018). This chapter's purpose is to highlight the major contributions of nanoparticles to modern medical science.

Background History

It is quite difficult to exactly date back to the era when nanosized substances were first utilized by humans. However, the history of utilization of nanomaterial is not new. It is evident that approximately 4500 years ago nanofibers had been used to stiffen a mixture of ceramics (Heiligtag and Niederberger, 2013). In 1959 during the annual meeting of the American Physical Society, the concept of nanotechnology was introduced by Richard Feynman an American Nobel Prize physicist in his speech. This was the first time when nanotechnology was discussed at the academic level (Langer, 2000). About 4000 years ago, lead sulphide (PbS) nanoparticles were used in hair-dyeing formula by ancient Egyptians (Walter et al., 2006; Jeevanandam et al., 2018). In the fourth century, Romans were producing the "Lycurgus Cup" which is a dichroic cup. In direct light, it looks like a jade (green gemstone) while under transmitted light it gives a luminous ruby color. The variations of color were due to the presence of silver and gold nanoparticles and incident light (Freestone et al., 2007). Nanotechnology is considered the most promising technology of the 21st century (Emerich and Thanos, 2003).

Need for Nanotechnology in Biomedical Science

The discoveries in the field of nanotechnology and nanomedicine are massive and widespread. Nano drugs have undergone remarkable modifications, pushing the creativeness of the drug to a novel level with noteworthy healthcare results. Still there is a significant need to study the substantial capabilities of nanotechnology in the healthcare sector. In medicine, wide-range research is conducted to find best practices and methods to be used in cancer therapy, nephrology, gene therapy and cardiovascular disease. Remarkable development and improvement in the traditional treatment, along

with the improvement in the quality of nanotechnology and nanoparticles leads to stirring results (Vishwakarma et al., 2013; Keskinbora and Jameel, 2018).

Classification of Nanoparticles

The nanomaterials are classified on the basis of (a) nature and (b) dimension (Fig. 1).

Classification of Nanoparticles based on Nature

Based on nature, the nanoparticles typically fall into three categories which are the following

Organic Nanoparticles

Organic nanoparticles include liposomes, dendrimers ferritin and micelles etc. Organic nanoparticles have some unique characteristics such as they are nontoxic, biodegradable and some organic nanoparticles have a hollow core i.e. liposomes and micelles are which recognized as nanocapsules and are sensitive to heat and light (Tiwari et al., 2008). These unique properties make them a perfect choice for drug delivery systems. Organic nanoparticles are extensively used in the field of biomedical sciences for example in drug delivery system as well as in targeted drug delivery.

Inorganic Nanoparticles

Nanoparticles not made up of carbon are commonly known as inorganic nanoparticles. The inorganic nanoparticles are further categorized into metal based and metal oxide based inorganic nanoparticles.

Metal based

The synthesis of nano-sized particles from metals is known as metal based inorganic nanoparticles. Either constructive or destructive methods are used in the production of metal-based nanoparticles. Nearly the nanoparticles of all the metals can be synthesized (Salavati-niasari et al., 2008). Silver (Au), gold (Au), aluminium (Al), copper (Cu), lead (Pb), cadmium (Cd), zinc (Zn), iron (Fe) and cobalt (Co) are the most commonly used metals for the synthesis of the nanoparticle.

Metal Oxides based

The synthesis of nano sized particles from metal oxides is known as metal oxide based inorganic nanoparticles. Their synthesis modifies the properties of their particular metal-based nanoparticles. Iron oxide (Fe_2O_3) is one good example where under aerobic conditions, the iron (Fe) nanoparticles are instantaneously oxidized into iron oxide nanoparticles at room temperature. This conversion increases the reactivity of Fe_2O_3 nanoparticles compared to the Fe nanoparticles. Mainly due to high efficiency and increased reactivity metal oxide-based nanoparticles are synthesized (Tai et al., 2007). Iron oxide (Fe_2O_3), Zinc oxide (ZnO), Silicon dioxide (SiO_2), Aluminium oxide (Al_2O_3), Titanium oxide (TiO_2), Cerium oxide (CeO_2) and Magnetite (Fe_3O_4) commonly used metal oxides for the synthesis of nanoparticle

Carbon based

Entirely, carbon-made nanoparticles are recognized as carbon-based nanoparticles (Bhaviripudi et al., 2007). Carbon nano-tubes (CNT), carbon black, fullerenes, carbon nanofibers, graphene, carbon nanofibers and occasionally activated nano-sized carbon are included in carbon-based nanoparticles.

Classification of Nanoparticles based on Dimension

Nanoparticles have numerous dimensions. Siegel also classified nanoparticles on the basis of dimension into four types such as zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanoparticles. (Jeevanandam et al., 2018).

Zero-Dimensional Nanoparticles

The nanoparticles that with no dimension larger than 100 nm (nanoscale) are known as zero-dimensional nanoparticles. They are the most common type of nanoparticles. These are small point-like particles. The most common examples include Quantum dots, nano lenses and hollow spheres (Jeevanandam et al., 2018).

One-Dimensional Nanoparticles

The nanoparticles having at least one dimension that is larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as one-dimensional nanoparticles. The most common examples include nanotubes, nanofibers and nanorods (Jeevanandam et al., 2018).

Two-Dimension Nanoparticles

The nanoparticles having two dimensions that are larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as two-dimensional nanoparticles. The most common examples include nanocoating, nanofilms and nanolayers (Jeevanandam et al., 2018).

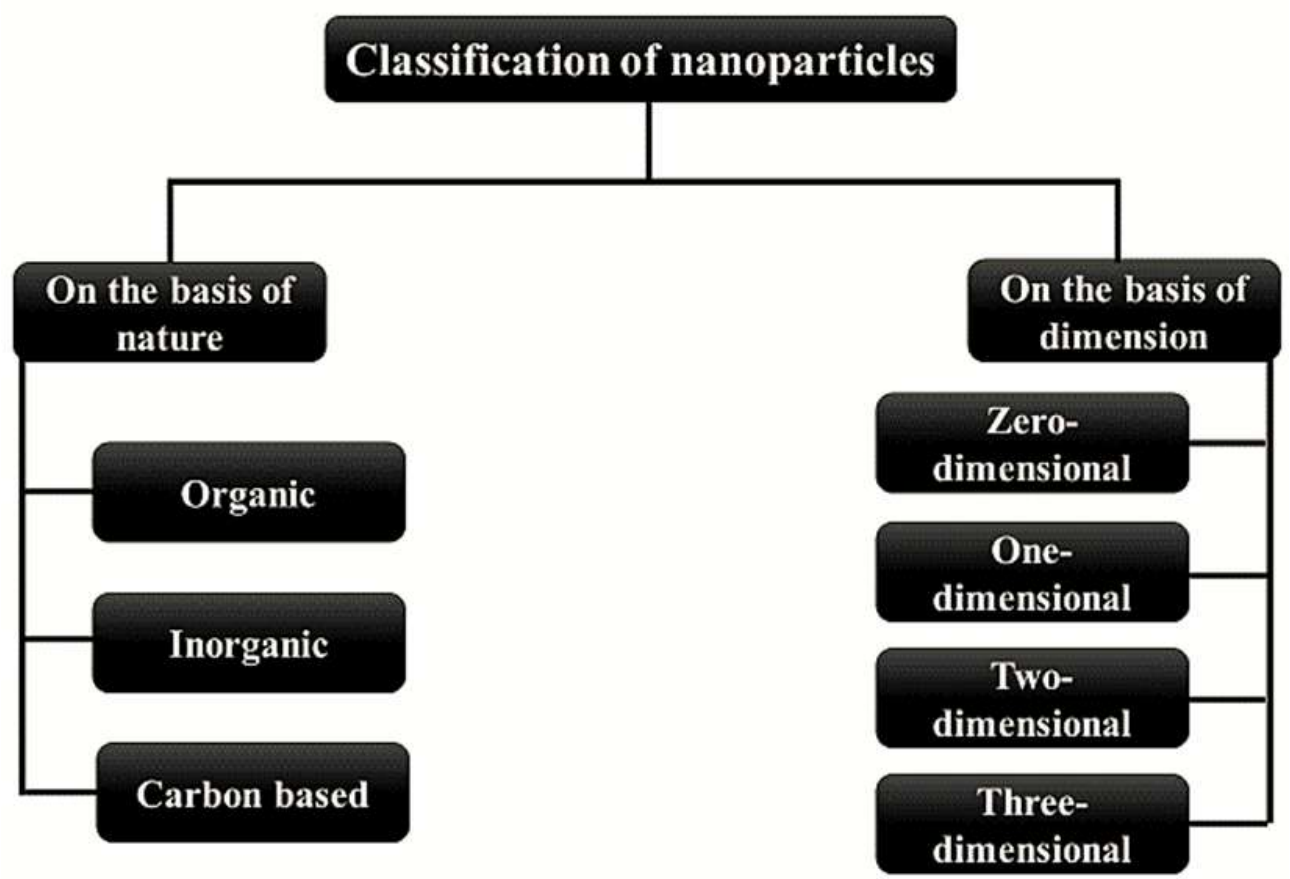


Fig: 1: Classification of nanoparticles

Three-Dimensional Nanoparticles

The nanoparticles having three dimensions that are larger than 100 nm (nanoscales) while other dimensions are within nano scale range are known as two-dimensional nanoparticles. These particles have numerous applications and are usually nonporous. The most common examples include multi nano-layer type structure, nanocomposites and bundles of nanofibers (Jeevanandam et al., 2018).

Applications of Nanotechnology in Biomedical Science

Nanoparticles have a large number of applications in the biomedical field (Table. 1). Some of these applications are discussed here.

Nanoparticles used in Cancer Therapy

In clinical trials, the nanomedicines used for the cancer treatment are considered to be the most important application (therapeutic) of nanoparticles among others. Many different formulations of nanoparticles are clinically approved to be used in the treatment of various cancers at different stages.

Remarkably, all of these systems but one such as Abraxane are liposomal systems that encapsulate an ant cancerous drug. The first cancer nanomedicine approved by FDA, in 1995 was Doxil. It was a PEG (polyethylene glycol) liposomal doxorubicin formulation (Barenholz, 2012). Soon after this, other formulations of liposomes were approved by the Food and Drug Administration (FDA) such as liposomal vincristine (Marqibo), liposomal daunorubicin (DaunoXome), and most new liposomal irinotecan (Onivyde) (Fox, 1995; Silverman and Deitcher, 2013; Carnevale and Ko, 2016). While non-PEGylated liposomal mifamurtide (MEPACT) and liposomal doxorubicin (Myocet) were approved by the European Medicines Agency (EMA) (Leonard et al., 2009; Ando et al., 2011). Abraxane, a paclitaxel albumin-bound nanoparticle is recently approved lone nonliposomal nanoparticle system for the treatment of cancer nanoparticles (Miele et al., 2009). Except, for Doxil and Onivyde most of these drugs formulations are not PEGylated (Chang et al., 2015; Otsuka et al., 2003; Suk et al., 2016; Gref et al., 1994). Furthermore, despite preclinically proven advantages of active targeting, all of these drug formulations are passively targeted, having no chemical or active based targeting moieties; (Wang et al., 2012; Byrne et al., 2008; Peer et al., 2020). It is expected that the other advantages, especially their reduced toxicity restricting their ability to specially accumulate at the site of the tumor and limit side effects on non-target area through the enhanced permeation and retention (EPR) effect (Maeda, 2012).

Nanoparticles in Gene Delivery

In the case of polynucleotide-based vaccines, the relevant genes are delivered, encode a specific antigen to the host cells, expressed and produce antigenic protein within the locality of original antigen presenting cells to trigger immunological response (Gurunathan et al., 2000). However, the applications of polynucleotides have been limited due to numerous issues associated with their delivery. Plasmid DNA-loaded nanoparticles could also serve as an effective sustained release gene delivery system because of their speedy escape to the cytoplasmic potion from the degradative endo-lysosomal portion (Panyam et al., 2002). This strategy of gene delivery could be applied to enable bone healing by using poly (lactic-co-glycolic acid) (PLGA) nanoparticles comprising therapeutic genes i.e. bone morphogenic protein (Hadley et al., 1998).

Nanoparticles used in the Treatment of Cardiovascular Diseases

Several kinds of nanoparticles are broadly utilized in the site-specific delivery of cardioprotective drugs for the treatment of cardiovascular diseases (CVDs). Gold (Au) nanoparticles are one among them. They have extensively used nanocarriers for the delivery of drugs (cardioprotective) to treat CVDs (Zhang et al., 2018). Clinical drugs are reported to have high efficacy and accuracy in combined form. One such example is combine cardioprotective effect of gold nanoparticles and simdax are far superior to their effect (Spivak et al., 2013). Liposomes, spherical nanoparticles have a bilayer structure composed of natural lipids or synthetic cholesterol. Biological benefits and delivery systems can be improved by using them in conjugated form with peptides or proteins (Mufamadi et al., 2011; Maurer et al., 2001). The first FDA-approved liposomal therapeutic drug prescribed to patients is Doxil (Liposomal doxorubicin). It is used in the treatment of different types of cancers (Hamilton et al., 2002). A study conducted by Basu (2018) reported that in cardiac grafting starburst dendrimers can be used for genes transfer (DNA or RNA).

Nanoparticles in Dentistry

Teeth are present inside the buccal cavity and consist of different parts like enamel, pulp, dentin, cementum, and periodontal ligament. The teeth are used to cut and crush food thus, aiding the process of swallowing and digestion (Tortora and Derrickson, 2018). In dentistry, nanotechnology using nanoparticles acts as a promising approach that can help in the prevention, shortening of treatment duration and in the eradication of oral related problems i.e. dental caries, periodontal disease, oral candidiasis, and hyposalivation (Ghafar et al., 2020). Typically, the fluoride level in the buccal cavity is greatly increased by using nanoparticles of calcium fluoride (CaF_2NPs). According to Kulshrestha et al. (2016) CaF_2NPs inhibit exopolysaccharide production by *Streptococcus mutans*. Nanotechnology is capable of overcomig such complications (Niemirowicz et al., 2017). Periodontal is an infectious disease that occurs due to the imbalancement between the colonization of pathogenic bacteria and the immune response of the host toward infection (Bao, 2018). Azithromycin and clarithromycin conjugated with silver nanoparticles are reported to have an efficient synergistic effect against microorganisms that cause periodontal infection (Emmanuel et al., 2015).

Nanoparticles in Drug Delivery

Nanoparticles and nanomaterials are progressively being sightseen for their possible applications in the field of medicine. Drug delivery is one such promising application. Nanoparticles are used as carriers in delivering of drugs to precise cells or tissues in the body. Nanoparticles can be engineered, having particular surface properties, enabling them to target diseased cells selectively and avoid healthy cells. Thus, increasing their efficiency and decreasing the side effects of drugs (Huang et al., 2010). In the research field, the widely used nanoparticles for therapeutic purposes comprise encapsulated mRNA (siRNA) or DNA (in gene therapy), metal complexes and inorganic metal, or chemotherapeutic agents with pharmacological capabilities (Khurana et al., 2019; Sharma et al., 2022).

Nanoparticles in Molecular Imaging

In molecular imaging, nanoparticles have great potential and formed a new set of diagnostic tools (Jokerst et al., 2011). There are different molecular imaging (MI) techniques, comprising of magnetic resonance imaging, ultrasound imaging, optical imaging, computed tomography and nuclear imaging and imaging with theranostics nanoparticles. The efficacy of ultrasound therapy can be enhanced by using distinct sound-active materials such as nanoparticles (Janib et al., 2010). From a clinical view, magnetic resonance imaging (MRI) is one of the most significant and non-invasive diagnostic tools for monitoring of disease (Shubayev et al., 2009). Currently, a multipurpose liposome incorporated with gadolinium-DOTA (MRI distinct agent) functionalizing with anticancer drugs such as αvβ3 integrin (targeted peptide) and paclitaxel was developed by the Xin Zhou group (Ren et al., 2015). Computed tomography (CT) is a documented and widely used technique that permits spatial imaging of tissues, providing comprehensive visualization of anatomy. Korean researchers designed gold nanoparticles (GNP) designed for the immediate therapy and imaging of prostate cancer (Kim et al., 2010).

Nanoparticles as Biosensors

Various types of nanoparticles are used as biosensors components. Mostly they work as probes identifying, and discriminating an analytical interest for screening and diagnostic purposes. Such approaches involve the attachment of

nanoparticles with biological molecular species through an exclusive modification process. The probes are used to bind with the sample and also signal the target's presence on the basis of their mass, color and other physical properties. Quantum dots, metallic nanobeads, nanobarcodes, carbon nanotubes, magnetic beads and silica nanoparticles-based biosensors are capable of to be skilled to the nanoprobe's group. Some other biosensors use nanoparticles in a different way (Kubik et al., 2005).

Table 1: Applications of nanoparticles in biomedical sciences

Nanoparticle	Application	Reference
Silver nanoparticles	Reduce orthopaedic infections	Jeyaraman et al., 2023
	High potential for use in the treatment of anticancer, antidiabetic	Stasyuk et al., 2016
	Antifungal activity against *Puccinia graminis tritci, Aspergillus flavus, Aspergillus niger* and *Candida albicans*	Terentyuk et al., 2014
	Antibacterial activity against *Escherichia coli*	Seo et al., 2014
	Used to treat urinary tract infections (UTI)	Jacob et al., 2011
	Antibacterial activity against Gram-negative and Gram-positive bacteria	Thakkar et al., 2010
Gold nanoparticles	Used in prostate cancer's therapy and imaging	Kim et al., 2010
Poly(butylcyanoacrylate)	Enable drug delivery to brain by crossing Blood-brain barrier (BBB)	Kreuter, 2004
Liposome	Deliver siRNA to the tumor tissues	Ozpolatet al., 2014
	Used to treat hepatitis B and hepatic fibrosis	Bobbin and Rossi, 2016
	Enable drug delivery to brain by crossing Blood-brain barrier (BBB)	Sato et al., 2008 Pardridge, 2005
Silver nanoparticles in glass ionomer cements (NanoAg-GIC)	Antibacterial properties Inhibit growth of *E. coli* and *S. mutans*	Paiva et al., 2018
Silver and zinc oxide nanoparticles	Inhibit growth of *Mycobacterium tuberculosis*	Jafari et l., 2016
Zinc oxide	Used to treat a respiratory infection caused by *Klebsiella pneumonia*	Reddy et al., 2014
Aptamers and Au nanoparticle modified Morin pH-sensitive liposome (AptAu@MSL)	Used in targeted drug delivery for cancer treatment	Ding et al., 2020
Gold nanoparticle (Au NPs) conjugated Gentamicin	Used to treat of serious kind of microbial infection	Yeluri et al., 2015
Gold nanoparticle (Au NP) conjugated everolimus	Used in Bronchiolitis obliterans syndrome to inhibit proliferation and increasing mesenchymal cell's apoptosis	Meloni et al., 2014
Abraxane (albumin-based nanoparticle)	Used in the treatment of breast cancer	Kadri et al., 2024 Miele et al., 2009
Abraxane in combination with narmafotinib and gemcitabine	Used in pancreatic cancer therapy	Cock et al., 2024
Pegylated Liposomal Doxorubicin (Doxil®)	Used in the treatment of ovarian and breast cancer	Perez et al., 2002 Barenholz, 2012
Simdax, conjugated on Au nanoparticles	Cardioprotective effect against doxorubicin-induced heart failure in rats	Spivak et al., 2013
Liposomal vincristine (Marqibo), liposomal daunorubicin (DaunoXome), liposomal irinotecan (Onivyde)	Used in cancer treatment	Silverman and Deitcher, 2013 Carnevale and Ko, 2016
Plasmid DNA loaded nanoparticles	Used in gene delivery	Panyam et al., 2002
Dendrimers	Used to transfer in cardiac grafting	Basu, 2018
Quercetin loaded PLGA nanoparticles	Used to prevent CVDs	Zhang et al., 2018
Calcium fluoride nanoparticles	Inhibit exopolysaccharide production by *Streptococcus mutans*	Kulshrestha et al., 2016

Nanoparticles in Orthopedic Infection

In orthopaedic infections, unreasonable and continued use of antibiotics is a major threat that leads to the development of antimicrobial resistance. In the field of orthopaedics, implant infections can be reduced by silver nanoparticles (AgNP) (Jeyaraman et al., 2023). The orthopaedic implants have been modified by using silver nanoparticles that increases antimicrobial effects through various processes i.e. plasma electrolytic oxidation, plasma immersion ion implantation (PIII), 3DP-Ag-containing scaffolds and magnetron sputtering (Qing et al., 2018).

Nanoparticles in Infectious Diseases

The diseases caused by bacteria, viruses, fungi and parasites are known as infectious diseases. Globlly, many deaths occurred due to these infectious diseases. The treatment and control of these infectious diseases are difficult as they undergo drug resistance (Fauci and Morens, 2012; Morens and Fauci, 2013; Parrish et al., 2008). Metal-based nanoparticles, have been utilized to treat infectious diseases. Metal-based nanoparticles are usually small-sized ranges between 10–100 nm enabling their efficient interaction with biomolecules on the surface of cell or inside the cell (Mody et al., 2010).

Mycobacterium tuberculosis, a bacterium causes an infectious disease of lungs known as Tuberculosis. The use of antibiotics against tuberculosis for extended period of time leads to drug resistance thus, hindering treatment. The growth rate of *Mycobacterium tuberculosis* can be inhibited by using mixture of silver and zinc oxide nanoparticles (Reddy et al., 2014).

Conclusion

The future potential of nanotechnology in the sector of medicine and healthcare is very vast. This technology has revolutionized our mode of diagnosis, treatment and disease preventions. In nanotechnology the materials are manipulated at a very small scale substantially varying the properties of materials from their bulk complements, enabling specific control of their biological, physical and chemical properties. Thus, opening new ways for the development of innovative therapies, highly sensitive diagnostic tools and targeted drug delivery systems. Moreover, nanoparticles can also be used to increase the efficiency of current drugs by enhancing their stability, bioavailability and solubility, stability. Furthermore, devices and sensors that are nanotechnology-based can be used in monitoring the health of patient in real-time, allowing early detection and improved personalized treatment plans. In the future, nanotechnology may even develop nanorobots that can move through the bloodstream, navigate the target and cause the destruction of cancer cells or deliver a precise load of drugs at a specific tissue.

REFERENCES

Ando, K., Mori, K., Corradini, N., Redini, F., and Heymann, D. (2011). Mifamurtide for the treatment of nonmetastatic osteosarcoma. *Expert Opinion on Pharmacotherapy*, *12*(2), 285-292.

Bao, X., Zhao, J., Sun, J., Hu, M., and Yang, X. (2018). Polydopamine nanoparticles as efficient scavengers for reactive oxygen species in periodontal disease. *ACS Nano*, *12*(9), 8882-8892.

Barenholz, Y. C. (2012). Doxil®—The first FDA-approved nano-drug: Lessons learned. *Journal of Controlled Release*, *160*(2), 117-134.

Basu, S. (2018). Novel drug delivery systems in management of cardiovascular diseases. *Pharmatutor*, *6*(6), 19-23.

Bhaviripudi, S., Mile, E., Steiner, S. A., Zare, A. T., Dresselhaus, M. S., Belcher, A. M., and Kong, J. (2007). CVD synthesis of single-walled carbon nanotubes from gold nanoparticle catalysts. *Journal of the American Chemical Society*, 129(6), 1516-1517.

Bobbin, M. L., and Rossi, J. J. (2016). RNA interference (RNAi)-based therapeutics: delivering on the promise. *Annual Review of Pharmacology and Toxicology*, *56*, 103-122.

Boulaiz, H., Alvarez, P. J., Ramirez, A., Marchal, J. A., Prados, J., Rodríguez-Serrano, F., and Aranega, A. (2011). Nanomedicine: application areas and development prospects. *International Journal of Molecular Sciences*, *12*(5), 3303-3321.

Byrne, J. D., Betancourt, T., and Brannon-Peppas, L. (2008). Active targeting schemes for nanoparticle systems in cancer therapeutics. *Advanced Drug Delivery Reviews*, *60*(15), 1615-1626.

Carnevale, J., and Ko, A.H. (2016). MM-398 (nanoliposomal irinotecan): emergence of a novel therapy for the treatment of advanced pancreatic cancer. *Future Oncol*, 12, 453–464.

Chang, T. C., Shiah, H. S., Yang, C. H., Yeh, K. H., Cheng, A. L., Shen, B. N., and Chen, L. T. (2015). Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients. *Cancer Chemotherapy and Pharmacology*, *75*, 579-586.

Chen, Z., Meng, H., Xing, G., Chen, C., Zhao, Y., Jia, G., and Wan, L. (2006). Acute toxicological effects of copper nanoparticles in vivo. *Toxicology Letters*, *163*(2), 109-120.

Christian, P., Von der Kammer, F., Baalousha, M., and Hofmann, T. (2008). Nanoparticles: structure, properties, preparation and behaviour in environmental media. *Ecotoxicology*, *17*, 326-343.

Cock, T. A., Bishop, A., Kruger, N., McCormack, S., Harris, M., Ananda, S., and Burns, C. (2024). Abstract CT220: Phase 1b/2a of narmafotinib (AMP945) in combination with gemcitabine and nab-paclitaxel (Abraxane) standard of care as first-line therapy in patients with advanced pancreatic cancer (ACCENT trial): interim analysis. *Cancer Research*, *84*(7_Supplement), CT220-CT220.

Ding, X., Yin, C., Zhang, W., Sun, Y., Zhang, Z., Yang, E., and Wang, W. (2020). Designing aptamer-gold nanoparticle-loaded pH-sensitive liposomes encapsulate morin for treating cancer. *Nanoscale Research Letters*, *15*, 1-17.

Emerich, D. F., and Thanos, C. G. (2003). Nanotechnology and medicine. *Expert Opinion on Biological Therapy*, *3*(4), 655-663.

Emmanuel, R., Palanisamy, S., Chen, S. M., Chelladurai, K., Padmavathy, S., Saravanan, M., and Al-Hemaid, F. M. (2015). Antimicrobial efficacy of green synthesized drug blended silver nanoparticles against dental caries and periodontal disease-causing microorganisms. *Materials Science and Engineering: C*, *56*, 374-379.

Fauci, A. S., and Morens, D. M. (2012). The perpetual challenge of infectious diseases. *New England Journal of Medicine*, 366(5), 454-461.

Fox, J. (1995). FDA advisors okay NeXstar's DaunoXome. *Nature Biotechnology,* 13(7), 635–636.

Freestone, I., Meeks, N., Sax, M., and Higgitt, C. (2007). The Lycurgus cup—a roman nanotechnology. *Gold Bulletin*, *40*, 270-277.

Ghafar, H., Khan, M. I., Sarwar, H. S., Yaqoob, S., Hussain, S. Z., Tariq, I., and Sohail, M. F. (2020). Development and characterization of bioadhesive film embedded with lignocaine and calcium fluoride nanoparticles. *Aaps Pharmscitech*, *21*, 1-12.

Gref, R., Minamitake, Y., Peracchia, M. T., Trubetskoy, V., Torchilin, V., and Langer, R. (1994). Biodegradable long-circulating polymeric nanospheres. *Science*, *263*(5153), 1600-1603.

Gurunathan, S., Wu, C. Y., Freidag, B. L., and Seder, R. A. (2000). DNA vaccines: a key for inducing long-term cellular immunity. *Current Opinion in Immunology*, *12*(4), 442-447.

Hamilton, A., Biganzoli, L., Coleman, R., Mauriac, L., Hennebert, P., Awada, A., and de Valeriola, D. (2002). EORTC 10968: a phase I clinical and pharmacokinetic study of polyethylene glycol liposomal doxorubicin (Caelyx®, Doxil®) at a 6-week interval in patients with metastatic breast cancer. *Annals of Oncology*, *13*(6), 910-918.

Hadley, M. L., Curley, J., and Urban, R. (1998). Microspheres containing plasmid-encoded antigens elicit cytotoxic T-cell responses.

Heiligtag, F. J., and Niederberger, M. (2013). The fascinating world of nanoparticle research. *Materials Today*, *16*(7-8), 262-271.

Huang, Q., Yu, H., and Ru, Q. (2010). Bioavailability and delivery of nutraceuticals using nanotechnology. *Journal of Food Science*, *75*(1), R50-R57.

Jacob Inbaneson, S., Ravikumar, S., and Manikandan, N. (2011). Antibacterial potential of silver nanoparticles against isolated urinary tract infectious bacterial pathogens. *Applied Nanoscience*, 1, 231-236.

Jafari, A. R., Mosavi, T., Mosavari, N., Majid, A., Movahedzade, F., Tebyaniyan, M... and Arastoo, S. (2016). Mixed metal oxide nanoparticles inhibit growth of Mycobacterium tuberculosis into THP-1 cells. *The International Journal of Mycobacteriology*, 5(Suppl 1), S181-S183.

Janib, S. M., Moses, A. S., and MacKay, J. A. (2010). Imaging and drug delivery using theranostic nanoparticles. *Advanced Drug Delivery Reviews*, *62*(11), 1052-1063.

Jeevanandam, J., Barhoum, A., Chan, Y. S., Dufresne, A., and Danquah, M. K. (2018). Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. *Beilstein Journal of Nanotechnology*, *9*(1), 1050-1074.

Jeyaraman, M., Jeyaraman, N., Nallakumarasamy, A., Iyengar, K. P., Jain, V. K., Potty, A. G., and Gupta, A. (2023). Silver nanoparticle technology in orthopaedic infections. *World Journal of Orthopedics*, *14*(9), 662.

Jokerst, J. V., Lobovkina, T., Zare, R. N., and Gambhir, S. S. (2011). Nanoparticle PEGylation for imaging and therapy. *Nanomedicine*, *6*(4), 715-728.

Kadri, H., Alshatfa, M., Alsalloum, F. Z., Elhissi, A., Daou, A., and Khoder, M. (2024). Albumin Nanoparticles in Cancer Therapeutics: Clinical Status, Challenges, and Future Directions.

Keskinbora, K. H., and Jameel, M. A. (2018). Nanotechnology applications and approaches in medicine: a review. *Journal Nanoscience Nanotechnology Research*, *2*(2), 6.

Khurana, A., Tekula, S., Saifi, M. A., Venkatesh, P., and Godugu, C. (2019). Therapeutic applications of selenium nanoparticles. *Biomedicine and Pharmacotherapy*, *111*, 802-812.

Khursheed, R., Dua, K., Vishwas, S., Gulati M., Jha N.K., Aldhafeeri G.M., Alanazi F.G., Goh B.H., Gupta G., Paudel K.R., (2022). Biomedical applications of metallic nanoparticles in cancer: Current status and future. Historical overview of nanotechnology and nanotoxicology. *Nanotoxicity: Methods and Protocols*, 1-12.

Kim, D., Jeong, Y. Y., and Jon, S. (2010). A drug-loaded aptamer− gold nanoparticle bioconjugate for combined CT imaging and therapy of prostate cancer. *ACS Nano*, *4*(7), 3689-3696.

Kreuter, J. (2004). Influence of the surface properties on nanoparticle-mediated transport of drugs to the brain. *Journal of Nanoscience and Nanotechnology*, *4*(5), 484-488.

Kubik, T., Bogunia-Kubik, K., and Sugisaka, M. (2005). Nanotechnology on duty in medical applications. *Current Pharmaceutical Biotechnology*, *6*(1), 17-33.

Kulshrestha, S., Khan, S., Hasan, S., Khan, M. E., Misba, L., and Khan, A. U. (2016). Calcium fluoride nanoparticles induced suppression of Streptococcus mutans biofilm: an in vitro and in vivo approach. *Applied Microbiology and Biotechnology*, *100*, 1901-1914.

Langer, R. (2000). Biomaterials in drug delivery and tissue engineering: one laboratory's experience. *Accounts of Chemical Research*, *33*(2), 94-101.

Leonard, R. C. F., Williams, S., Tulpule, A., Levine, A. M., and Oliveros, S. (2009). Improving the therapeutic index of anthracycline chemotherapy: focus on liposomal doxorubicin (Myocet™). *The Breast*, *18*(4), 218-224.

Maeda, H. (2012). Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. *Journal of Controlled Release*, *164*(2), 138-144.

Maurer, N., Fenske, D. B., and Cullis, P. R. (2001). Developments in liposomal drug delivery systems. *Expert Opinion on*

Biological Therapy, *1*(6), 923-947.

Meloni, F., Cova, E., Inghilleri, S., Oggionni, T., Magni, S., Morosini, M., and Prosperi, D. (2014). Novel Antibody-Engineered Gold Nanoparticles as Targeted Drug Delivery for Primary Mesenchimal Cells Do Not Elicit an Inflammatory Response. *The Journal of Heart and Lung Transplantation*, *33*(4), S166.

Miele, E., Spinelli, G. P., Miele, E., Tomao, F., and Tomao, S. (2009). Albumin-bound formulation of paclitaxel (Abraxane® ABI-007) in the treatment of breast cancer. *International Journal of Nanomedicine*, 99-105.

Mody, V. V., Siwale, R., Singh, A., and Mody, H. R. (2010). Introduction to metallic nanoparticles. *Journal of Pharmacy and Bioallied Sciences*, 2(4), 282-289.

Morens, D. M., and Fauci, A. S. (2013). Emerging infectious diseases: threats to human health and global stability. *PLoS Pathogens*, 9(7), e1003467.

Mufamadi, M. S., Pillay, V., Choonara, Y. E., Du Toit, L. C., Modi, G., Naidoo, D., and Ndesendo, V. M. (2011). A review on composite liposomal technologies for specialized drug delivery. *Journal of Drug Delivery*, *2011*.

Niemirowicz, K., Durnaś, B., Tokajuk, G., Piktel, E., Michalak, G., Gu, X., and Bucki, R. (2017). Formulation and candidacidal activity of magnetic nanoparticles coated with cathelicidin LL-37 and ceragenin CSA-13. *Scientific Reports*, *7*(1), 4610.

Otsuka, H., Nagasaki, Y., and Kataoka, K. (2003). PEGylated nanoparticles for biological and pharmaceutical applications. *Advanced Drug Delivery Reviews*, *55*(3), 403-419.

Ozpolatet, B., Sood, A. K., and Lopez-Berestein, G. (2014). Liposomal siRNA nanocarriers for cancer therapy. *Advanced Drug Delivery Reviews*, *66*, 110-116.

Paiva, L., Fidalgo, T. K. S., Da Costa, L. P., Maia, L. C., Balan, L., Anselme, K., and Thiré, R. M. S. M. (2018). Antibacterial properties and compressive strength of new one-step preparation silver nanoparticles in glass ionomer cements (NanoAg-GIC). *Journal of Dentistry*, *69*, 102-109.

Panyam, J., Zhou, W. Z., Prabha, S., Sahoo, S. K., and Labhasetwar, V. (2002). Rapid endo-lysosomal escape of poly (DL-lactide-coglycolide) nanoparticles: implications for drug and gene delivery. *The FASEB Journal*, *16*(10), 1217-1226.

Pardridge, W. M. (2005). Drug and gene targeting to the brain via blood–brain barrier receptor-mediated transport systems. In *International Congress Series* (Vol. 1277, pp. 49-62). Elsevier.

Parrish, C. R., Holmes, E. C., Morens, D. M., Park, E. C., Burke, D. S., Calisher, C. H., and Daszak, P. (2008). Cross-species virus transmission and the emergence of new epidemic diseases. *Microbiology and Molecular Biology Reviews*, 72(3), 457-470.

Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., and Langer, R. (2020). Nanocarriers as an emerging platform for cancer therapy. *Nano-enabled Medical Applications*, 61-91.

Perez, A. T., Domenech, G. H., Frankel, C., and Vogel, C. L. (2002). Pegylated liposomal doxorubicin (Doxil®) for metastatic breast cancer: the Cancer Research Network, Inc., experience. *Cancer Investigation*, *20*(sup2), 22-29.

Qing, Y. A., Cheng, L., Li, R., Liu, G., Zhang, Y., Tang, X., and Qin, Y. (2018). Potential antibacterial mechanism of silver nanoparticles and the optimization of orthopedic implants by advanced modification technologies. *International Journal of Nanomedicine*, 3311-3327.

Reddy, L. S., Nisha, M. M., Joice, M., and Shilpa, P. N. (2014). Antimicrobial activity of zinc oxide (ZnO) nanoparticle against Klebsiella pneumoniae. *Pharmaceutical Biology*, 52(11), 1388-1397.

Ren, L., Chen, S., Li, H., Zhang, Z., Ye, C., Liu, M., and Zhou, X. (2015). MRI-visible liposome nanovehicles for potential tumor-targeted delivery of multimodal therapies. *Nanoscale*, *7*(30), 12843-12850.

Salavati-Niasari, M., Davar, F., and Mir, N. (2008). Synthesis and characterization of metallic copper nanoparticles via thermal decomposition. *Polyhedron*, *27*(17), 3514-3518.

Sato, Y., Murase, K., Kato, J., Kobune, M., Sato, T., Kawano, Y., and Niitsu, Y. (2008). Resolution of liver cirrhosis using vitamin A–coupled liposomes to deliver siRNA against a collagen-specific chaperone. *Nature Biotechnology*, *26*(4), 431-442.

Seo, S. H., Kim, B. M., Joe, A., Han, H. W., Chen, X., Cheng, Z., and Jang, E. S. (2014). NIR-light-induced surface-enhanced Raman scattering for detection and photothermal/photodynamic therapy of cancer cells using methylene blue-embedded gold nanorod@ SiO2 nanocomposites. *Biomaterials*, *35*(10), 3309-3318.

Sharma, A. R., Lee, Y. H., Bat-Ulzii, A., Bhattacharya, M., Chakraborty, C., and Lee, S. S. (2022). Recent advances of metal-based nanoparticles in nucleic acid delivery for therapeutic applications. *Journal of Nanobiotechnology*, *20*(1), 501.

Shubayev, V. I., Pisanic II, T. R., and Jin, S. (2009). Magnetic nanoparticles for theragnostics. *Advanced Drug Delivery Reviews*, *61*(6), 467-477.

Silverman, J. A., and Deitcher, S. R. (2013). Marqibo®(vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemotherapy and Pharmacology*, *71*(3), 555-564.

Spivak, M. Y., Bubnov, R. V., Yemets, I. M., Lazarenko, L. M., Tymoshok, N. O., and Ulberg, Z. R. (2013). Development and testing of gold nanoparticles for drug delivery and treatment of heart failure: a theranostic potential for PPP cardiology. *Epma Journal*, *4*, 1-23.

Stasyuk, N., Gayda, G., Serkiz, R., and Gonchar, M. (2016). The green" synthesis of gold nanoparticles by the yeast Hansenula polymorpha. (73), 96-102.

Suk, J. S., Xu, Q., Kim, N., Hanes, J., and Ensign, L. M. (2016). PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Advanced Drug Delivery Reviews*, *99*, 28-51.

Tai, C. Y., Tai, C. T., Chang, M. H., and Liu, H. S. (2007). Synthesis of magnesium hydroxide and oxide nanoparticles using a

spinning disk reactor. *Industrial and Engineering Chemistry Research*, 46(17), 5536-5541.

Terentyuk, G., Panfilova, E., Khanadeev, V., Chumakov, D., Genina, E., Bashkatov, A., and Khlebtsov, B. (2014). Gold nanorods with a hematoporphyrin-loaded silica shell for dual-modality photodynamic and photothermal treatment of tumors in vivo. *Nano Research*, *7*, 325-337.

Thakkar, K. N., Mhatre, S. S., and Parikh, R. Y. (2010). Biological synthesis of metallic nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *6*(2), 257-262.

Tiwari, D. K., Behari, J., and Prasenjit Sen, P. S. (2008). Application of nanoparticles in waste water treatment.

Tortora, G. J., and Derrickson, B. H. (2018). *Principles of anatomy and physiology*. John Wiley and Sons.

Vishwakarma, K., Vishwakarma, O. P., and Bhatele, M. (2013). A brief review on role of nanotechnology in medical sciences. In *Proceedings of All India Seminar on Biomedical Engineering 2012 (AISOBE 2012)* (pp. 53-63). Springer India.

Walter, P., Welcomme, E., Hallégot, P., Zaluzec, N. J., Deeb, C., Castaing, J., and Tsoucaris, G. (2006). Early use of PbS nanotechnology for an ancient hair dyeing formula. *Nano Letters*, *6*(10), 2215-2219.

Wang, A. Z., Langer, R., and Farokhzad, O. C. (2012). Nanoparticle delivery of cancer drugs. *Annual Review of Medicine*, *63*, 185-198.

Yeluri, T., Bhosale, R. S., Ghule, N. V., Raynor, A. M., Bhosale, S. V., and Bhosale, S. V. (2015). Retracted Article: Neomycin and gentamicin detection via molecular recognition with cyclam-decorated gold nanoparticles. *Supramolecular Chemistry*, *27*(11-12), 772-779.

Zhang, J., Ma, A., and Shang, L. (2018). Conjugating existing clinical drugs with gold nanoparticles for better treatment of heart diseases. *Frontiers in Physiology*, *9*, 642.

Chapter 22

Trends in Application of Nanotechnology for Poultry Production

Iqra Zaheer[1], Muhammad Arslan[2], Tahreem Asad[2], Uzair Safdar[3], Umar Iqbal[2], Abdul Qudoos[2], Saad Ahmad Khan[2], Rana Kamal Elahi[2], Sana Ali[2] and Mahreen Fatima[4]

[1]Health Control Division, Livestock Production Research Institute, Okara, Pakistan
[2]Department of Poultry Science, Faculty of Animal Production and Technology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
[3]Department of Animal Nutrition, Faculty of Animal Production and Technology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
[4]Faculty of Biosciences, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
*Corresponding author: dr.iqzaheer@gmail.com

ABSTRACT

Nanotechnology, an innovative technology operated at the nanoscale that has a great scope of applications as well as a socioeconomic potential in the poultry sector. This chapter provides an overview of nanotechnology and provides the basic concepts about nanotechnology, nanoparticles, nano-biosensors, nano-carriers vaccines, nano-minerals, essential oils, and nano-emulsions. Moreover, nanotechnology is an emerging field in poultry science, it plays a vital role in poultry nutrition. Nano-minerals and nanoencapsulation can improve the bioavailability and absorption of essential nutrients and improve the gut health and immunity of broiler birds with disease resistance to antimicrobial meat packaging and overall flock health. Nano-carriers are used for the targeted delivery of vaccines and antibiotics described with problems and solutions of nano-carrier based vaccine in poultry, moreover, nano-carriers play a vital role in early chick detection. This chapter highlights the nanoparticles improve the hygiene of poultry houses, challenges, prospects, and recent emerging trends like gene editing and target genes. The advantages of nanotechnology as traditional methods are described as well.

KEYWORDS
Nanotechnology, Poultry, Nanoencapsulation, Nanosensors, Nanoemulsions, Nanovaccines

Received: 19-Jun-2024
Revised: 18-Jul-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Zaheer I, Arslan M, Asad T, Safdar U, Iqbal U, Qudoos A, Khan SA, Elahi RK, Ali S and Fatima M, 2024. Trends in application of nanotechnology for poultry production. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 189-197. https://doi.org/10.47278/book.CAM/2024.159

INTRODUCTION

Nanotechnology is widely regarded as one of the most promising technologies in the 21st century. Nanotechnology is an emerging field in poultry sciences and can be possibility defined as the process of designing, characterization, producing, and application of structures, by controlling shape and size at the nanoscale (1-100 nm) at least in one dimension (Bayda et al., 2020). Nanotechnology is commonly associated with nanoparticles which are antimicrobial activity, cytotoxicity from reactive oxygen species (ROS), and genotoxicity. Various factors, such as size, shape, dose, and concentration, have been shown to influence the effects of nanoparticles (Rawat et al., 2018). The mode of action associated with nanoparticles in poultry is as explained Fig 1.

The two approaches used to form nanoparticles are top down and bottom-up (Sadr et al., 2023). In the Bottom-Up approach (Fig 2), Plasma arcing is used which relies on ionized gas atoms, which require a high energy level to remove an electron from its valence shell and create a positively charged atom. This process ensures an overall state of neutrality. Another method in bottom-up is the Chemical vapor deposition process in which the Reactants are transported onto the growth surface and chemical reactions take place on the growth surface and by-products formed by the gas-phase reaction are removed and the nanoparticles are generated. In Molecular beam epitaxy thermal molecular and atomic beams are directly onto a heated substrate under ultra-high vacuum conditions to produce nanoparticles. In Self-assembly bottom-up method atoms or molecules come together under equilibrium conditions to form a stable and well-defined nano-phase through non-covalent bonds to form nanoparticles (Kumar et al., 2018). Different type of material is used in the preparation of nanoparticles which include polymers such as copper particles, zinc oxide particles, gold, silver, chitosan, polyethylene glycol, and inulin are effectively used. The materials such as liposomes, fullerenes, solid lipids, nano-

emulsions, bulky tubes, magnetic ions oxide, and metallic particles also play a carrier role in the field of nanotechnology (Sadr et al., 2023).

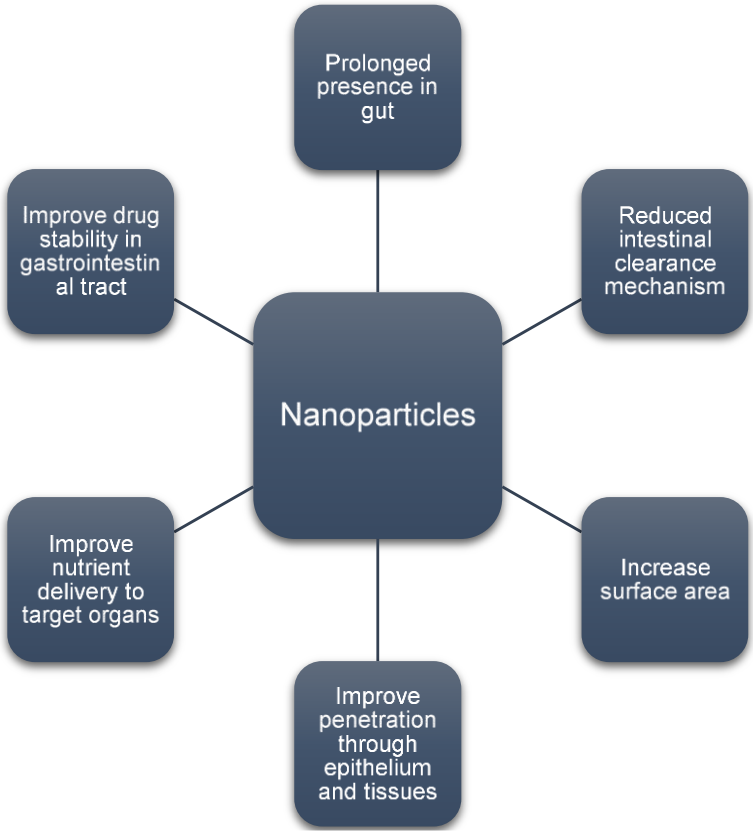


Fig. 1: Mode of Action of Nanoparticles (Suk et al., 2016).

The top-down method (Fig 2) begins with macroscopic structures that are converted to nanoparticles through a series of activities. The method includes material grinding by externally controlled tools to cut, grind, and shape materials into nanoscale structures except for soft materials. There are different methods of top-down approach but Mechanical milling is a widely used method in which the rotatory tools are used to generate shear force which produces nanoparticles. Nano-lithography is another process that uses optical, electron-beam, multi-photon, nano-imprint, and scanning probe lithography to break large particles into nanoparticles another method used is the Arc Discharge method in which a chamber containing 2 graphite rods, and helium pressure is used to produce nanoparticles from larger molecules. In sputtering nanoparticles are produced by hitting solid particles with high energy (Kraft et al., 2014) particles such as plasma or gas. As the advances continue in nanotechnology laser ablation method also gets it ground in which nanoparticles are produced by striking the target material with a strong laser beam another method that is effective works in the field is the Pulse wire discharge method in this method metal wire is exposed to pulsing current which evaporated and vapor is cooled by ambient gas to produce nanoparticles (Altammar, 2023).

Nanotechnology is becoming more popular in modern animal production systems than traditional methods due to several advantages. The nanotechnology has provided efficient drug delivery compounds with better safety profiles, better quality of feed additives with no drug resistance complications, and minimized the usage of antimicrobials. The nanotechology-based compounds are an eco-friendly and economically viable options for animal production industry (Malik et al., 2023) as discussed in Table 1.

Role of Nanoparticles in Poultry Nutrition

The feed additives used in the poultry industry are costly and good quality ingredient availability is a challenge (Sayee et al., 2019). The anti-nutritional factors present in feed ingredients cause low utilization of nutrients and most nutrients are excreted undigested (Kiarie and Mills, 2019). Nanotechnology is opening an exciting possibility in the field of nutrition by enhancing nutrient delivery and bioavailability by improving the digestion of nutrients. Some nutrients are poorly soluble and some are highly degradable losing their nutritional potential to resolve this issue and improve their absorption nanoparticle play a role as nano-carriers such as liposomes which increase the solubility of a nutrient and increase their absorption, they also protect against degradation of nutrient by forming a protective covering around them and deliver them to a particular site for absorption in this way they carry a particular nutrient to a specific site without being wasted or utilized by other organ (Van Tran et al., 2019).

Role of Nanotechnology in Bioavailability and Nutrient Utilization of Essential Nutrients

Nano-encapsulation aims to enhance the solubility of insoluble ingredients by binding them, protecting highly

degradable nutrients with a covering, and transporting them to the absorption site intact. This process increases surface area for optimal absorption, ensuring prolonged availability. The nano-encapsulation can pass from small capillaries and barriers and then reach the brain and groan region. They remain longer in birds due to their small size and slow metabolism excretion (Barua and Mitragotri, 2014).

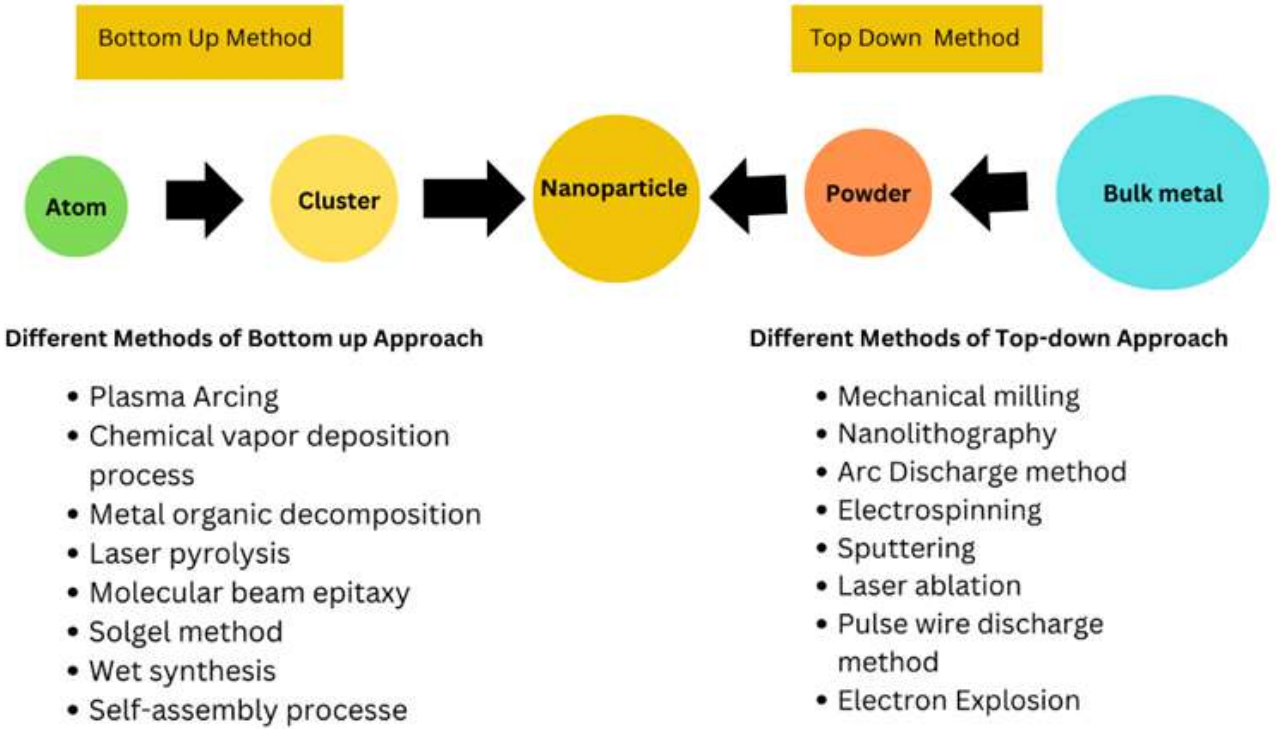


Fig. 2: Nanoparticles production approaches through bottom-up and top-down methods (Kumar et al., 2018).

Table 1: Advantages of using Nanotechnology over Traditional Methods

Sr #	Usage of Nanotechnology	Nanotechnology advantages	Traditional Methods limitations	Reference
1	Drug Delivery	Enhance solubility, absorb-ability, bio-availability, and half-life of products.	Limited by Conventional formulations	Danchuk et al., 2023
2	Disease Prevention	Smart technology for diagnosis and treatment of poultry diseases.	Relies on traditional Vaccines and medications.	Danchuk et al., 2023
3	Growth Promotion	Nanoparticles are used as an alternative to antibiotics as growth promoters.	Dependence on antibiotics can lead to resistance.	Gelaye, (2023).
4	Feed Additives	Improve growth rate, performance, immunity, and resistance to pathogens.	Less targeted and efficient feed additives.	Gelaye, (2023).
5	Animal Product Quality control	It enhances meat quality and can reduce supplemental doses of minerals.	Animal product quality depends on varied factors, therefore less controlled.	Mekonnen, G. (2021).
6	Environmental Impact	Nanoparticles are used without affecting animal health and welfare.	Greater environmental footprint.	Poddar and Kishore, (2022).
7	Cost Efficiency	Potential to reduce costs and enhance final product quality.	Higher costs due to less efficient processes.	Malik et al., 2023

Role of Nanominerals in Poultry Production

In poultry, dietary minerals are essential for immune function and gastrointestinal health. They function as vital components and mediators of numerous physiological processes, influencing everything from the formation of immune cells to the integrity of the gut barrier. Minerals like zinc, calcium, and magnesium contribute to maintaining the tight junctions between intestinal cells, fortifying this barrier. Minerals like copper, manganese, and selenium are essential co-factors for enzymes involved in digestion. They help break down complex nutrients in feed for proper nutrient absorption and gut health. Minerals like manganese or chromium can promote the growth of beneficial bacteria, creating a healthy

gut environment. Zinc, iron, and selenium are crucial for the development and function of immune cells. Selenium and manganese act as antioxidants which neutralize harmful free radicals. Zinc and copper have anti-inflammatory properties (Sadr et al., 2023). Selenium nanoparticles improve growth performance, egg production, feed conversion ratio, immune response, and antioxidant status which enhance meat quality and intestinal microbiota (Abdel-Moneim et al., 2022).

How Nano-minerals can Improve Mineral Absorption and Utilization?

Regular dietary minerals have low absorption and utilization in the body which encourages scientists to explore the potential of nano-minerals to increase digestion. Essential minerals like iron, calcium, and magnesium often have low solubility and absorption in the digestive system. Nano-minerals, ranging from 1-100 nanometre, such as; silver, copper, and zinc (Vazhacharickal and Thomas, 2022) interact more effectively with water due to their smaller size, improving solubility and bioavailability (Table 2). To protect minerals from degradation by stomach acid, enzymes, or other factors, nano-minerals can be encapsulated in carriers such as liposomes or nanoparticles. Nano-minerals also offer targeted

Table 2: Effect of various types of nanoparticles on poultry production

Sr #	Nano- encapsulation	Dose	Output/impact	Reference
1.	Silver- NPs	900 ppm/ kg diet	Body weight gain and feed intake increase and FCR value decreases	(Anwar et al., 2019)
2.	Gold- NPs		Growth performance increases	
3.	Copper-loaded chitosan	100 mg/kg diet	Increased growth performance, Immunity improved, Protein synthesis increased, Beneficial cecal microbiota population increase	
4.	Zinc oxide- NPs	20 mg/kg diet	Growth performance improves Anti-oxidative bio-marker increases	
5.	Montmorillonite- NPs	3 g/kg feed	Decrease the toxicity of aflatoxins	
6.	Zinc- NPs	80 mg/kg diet	Increased egg production, Size, and shell quality of egg improve, Culminates oxidative stress	(Abedini et al., 2017)
7.	Nano-encapsulated Ginger essential oil with chitosan	100 mg/kg feed	Improved weight gain, Growth of Lactobacilli population ileo-caecum appreciates, Mucin2 gene expression	(Amiri et al., 2021)
8.	Curcumin-cinnamon essential oil nano-emulsion	Sprinkled on meat	Decrease the total plate count (TPC), psychrophilic bacteria, yeast, and mold growth, and preserve the broiler meat from spoilage.	(Abdou et al., 2018)
9.	Curcumin-garlic essential oil nano-emulsion	Sprinkled on broiler meat	The lowest values of total volatile nitrogen (TVN) show meat is fresh and protein does not degrade Low thiobarbituric acid (TBA) value which shows low lipid oxidation. Showed the best values for water-holding	
10.	Eugenol nano-emulsion (E. coli challenged)	400 mg/kg feed	BWG, FI, and livability, digestive enzyme level increases, Lactobacillus species count in cecum increases, E*nterobacteriaceae* and *Bacteroid* count decrease, Bird challenged with E.coli strain show reduction in APEC O78 loads with downregulation of *papc, iron, iuta*, and *iss* virulence genes	(Ibrahim et al., 2022)
11.	Encapsulated trace mineral premix containing Zn, Cu, Mn, Fe, Se and I	250mg/kg 375mg/kg feed	Same effects on poultry as organic and inorganic minerals but less excretion of mineral	(Ramirez et al., 2022)
12.	Encapsulated form of lactic acid VS encapsulated form	0.6%	Improved broiler performances Reduced intestinal pH, Increased intestinal villi length and reduced only the number of S*almonella* sp	(Natsir et al., 2010)
13.	Fe- NPs	100mg/kg feed	Egg quality traits, immune response and biochemical blood indices without negatively affecting productive performance traits in laying hens, Increase the per-oxidation of egg lipids at this level.	(Javadifar, et al., 2020)

delivery in the intestine by attaching specific ligands to the nano-carrier for maximum absorption. These controlled release mechanisms optimize mineral efficacy (Barua and Mitragotri, 2014). The encapsulated nano-minerals improve the absorption and utilization of nutrients than traditional minerals (Sadr et al., 2023).

Role of Nanotechnology in Poultry Health Management

Challenges of Maintaining Hygiene in Poultry Houses

Maintaining hygiene in poultry houses is a complex task that involves addressing various challenges such as bio-security, waste management, ventilation, water quality, cleaning and disinfection, pest control, and worker hygiene practices (Pagar et al., 2020). Nanoparticles with antimicrobial properties, such as silver, copper, zinc oxide, titanium dioxide, and chitosan, have shown potential in surface disinfection due to their small size and high surface area-to-volume ratio. These nanoparticles can disrupt microbial membranes, interfere with cellular processes, and generate ROS that damage microbial DNA (Rai et al., 2009). TiO2 nanoparticles exhibit photo-catalytic activity when exposed to UV light, effectively killing bacteria and viruses. Airborne nanoparticles are also used for surface disinfection (Lara et al., 2010).

Early Disease Detection Challenges

Early disease diagnosis in poultry flocks is crucial for timely intervention and disease control, but it presents several challenges due to factors such as asymptomatic carriers, limited diagnostic tools, and the rapid spread of pathogens within flocks. Numerous diseases that affect poultry, like avian influenza and infectious bronchitis, can appear as sub-clinical infections, meaning that even if the birds carry the pathogens, they only exhibit minimal or no symptoms (Brown et al., 2006). Numerous pathogens, such as bacteria, viruses, and parasites, may cause poultry diseases; precise identification of each requires specialized diagnostic testing (Bello et al., 2018). Particularly in the early stages of infection, traditional diagnostic methods like culture-based methods and serological assays may lack sensitivity and specificity, causing false-negative or inconclusive results (Stärk et al., 2014).

Role of Nano-sensors in Early Disease Detection

Nano-sensors, have rapid and sensitive detection capabilities and have a lot of potential for in-field disease monitoring in poultry (Dhumpa et al., 2011). Nano-sensors generate a detectable signal such as fluorescence, electrochemical, or colorimetric changes that can be quantitatively evaluated after the target pathogen binds to the sensor surface (Lee et al., 2007). Early diagnosis and intervention are made possible by the sensitive detection of infections at low concentrations enabled by the signal transduction pathways (Stephen Inbaraj and Chen, 2016). Although nano-sensors can be reduced to micro or nanoscale dimensions, portable and point-of-care devices for pathogen detection on-site can be created (Yetisen et al., 2013). Portable nano-sensor platforms are suitable for environments with restricted resources or field applications because they offer rapid results and enable decentralized testing. Through the use of multiplexed detection techniques or arrays of different recognition elements, nano-sensors can be designed to detect multiple pathogens simultaneously. Multiplexed nano-sensor platforms enable comprehensive pathogen screening, identification of multiple infections, and efficient use of resources in diagnostic work flows (Guo et al., 2020). Bio-sensors can identify poultry products parameters like freshness, spoilage, and nutritional content in chicken meat which will ensure the quality of poultry products. Nano-biosensors are used in monitoring physiological parameters (Fig 3) including heart rate, temperature, and stress level (Sadr et al., 2023).

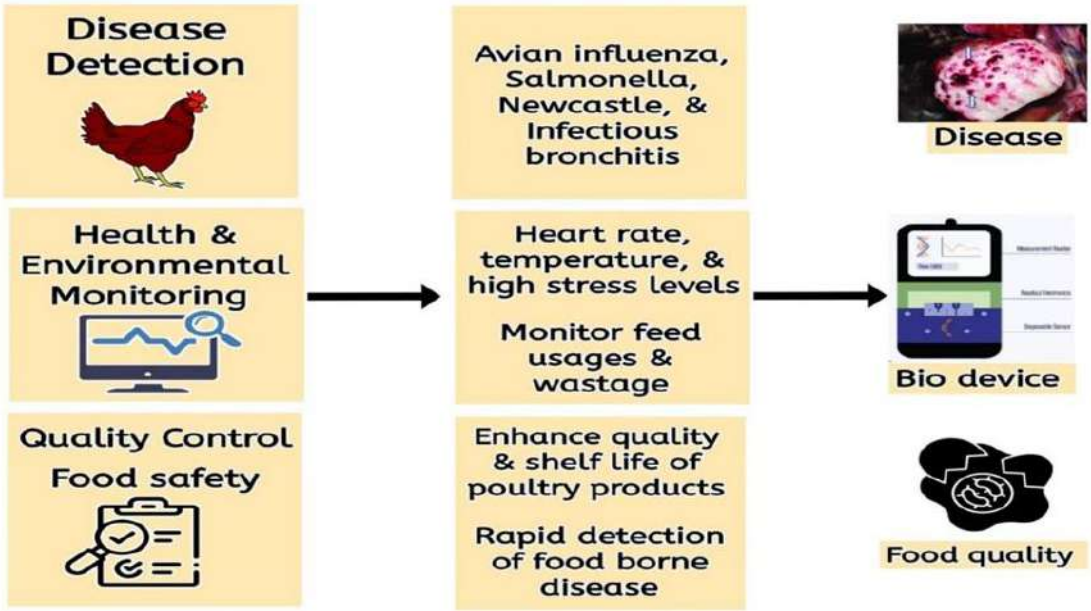


Fig. 3: Nano-biosensors application quality control, food safety, disease detection and environment monitoring (Sadr et al., 2023)

Nano-carriers for Targeted Delivery of Vaccines and Antibiotics

Challenges with Conventional Vaccines and Antibiotics

Conventional vaccines and antibiotics are used extensively in poultry production to prevent diseases and treat

bacterial infections but there are several limitations that lower their efficacy and sustainability. Conventional vaccines may produce sub-optimal immune responses in poultry due to factors such as antigen degradation, poor immunogenicity of antigens, and interference from maternal antibodies (Marangon and Busani, 2007). Many conventional vaccines require strict temperature control throughout storage and transportation, posing logistical challenges in regions with limited access to the cold chain. Traditional vaccines often target a single antigen, limiting their ability to provide broad-spectrum protection against diverse pathogens or emerging strains. The onset of immunity after vaccination with conventional vaccines may be delayed, leaving poultry susceptible to infections during the vulnerable period post-vaccination (Rauw et al., 2009). Continuous misuse of antibiotics in poultry production has developed antibiotic-resistant bacterial strains, posing a significant threat to both animal and human health (Zhu et al., 2013). Conventional antibiotics can disrupt the gut microbiota of poultry, causing dysbiosis, poor nutrient absorption, and increased susceptibility to opportunistic pathogens (Oakley and Kogut, 2016).

Nano-carriers as a Promising Solution to Conventional Vaccines and Antibiotics Challenges

Nano-carriers offer significant advantages for enhancing drug delivery to specific target sites within the body, including good vaccine delivery, improved targeting capabilities, and controlled release profiles. Nano-carriers can protect drug molecules from degradation in the body, leading to increased bioavailability and prolonged circulation in the bloodstream (Torchilin, 2014). The danger of systemic toxicity and adverse effects can be decreased by encasing antibiotics inside nano-carriers, which will enhance antibiotics effectiveness (Anselmo and Mitragotri, 2019). By responding to particular stimuli at the target region, such as pH, temperature, or enzyme activity, nano-carriers can be made to release encapsulated drugs in a regulated manner (Meng et al., 2014)

In 2014, Chinese scientists explored the encapsulation of the Newcastle disease virus (NDV) vaccine in chitosan nanoparticles, demonstrating enhanced mucosal immune responses and protection against NDV infection in chickens (Sun et al., 2014). Nanoemulsions and nanoparticles have shown promise in delivering poultry vaccines via oral or intranasal routes, offering convenient and effective administration in poultry farming (Jazayeri et al., 2021).

Ongoing Research on Nano-carrier based Vaccines against Poultry Diseases

In 2017, Indian scientists investigated the development of polymeric nanoparticles as carriers for the Marek's disease virus (MDV) vaccine in poultry. The study focused on evaluating the immunogenicity and protective efficacy of the polymeric nanoparticle- encapsulated MDV vaccine in chickens (Reddy et al., 2017). In Iran, explored the use of chitosan nanoparticles as carriers for the NDV vaccine in poultry. The study investigated the immunogenicity and protective efficacy of the chitosan nanoparticle- encapsulated NDV vaccine in chickens (Mohammadi et al., 2021). Most recently, the liposome-based vaccines for AIV in poultry showcased the increased stability and better immune responses elicited by the liposome-encapsulated AIV vaccine in chickens (Elbohy et al., 2024).

Improved Bio-security and Sanitation

Antimicrobial nano-materials have demonstrated significant potential to enhance poultry premises hygiene by efficiently inhibiting the growth of microorganisms that may infect poultry. Antimicrobial nanoparticles have the ability to reduce bacteria's adherence to surfaces, which reduces their ability to colonize and form bio-films (Sonawane et al., 2022). Metal and metal oxide nanoparticles are good antimicrobial agents i.e. Titanium dioxide and Zinc oxide (Elbourne et al., 2017).

Antimicrobial Meat Packaging

A tremendous increase in the population and growing demand for meat has taken the poultry industry to the sky heights. Industry focused on the quality production and packaging of meat. Nanotechnology is used in food packaging which enhances antimicrobial properties, microbial barrier, and chemical, thermal, and mechanical properties of packaging materials. Nano- composites are used for packaging meat. Natural or synthetic bio-polymers like chitosan, cellulose, polyvinyl alcohol and polylactide nanoparticles are used in biodegradable packaging. Nano device-combined polymers such as bio-sensors are able to detect microbes and toxins in the packaging (Ramachandraiah et al., 2015).

Emerging Trends and Future Prospects

Research on gene editing using nanoparticles for improving poultry traits, such as disease resistance and feed efficiency, is promising. CRISPR/Cas9 technology allows for precise gene editing by targeting specific DNA sequences. Nanoparticles, like liposomes and polymeric nanoparticles, can efficiently deliver CRISPR/Cas9 components into poultry cells (Khwatenge and Nahashon, 2021). Gene editing can enhance disease resistance by modifying immunity genes, such as the CD163 gene, and improve feed efficiency by targeting genes involved in nutrient metabolism and utilization (Cheng et al., 2019). Nano-material coatings are being developed to improve hygiene, reduce disease transmission, and enhance poultry production efficiency. These coatings consist of nanoparticles dispersed in a matrix, such as titanium dioxide (TiO2), zinc oxide (ZnO), and silver nanoparticles. These coatings have antimicrobial properties and photo-catalytic activity, which can inhibit the growth of bacteria, viruses, and fungi on poultry house surfaces. Nano-material coatings also contribute to improved air quality by reducing dust accumulation. Research is focused on developing environmentally friendly coatings

that do not leach into the environment. Although initial costs may be higher than traditional methods, the long-term benefits, such as reduced cleaning and maintenance requirements, improved poultry health, and increased productivity, make them cost-effective in the long run (Lead et al., 2018). Nano-biosensors are a revolutionary approach to personalized nutrition in poultry, enabling real-time monitoring of physiological parameters and nutrient levels. These sensors can be integrated into feed delivery systems or implanted in birds to continuously monitor bio-markers. By analyzing these parameters, personalized feed formulations can be created to meet individual nutritional needs, leading to improved growth performance, feed efficiency, and overall health. By detecting early signs of health problems or nutrient deficiencies. Nano-biosensors can help prevent disease outbreaks and reduce antibiotic needs (Hill and Li, 2017).

Nanotechnology in poultry production poses potential environmental and health risks, including toxicity, environmental release, and unintended consequences. If not managed properly, nanoparticles can cause environmental contamination, persist in soil, water, and air, and potentially enter the food chain. They may also contribute to antibiotic-resistant bacteria. To mitigate these risks, responsible development and application of nanotechnology in poultry production are essential, including thorough risk assessments, regulation of nanoparticles use, and best practices (Li et al., 2017).

Conclusion

Nanoparticles are highly promising technology with a wide range of applications in the poultry industry. However, their optimal usage still needs to be studied. Common modes of action associated with nanoparticles include antimicrobial activity, cytotoxicity induced by ROS, and genotoxicity. It is crucial to study how nanoparticles can effectively reduce disease prevalence in the poultry industry in order to achieve better growth, production, and the production of healthier and safer products. A recent study has shown that adding various dietary nanoparticles to poultry feed significantly improves growth, production, and the quality of meat and eggs. Additionally, incorporating these particles during the processing and storage of meat products enhances and maintains their quality. However, further research is needed to investigate the correct dosage, sizes, and shapes of these materials. It is also important to study the accumulation of nanoparticles in the body, the number of residual particles in body tissues, and the potential toxic effects.

REFERENCES

Abdel-Moneim, A. M. E., Shehata, A. M., Mohamed, N. G., Elbaz, A. M., and Ibrahim, N. S. (2022). Synergistic effect of Spirulina platensis and selenium nanoparticles on growth performance, serum metabolites, immune responses, and antioxidant capacity of heat-stressed broiler chickens. *Biological Trace Element Research*, *200*(2). https://doi.org/10.1007/s12011-021-02662-w

Abdou, E. S., Galhoum, G. F., and Mohamed, E. N. (2018). Curcumin loaded nanoemulsions/pectin coatings for refrigerated chicken fillets. *Food Hydrocolloids*, *83*. https://doi.org/10.1016/j.foodhyd.2018.05.026

Abedini, M., Shariatmadari, F., Torshizi, M. A. K., and Ahmadi, H. (2017). Effects of a dietary supplementation with zinc oxide nanoparticles, compared to zinc oxide and zinc methionine, on performance, egg quality, and zinc status of laying hens. *Livestock Science*, *203*. https://doi.org/10.1016/j.livsci.2017.06.010

Altammar, K. A. (2023). A review on nanoparticles: characteristics, synthesis, applications, and challenges. In *Frontiers in Microbiology* (Vol. 14). https://doi.org/10.3389/fmicb.2023.1155622

Amiri, N., Afsharmanesh, M., Salarmoini, M., Meimandipour, A., Hosseini, S. A., and Ebrahimnejad, H. (2021). Nanoencapsulation (in vitro and in vivo) as an efficient technology to boost the potential of garlic essential oil as alternatives for antibiotics in broiler nutrition. *Animal*, *15*(1). https://doi.org/10.1016/j.animal.2020.100022

Anselmo, A. C., and Mitragotri, S. (2019). Nanoparticles in the clinic: An update. *Bioengineering and Translational Medicine*, *4*(3). https://doi.org/10.1002/btm2.10143

Anwar, M. I., Awais, M. M., Akhtar, M., Navid, M. T., and Muhammad, F. (2019). Nutritional and immunological effects of nano-particles in commercial poultry birds. In *World's Poultry Science Journal* (Vol. 75, Issue 2). https://doi.org/10.1017/S0043933919000199

Barua, S., and Mitragotri, S. (2014). Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects. In *Nano Today* (Vol. 9, Issue 2). https://doi.org/10.1016/j.nantod.2014.04.008

Bayda, S., Adeel, M., Tuccinardi, T., Cordani, M., and Rizzolio, F. (2020). The history of nanoscience and nanotechnology: From chemical-physical applications to nanomedicine. In *Molecules* (Vol. 25, Issue 1). https://doi.org/10.3390/molecules25010112

Bello, M. B., Yusoff, K., Ideris, A., Hair-Bejo, M., Peeters, B. P. H., and Omar, A. R. (2018). Diagnostic and Vaccination Approaches for Newcastle Disease Virus in Poultry: The Current and Emerging Perspectives. In *BioMed Research International* (Vol. 2018). https://doi.org/10.1155/2018/7278459

Brown, J. D., Stallknecht, D. E., Beck, J. R., Suarez, D. L., and Swayne, D. E. (2006). Susceptibility of North American ducks and gulls to H5N1 highly pathogenic avian influenza viruses. *Emerging Infectious Diseases*, *12*(11). https://doi.org/10.3201/eid1211.060652

Cheng, Y., Lun, M., Liu, Y., Wang, H., Yan, Y., and Sun, J. (2019). CRISPR/Cas9-mediated chicken TBK1 gene knockout and its essential role in STING-mediated IFN-β induction in chicken cells. *Frontiers in Immunology*, *10*(JAN).

https://doi.org/10.3389/fimmu.2018.03010

Danchuk, O., Levchenko, A., da Silva Mesquita, R., Danchuk, V., Cengiz, S., Cengiz, M., and Grafov, A. (2023). Meeting Contemporary Challenges: Development of Nanomaterials for Veterinary Medicine. *Pharmaceutics*, 15(9), 2326.

Dhumpa, R., Handberg, K. J., Jørgensen, P. H., Yi, S., Wolff, A., and Bang, D. D. (2011). Rapid detection of avian influenza virus in chicken fecal samples by immunomagnetic capture reverse transcriptase-polymerase chain reaction assay. *Diagnostic Microbiology and Infectious Disease*, *69*(3). https://doi.org/10.1016/j.diagmicrobio.2010.09.022

Elbohy, O. A., Iqbal, M., Daly, J. M., and Dunham, S. P. (2024). Development of Virus-like Particle Plant-Based Vaccines against Avian H5 and H9 Influenza A Viruses. *Veterinary Sciences*, *11*(2). https://doi.org/10.3390/vetsci11020093

Elbourne, A., Crawford, R. J., and Ivanova, E. P. (2017). Nano-structured antimicrobial surfaces: From nature to synthetic analogues. In *Journal of Colloid and Interface Science* (Vol. 508). https://doi.org/10.1016/j.jcis.2017.07.021

Gelaye, Y. (2023). Application of nanotechnology in animal nutrition: Bibliographic review. Cogent Food and Agriculture, 10(1). https://doi.org/10.1080/23311932.2023.2290308

Guo, Z., Huang, X., Li, Z., Shi, J., Zhai, X., Hu, X., Liang, N., and Zou, X. (2020). Rapid and highly sensitive detection of Salmonella typhimurium in lettuce by using magnetic fluorescent nanoparticles. *Analytical Methods*, *12*(48). https://doi.org/10.1039/d0ay01744b

Hill, E. K., and Li, J. (2017). Current and future prospects for nanotechnology in animal production. In *Journal of Animal Science and Biotechnology* (Vol. 8, Issue 1). https://doi.org/10.1186/s40104-017-0157-5

Ibrahim, D., Eldemery, F., Metwally, A. S., Abd-Allah, E. M., Mohamed, D. T., Ismail, T. A., Hamed, T. A., Al Sadik, G. M., Neamat-Allah, A. N. F., and Abd El-Hamid, M. I. (2022). Dietary Eugenol Nanoemulsion Potentiated Performance of Broiler Chickens: Orchestration of Digestive Enzymes, Intestinal Barrier Functions and Cytokines Related Gene Expression With a Consequence of Attenuating the Severity of E. coli O78 Infection. *Frontiers in Veterinary Science*, *9*. https://doi.org/10.3389/fvets.2022.847580

Islam, M. S. Bin, Miah, M., Hossain, M. E., and Kibria, K. M. K. (2020). A conserved multi-epitope-based vaccine designed by targeting hemagglutinin protein of highly pathogenic avian H5 influenza viruses. *3 Biotech*, *10*(12). https://doi.org/10.1007/s13205-020-02544-3

Javadifar, A., Hosseini-vashan, S. J., Montazer Torbati, M. B., and Shamshirgran, Y. (2020). The effect of iron nano oxide on performance, egg quality indices and antioxidant status of laying hen. *Animal Sciences Journal*, 33(128), 125–140.

Jazayeri, S. D., Lim, H. X., Shameli, K., Yeap, S. K., and Poh, C. L. (2021). Nano and Microparticles as Potential Oral Vaccine Carriers and Adjuvants Against Infectious Diseases. In *Frontiers in Pharmacology* (Vol. 12). https://doi.org/10.3389/fphar.2021.682286

Khwatenge, C. N., and Nahashon, S. N. (2021). Recent Advances in the Application of CRISPR/Cas9 Gene Editing System in Poultry Species. In *Frontiers in Genetics* (Vol. 12). https://doi.org/10.3389/fgene.2021.627714

Kiarie, E. G., and Mills, A. (2019). Role of feed processing on gut health and function in pigs and poultry: Conundrum of optimal particle size and hydrothermal regimens. In *Frontiers in Veterinary Science* (Vol. 6, Issue FEB). Frontiers Media S.A. https://doi.org/10.3389/fvets.2019.00019

Kraft, J. C., Freeling, J. P., Wang, Z., and Ho, R. J. Y. (2014). Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. In *Journal of Pharmaceutical Sciences* (Vol. 103, Issue 1). https://doi.org/10.1002/jps.23773

Kumar, S., Bhushan, P., and Bhattacharya, S. (2018). Fabrication of Nanostructures with Bottom-up Approach and Their Utility in Diagnostics, Therapeutics, and Others. In *Energy, Environment, and Sustainability*. https://doi.org/10.1007/978-981-10-7751-7_8

Lara, H. H., Ayala-Nuñez, N. V., Ixtepan-Turrent, L., and Rodriguez-Padilla, C. (2010). Mode of antiviral action of silver nanoparticles against HIV-1. *Journal of Nanobiotechnology*, *8*. https://doi.org/10.1186/1477-3155-8-1

Lead, J. R., Batley, G. E., Alvarez, P. J. J., Croteau, M. N., Handy, R. D., McLaughlin, M. J., Judy, J. D., and Schirmer, K. (2018). Nanomaterials in the environment: Behavior, fate, bioavailability, and effects—An updated review. In *Environmental Toxicology and Chemistry* (Vol. 37, Issue 8). https://doi.org/10.1002/etc.4147

Lee, J. S., Han, M. S., and Mirkin, C. A. (2007). Colorimetric detection of mercuric ion (Hg2+) in aqueous media using DNA-functionalized gold nanoparticles. *Angewandte Chemie - International Edition*, *46*(22). https://doi.org/10.1002/anie.200700269

Li, Y., Qin, T., Ingle, T., Yan, J., He, W., Yin, J. J., and Chen, T. (2017). Differential genotoxicity mechanisms of silver nanoparticles and silver ions. *Archives of Toxicology*, *91*(1). https://doi.org/10.1007/s00204-016-1730-y

Malik, S., Muhammad, K., and Waheed, Y. (2023). Nanotechnology: A revolution in modern industry. Molecules, 28(2), 661.

Marangon, S., and Busani, L. (2007). The use of vaccination in poultry production. *OIE Revue Scientifique et Technique*, *26*(1). https://doi.org/10.20506/rst.26.1.1742

Mekonnen, G. (2021). Review on application of nanotechnology in animal health and production. *Journal Nanomedicine Nanotechnology*, 12, 559.

Meng, F., Zhong, Y., Cheng, R., Deng, C., and Zhong, Z. (2014). PH-sensitive polymeric nanoparticles for tumor-targeting doxorubicin delivery: Concept and recent advances. In *Nanomedicine* (Vol. 9, Issue 3). https://doi.org/10.2217/nnm.13.212

Mohammadi, A. R., Zamani Moghaddam, A., and Shahsavandi, S. (2021). Encapsulation of inactivated Newcastle disease

virus onto the chitosan nanoparticles for use in mucosal immunity. *Iranian Journal of Virology*, 15(1), 32-39.

Natsir, M. H., Sjofjan, O., Umam, K., Manab, A., and Widodo, E. (2010). Effects of liquid and encapsulated lactic acid in broiler diets on performances, intestinal characteristics and intestinal microflora. *Journal of Poultry Science*, *47*(3). https://doi.org/10.2141/jpsa.009099

Oakley, B. B., and Kogut, M. H. (2016). Spatial and temporal changes in the broiler chicken cecal and fecal microbiomes and correlations of bacterial taxa with cytokine gene expression. *Frontiers in Veterinary Science*, *3*(FEB). https://doi.org/10.3389/fvets.2016.00011

Pagar, T., Ghotekar, S., Pansambal, S., Pagar, K., and Oza, R. (2020). Biomimetic Synthesis of CuO Nanoparticle using Capparis decidua and their Antibacterial Activity. *Advanced Journal of Science and Engineering*, *1*(4).

Poddar, K., and Kishore, A. V. (2022). Nanotechnology in animal production. In Emerging Issues in Climate Smart Livestock Production (pp. 149-170). Academic Press.

Rai, M., Yadav, A., and Gade, A. (2009). Silver nanoparticles as a new generation of antimicrobials. In *Biotechnology Advances* (Vol. 27, Issue 1). https://doi.org/10.1016/j.biotechadv.2008.09.002

Ramachandraiah, K., Han, S. G., and Chin, K. B. (2015). Nanotechnology in meat processing and packaging: Potential applications - A review. *Asian-Australasian Journal of Animal Sciences*, *28*(2). https://doi.org/10.5713/ajas.14.0607

Ramirez, S., Lu, W.-B., Davin, R., Broek, H. van der, and Liu, Y.-G. (2022). Effect of Encapsulated Trace Minerals Premix in Comparison with Inorganic and Organic Microminerals on Growth Performance and Mineral Excretion of Broiler. *Journal of Food Science and Nutrition Research*, *05*(01). https://doi.org/10.26502/jfsnr.2642-11000085

Rauw, F., Gardin, Y., Palya, V., van Borm, S., Gonze, M., Lemaire, S., van den Berg, T., and Lambrecht, B. (2009). Humoral, cell-mediated and mucosal immunity induced by oculo-nasal vaccination of one-day-old SPF and conventional layer chicks with two different live Newcastle disease vaccines. *Vaccine*, *27*(27). https://doi.org/10.1016/j.vaccine.2009.03.068

Rawat, M., Yadukrishnan P., and Kumar, N. (2018). *Mechanisms of Action of Nanoparticles in Living Systems*. https://doi.org/10.4018/978-1-5225-3126-5.ch014

Reddy, S. M., Izumiya, Y., and Lupiani, B. (2017). Marek's disease vaccines: Current status, and strategies for improvement and development of vector vaccines. *Veterinary Microbiology*, *206*. https://doi.org/10.1016/j.vetmic.2016.11.024

Sadr, S., Lotfalizadeh, N., Ghafouri, S. A., Delrobaei, M., Komeili, N., and Hajjafari, A. (2023). Nanotechnology innovations for increasing the productivity of poultry and the prospective of nanobiosensors. In *Veterinary Medicine and Science* (Vol. 9, Issue 5). https://doi.org/10.1002/vms3.1193

Sayee, H., Thirumalaisamy, G., Muralidharan, J., Senthilkumar, S., Sayee, R. H., and Priyadharsini, M. (2019). COST-EFFECTIVE FEEDING OF POULTRY. In *Article in International journal of Environmental Science and Technology*. https://www.researchgate.net/publication/335054995

Sonawane, J. M., Rai, A. K., Sharma, M., Tripathi, M., and Prasad, R. (2022). Microbial biofilms: Recent advances and progress in environmental bioremediation. *Science of the Total Environment*, *824*. https://doi.org/10.1016/j.scitotenv.2022.153843

Stärk, K. D. C., Alonso, S., Dadios, N., Dupuy, C., Ellerbroek, L., Georgiev, M., Hardstaff, J., Huneau-Salaün, A., Laugier, C., Mateus, A., Nigsch, A., Afonso, A., and Lindberg, A. (2014). Strengths and weaknesses of meat inspection as a contribution to animal health and welfare surveillance. *Food Control*, *39*(1). https://doi.org/10.1016/j.foodcont.2013.11.009

Stephen Inbaraj, B., and Chen, B. H. (2016). Nanomaterial-based sensors for detection of foodborne bacterial pathogens and toxins as well as pork adulteration in meat products. In *Journal of Food and Drug Analysis* (Vol. 24, Issue 1). https://doi.org/10.1016/j.jfda.2015.05.001

Suk, J. S., Xu, Q., Kim, N., Hanes, J., and Ensign, L. M. (2016). PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. In *Advanced Drug Delivery Reviews* (Vol. 99). https://doi.org/10.1016/j.addr.2015.09.012

Sun, Y., Zhang, Y., Shi, C., Li, W., Chen, G., Wang, X., and Zhao, K. (2014). Newcastle disease virus vaccine encapsulated in biodegradable nanoparticles for mucosal delivery of a human vaccine. In *Human Vaccines and Immunotherapeutics* (Vol. 10, Issue 8). https://doi.org/10.4161/hv.29201

Torchilin, V. P. (2014). Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. In *Nature Reviews Drug Discovery* (Vol. 13, Issue 11). https://doi.org/10.1038/nrd4333

Van Tran, V., Moon, J. Y., and Lee, Y. C. (2019). Liposomes for delivery of antioxidants in cosmeceuticals: Challenges and development strategies. In *Journal of Controlled Release* (Vol. 300). https://doi.org/10.1016/j.jconrel.2019.03.003

Vazhacharickal, P. (2022) 'Synthesis and Characterization of Metal Nanoparticles', *Journal of Nanoscience and Technology*, 3:1-9.

Yetisen, A. K., Akram, M. S., and Lowe, C. R. (2013). Paper-based microfluidic point-of-care diagnostic devices. In *Lab on a Chip* (Vol. 13, Issue 12). https://doi.org/10.1039/c3lc50169h

Zhu, Y. G., Johnson, T. A., Su, J. Q., Qiao, M., Guo, G. X., Stedtfeld, R. D., Hashsham, S. A., and Tiedje, J. M. (2013). Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(9). https://doi.org/10.1073/pnas.1222743110

Chapter 23

Exploring the Potential of Plant Extract, Green Nanoparticles, and Oil Formulation for the Control of Disease Caused by Cestodes: Trends and Challenges

Farhana Yousaf[1], Saba Kousar[1], Kainat Farooq Khokhar[1], Maher Nigar[1], Mahnoor Aslam[1], Madiha Fatima[1,2], Madiha Rasool[1,3], Amina Riaz[4], Hira Muqaddas[1*] and Naunain Mehmood [5,6*]

[1]Department of Zoology, The Women University Multan, Multan, Pakistan
[2]Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan
[3]Institute of Zoology, Bahauddin Zakariya University, Multan, Pakistan.
[4]Department of Pharmacy, The Women University Multan, Multan, Pakistan
[5]Department of Zoology, University of Sargodha, Sargodha, Pakistan
[6]Department of Veterinary Medicine, University of Sassari, Sassari, Italy
*Corresponding author: naunain.mahmood@uos.edu.pk; hira.6385@wum.edu.pk

ABSTRACT

Cestode infestations severely compromise animal health and result in significant financial losses because of excessive levels of sickness and death, costly medication, and decreased production. Because of the emergence of drug susceptibility and climate change, the efficacy of conventional control methods, such as periodic anthelmintic medication along with control measures, are being put under increasing pressure. This chapter highlights the importance of using plant extracts, essential oils, and green nanoparticle technologies to reduce livestock cestode infestations. The increasing acceptance of natural remedies can be attributed to their strong antiparasitic characteristics and ability to offer a persistent resolution for problems related to animal infestation. Plant extracts that are effective in the management of parasitic diseases include ginger, eucalyptus, coriander seeds, neem, garlic, and pumpkin seeds. These extracts are rich in bioactive components that demonstrate potent anti-cestode activity. Similarly, essential oils derived from Ajowan, European black pine, garlic, black cumin, and turmeric, along with green nanoparticles manufactured from plant sources, such as eucalyptus and neem, possess beneficial antiparasitic, antibacterial, and antifungal qualities. Future proposals call for the undertaking of further research and studies to improve formulations for the large-scale production and application of essential oils, green nanoparticles, and plant extracts with a specific focus on the management of cestode infections. Furthermore, there is need of effective integration of these natural therapies into current frameworks for controlling livestock illness necessitates collaboration between researchers, veterinarians, and legislators.

KEYWORDS
Cestode, *Moniezia, Echinococcus granulosus*, *Hymenolepis*, *Raillietina*, *Taenia,* Anthelmintic treatment, Plant extracts, Essential oil, Green nanoparticles, Scolicidal, protoscolex.

Received: 19-Jun-2024
Revised: 18-Jul-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Yousaf F, Kousar S, Khokhar KF, Nigar M, Aslam M, Fatima M, Rasool M, Riaz A, Muqaddas H and Mehmood N, 2024. Exploring the potential of plant extract, green nanoparticles, and oil formulation for the control of disease caused by cestodes: trends and challenges. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 198-207. https://doi.org/10.47278/book.CAM/2024.486

INTRODUCTION

Cestodes, also referred to as tapeworms, are significant endoparasites that affect both livestock and humans (Siles-Lucas and Hemphill, 2002). The genus cestode consists of around 5,000 species that are distributed globally (Trevisan et al., 2021). These parasites can be transmitted from animals to humans and vice versa (Jeon and Eom, 2024), thereby having a major impact on both the human and livestock sectors. Almost all the cestodes have complicated life cycles (Fig. 1), involving both final and intermediate hosts with severe clinical manifestations such as sparganosis, neurocysticercosis, and echinococcosis (Jeon and Eom, 2024). Apart from the complex life cycle, they are distinct in a few ways, such as tapeworms absorbing nutrients through the integument and lacking an alimentary canal. They have a scolex (head) and neck that are joined to repeating segments called proglottids. Terminal proglottids release eggs that are expelled through the stool, where they hatch into oncospheres. These oncospheres then move to the various organs, where they mature into cysticercus larvae (or hydatid larvae, depending on the species) (Panda et al., 2022). Cestodes species cause infection in

livestock, leading to significant economic losses and jeopardizing food production in many parts of the world. (Abdel-Ghaffar et al., 2011).

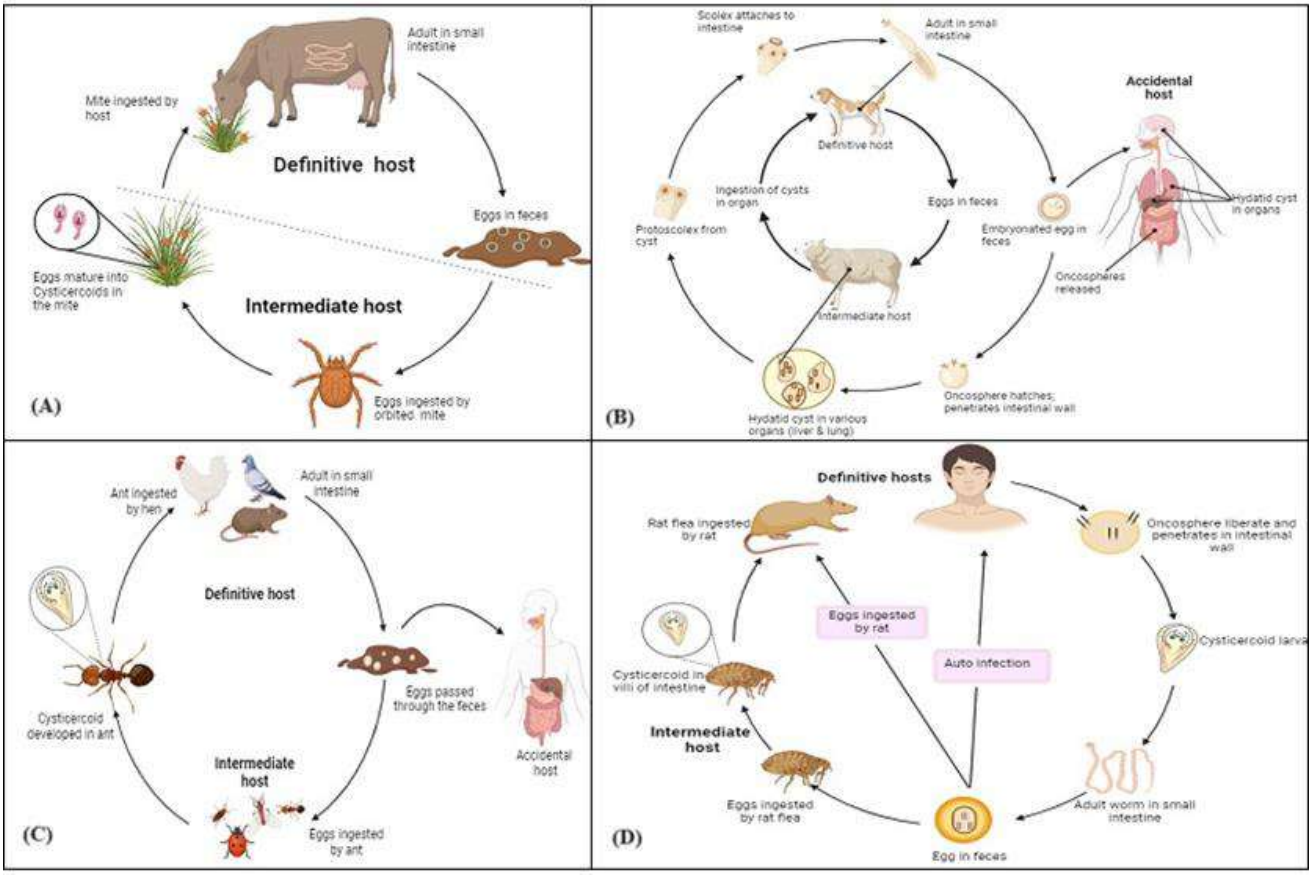


Fig. 1: Life cycle of cestodes along with their intermediate and definite host (a) *Moniezia* spp. (b) *Echinococcus granulosus* (c) *Raillietina* spp. (d) *Hymenolepis* spp.

Recently, many studies have primarily focused on natural therapies because of increasing anthelmintic resistance and side effects of synthetic drugs. Some plants have been proven to be effective against helminthic parasites, but there are many more plants that haven't been studied so far (Kundu et al., 2012). For this purpose, a program launched by the World Health Organization (WHO) in 2000 formally advocated the study of goods produced from plants (Abdel-Ghaffar et al., 2011), that will ultimately have a beneficial outcome for the development of new and effective green anthelmintic drug. Although there are a limited number of medications that are effective against intestinal helminths, over one-third of the world's population does not have access to basic medications, and that number rises to over 50% in many under-developed nations. In this context, traditional medicines, primarily relying on herbs and trees, can provide a significant and readily available source of healthcare for people and their livestock. Medicinal plants have served as crucial sources of therapeutic remedies for thousands of years and remain essential in modern times too (Yadav and Temjenmongla, 2011). With advances in technologies, Plant-based natural products (NP) are being produced and experimentally studied to determine their efficacy against cestode parasites. The production of green nanoparticles (NPs) is inexpensive, scalable, and environmentally harmless (Gour and Jain, 2019). Concurrently Maggiore and Elissondo (2014) have found that certain essential oils and their constituents exhibit anthelminthic effects, however, additional research is needed.

This chapter discusses the utilization of naturally occurring compounds, such as essential oils, green nanoparticles, and plant extracts, as pharmaceuticals for treating cestodes of veterinary importance. There are many benefits of these naturally occurring compounds as they are safe to consume, readily available, and do not have any detrimental effect on our ecosystem.

Current Challenges to Anthelminthic Research and its Application

Pakistan's economy depends heavily on its livestock sector. Livestock can contract several parasite illnesses because of insufficient care, an unhygienic environment, severe weather conditions, and close proximity to infected animals (Gadahi et al., 2009). Tropical countries in South Asia have a rich biodiversity that could offer natural products for anthelmintic activity. However, challenges like limited research, funding, awareness, industry partnerships, and technological innovations hinder anthelmintic research in the region (Kamal et al., 2023). Systematic deworming of livestock with a broad-spectrum anthelminthic cannot be suggested to pastoralists due to high pricing, unavailability or inaccessibility of medications and veterinary services. As a result, low-cost locally applied measures such as the use of plant-based remedies against GI

parasites should be systematically evaluated for their effectiveness against the most common helminth species in the South Asia region (Raza et al., 2014).

Exploring the Efficacy of Medicinal Plants in Cestode Parasite Control

The control of parasites often relies on commercial drugs, but these are expensive, making them inaccessible to many low-income farmers. Additionally, some parasites have developed resistance to these drugs and their use can contribute to environmental pollution (James et al., 2009). Because of the challenges with expensive and potentially environmentally harmful commercial drugs, farmers have turned to alternative methods, such as using the medicinal plant to treat and control livestock parasites. There's a belief that natural products are perceived as safe and harmonious with the biological system (Sanhokwe et al., 2016).

Plants have the ability to produce beneficial synthetic compounds. Extracting and identifying these active compounds from medicinal plants have led to the discovery of new drugs with significant therapeutic benefits (Huie, 2002). Plant extracts can function as scolicidal agents for cestodes, in the distant past plant-based helminthic treatments were widely used. In 1974, a successful treatment in Taiwan involved thirty-two individuals with taeniasis using a combination of a mixture of boiled areca nuts and pumpkin seeds (Chung and Ko, 1976). In 2009, extracts from pumpkin seeds were utilized for the treatment of *Tenia solium* (Ito et al., 2013). The efficacy of wormicidal plant extracts from *Melia azedarach* surpassed that of piperazine phosphate in the treatment of *T. solium* (Szewezuk et al., 2003). In general, the efficacy of an extract against a specific worm load is influenced by the choice of extraction fluid, such as methanolic, ethanolic, aqueous, acetonitrile, chloroform, etc. (Mehlhorn et al., 2011) (Fig. 2). Below, we shall discuss promising studies on the plant extract produced by using various extraction fluids.

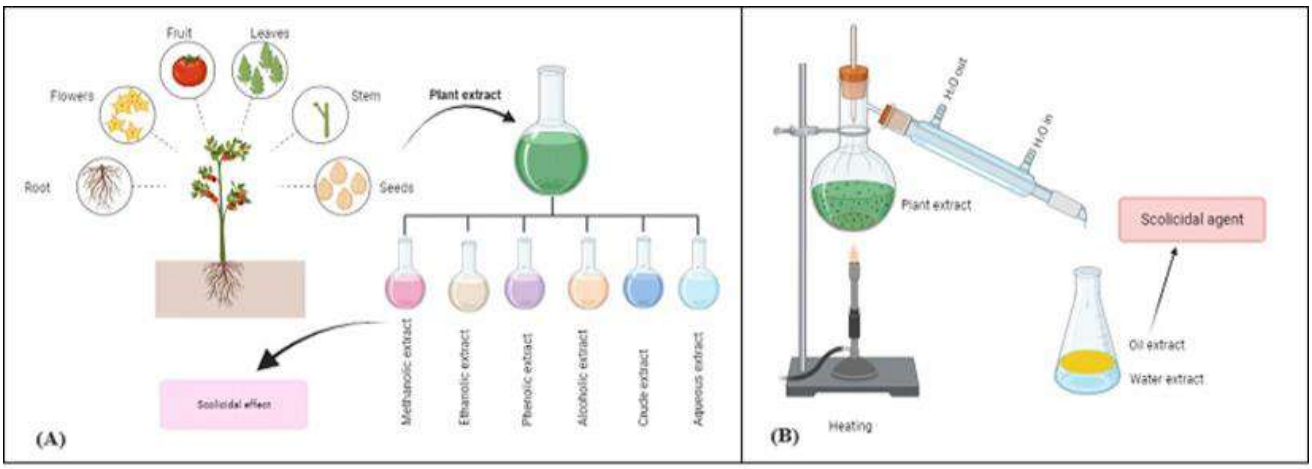


Fig. 2: Various plant parts can be utilized to make plant extracts (A) and essential oils (B) through the use of different extraction mediums.

Methanolic Extract

The methanolic extracts of ginger (*Zingeber officinale*) and eucalyptus can be used to treat *E. granulosus*. The extract of ginger at a concentration of 100mg/ml and eucalyptus at concentrations of 50 and 100mg/ml exhibited a 100% kill rate of protoscolices after 40 minutes. Additionally, all concentrations of the methanolic extract of ginger and eucalyptus can show a significant effect on protoscolex (Faizei et al., 2015) (Table 1). Another methanolic extract of Shirazi thyme (*Zataria multiflora)* is used for the treatment of cestodes at a concentration of 25mg/ml shows 100% scolicidal effect after 1 minute. These findings suggest that the methanolic extract of *Z. multiflora* exhibits strong scolicidal activity and could be considered an effective agent against parasites (Moazeni and Roozitalab, 2012).

Phenolic Extract

Phenolic extract obtained from coriander (*Coriandrum sativum)* seeds can be used to treat *E. granulosus*. Further study revealed that higher concentrations of this extract correlated with reduced protoscolices viability, and the number of deceased protoscolices increased over time. Particularly, after three days of therapy, a concentration of 0.75gm/ml had the greatest effect on the persistence of protoscolices, therefore could help in eliminating the parasite (Dawwas, 2008) (Table 1).

Ethanolic Extract

Ethanolic extract of ginger (*Zingeber officinale*) has anti-protoscolicidal properties. Ginger is one of the most well-known spices in the world, and it has been used for centuries for its medicinal advantages. Protoscolices of *E. granulosus* can be eliminated at concentrations of 150mg per milliliter after one hour of exposure (Baqer et al., 2014). There is another ethanolic extracts of mint (*Mentha spicata*), garden thyme (*Thymus vulgaris*), and tulsi (*Ocimum basilicum*) which may act as an effective alternative to anti-protoscolices. The garden thyme and mint extracts had the maximum efficacy at 100%,

whereas tulsi had 98.8% efficacy after a 20-minute exposure to 75 milligrams per milliliter, greatly diminishing the viability of protoscolices. However, the extract revealed time-dependent consequences (Abed and Ibrahim, 2021).

Alcoholic Extract

An alcoholic extract from coriander (*Coriandrum sativum*) seeds has been used to treat parasitic illnesses. Specifically, administering doses of *C. sativum* at five hundred and seven hundred fifty milligrams per kilogram shows complete efficacy after fifteen days of therapy. The addition of a thousand milligrams per milliliter of *C. sativum* extract has been shown to remove worms in a thirty-minute timeframe. According to Hosseinzadeh et al. (2016), the extract of *C. sativum* has potential in combating *Hymenolepis nana* (Table 1).

Aqueous Extract

A scolicidal agent has been found in the aqueous extract of Mediterranean saltbush (*Atriplex halimus*) leaves. Following 120 minutes of incubation, the death rates were 99.36 and 100%, at doses of 60 and 100mg/ml, respectively. Scanning electron microscopy (SEM) pictures showed these plant's extracts affected the parasite tegument, illustrating the potential benefits of *A. halimus* extract as a possible scolicidal therapy for hydatid cysts (Bouaziz et al., 2021).

Raw Extract

The unrefined extract of santonica (*Artemisia cina*), has anthelmintic properties. Through *in-vitro* and *in-vivo* experiments, the efficacy of the raw plant extract has been demonstrated at different concentrations. The plant extract was effective in vitro at all doses, and microscopy examination demonstrated that the worms' different structures such as scolex and microtriches of the external tegumental surface, were notably damaged. Using anthelminthic treatment to treat severely affected animals resulted in the complete elimination of infection. The results of fecal examinations after the treatment showed that there are no eggs of parasites in the feces of animals (Bashtar et al., 2010). A mixture of onion extract (*Allium cepa*) and coconut extract (*Cocos nucifera*) combined with milk powder has shown effectiveness in treating Moniezia spp. When a dose of 60g of this extract was administered daily for 8 days, the worm stages disappeared from the feces (Mehlhorn et al., 2010).

Table 1: An overview of the latest findings on the efficacy of plant extract in controlling Cestodes of veterinary importance

Plant Extract	Parasites	Dose	Exposure Time	Mortality (%)	Effects	References
Ocimum basilicum, *Mentha spicata* and *Thymus vulgaris*	*Echinococcus granulosus*	75mg/ml	20 min	98.8, 100	Kill protoscolex	Abed and Ibrahim (2021)
Allium cepa and *Cocos nucifera*	Moniezia spp.	60gm	9 - 20 days	100	Disappearance of proglottids	Mehlhorn et al. (2010)
Coconut and Onion	*Hymenolepis diminuta, Hymenolepis microstoma* and*Taenia taeniaeformis*	Variable	33 days	100	Death of worms	Ghaffar et al. (2010)
Coriandrum sativum	*Hymenolepis nana*	500 and750mg/kg	15 days	100	Death of worms	Hosseinzadeh et al. (2016)
Zingiber officinale, *Artemisia aucheri* and Eucalyptus	*E. granulosus*	50,100mg/ml	40 min	100	Scolicidal effect	Faizei et al. (2015)
Atriplex halimus	*E. granulosus*	60mg/ml,100mg/ml	120 min	93.36, 100	Scolicidal effect	Bouaziz et al. (2021)
Artemisia cina	Moniezia spp.	40mg/ml	9 days	100	Absence of eggs in faeces	Bashtar et al. (2010)
Zingiber officinale	*E. granulosus*	150mg/ml	60 min	100	Zero percent viability rate of protoscolex	Bakqer et al. (2014)
Coriandrum sativum	*E. granulosus*	0.75gm/ml	3 days	100	Kill protoscolex	Dawwas (2008)
Zataria multiflora	*E. granulosus*	10mg/ml	1,2,3 min	68.9, 93.7, 100	Scolicidal effect	Moazeni and Roozidalab (2012)
Sambucus ebulus	*E. granulosus*	100 mg/ml	60 min	98.60	Scolicidal effect	Gholami et al. (2013)
Dendrosicyos socotrana and *Jatropha unicostata*	*E. granulosus*	1000µg/ml	N.A	N.A	Significantly reducing protoscolex	Barzinji et al. (2009)
Zingiber officinale	*E. granulosus*	150g/ml	60 min	100	Scolicidal agent	Baqer et al. (2014)

Green Defense: the Role of Essential Oil in Managing Cestode Parasites

Essential oils (EO), or volatile oils, are aromatic and oily liquids extracted through distillation from various plant parts

such as buds, seeds, leaves, twigs, bark, wood, fruits, and roots (Mrabti et al., 2023). These oils are organic solvent extracts (using substances like ethanol, methanol, toluene, or other organic solvents) or steam-volatile extracts that have been traditionally used for centuries in various regions worldwide. Approximately all the essential oils can be obtained through hydrodistillation method; encompasses three key physicochemical processes: hydro diffusion, hydrolysis, and heat decomposition (Oreopoulou et al., 2019).

Essential oils have scolicidal effect against many cestodes species. Research has revealed that the root oils of *Hedychium coronarium* and *H. spicatum* exhibited more effective results against tapeworms compared to piperazine phosphate. Additionally, oils derived from *Gardenia lucida*, *Cyperus rotundus*, *Inula racemose*, *Psitacia integrrima*, *Litsea chinensis* and *Randia dumetorum* demonstrated notable effects on tapeworms (Tandon et al., 2011). In another study, oils from plants *Artemisia pallens*, *Eupatorium triplinerve*, *Artabotrys odoratissimus*, *Capillipedium foetidum* and *Cymbopogon martini* exhibited strong impacts on Ascaris and *T. solium* (Nakhare and Garg, 1991).

Pelargonium roseum and *Ferula gummosa* are identified as potential sources of novel natural products with the potential for developing effective and environmentally friendly scolicidal drugs. The main chemical components, β-pinene and citronellol, present in both essential oils, demonstrate scolicidal activity against *E. granulosus*, with 50% lethal concentration (LC50) values of 8.52 and 17.18µg/mL, respectively (Tabari et al., 2019) (Table 2). Ajowan (*Trachyspermum ammi*), known for its various therapeutic properties, investigated for its scolicidal properties against *E. granulosus*. Their main chemical components thymol, γ-terpinene and p-cymene showed scolicidal activity. Moazeni et al. in 2012 reported, the ajowan EO with a concentration of 10 milligrams per milliliter after ten minutes demonstrated complete scolicidal efficacy. Similarly, the EO obtained from European black pine kills protoscolices of *E. granulosus*. Varied outcomes were observed when different doses were administered at different time intervals. Best efficiency (100%) shown at the higher concentration of 50 milligrams per milliliter (Kozan et al., 2019) (Table 2).

The essential oil of black cumin (*Nigella sativa*), together with its main chemical constituents (thymoquinone, p-cymene, carvacrol, and longifolene) exhibited scolicidal activity against *E. granulosus*. A study conducted by Mahmoudvand et al. (2014) showed various concentrations of the black cumin EO (ranging from 0.01 to 10mg/ml) applied for different time durations (5 to 60 minutes) had different scolicidal effects. Moreover, *Myrtus communis* EO has also shown promising scolicidal results on hydatid cyst protoscolices. The results of the investigation revealed that after five minutes of exposure, 100µl/ml of *M. communis* EO killed 100% of protoscoleces. Hence can be used as a natural scolicidal drug during hydatid cyst removal (Mahmoudvand et al., 2016). Similarly, the turmeric EO is useful against protoscolices of *E. granulosus* following a five-minute treatment with 200µl/mL, all protoscolices were completely destroyed (Mahmoudvand et al., 2019) (Table 2).

The EO from dried garlic bulbs has the capability to damage the scolex of *Moniezia expansa*. After 24h of incubation with 100µg/ml, the scolex appears shrunken with a highly deformed and folded tegument (Shalaby and Farag, 2014).

Table 2: Updates on the effectiveness of essential oil against cestodes.

Essential Oil	Parasites	Dose	Mortality (%)	Effect	Reference
Pelargonium roseum and *Ferula gummosa*	*Echinococus granulosus*	50µg/ml	100	Kill protoscolex	Tabari et al. (2019)
Trachyspermum ammi sprague	*E. granulosus*	10,000µg/ml	100	Kill protoscolex	Moazeni et al. (2012)
Pinus nigra spp. *pallasiana,*	*E. granulosus*	10mg/ml	61.69	Kill protoscolex	Kozan et al. (2019)
Allium sativum	*Moniezia expansa*	100µg/ml	100	Shrunken scolex with distorted and folded tegument	Shalby and Farag (2014)
Nigella sativa	*E. granulosus*	100µg/ml	21.60	Scolicidal activities	Mahmoudvand et al. (2014)
Myrtus communis	*E. granulosus*	100µl/ml	100	Natural scolicidal agent for hydatid cyst	Mahmoudvand et al. (2016)
Curcuma longa	*E. granulosus*	200µl/ml	100	Kill protoscolex	Mahmoudvand et al. (2019)
Ferula macrecolea	*E. granulosus*	150and300µl/ml	100	Kill protoscolex	Alyousif et al. (2021)
Saturega khuzistanica	*E. granulosus*	5mg/ml	100	Scolicidal activities	Moazeni et al. (2012)
Bunium persicum	*E. granulosus*	25µl/ml	100	Kill protoscolex	Mahmoudvand et al. (2016)

Sustainable Green Nanoparticle Solutions for Cestode Control

Green nanoparticles are emerging as a promising eco-friendly alternative for controlling cestodes and are suggested as an alternative to traditional chemical methods. One way to integrate nanotechnology and plants is through the use of green chemistry, known as plant-mediated production of nanoparticles (Fig. 3). Chemical methods can be problematic because of their complex composition, potentially causing reactivity and toxicity

concerns. However the use of natural extract for the synthesis of nanoparticles is less toxic and more reliable (Hussain et al., 2016).

Fig. 3: Presents a potential method for synthesizing nanoparticles by using Plants (Green nanoparticle)

Green Gold Nanoparticle

Raziani et al. (2023) suggest that natural extract from the upper flowering part of savory (*Saturja khuzestanica*) can be used for the production of green gold nanoparticles and show a lethal effect for *E. granulosus*. The efficiency of these green nanoparticles depends on the dose and exposure time. At a concentration of 5mg/ml and 20 minutes exposure time, there was a maximum mortality rate of about 100 percent. Moreover, Barabadi et al. (2017) revealed the production of gold nanoparticles by the use of mycelia-free culture filtrate of *Penicillium aculeatum* showing scolocidal activity. These nanoparticles exhibit 94% scolocidal effect at a dose of 0.3mg/ml with a long exposure time of 2 hours. These experiments are helpful for understanding the efficiency of nanoparticles. However, further research is necessary to reveal the efficacy of Au NPs in both *in-vivo* and *in-vitro* studies.

Green Silver (Ag) Nanoparticles

Green silver nanoparticles (Ag NPs) were prepared from the aerial extract of *Penicillium aculeatum* that were effective scolocidal agent against *E. granulosus*. Dosage of 0.1 and 0.15 milligram per milliliter after two hours of exposure time results in death rates of 83 and 90% respectively (Rahimi et al., 2015). These nanoparticles can also be synthesized from *Ziziphus spinachristi*, according to Salih et al. (2020) which is commonly referred to as Christ's thorn jujube. They have considerable activity against protoscolices of *E. granulosus*. Scolocidal activity varies according to the dose and exposure time. Maximum efficiency was 100% at a dose of 0.4mg/mL for 120 minutes (Jalil et al., 2021). These results are consistent with the findings of Norouzi et al. (2020), who showed the highest scolocidal activity of Ag NPs at 1mg/mL after one hour, with an 80 percent death rate by inducing major changes in their external encasing of protoscolices. Another study reported that the anthelmintic action of plants (flowers of hill glory bower; *Clerodendrum infortunatum*) can be improved by blending it with Ag NPs. When these green nanoparticles were used against *Raillietina* spp. there was destruction of the scolex and alterations in morphology (Majumdar and Kar, 2023).

Green Zinc Oxide (ZnO) Nanoparticle

Shnawa et al. (2021) reported Zinc oxide nanoparticles with Horse mint (*Mentha longifolia*) leaf extract with notable in vitro protoscolicidal efficacy. In the latter studies, ZnO-NPs synthesized from Christ's thorn jujube (*Z. spinachristi*) displayed the highest antiparasitic activity at 400µg/ml after 60 minutes, resulting in 100 percent mortality of treated protoscolices. Both findings emphasize the effectiveness of the green manufacturing of nanoparticles of zinc oxide with strong scolicidal

potential (Shnawa et al., 2021)**.**

The anthelminthic activity of the bark or leaves of willow has also been shown to be improved by the addition of ZnO nanoparticles. It has been shown that *E. granulosus* can be treated by using salicylate-coated zinc oxide nanoparticles (SA-ZnO NPs). The remarkable efficacy of SA-ZnO-NPs against protoscoleces resulted in 100% mortality after 20 minutes of treatment at 2000µg/ml. The drug has a significant effect on the survival and morphology of these parasites as the rostellum of protoscoleces showed abnormalities, external wrinkling of the tegument, and apoptogenic changes after administration (Cheraghipour et al., 2023). Similarly, according to recent study an aqueous extract of grape (*Vitis vinifera*) seeds and ZnO showed effective therapy against *E. granulosus*. The treatment was administrated twice, one with 0.100mg/ml and other with 0.050mg/ml concentration. The mortality rates for these therapies were 97 and 100% respectively (Mahmmoud et al. 2020). The aforementioned research demonstrates that green synthetic ZnO-NPs exhibit scolicidal efficacy against *E. granulosus*.

Biosynthesis of Copper Nanoparticles

The study found that an in vitro combination of albendazole, capparis fruit and Cu nanoparticles at a dose of 750mg/mL demonstrated the greatest protoscolicidal activity.

After 60 min of exposure, 73.3% of protoscoleces were killed. Moreover, when Cu nanoparticles at the same concentration were combined with albendazole (200mg/mL), the mortality of protoscoleces reached 100% after only 10 minutes of exposure (Ezzatkhah et al., 2021).

Biosynthesis of Chitosan Nanoparticle

Chitosan nanoparticles containing curcumin have an impact on protoscolices of the hydatid cyst *in-vitro*, with highest fatality rate 68% at a concentration of 4mg/mL. The most significant effect was observed at 4mg/mL after 60 min of exposure, impacting the tegument, hooks, and suckers, including the collapse of the sucker region (Napooni et al., 2019).

Table 3: An overview of the latest findings about the efficacy of green nanoparticles in combating Cestodes.

Green Nanoparticles	Parasites	Dose	Exposure time	Mortality (%)	Effects	References
Au+ *Saturja khuzestanica*	*Echinococus granulosus*	5mg/ml	20min	100	Morphological changes	Raziani et al. (2023)
Ag+ *Pencillium aculleatum*	*E. granulosus*	0.1 and 0.15mg/ml	120min	83, 90	Larvicidal effect	Rahimi et al. (2015)
Ag+ *Zizyphus spinachristi*	*E. granulosus*	0.4mg/ml	120min	100	Morphological changes, no viable protoscolex	Jalil et al. (2021)
ZnO + *Mentha longifolia*	*E. granulosus*	400ppm	150min	100	Destruction of protoscolex	Shnawa et al. (2021)
Ag and Au+ *Clerodendrum infortunatum*	*Raillietina* spp.	125mg/ml			Destruction of scolex and morphological changes	Majumdar and Kumar (2023)
Aaronsohnia factorovskyi	*Hymenolepis nana*	0.5mg/kg	More than 10 days	100	Reduction of worms	Olayan et al. (2023)
ZnO+ grape seeds extract	*E. granulosus*	0.050mg/ml	60min	100	Destruction of protoscolex	Mahmmoud et al. (2020)
Cu + Capparis fruit+ Albendazole	*E. granulosus*	Cu-NPs 750mg/ml +ALZ 200mg/ml	10min	100	Destruction of protoscolex	Ezzatkhah et al. (2021)
Chitosan-Curcumim	*E. granulosus*	4mg/ml	60min	68	Collapsing of suckers and reduction in length of protoscoles.	Napooni et al. (2019)

Challenges

Plant extracts can be used to treat diseases caused by cestodes. Literature has shown notable progress in the treatment of animals from cestodes parasites. However, there are certain difficulties in treating parasitic infections using natural therapies. Such as, we need to utilize a very particular concentration of extract to get good outcomes. The determination of which extracts, at what concentration, should be mixed for a certain parasite is also essential. Another important aspect is the organism's body's weight. Because the dosage concentration changes with the age of the organism, therefore it is important to consider the age of the organism for efficient therapy (Abdel-Ghaffar et al., 2011).

Conclusion

The cestodes can be effectively treated by the use of plant products, e.g. green nanoparticles, plant extract, and essential oils. These remedies are frequently used for the treatment of parasitic infections like Monieziasis, Echinococcosis, Hymenolopsis and Taeniasis in livestock. Parasites have developed resistance against traditional drugs to overcome this

problem; we should use plant products to cure livestock from parasitic infections. Commercial medicines are expensive and cause pollution in the environment, but these remedies are easily available and have no side effects. The utilization of these eco-friendly alternatives shows the potential for sustainable and effective practices in animal health.

REFERENCES

Abdel-Ghaffar, F., Semmler, M., Al-Rasheid, K. A., Strassen, B., Fischer, K., Aksu, G., Klimpel, S., and Mehlhorn, H. (2011). The effects of different plant extracts on intestinal cestodes and on trematodes. *Parasitology Research*, *108*, 979-984.

Abed, A., and Ibrahim, O. (2021). Antioxidant, antiprotoscolices activity of ethanolic extracts of some medicinal plants against *Echinococcus granulosus* as eco-friendly system. *Asian Journal of Water, Environment and Pollution*, *18*(4), 87-94.

Al-Olayan, E., Almushawah, J., Alrsheed, H., Dawoud, T., and Abdel-Gaber, R. (2023). Potential role of biosynthesized silver nanoparticles from *Aaronsohnia factorovskyi* on *Hymenolepis nana* in BALB/c mice. *Arquivo Brasileiro de Medicina Veterinária e Zootecnia*, *75*, 849-856.

Al-Otaibi, B. O., Degheidy, N. S., and Al-Malki, J. S. (2021). Prevalence, incidence and molecular characterization of tape worms in Al Taif governorate, KSA and the effectiveness of *Spirulina platensis* as a biological control in vitro. *Saudi Journal of Biological Sciences*, *28*(11), 6272-6278.

Alyousif, M. S., Al-Abodi, H. R., Almohammed, H., Alanazi, A. D., Mahmoudvand, H., Shalamzari, M. H., and Salimikia, I. (2021). Chemical composition, apoptotic activity, and antiparasitic effects of *Ferula macrecolea* essential oil against *Echinococcus granulosus* protoscoleces. *Molecules*, *26*(4), 888.

Baqer, N. N., Khuder, M. H., and Amer, N. (2014). Antiprotoscolices effects of ethanolic extract of *Zingiber officinale* against *Echinococcus granulosus* invitro and invivo. *International Journal*, *2*(10), 59-68.

Barabadi, H., Honary, S., Ali Mohammadi, M., Ahmadpour, E., Rahimi, M. T., Alizadeh, A., Naghibi, F., and Saravanan, M. (2017). Green chemical synthesis of gold nanoparticles by using *Penicillium aculeatum* and their scolicidal activity against hydatid cyst protoscolices of *Echinococcus granulosus*. *Environmental Science and Pollution Research*, *24*, 5800-5810.

Barzinji, A. K. R., Mothana, R. A., and Nasher, A. K. (2009). Effect of leaf extracts of *Dendrosicyos socotrana* and *Jatropha unicostata* on the viability of *Echinococcus granulosus* protoscoleces. *EurAsian Journal of BioSciences*, *3*(3), 122-129.

Bashtar, A. R., Abdel-Ghaffar, F., Al-Rasheid, K. A., Mehlhorn, H., and Al Nasr, I. (2010). Light microscopic study on *Eimeria* species infecting Japanese quails reared in Saudi Arabian farms. *Parasitology Research*, *107*, 409-416.

Bouaziz, S., Amri, M., Taibi, N., Zeghir-Bouteldja, R., Benkhaled, A., Mezioug, D., and Touil-Boukoffa, C. (2021). Protoscolicidal activity of *Atriplex halimus* leaves extract against *Echinococcus granulosus* protoscoleces. *Experimental Parasitology*, *229*, 108155.

Cheraghipour, K., Azarhazine, M., Zivdari, M., Beiranvand, M., Shakib, P., Rashidipour, M., Mardanshah, O., Mohaghegh, M. A., and Marzban, A. (2023). Evaluation of scolicidal potential of salicylate coated zinc nanoparticles against *Echinococcus granulosus* protoscoleces. *Experimental Parasitology*, *246*, 108456.

Chung, W., and Ko, B. (1976). Treatment of *Taenia saginata* infection with mixture of areca nuts and pumpkin seeds. *Zhonghua Minguo wei Sheng wu xue za zhi,Chinese Journal of Microbiology*, *9*(1-2), 31-35.

Dawwas, A. (2008). Investigation of biochemical effect of phenols extract isolated from *Coriandrum sativum* seeds against *Echinococcus granulosus* parasite in vitro. *University of Thi-Qar Journal of Science*, *1*(1), 2-9.

Ezzatkhah, F., Khalaf, A. K., and Mahmoudvand, H. (2021). Copper nanoparticles: Biosynthesis, characterization, and protoscolicidal effects alone and combined with albendazole against hydatid cyst protoscoleces. *Biomedicine and Pharmacotherapy*, *136*, 111257.

Faizei, F., Maghsood, A. H., Parandin, F., Matini, M., Moradkhani, S., and Fallah, M. (2015). Antiprotoscolices effect of methanolic extract of *Zingiber officinale, Artemisia aucheri* and *Eucalyptus globulus* against *Echinococcus granulosus* in vitro. *Iranian Journal Pharmacology Thereology*, *14*(1), 7-11.

Gadahi, J., Arshed, M., Ali, Q., Javaid, S., and Shah, S. (2009). Prevalence of gastrointestinal parasites of sheep and goat in and around Rawalpindi and Islamabad, Pakistan. *Veterinary World, 2*(2), 51-53.

Gholami, S., Rahimi-Esboei, B., Ebrahimzadeh, M., and Pourhajibagher, M. (2013). In vitro effect of *Sambucus ebulus* on scolices of Hydatid cysts. *Europe Review Medicine Pharmacology Science*, *17*(13), 1760-1765.

Gour, A., and Jain, N. K. (2019). Advances in green synthesis of nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology*, *47*(1), 844-851.

Hosseinzadeh, S., Ghalesefidi, M. J., Azami, M., Mohaghegh, M. A., Hejazi, S. H., and Ghomashlooyan, M. (2016). In vitro and in vivo anthelmintic activity of seed extract of *Coriandrum sativum* compared to Niclosamid against *Hymenolepis nana* infection. *Journal of Parasitic Diseases*, *40*, 1307-1310.

Huie, C. W. (2002). A review of modern sample-preparation techniques for the extraction and analysis of medicinal plants. *Analytical and Bioanalytical Chemistry*, *373*, 23-30.

Hussain, I., Singh, N., Singh, A., Singh, H., and Singh, S. (2016). Green synthesis of nanoparticles and its potential application. *Biotechnology Letters*, *38*, 545-560.

Ito, A., Li, T., Chen, X., Long, C., Yanagida, T., Nakao, M., Sako, Y., Okamoto, M., Wu, Y., and Raoul, F. (2013). Review Paper

Mini review on chemotherapy of taeniasis and cysticercosis due to *Taenia solium* in Asia, and a case report with 20 tapeworms in China. *Tropical Biomedicine*, *30*(2), 164-173.

Jalil, P. J., Shnawa, B. H., and Hamad, S. M. (2021). Silver Nanoparticles: Green Synthesis, Characterization, Blood Compatibility and Protoscolicidal Efficacy against *Echinococcus granulosus*. *Pakistan Veterinary Journal*, *41*(3).

James, C. E., Hudson, A. L., and Davey, M. W. (2009). Drug resistance mechanisms in helminths: is it survival of the fittest? *Trends in Parasitology*, *25*(7), 328-335.

Jeon, H.-K., and Eom, K. S. (2024). Cestodes and cestodiasis. In Y. W. Tang, M. Y. Hindiyeh, D. Liu, A. Sails, P. Spearman, and J. R. Zhang (Eds.), *Molecular Medical Microbiology, 149*(pp. 2941-2963). Acedemic press, Elsevier.

Kamal, M., Mukherjee, S., Joshi, B., Wangchuk, P., Haider, S., Ahmed, N., Talukder, M. H., Geary, T. G., and Yadav, A. K. (2023). Model nematodes as a practical innovation to promote high throughput screening of natural products for anthelmintics discovery in South Asia: Current challenges, proposed practical and conceptual solutions. *Molecular and Biochemical Parasitology*, *256*, 111594.

Kozan, E., Ilhan, M., Tümen, I., and Akkol, E. K. (2019). The scolicidal activity of the essential oil obtained from the needles of *Pinus nigra* Arn. subsp. *pallasiana* (Lamb.) Holmboe on hydatid cyst. *Journal of Ethnopharmacology*, *235*, 243-247.

Kundu, S., Roy, S., and Lyndem, L. M. (2012). Cassia alata L: potential role as anthelmintic agent against *Hymenolepis diminuta*. *Parasitology Research*, *111*, 1187-1192.

Maggiore, M., and Elissondo, M. C. (2014). In vitro cestocidal activity of thymol on *Mesocestoides corti* tetrathyridia and adult worms. *Interdisciplinary Perspectives on Infectious Diseases*, *2014*, (1), 268135.

Mahmmoud, S. M., ALBayati, N. Y., and Abdullah, A. H. (2020). Effect of ZnO nanoparticles on protoscolices of *Echinococcus granulosus* and comparing them with aqueous extract of the grape seeds. *Biochemical and Cellular Archives*, *20*(1), 2209.

Mahmoudvand, H., Dezaki, E. S., Kheirandish, F., Ezatpour, B., Jahanbakhsh, S., and Harandi, M. F. (2014). Scolicidal effects of black cumin seed (*Nigella sativa*) essential oil on hydatid cysts. *The Korean Journal of Parasitology*, *52*(6), 653.

Mahmoudvand, H., Fallahi, S., Mahmoudvand, H., Shakibaie, M., Harandi, M. F., and Dezaki, E. S. (2016). Efficacy of *Myrtus communis* L. to inactivate the hydatid cyst protoscoleces. *Journal of Investigative Surgery*, *29*(3), 137-143.

Mahmoudvand, H., Pakravanan, M., Aflatoonian, M. R., Khalaf, A. K., Niazi, M., Mirbadie, S. R., Tavakoli Kareshk, A., and Khatami, M. (2019). Efficacy and safety of *Curcuma longa* essential oil to inactivate hydatid cyst protoscoleces. *BMC Complementary and Alternative Medicine*, *19*, 1-7.

Majumdar, R., and Kar, P. K. (2023). Biosynthesis, characterization and anthelmintic activity of silver nanoparticles of *Clerodendrum infortunatum* isolate. *Scientific Reports*, *13*(1), 7415.

Mehlhorn, H., Al-Quraishy, S., Al-Rasheid, K. A., Jatzlau, A., and Abdel-Ghaffar, F. (2011). Addition of a combination of onion (*Allium cepa*) and coconut (*Cocos nucifera*) to food of sheep stops gastrointestinal helminthic infections. *Parasitology Research*, *108*, 1041-1046.

Moazeni, M., and Roozitalab, A. (2012). High scolicidal effect of *Zataria multiflora* on protoccoleces of hydatid cyst: an in vitro study. *Comparative Clinical Pathology*, *21*, 99-104.

Moazeni, M., Saharkhiz, M. J., and Hosseini, A. A. (2012). In vitro lethal effect of ajowan (*Trachyspermum ammi* L.) essential oil on hydatid cyst protoscoleces. *Veterinary Parasitology*, *187*(1-2), 203-208.

Mrabti, H. N., Jaouadi, I., Zeouk, I., Ghchime, R., El Menyiy, N., El Omari, N., Balahbib, A., Al-Mijalli, S. H., Abdallah, E. M., and El-Shazly, M. (2023). Biological and pharmacological properties of myrtenol: a review. *Current Pharmaceutical Design*, *29*(6), 407-414.

Nakhare, S., and Garg, S. (1991). Anthelmintic Activity Of The Essential Oil Of Artemisia Pallens Wall. *Ancient Science of life*, *10*(3), 185-186.

Napooni, S., Delavari, M., Arbabi, M., Barkheh, H., Rasti, S., Hooshyar, H., and Mostafa Hosseinpour Mashkani, S. (2019). Scolicidal effects of chitosan–curcumin nanoparticles on the hydatid cyst protoscolices. *Acta Parasitologica*, *64*, 367-375.

Norouzi, A., Adeli, M., and Zakeri, A. (2020). An innovative hydrometallurgical process for the production of silver nanoparticles from spent silver oxide button cells. *Separation and Purification Technology*, *248*, 117015.

Oreopoulou, A., Tsimogiannis, D., and Oreopoulou, V. (2019). Extraction of polyphenols from aromatic and medicinal plants: an overview of the methods and the effect of extraction parameters. In R. R. Watson (Eds.), *Polyphenols in Plants*, *15* (pp. 243-259). Acedmic press, Elesvier.

Panda, S. K., Daemen, M., Sahoo, G., and Luyten, W. (2022). Essential oils as novel anthelmintic drug candidates. *Molecules*, *27*(23), 8327.

Rahimi, M. T., Ahmadpour, E., Esboei, B. R., Spotin, A., Koshki, M. H. K., Alizadeh, A., Honary, S., Barabadi, H., and Mohammadi, M. A. (2015). Scolicidal activity of biosynthesized silver nanoparticles against *Echinococcus granulosus* protoscolices. *International Journal of Surgery*, *19*, 128-133.

Raza, M. A., Younas, M., and Schlecht, E. (2014). Prevalence of gastrointestinal helminths in pastoral sheep and goat flocks in the Cholistan desert of Pakistan. *JAPS: Journal of Animal and Plant Sciences*, *24*(1), 127-134.

Raziani, Y., Shakib, P., Rashidipour, M., Cheraghipour, K., Ghasemian Yadegari, J., and Mahmoudvand, H. (2023). Green synthesis, characterization, and Antiparasitic Effects of Gold nanoparticles against *Echinococcus granulosus* Protoscoleces. *Tropical Medicine and Infectious Disease*, *8*(6), 313.

Salih, T. A., Hassan, K. T., Majeed, S. R., Ibraheem, I. J., Hassan, O. M., and Obaid, A. (2020). In vitro scolicidal activity of synthesised silver nanoparticles from aqueous plant extract against *Echinococcus granulosus*. *Biotechnology Reports*, *28*, e00545.

Sanhokwe, M., Mupangwa, J., Masika, P. J., Maphosa, V., and Muchenje, V. (2016). Medicinal plants used to control internal and external parasites in goats. *Onderstepoort Journal of Veterinary Research*, *83*(1), 1-7.

Shalaby, H. A., and Farag, T. K. (2014). Body surface changes in gastrointestinal helminthes following in vitro treatment with *Allium sativum* oil. *Journal of Veterinary Science and Technology*, *5*(1), 1000153.

Shnawa, B. H., Hamad, S. M., Barzinjy, A. A., Kareem, P. A., and Ahmed, M. H. (2022). Scolicidal activity of biosynthesized zinc oxide nanoparticles by *Mentha longifolia* L. leaves against *Echinococcus granulosus* protoscolices. *Emergent Materials*, *5*(3), 683-693.

Shnawa, B. H., Jalil, P. J., Aspoukeh, P., Mohammed, D. A., and Biro, D. M. (2022). Protoscolicidal and Biocompatibility Properties of Biologically Fabricated Zinc Oxide Nanoparticles Using *Ziziphus spina-christi* Leaves. *Pakistan Veterinary Journal*, *42*(4), 517-525.

Siles-Lucas, M., and Hemphill, A. (2002). Cestode parasites: application of in vivo and in vitro models for studies on the host-parasite relationship. *Advances in Parasitology, 51,* 133-230.

Szewezuk, V., Mongelli, E. R., and Pomilio, A. B. (2003). Antiparasitic activity of *Melia azadirach* growing in Argentina. *Molecular Medicine Chemistry*, *1*(1), 54-55.

Tabari, M. A., Youssefi, M. R., Nasiri, M., Hamidi, M., Kiani, K., Samakkhah, S. A., and Maggi, F. (2019). Towards green drugs against cestodes: Effectiveness of *Pelargonium roseum* and *Ferula gummosa* essential oils and their main component on *Echinococcus granulosus* protoscoleces. *Veterinary Parasitology*, *266*, 84-87.

Tandon, V., Yadav, A., Roy, B., and Das, B. (2011). Phytochemicals as cure of worm infections in traditional medicine systems. In U.C. Srivastava, and S. Kumar (Eds.), *Emerging trends in Zoology, 16* (351-378). *Narendra Publishing House, New Delhi*, India.

Trevisan, B., Jacob Machado, D., Lahr, D. J., and Marques, F. P. (2021). Comparative characterization of mitogenomes from five orders of cestodes (Eucestoda: tapeworms). *Frontiers in Genetics*, *12*, 788871.

Yadav, A. K., and Temjenmongla. (2011). Anticestodal activity of *Houttuynia cordata* leaf extract against *Hymenolepis diminuta* in experimentally infected rats. *Journal of Parasitic Diseases*, *35*, 190-194.

Chapter 24

Nanotechnology in Parasite Control: New Therapeutic Horizons

Maryam Bashir[1], Naseer Khan[2], Nimra Mushtaq[3], Muhammad Kasib Khan[4*], Kashif Hussain[1*], Maryam Arshad[5], Fouzia Tabassum[1], Mah Noor[3], Ali Haider[6], Muhammad Umair Waqas[1], Rana Muhammad Shahbakht[7] and Asghar Abbas[1]

[1]Department of Pathobiology and Biomedical Sciences, MNS University of Agriculture, Multan
[2]Deparment of Poultry Science, University of Agriculture, Faisalabad
[3]Department of Microbiology and Molecular Genetics, The Women University, Multan
[4]Department of Parasitology, University of Agriculture, Faisalabad
[5]Institute of Microbiology, University of Agriculture, Faisalabad
[6]Department of Clinical Sciences, MNS University of Agriculture, Multan
[7]Department of Animal and Dairy Sciences, MNS University of Agriculture, Multan
*Corresponding author: mkkhan@uaf.edu.pk; kashif.hussain@mnsuam.edu.pk

ABSTRACT

Production animals and humans in underdeveloped and developing countries face significant risks from parasitic infections, leading to serious economic losses. In endemic regions, these parasites cause considerable mortality and morbidity each year. Current vaccines and treatment methods are limited and can have adverse side effects. Therefore, there is an urgent need for novel, safe, and effective treatment approaches. Recently, nanotechnology has emerged as a promising solution for treating parasitic diseases due to its lower toxicity and improved bioavailability. Nanoparticles can lead to the death of infected cells through mechanisms such as inhibiting the electron transport chain by causing cell membrane damage, oxidative stress, and ribosome disassembly, which results in protein denaturation and DNA damage. This chapter provides an overview of the current state of nanotechnology for treating parasitic infections. It discusses the advantages, challenges, and future directions in developing nanotechnology-based treatments. Various metals are used to synthesize nanoparticles, with silver and gold being common due to their wide spectrum of antiparasitic properties against protozoa, helminths, and ectoparasites. Nanotechnology offers several benefits for treating parasitic diseases, including enhanced drug delivery, improved drug solubility, overcoming drug resistance, and reduced side effects. However, challenges remain, such as the complexity of parasitic infections, targeted drug delivery, cost and affordability, and toxicity and safety concerns. Despite these challenges, nanotechnology holds great promise for revolutionizing the treatment of parasitic diseases, providing a potentially effective alternative to traditional methods.

KEYWORDS
Nanotechnology, Parasitic infections, Nanoparticles, Antiparasitic properties, Bioavailability

Received: 19-Jun-2024
Revised: 12-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Bashir M, Khan N, Mushtaq N, Khan MK, Hussain K, Arshad M, Tabassum F, Mah Noor, Haider A, Waqas MU, Rana Shahbakht RM and Abbas A, 2024. Nanotechnology in parasite control: new therapeutic horizons. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 208-217. https://doi.org/10.47278/book.CAM/2024.487

INTRODUCTION

Production animals and humans in underdeveloped and developing countries are significantly at risk from parasitic infections, which can result in serious economic losses (Mehmood et al., 2017). In the various endemic countries, these parasites cause significant mortality and morbidity each year. The vaccines and treatment methodologies available today are associated with certain limitations and adverse side effects (Palomo-Ligas et al., 2023). To mitigate these risks, there is an urgent need for novel, safe, and effective treatment approaches (Ndjonka et al., 2013). In recent years, nanotechnology has emerged as a promising approach for the treatment of parasitic diseases due to its lower toxicity and improved bioavailability (Gutiérrez et al., 2016). Nanoparticles leads to the death of infected cells within the body either through inhibition of electron transport chain by cell membrane damage and oxidative stress or through ribosome disassembly which leads to the protein denaturation and DNA damage as shown in Fig. 1 (AlGabbani 2023).

This chapter provides an overview of the current state of nanotechnology for the treatment of parasitic infections. Furthermore, it discusses the advantages, challenges, and future directions in the development of nanotechnology-based treatments for parasitic infections.

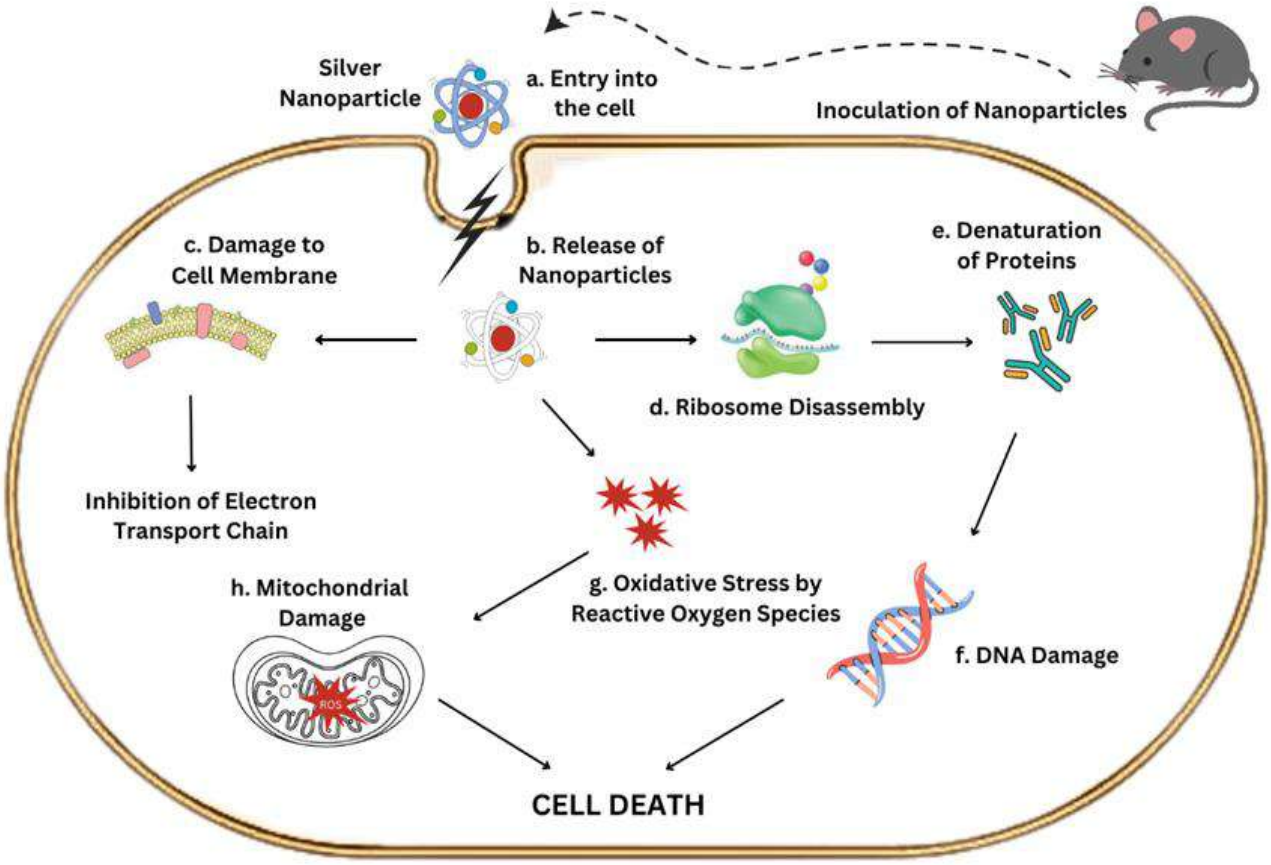


Fig. 1: Nanoparticles general mechanism of action against parasitic infections

Antiparasitic Spectrum of Nano-particles

Many metals are commonly used to synthesize nanoparticles-based treatments. The common metals used for NP synthesis is silver and gold having a wide spectrum of antiparasitic properties against protozoa, helminth and ectoparasites i.e., mosquitoes as shown in Fig. 2 (AlGabbani 2023).

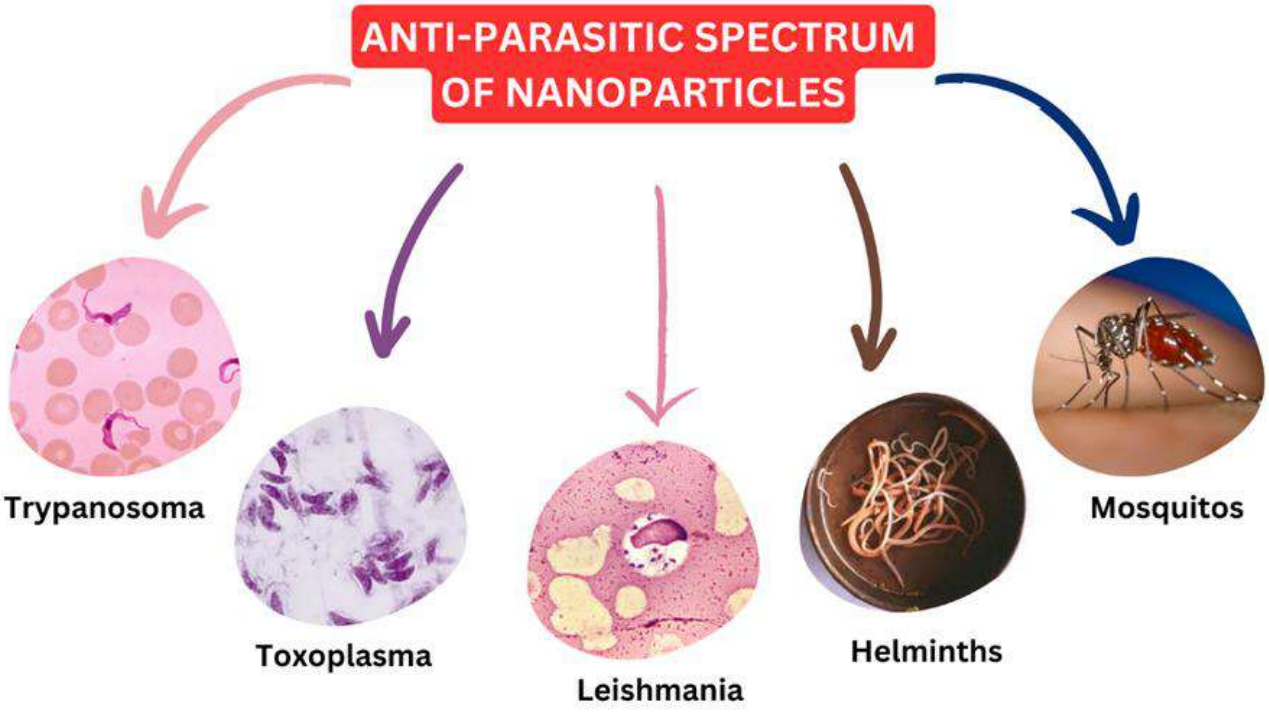


Fig. 2: Antiparasitic spectrum of nanoparticles

Anti-protozoan Spectrum of AuNPs

Aurum-based nanoparticles (AuNPs) are being commonly used to control various parasitic infections (Baek et al., 2020). These nanoparticles are usually found in two oxidized and one non-oxidized form. The oxidized form is converted in to non-oxidized form through a precursor chloroauric acid. After preparation by in vitro or conventional method, these NPs are stored in the dark place to avoid oxidation by light (Jain et al., 2019). AuNPs have a broad spectrum of antiparasitic properties against *Cryptosporidium parvum, Leishmania (L.) tropica, L. donovani*, *Toxoplasma gondii* and *Trypanosoma spp.* (Hancock et al., 2022; Campbell and Soman-Faulkner, 2019), *Raillietina spp.* and *Schistosoma spp.* (Dykman, 2020), mosquitoes of genus *Aedes, Anopheles* and *Culex* and dipteran flies (Moodley et al., 2018). It is now considered as a novel product to develop a new drug but still needs a lot of research on dose requirement and efficacy (Bahuguna and Rawat, 2020).

AuNPs against *Plasmodium*

Malaria is a dangerous disease caused by the protozoan parasites of genus *Plasmodium* i.e., *Plasmodium (P.) falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*, mainly infecting young children and pregnant women of third world countries especially those residing in sub-Saharan Africa (Laurens, 2018_Husnain Chapter). The control of malaria is a matter of concern since parasite documentation in 1897. Many attempts i.e., artemisinin-based combination therapy (ACT), insecticide-treated bed nets (ITNs) and control through vaccination, have already been made for its control but antigenic shift of the parasite enables it to dodge the immune system of host (Hayder et al., 2023). Use of AuNPs is an effective alternative strategy that provide protection in patients infected with malarial parasite (Wicht et al., 2020). According to a study, AuNPs provide tremendous protection in the mice infected with *Plasmodium* (Daptardar et al., 2016). The use of AuNPs also play an important role in malaria diagnosis (Gruessner and Weathers, 2021). Histidine-enriched protein II is a biomarker of *Plasmodium* parasite which is being detected in the patient serum by AuNPs-based kit (Abdellahi et al., 2022).

AuNPs against *Leishmania*

Leishmaniasis is considered as a Neglected Tropical Disease (NTD) for the long time. According to the recent estimates, it is a deadliest NTD reported worldwide (Álvarez-Hernández et al., 2020). Leishmaniasis is a spectrum of various diseases caused by 20 different species of *Leishmania* which are transmitted by phlebotomine sand fly (Cecílio et al., 2022). It has now become a priority disease regarding public health importance due to various factors including its potential lethality, spread across the world, at risk population and development of peculiar lesion in tropical and visceral form of the disease. The drugs that are commonly used to treat the disease is costly and not easily available (Uliana et al., 2018). Various chemotherapeutic agents can be used for treatment (Bruni et al., 2017) but have few limitations which include development of resistance, side effects and treatment failure (Yasinzai et al., 2013). Due to intracellular nature of parasite, the drug delivery to the target site is usually difficult resulting in the development of resistance. Scientists also revealed that different *Leishmania spp.* have already developed resistance against commonly used anthelmintics (AlGabbani, 2023). Due to raise of question, "there is always an onset of disease but is there an end", there is a need of an immediate alternate control strategy to overcome the spread of disease (Conceição-Silva and Morgado, 2019). To ensure efficient drug delivery to the target site, scientist have developed nanoparticles-based approach. Moreover, the use of NPs showed an efficient drug release, less toxicity and improved efficacy (Karimkhani et al., 2016).

In a study, the use of AuNPs showed decrease in life span and growth of promastigote stage resulted in improved recovery of skin lesions (Hancock et al., 2022). Additionally, the use of AuNPs also stimulate the process of angiogenesis in skin of infected individual. A study proved better efficacy of AuNPs while used in combination with microwave radiation but more research needs to be conducted to confirm this thing (Nafari et al., 2020).

AuNPs against *Toxoplasma gondii*

Toxoplasmosis is a zoonotic disease affecting a wide range of host including human, livestock and companion animals. It is caused by a protozoan parasite *Toxoplasma (T.) gondii* which is the only pathogenic species found in *Toxoplasma* genus (Dubey, 2016). Domestic and wild felids act as its definitive host shedding oocyst in the environment and human and livestock animals serve as the intermediate host (Havelaar et al., 2012). It is a parasite of paramount importance in the list of food and water borne parasites (FAO/WHO, 2014). Regarding public health significance, the healthy individuals remain asymptomatic during the course of infection but neonates and immunocompromised individuals may experience severe clinical illness leading to death (Robert-Gangneux et al., 2018; Mcleod et al., 2020). Pyrimethamine (PYR) and sulfadiazine (SDZ) are the drugs commonly used to treat *Toxoplasma* infection. However, several failure cases suggested the existence of drug resistance in various strains of parasite (Montazeri et al., 2018). Several other drugs including azithromycin, sipramycin, dapsone, clarithromycin, cotrimoxazole and atovaquone have also been reported to treat toxoplasmosis but no effect have been reported on the bradyzoite form of parasite (Montazeri et al., 2017). This indicated the need to develop an alternative strategy to control toxoplasmosis in affected individuals. To ensure efficient treatment of infection, scientists have developed nanoparticles-based approaches (Etewa et al., 2018; Hagras et al., 2019; da Silva Sanfelice et al., 2022; Ifijen et al., 2023).

A study was conducted to check the effect of AuNPs on tachyzoite stage of *T. gondii* for various time periods. The results showed a significant decrease in the number of tachyzoite depending on the time of exposure (Shen et al., 2020). Another study showed better results of antibodies and AuNPs combination for the treatment of infection as compared to the antibodies alone (Baek et al., 2020). Apart from treatment, scientists have developed a diagnostic kit for the detection of antibodies, developed against *Toxoplasma,* by using AuNPs through piezoelectric device (Ibarra-Cerdena et al., 2017).

AuNPs against *Trypanosoma*

Trypanosomes are the unicellular flagellates belongs to the genus *Trypanosoma* and family *Trypanosomatidae*. Multiple species belong to this genus including, *Trypanosoma (T.) brucei, T. cruzi, T. congolense, T. equiperdum, T. envansi, T. simiae, T. suis* and *T. vivax* causing traypanosomiasis in various mammalian hosts (Aslam et al., 2023; Pays et al., 2023). According to World Health Organization (WHO), trypanosomiasis is considered among Neglected Tropical Diseases (NTDs) found worldwide mainly in low- and middle-income countries. More than 20% of the world population lives in NTDs endemic areas affecting more than 1 billion people each year (Lancet, 2019). The diseases caused by *Trypanosoma* are mainly classified in to 2 major categories including 1- Human African Trypanosomiasis (HAT) which is prevalent in Central Africa and transmitted by tsetse fly and 2- Chagas Disease (CD) which is prevalent in Latin America and transmitted by triatomine bug (Dickie et al., 2020; Abras et al., 2022).

Pentamidine and suramin have been used since decades to treat blood stages of *T. brucei* and melarsoprol to treat second stage infection. Due to high occurrence of post-treatment encephalopathy, these drugs are not recommended to use specially in chronic infections (Álvarez-Rodríguez et al., 2022). Currently, there is no successful treatment option available to treat these diseases. The use of metal nanoparticles i.e., AuNPs, AnNPs and AgNPs to treat trypanosomiasis showed promising results. In a study, use of AnNPs and AgNPs showed a significant reduction of parasites (*T. evansii, T. congolense, T. brucei* and *T. cruzi*) growth (Morones et al., 2005). In another study, arginine kinase (phosphotransferase required for the parasite energy metabolism) was targeted by using AuNPs and AgNPs and showed a reduction in parasite growth (Eger and Soares, 2012).

Anti-parasitic Spectrum of AgNPs

Silver based nanoparticles (AgNPs) have been used for multiple purpose i.e., in the pharmaceuticals, biomedical devices, bioimaging and as antipathogenic agents (Roy et al., 2019). Recently, scientist reported anti-parasitic potential of AgNPs prepared through various in vitro techniques (Parashar et al., 2020). Among these, green synthesis is the most widely used technique for NP synthesis as it is less toxic and economically feasible. It showed good results in control of parasitic infection. The only disadvantage of this technique is the synthesis of uneven size NP (Colwell et al., 2011). So, there is a need to synthesize even size NP for the effective control of parasitic infections.

AgNPs against Vector

There is a list of parasitic i.e., protozoan and helminth infections being transmitted by the vector. So, vector control is considered as a necessary step to prevent these infections. Various chemical and biological methods have been used to control vectors but due to the development of resistance through genetic variation, these techniques are no more effective (Varela-Aramburu et al., 2020). The researches in last ten years showed an effective control of mosquito through AgNPs. According to a study, AgNPs prepared from *Mimosa pudica* showed an excellent control of Anopheles mosquito (Moodley et al., 2018). In another study, AgNPs prepared from *Euphorbia hirta* also gave good results against *Anopheles stephensi* (Sardana et al., 2018). Similarly, AgNPs synthesized from leaves and flowers of *Jatropha integerrima* showed insecticidal potential against *Aedes aegypti* (Verma and Preet, 2022). These studies indicate the insecticidal activity of AgNPs that can be used as an alternative strategy for control of parasitic infections.

AgNPs against *Plasmodium*

AgNPs have also been used in past to control malaria caused by *Plasmodium* which is a serious threat for third world countries especially in sub-Saharan Africa. In a study, AgNPs synthesized from plant extracts was used against *Plasmodium* and showed excellent results (Moodley et al., 2018). In another study, AgNPs prepared from the leaves of *Madhuca longifolia* showed significant antimalarial activity against *Plasmodium falciparum* (Shater et al., 2023).

AgNPs against *Leishmania*

AgNPs can effectively be used to control leishmaniasis through the production of reactive oxygen species (ROS). Mainly, AgNPs impair the parasite metabolism resulting in the reduction of promastigote proliferation and growth leading to the death of parasite (Boukthir et al., 2020). By using these with UV light increases the efficacy up to six-folds (Ali et al., 2021). In a study, miltefosine was used with AgNPs and showed a significant decrease in amastigote and promastigote stages of parasite (Roy et al., 2019). In another study, AgNPs coated with curcumin showed a significant reduction of parasitic burden both in vitro and in mouse models (Badirzadeh et al., 2022). Nanoparticles may be considered as a reliable treatment against parasitic infections in near future. Various studies have been conducted so far against other parasites as well. Summary of these studies are given in Table 2.

Benefits of Nanotechnology for Treatment of Parasitic Diseases

Parasitic diseases continue to pose significant health challenges worldwide, particularly in regions with limited access to effective healthcare resources. These diseases are caused by various parasites and can lead to a range of debilitating symptoms and long-term health complications if left untreated (Kirtane et al., 2021). Traditional treatment methods often face limitations due to factors such as drug resistance, adverse effects, and difficulties in drug delivery. In recent years, nanotechnology has emerged as a promising approach to address these challenges and revolutionize the treatment of parasitic diseases (Bajwa et al., 2022).

Table 2: Summary of parasitic susceptibility to nanoparticles

Treatment	Pathogen	Outcome	Reference
Gold nanoparticles + Aqueous extract of *Citrullus colocynthis* fruits	*Giardia lamblia*	The combination therapy reduced the cyst count in fecal sample and trophozoite count in the intestine	Al-Ardi, 2020
Gold nanoparticles vs metronidazole	*Giardia lamblia*	NPs significantly reduced oocyst count in the stool samples and intestinal sections of albino rats as compared to metronidazole	Baz et al., 2022
Biosynthesized silver nanoparticles	*Cryptosporidium parvum*	Time and dose dependent oocyst reduction in faecal samples from pigeons was observed	Abou Elez et al., 2023
Chitosan nanoparticles loaded with ginger (ginger CSNPs) vs Nanazoxid (NZX)	*Cryptosporidium* spp.	Ginger CSNPs significantly reduced the oocyst count in the stool samples of mice. Intact intestinal mucosa was observed upon histopathological examination	Abdelmaksoud et al., 2023
In vitro efficacy of mesoporous silica nanoparticles (MSNs) loaded with metronidazole (MTZ)	*Trichomonas vaginalis*	MSNs/MTZ combination showed cytotoxic effects on trophozoite and improved drug efficacy.	Altememy et al., 2020
ZnO nanoparticles prepared through green synthesis from leaf extract of *Terminalia mantaly*	*Balantidium coli* and *Escherichia coli*	The antibacterial efficacy of NPs was evaluated through well diffusion method and results showed zone of inhibition against these pathogens	Lavanya et al., 2023
Silver nanoparticles (AgNPs) from *Bacillus cereus* and *Chromobacterium violaceum* bacteria	*Entamoeba (E.) histolytica, E. coli* and *Giardia lamblia*	A significant reduction in oocyst count of *G. lamblia* followed by *E. histolytica* and *E. coli* was observed.	Obaid, 2022
Silica nanoparticles	*Plasmodium falciparum* and *Leishmania infantum*	Artemisinin loaded nanoparticles showed anti-leishmanial and anti-malarial properties.	Tsamesidis et al., 2021
MgO nanoparticles	*Leishmania (L.) tropica* and *L. infantum*	MgO NPs showed in-vitro fatality effect on promastigote and amastigote stages of parasites	Karimipour-Saryazdi et al., 2022
AgNPs prepared from fruit extracts of *Sambucus (S.) ebulus* and *Feijoa (F.) sellowiana*	*Toxoplasma (T.) gondii*	These AgNPs showed a significant reduction in the growth of parasite both in-vitro and in-vivo. AgNPs from *S. ebulus* showed more lethal effect.	Hematizadeh et al., 2023
Tellurium oxide (TeO_2) nanoparticles	*T. gondii*	TeO_2 NPs showed destructive effect on *T. gondii*. Flow cytometric analysis also showed good apoptosis percentage.	KarimiPourSaryazdi et al., 2021
Zinc oxide (ZnO) nanoparticles vs amprolium	*Eimeria tenella*	ZnO NPs showed dose dependent reduction in oocyst excretion from the infected birds	Anah et al., 2022
AgNPs prepared from the rhizomes of *Zingiber officinale*	*Eimeria papillata*	AgNPs reduced the oocyst secretion in feces of infected mice along with the reduction in meronts and gamonts in the jejunum	Dkhil et al., 2023
Salicylate coated zinc oxide nanoparticles (SA-ZnO-NPs)	*Echinococcus granulosus*	SA-ZnO-SPs showed significant reduction of hydatid cyst protoscolices	Cheraghipour et al., 2023
AgNPs vs albendazole	*Trichinella spiralis*	SEM analysis showed dose and time dependent mortalities of adult worms by using AgNPs	Taha et al., 2022
Ginger-loaded chitosan nanoparticles vs Praziquantel	*Schistosoma mansoni*	NPs showed a significant decrease in the count of cellular granuloma and granuloma diameter of infected mice. Immunological analysis revealed reduction in TNF-α, IL-4 and IL-10 levels	El-Derbawy et al., 2022

Enhanced Drug Delivery

One of the significant challenges to treat parasitic diseases is ensuring that the drugs reach to their target sites within the body, where the parasites reside. Nanotechnology enables the design and fabrication of drug delivery systems that can enhance the specificity and efficiency of drug delivery. Nanoparticles can encapsulate antiparasitic drugs, protecting them from degradation and improving their bioavailability. These nanoparticles can also be engineered to release the drugs gradually, extending their therapeutic effect (AlGabbani, 2023).

Improved Drug Solubility

Many antiparasitic drugs suffer from poor solubility, which is limiting their effectiveness in the body. Nanotechnology offers solutions to this challenge by enabling the formulation of drugs in nanoparticle carriers that enhance solubility. This

approach not only improves drug absorption but also enhances the distribution of drugs throughout the body (Tundisi et al., 2022). Nanoparticles have the advantage of increasing the solubility of hydrophobic drugs, which is particularly relevant for improving the efficacy of antiparasitic medications (Nafari et al., 2020).

Overcoming Drug Resistance

The development of drug resistance is a significant issue for treatment of parasitic diseases (Shibeshi et al., 2020). Nanotechnology helps to overcome this issue by enabling the targeted delivery of combination therapies or by modifying drug structures to improve their efficacy against resistant strains. Nanoparticles can carry multiple drugs simultaneously that enhances their synergistic effects and reduces the likelihood of resistance development (Gujjari et al., 2022).

Reduced Side Effects

Traditional treatments for parasitic diseases often result in systemic toxicity and adverse effects due to the high doses required to effectively combat parasites (Cortez-Maya et al., 2020). Nanotechnology allows for precise targeting of parasites, reducing the exposure of healthy tissues to the drugs and minimizing side effects. Additionally, nanoparticles can be engineered to release drugs in response to specific triggers, such as pH changes or enzymatic activity, further enhancing the therapeutic index of the drugs (Mengarda et al., 2022).

Challenges of Nanotechnology for the Treatment of Parasitic Diseases

The utilization of nanotechnology for treating parasitic diseases has garnered considerable attention due to exceptional physical and chemical characteristics (Ebrahimzadeh et al. 2023). Nanotechnology has provided resources to enhance therapies and to establish effective immune responses against infectious pathogens (Molento and Arenal, 2020). Nanomaterials and different chemical and natural antiparasitic substances have shown considerable potential in pharmaceutical research for safe pharmacological therapy with maximal antiparasitic effects and effective treatment (Amini et al., 2023). This dynamic field comes with a series of intricate challenges that must be confronted and surmounted, that are;

Complexity of Parasitic Infections

Parasitic infections encompass a diverse array of pathogens, each characterized by complex life cycles and intricate interactions with their hosts (Bennett et al., 2023). The dynamic interplay between parasites and their hosts adds layers of complexity that demand precise and adaptable nanoparticle-based interventions (Jain et al., 2019). Additionally, host immune responses can vary greatly, affecting the parasites' susceptibility to treatment and leading to unpredictable outcomes (Zaman et al., 2023). A fundamental challenge in the realm of nanotechnology is the development of nanoparticles that can efficiently target various pathogen life stages, avoid immune evasion tactics, and overcome host-specific variances (Wu et al., 2020).

Targeted Drug Delivery

Targeted drug distribution to disease sites is a significant challenge in nano-medicine because most commonly prescribed medications are given orally or by intravenous injection. The drugs must successfully navigate several biological barriers before they are able to treat disease locations. Oral nanoparticles must be extremely stable inside the digestive system, have the potential to cross intestinal epithelial barriers, and maintain high systemic drug bioavailability after overcoming several physiological hurdles (Wu et al., 2020).

Cost and Affordability

The development and production of nanoparticles e.g., gold nanoparticles, often involves specialized materials and technologies, that can be resource-intensive. This can lead to higher research and development costs compared to traditional therapies (Aljabali et al., 2018). Due to the high cost of raw materials and the necessity of a laborious and multistep production process, nanomedicine-based therapy is relatively expensive (Zheng et al., 2021). Balancing the need for extensive research, optimization, and safety evaluations with the ultimate goal of making these therapies accessible to populations in need presents a significant challenge. Manufacturing processes, quality control measures, and regulatory compliance further contribute to the overall cost of nanoparticle-based therapies (Crist et al., 2021).

Toxicity and Safety Challenges

Nanoparticles have distinctive characteristics and differ greatly in terms of their size, shape, composition, aggregation, and uniformity states. After inhalation, ingestion, and skin contact, nanoparticles are prone to accumulate in sensitive organs such the heart, liver, spleen, kidney, and brain. Reactive oxygen species (ROS), which are a major factor in toxicity, are thought to be produced when nanoparticles are exposed to in-vitro and in-vivo investigations. For example; different cell types have been observed to show inflammatory response and undergo morphological changes when exposed to cobalt or cobalt-containing nanoparticles (Sengul and Asmatulu, 2020).

Conclusion and Future Prospects

Various chemotherapeutic agents have been used to control parasitic infections but due to their overuse, parasites developed resistance against these agents. Alternatively, ethnobotanicals showed good efficacy against parasites but limited funding and lack of interest from investors made this option not feasible. Moreover, lack of information regarding dosage of ethnobotanicals limited their use. Another option for control of parasitic infections is vaccination but high antigenic variation among protozoan parasites made it a challenging option. According to parasitologists, the use of nanoparticles is the best option to control parasitic infections. NPs can be prepared through different techniques and have ability to arrest the parasitic growth and kill them. These can also be used for diagnostic purposes. The most commonly used NPs against human and animal parasites are gold and silver. There is a need to conduct further research to understand their mode of action to develop safe diagnostic and treatment options. It is likely to offer a major breakthrough in the field of medical and pharmaceutical science.

REFERENCES

Abdellahi, L., Iraji, F., Mahmoudabadi, A., and Hejazi, S.H. (2022). Vaccination in Leishmaniasis: A Review Article. *Iranian Biomedical Journal, 26*, 1–35.

Abdelmaksoud, H., Nahas, E., Ismail, M., Abu-Sarea, E., El-Askary, H., Zalat, R., and Ibrahim, S. (2023). Evaluation of the therapeutic effect of Zingiber Officinale loaded on nanoparticles for cryptosporidiosis in experimentally immunosuppressed mice. *Parasitologists United Journal*, *16*(2), 133-138.

Abou Elez, R. M., Attia, A. S., Tolba, H. M., Anter, R. G., and Elsohaby, I. (2023). Molecular identification and antiprotozoal activity of silver nanoparticles on viability of Cryptosporidium parvum isolated from pigeons, pigeon fanciers and water. *Scientific Reports*, *13*(1), 3109.

Abras, A., Ballart, C., Fernández-Arévalo, A., Pinazo, M. J., Gascón, J., Muñoz, C., and Gállego, M. (2022). Worldwide control and management of Chagas disease in a new era of globalization: a close look at congenital Trypanosoma cruzi infection. *Clinical Microbiology Reviews*, *35*(2), e00152-21.

Al-Ardi, M. H. (2020). The uses of gold nanoparticles and Citrullus colocynthis L. nanoparticles against Giardia lamblia in vivo. *Clinical Epidemiology and Global Health*, *8*(4), 1282-1286.

AlGabbani, Q. (2023). Nanotechnology: A promising strategy for the control of parasitic infections. *Experimental Parasitology*, 108548.

Ali, K. M., Hassan, E. A., Abuowarda, M. M., Mahmoud, M. A., and Torad, F. A. (2021). Bilateral panophthalmia as a late sequel of leishmaniasis in dogs. *Pakistan Veterinary Journal*, *41*(1).

Aljabali, A. A., Akkam, Y., Al Zoubi, M. S., Al-Batayneh, K. M., Al-Trad, B., Abo Alrob, O., and Evans, D. J. (2018). Synthesis of gold nanoparticles using leaf extract of Ziziphus zizyphus and their antimicrobial activity. *Nanomaterials*, *8*(3), 174.

Altememy, D., Jafari, M., Naeini, K., Alsamarrai, S., and Khosravian, P. (2020). In-vitro Evaluation of Metronidazole loaded Mesoporous Silica Nanoparticles against Trichomonas Vaginalis. *International Journal of Pharmaceutical Research (09752366)*.

Álvarez-Hernández, D. A., Rivero-Zambrano, L., Martínez-Juárez, L. A., and García-Rodríguez-Arana, R. (2020). Overcoming the global burden of neglected tropical diseases. *Therapeutic Advances in Infectious Disease*, *7*, 2049936120966449.

Álvarez-Rodríguez, A., Jin, B. K., Radwanska, M., and Magez, S. (2022). Recent progress in diagnosis and treatment of Human African Trypanosomiasis has made the elimination of this disease a realistic target by 2030. *Frontiers in Medicine*, *9*, 1037094.

Amini, S. M., Hadighi, R., Najm, M., Alipour, M., Hasanpour, H., Vosoogh, M., and Badirzadeh, A. (2023). The therapeutic effects of curcumin-coated gold nanoparticle against Leishmania major causative agent of zoonotic cutaneous leishmaniasis (ZCL): an in vitro and in vivo study. *Current Microbiology*, *80*(4), 104.

Anah, S. A., Anah, S. A., and Al-Khalidy, K. A. H. (2022). Anti-parasitic activity of zinc oxide nanoparticles against Eimeria tenella in broilers experimentally infected. *Korean Journal Veterinary Research*, *62*(4), e30.

Aslam, S. M. A., Mughal, M. A. S., Khan, M. K., Prince, K., Rashid, J., Raza, A., and Usman, M. (2023). Chagas Disease. *One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan*, *2*, 119-124.

Badirzadeh, A., Alipour, M., Najm, M., Vosoogh, A., Vosoogh, M., Samadian, H., and Amini, S. M. (2022). Potential therapeutic effects of curcumin coated silver nanoparticle in the treatment of cutaneous leishmaniasis due to Leishmania major in-vitro and in a murine model. *Journal of Drug Delivery Science and Technology*, *74*, 103576.

Baek, S. H., Roh, J., Park, C. Y., Kim, M. W., Shi, R., Kailasa, S. K., and Park, T. J. (2020). Cu-nanoflower decorated gold nanoparticles-graphene oxide nanofiber as electrochemical biosensor for glucose detection. *Materials Science and Engineering: C*, *107*, 110273.

Bahuguna, A., and Rawat, D. S. (2020). An overview of new antitubercular drugs, drug candidates, and their targets. *Medicinal Research Reviews*, *40*(1), 263-292.

Bajwa, H. U. R., Khan, M. K., Abbas, Z., Riaz, R., Rehman, T. U., Abbas, R. Z., and Alouffi, A. (2022). Nanoparticles: Synthesis and their role as potential drug candidates for the treatment of parasitic diseases. *Life*, *12*(5), 750.

Baz, M. G., Elmarhoumy, S. M., Saied, E. M., and Zoghroban, H. S. (2022). Evaluation of the efficacy of gold nanoparticles on Giardia lamblia infection in experimental animals. *Experimental Parasitology*, *238*, 108277.

Bennett, J., Presswell, B., and Poulin, R. (2023). Tracking life cycles of parasites across a broad taxonomic scale in a marine ecosystem. *International Journal for Parasitology*, *53*(5-6), 285-303.

Boukthir, A., Bettaieb, J., Erber, A. C., Bouguerra, H., Mallekh, R., Naouar, I., and Ben Salah, A. (2020). Psycho-social impacts, experiences and perspectives of patients with Cutaneous Leishmaniasis regarding treatment options and case management: An exploratory qualitative study in Tunisia. *PloS one*, *15*(12), e0242494.

Bruni, N., Stella, B., Giraudo, L., Della Pepa, C., Gastaldi, D., and Dosio, F. (2017). Nanostructured delivery systems with improved leishmanicidal activity: a critical review. *International Journal of Nanomedicine*, 5289-5311.

Campbell, Sotonye, and Kristina Soman-Faulkner. "*Antiparasitic Drugs*," (2019).

Cecílio, P., Cordeiro-da-Silva, A., and Oliveira, F. (2022). Sand flies: Basic information on the vectors of leishmaniasis and their interactions with Leishmania parasites. *Communications Biology*, *5*(1), 1-12.

Cheraghipour, K., Azarhazine, M., Zivdari, M., Beiranvand, M., Shakib, P., Rashidipour, M., and Marzban, A. (2023). Evaluation of scolicidal potential of salicylate coated zinc nanoparticles against Echinococcus granulosus protoscoleces. *Experimental Parasitology*, *246*, 108456.

Colwell, D. D., Dantas-Torres, F., and Otranto, D. (2011). Vector-borne parasitic zoonoses: emerging scenarios and new perspectives. *Veterinary Parasitology*, *182*(1), 14-21.

Conceição-Silva, F., and Morgado, F. N. (2019). Leishmania spp-host interaction: there is always an onset, but is there an end?. *Frontiers in Cellular and Infection Microbiology*, *9*, 330.

Cortez-Maya, S., Moreno-Herrera, A., Palos, I., and Rivera, G. (2020). Old antiprotozoal drugs: Are they still viable options for parasitic infections or new options for other diseases?. *Current Medicinal Chemistry*, *27*(32), 5403-5428.

Crist, R. M., Dasa, S. S. K., Liu, C. H., Clogston, J. D., Dobrovolskaia, M. A., and Stern, S. T. (2021). Challenges in the development of nanoparticle-based imaging agents: Characterization and biology. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *13*(1), e1665.

da Silva Sanfelice, R. A., Silva, T. F., Tomiotto-Pellissier, F., da Silva Bortoleti, B. T., Lazarin-Bidóia, D., Scandorieiro, S., and Costa, I. N. (2022). Biogenic silver nanoparticles reduce Toxoplasma gondii infection and proliferation in RAW 264.7 macrophages by inducing tumor necrosis factor-alpha and reactive oxygen species production in the cells. *Microbes and Infection*, *24*(5), 104971.

Daptardar, M., Singh, B. B., Aulakh, R. S., and Gill, J. P. S. (2016). Prevalence and first molecular identification of Sarcocystis species in cattle and water buffaloes in India. *Acta Parasitologica*, *61*(3), 523-528.

Dickie, E. A., Giordani, F., Gould, M. K., Mäser, P., Burri, C., Mottram, J. C., and Barrett, M. P. (2020). New drugs for human African trypanosomiasis: a twenty first century success story. *Tropical Medicine and Infectious Disease*, *5*(1), 29.

Dkhil, M. A., Thagfan, F. A., Morad, M. Y., Al-Shaebi, E. M., Elshanat, S., Bauomy, A. A., and Abdel-Gaber, R. (2023). Biosynthesized silver nanoparticles have anticoccidial and jejunum-protective effects in mice infected with Eimeria papillata. *Environmental Science and Pollution Research*, *30*(15), 44566-44577.

Dubey, J. P. (2016). *Toxoplasmosis of Animals and Humans*. CRC press.

Dykman, L. A. (2020). Gold nanoparticles for preparation of antibodies and vaccines against infectious diseases. *Expert Review of Vaccines*, *19*(5), 465-477.

Ebrahimzadeh, A., Karamian, M., Alemzadeh, E., Solgi, R., Alemzadeh, E., and Mortazavi-Derazkola, S. (2023). Investigation of therapeutic potential in murine cutaneous leishmaniasis and antibacterial using biosynthesized silver nanoparticles using extract of Crocus sativus petals. *Biomass Conversion and Biorefinery*, 1-12.

Eger, I., and Soares, M. J. (2012). Endocytosis in Trypanosoma cruzi (Euglenozoa: Kinetoplastea) epimastigotes: Visualization of ingested transferrin–gold nanoparticle complexes by confocal laser microscopy. *Journal of Microbiological Methods*, *91*(1), 101-105.

El-Derbawy, M. M., Salem, H. S., Raboo, M., Baiuomy, I. R., Fadil, S. A., Fadil, H. A., and El Kholy, W. A. (2022). In vivo evaluation of the anti-schistosomal potential of ginger-loaded chitosan nanoparticles on schistosoma mansoni: histopathological, ultrastructural, and immunological changes. *Life*, *12*(11), 1834.

Etewa, S. E., El-Maaty, D. A. A., Hamza, R. S., Metwaly, A. S., Sarhan, M. H., Abdel-Rahman, S. A., and El-Shafey, M. A. (2018). Assessment of spiramycin-loaded chitosan nanoparticles treatment on acute and chronic toxoplasmosis in mice. *Journal of Parasitic Diseases*, *42*, 102-113.

Gruessner, B. M., and Weathers, P. J. (2021). In vitro analyses of Artemisia extracts on Plasmodium falciparum suggest a complex antimalarial effect. *PLoS One*, *16*(3), e0240874.

Gujjari, L., Kalani, H., Pindiprolu, S. K., Arakareddy, B. P., and Yadagiri, G. (2022). Current challenges and nanotechnology-based pharmaceutical strategies for the treatment and control of malaria. *Parasite Epidemiology and Control*, *17*, e00244.

Gutiérrez, V., Seabra, A. B., Reguera, R. M., Khandare, J., and Calderón, M. (2016). New approaches from nanomedicine for treating leishmaniasis. *Chemical Society Reviews*, *45*(1), 152-168.

Hagras, N. A. E., Allam, A. F., Farag, H. F., Osman, M. M., Shalaby, T. I., Mogahed, N. M. F. H., and Shehab, A. Y. (2019). Successful treatment of acute experimental toxoplasmosis by spiramycin-loaded chitosan nanoparticles. *Experimental Parasitology*, *204*, 107717.

Hancock, P. A., Lynd, A., Wiebe, A., Devine, M., Essandoh, J., Wat'senga, F., and Moyes, C. L. (2022). Modelling spatiotemporal trends in the frequency of genetic mutations conferring insecticide target-site resistance in African

mosquito malaria vector species. *BMC Biology*, *20*(1), 46.

Havelaar, A. H., Haagsma, J. A., Mangen, M. J. J., Kemmeren, J. M., Verhoef, L. P., Vijgen, S. M., and van Pelt, W. (2012). Disease burden of foodborne pathogens in the Netherlands, 2009. *International Journal of Food Microbiology*, *156*(3), 231-238.

Hayder, H., Uzair, M., Ahmad, S., Ashraf, U., Huzaifa, A., Mehmood, M. S., and Saleem, F. (2023). Strategies for malaria prevention and control. *One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan*, *3*, 157-163.

Hematizadeh, A., Ebrahimzadeh, M. A., Sarvi, S., Sadeghi, M., Daryani, A., Gholami, S., and Hosseini, S. A. (2023). In Vitro and In Vivo Anti-parasitic Activity of Sambucus ebulus and Feijoa sellowiana Extracts Silver Nanoparticles on Toxoplasma gondii Tachyzoites. *Acta Parasitologica*, *68*(3), 557-565.

Ibarra-Cerdena, C. N., Valiente-Banuet, L., Sanchez-Cordero, V., Stephens, C. R., and Ramsey, J. M. (2017). Trypanosoma cruzi reservoir—triatomine vector co-occurrence networks reveal meta-community effects by synanthropic mammals on geographic dispersal. *PeerJ*, *5*, e3152.

Ifijen, I. H., Atoe, B., Ekun, R. O., Ighodaro, A., and Odiachi, I. J. (2023). Treatments of Mycobacterium tuberculosis and Toxoplasma gondii with Selenium Nanoparticles. *BioNanoScience*, *13*(1), 249-277.

Jain, S., Melo, T. G. C., Dolabella, S. S., and Liu, J. (2019). Current and emerging tools for detecting protozoan cysts and oocysts in water. *TrAC Trends in Analytical Chemistry*, *121*, 115695.

KarimiPourSaryazdi, A., Ghaffarifar, F., Barati, M., and Omidi, R. (2021). Anti-Toxoplasma activity of tellurium oxide (TeO2) nanoparticle on Toxoplasma gondii in vitro. *Journal of Archives in Military Medicine*, *9*(4).

Karimipour-Saryazdi, A., Jafari, M. M., Omidi, R., Ghaffarifar, F., and Sadeghi, S. H. (2022). Anti-leishmania Effect of Magnesium Oxide Nanoparticles on Leishmania tropica/infantum and Leishmania-Infected Macrophages. *International Journal of Enteric Pathogens*, *10*(4), 144-154.

Karimkhani, C., Wanga, V., Coffeng, L. E., Naghavi, P., Dellavalle, R. P., and Naghavi, M. (2016). Global burden of cutaneous leishmaniasis: a cross-sectional analysis from the Global Burden of Disease Study 2013. *The Lancet Infectious Diseases*, *16*(5), 584-591.

Kirtane, A. R., Verma, M., Karandikar, P., Furin, J., Langer, R., and Traverso, G. (2021). Nanotechnology approaches for global infectious diseases. *Nature Nanotechnology*, *16*(4), 369-384.

Lancet, T. (2019). 2020: a crucial year for neglected tropical diseases. *Lancet (London, England)*, *394*(10215), 2126.

Laurens, M. B. (2018). The promise of a malaria vaccine—are we closer?. *Annual Review of Microbiology*, *72*, 273-292.

Lavanya, B., Aparna, Y., and Ramana, M. V. (2023). Synthesis, characterization of zinc oxide nanoparticles using Terminalia mantaly leaf extract and their antibacterial activity. *Materials Today: Proceedings*, *92*, 1011-1016.

McLeod, R., Cohen, W., Dovgin, S., Finkelstein, L., and Boyer, K. M. (2020). Human toxoplasma infection. In *Toxoplasma gondii* (pp. 117-227). Academic Press.

Mehmood, K., Zhang, H., Sabir, A. J., Abbas, R. Z., Ijaz, M., Durrani, A. Z., and Li, J. (2017). A review on epidemiology, global prevalence and economical losses of fasciolosis in ruminants. *Microbial Pathogenesis*, *109*, 253-262.

Mengarda, A. C., Iles, B., F. Longo, J. P., and de Moraes, J. (2022). Recent trends in praziquantel nanoformulations for helminthiasis treatment. *Expert Opinion on Drug Delivery*, *19*(4), 383-393.

Molento, M. B., and Arenal, A. (2020). The breakthrough of nanotechnology to veterinary parasitology research. *LALIOTIS, GP Current Research in Agriculture and Veterinary Science. London: Publisher International*, 71-77.

Montazeri, M., Mehrzadi, S., Sharif, M., Sarvi, S., Tanzifi, A., Aghayan, S. A., and Daryani, A. (2018). Drug resistance in Toxoplasma gondii. *Frontiers in Microbiology*, *9*, 299255.

Montazeri, M., Sharif, M., Sarvi, S., Mehrzadi, S., Ahmadpour, E., and Daryani, A. (2017). A systematic review of in vitro and in vivo activities of anti-Toxoplasma drugs and compounds (2006–2016). *Frontiers in Microbiology*, *8*, 228484.

Moodley, J. S., Krishna, S. B. N., Pillay, K., Sershen, F., and Govender, P. (2018). Green synthesis of silver nanoparticles from Moringa oleifera leaf extracts and its antimicrobial potential. *Advances in Natural Sciences: Nanoscience and Nanotechnology*, *9*(1), 015011.

Morones, J. R., Elechiguerra, J. L., Camacho, A., Holt, K., Kouri, J. B., Ramírez, J. T., and Yacaman, M. J. (2005). The bactericidal effect of silver nanoparticles. *Nanotechnology*, *16*(10), 2346.

Nafari, A., Cheraghipour, K., Sepahvand, M., Shahrokhi, G., Gabal, E., and Mahmoudvand, H. (2020). Nanoparticles: New agents toward treatment of leishmaniasis. *Parasite Epidemiology and Control*, *10*, e00156.

Ndjonka, D., Rapado, L. N., Silber, A. M., Liebau, E., and Wrenger, C. (2013). Natural products as a source for treating neglected parasitic diseases. *International Journal of Molecular Sciences*, *14*(2), 3395-3439.

Obaid, H. M. (2022). In Vitro assessment of biosynthesized silver nanoparticles effect on some intestinal protozoan cystic stages. *International Journal of Biology Research*, *7*(3), 22-27.

Palomo-Ligas, L., Vargas-Villanueva, J. R., Garza-Ontiveros, M., Gutiérrez-Gutiérrez, F., Castillo-Godina, R. G., Campos-Muzquiz, L. G., and Nery-Flores, S. D. (2023). New Alternatives of Treatment Against Intestinal Parasite Infection. In *Antimicrobials in Pharmaceutical and Medicinal Research* (pp. 203-239). CRC Press.

Parashar, M., Shukla, V. K., and Singh, R. (2020). Metal oxides nanoparticles via sol–gel method: a review on synthesis, characterization and applications. *Journal of Materials Science: Materials in Electronics*, *31*(5), 3729-3749.

Pays, E., Radwanska, M., and Magez, S. (2023). The pathogenesis of african trypanosomiasis. *Annual Review of Pathology: Mechanisms of Disease*, *18*, 19-45.

Robert-Gangneux, F., Meroni, V., Dupont, D., Botterel, F., Garcia, J. M. A., Brenier-Pinchart, M. P., and Manuel, O. (2018). Toxoplasmosis in transplant recipients, Europe, 2010–2014. *Emerging Infectious Diseases*, *24*(8), 1497.

Roy, A., Bulut, O., Some, S., Mandal, A. K., and Yilmaz, M. D. (2019). Green synthesis of silver nanoparticles: biomolecule-nanoparticle organizations targeting antimicrobial activity. *RSC Advances*, *9*(5), 2673-2702.

Sardana, M., Agarwal, V., Pant, A., Kapoor, V., Pandey, K. C., and Kumar, S. (2018). Antiplasmodial activity of silver nanoparticles: A novel green synthesis approach. *Asian Pacific Journal of Tropical Biomedicine*, *8*(5), 268-272.

Sengul, A. B., and Asmatulu, E. (2020). Toxicity of metal and metal oxide nanoparticles: a review. *Environmental Chemistry Letters*, *18*(5), 1659-1683.

Shater, A. F., Saleh, F. M., Mohammedsaleh, Z. M., Gattan, H., Al-Ahmadi, B. M., Saeedi, N. H., and Panneerselvam, C. (2023). Green nanoarchitectonics of the silver nanocrystal potential for treating malaria and their cytotoxic effects on the kidney Vero cell line. *Green Processing and Synthesis*, *12*(1), 20228111.

Shen, Y., Wang, Z., Li, J., Xu, R., Ji, R., Lin, J., and Zhu, C. (2020). Preparation of colloidal gold immunochromatographic test strips for the diagnosis of Toxoplasma gondii. *Food and Agricultural Immunology*, *31*(1), 630-641.

Shibeshi, M. A., Kifle, Z. D., and Atnafie, S. A. (2020). Antimalarial drug resistance and novel targets for antimalarial drug discovery. *Infection and Drug Resistance*, 4047-4060.

Taha, N. M., Abdel-Radi, S., Youssef, F. S., Auda, H. M., El-Bahy, M. M., and Ramadan, R. M. (2022). Parasiticidal efficacy of a new formulation of silver nanoparticles on Trichinella spiralis in vitro. *Journal of Advanced Veterinary Research*, *12*(4), 379-385.

Tsamesidis, I., Lymperaki, E., Egwu, C. O., Pouroutzidou, G. K., Kazeli, K., Reybier, K., and Kontonasaki, E. (2021). Effect of Silica Based Nanoparticles against Plasmodium falciparum and Leishmania infantum parasites. *Journal of Xenobiotics*, *11*(4), 155-162.

Tundisi, L. L., Ataide, J. A., Costa, J. S. R., de Freitas Coêlho, D., Liszbinski, R. B., Lopes, A. M., and Mazzola, P. G. (2023). Nanotechnology as a tool to overcome macromolecules delivery issues. *Colloids and Surfaces B: Biointerfaces*, *222*, 113043.

Uliana, S. R., Trinconi, C. T., and Coelho, A. C. (2018). Chemotherapy of leishmaniasis: present challenges. *Parasitology*, *145*(4), 464-480.

Varela-Aramburu, S., Ghosh, C., Goerdeler, F., Priegue, P., Moscovitz, O., and Seeberger, P. H. (2020). Targeting and inhibiting Plasmodium falciparum using ultra-small gold nanoparticles. *ACS applied Materials and Interfaces*, *12*(39), 43380-43387.

Verma, A., and Preet, S. (2022). Novel Green Synthesis of Combinational Silver Nanoparticles using Jatropha integerrima for Dengue Vector Control and Cytotoxicity Assessment. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, *92*(4), 747-757.

Wicht, K. J., Mok, S., and Fidock, D. A. (2020). Molecular mechanisms of drug resistance in Plasmodium falciparum malaria. *Annual Review of Microbiology*, *74*, 431-454.

Wu, L. P., Wang, D., and Li, Z. (2020). Grand challenges in nanomedicine. *Materials Science and Engineering: C*, *106*, 110302.

Yasinzai, M., Khan, M., Nadhman, A., and Shahnaz, G. (2013). Drug resistance in leishmaniasis: current drug-delivery systems and future perspectives. *Future Medicinal Chemistry*, *5*(15), 1877-1888.

Zaman, N., Rizwan, M., Sultana, K., Rauf, A., Al-Awthan, Y. S., and Bahattab, O. (2023). Animal Parasites: Insight into Natural Resistance. *Parasitic Infections: Immune Responses and Therapeutics*, 60-72.

Zheng, C., Li, M., and Ding, J. (2021). Challenges and opportunities of nanomedicines in clinical translation. *Bio Integration*, *2*(2), 57-60

Chapter 25

Characterization Techniques of Nanoparticles

Javeria Arshad[*1]

1Department of Chemistry, Government College Women University Sialkot, Pakistan
*Corresponding author: javeriaarshad777@gmail.com

ABSTRACT

This work examines numerous instrumental techniques used in the characterization of nanoparticles. The main emphasis is on X-ray diffraction (XRD), scanning electron microscopy (SEM), thermal analysis (TA), and electrochemical analysis techniques like cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). The principles, apparatus, and applications of each technique are described, providing insights into their utility for studying various structural, morphological, thermal, and electrochemical aspects of nanoparticles. Theoretical frameworks, equations, and experimental approaches are discussed, allowing for a thorough knowledge of the characterization procedures. This review provides academics and practitioners with essential information to guide their investigations and analysis of nanoparticle materials.

KEYWORDS
Nanoparticles, XRD, SEM, TA, Electrochemical analysis

Received: 19-Jun-2024
Revised: 15-Jul-2024
Accepted: 22-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Arshad J, 2024. Characterization techniques of nanoparticles. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 218-226. https://doi.org/10.47278/book.CAM/2024.306

INTRODUCTION

Several techniques are used for the characterization of nanomaterials. Some of them are explained below.

X-ray diffraction (XRD)

Because X-rays are non-destructive and inert, X-ray diffraction (XRD) is a commonly used characterization technique for fundamental structural study of both crystalline and non-crystalline materials. High-tech tools like X-ray diffraction (XRD) can clearly show the atomic or molecular structural features of crystals. Von Laue observed in 1912 that crystals can diffract X-rays due to their periodic arrangement. Every crystal has a distinct diffraction pattern that aids in determining its structure. The determination of particle size, d spacing, tension, phase equilibria, and crystal orientation are among the contemporary uses for this approach (Hanawalt et al., 1938).

Principle

In X-ray scattering (XRD), the crystal lattice and the incident monochromatic X-ray beam interact. When Bragg's law's requirements are met, constructive interference is observed.

$$n\lambda = 2d\sin\theta \quad (1)$$

Where θ is the angle between the incident beam and the diffracting planes, d is the distance between the crystal's planes participating in the diffraction, and n is an integer (Dinnebier and Billinge, 2008).

The scattering of photons caused by X-rays interacting with specific atom arrangements in the crystal lattice is known as diffraction. The specific phase relationship between the dispersed photons, which can result in either constructive or destructive interference, is caused by this periodic arrangement of atoms. Diffraction beams are created when constructive interference happens and all of the scattering rays from all of the atoms are in phase. Figure 1 shows how incident rays interact with various material planes diagrammatically.

Instrumentation

Three basic components make up a conventional x-ray diffractometer: an x-ray tube, a sample holder, and an x-ray detector (Bunaciu et al., 2015). X-ray tubes are made up of two metal electrodes with a high potential between them, often between 30,000 and 50,000 volts, and an electron source (Cullity, 1956). Copper, Cr, Fe, Co, and Mo are typically utilized as anode materials in x-ray tubes, and tungsten filament is used as the cathode material. By heating the filament to produce electrons, which are then accelerated toward and struck by the anode through the application of high voltage, X-rays are produced in an evacuated glass tube. The production of x-rays that radiate in all directions occurs if the bombarding electrons possess sufficient energy to remove the electrons from the target's inner shells. Figure 2 illustrates how these x-

rays combine to generate a spectrum that includes a variety of radiations, such as Kα, Kβ, Kα1, and Kα2. The equipment primarily uses Kα radiation for analysis, although Kβ and Kα1 are electronically blocked during data processing and are blocked by filters or monochromators (Jenkins and Snyder, 1996).

The x-rays are collimated by sending them through the Soller slits in order to evaluate the specimen perfectly. Goniometers, which rotate and orient the specimen in a certain direction with respect to the x-ray beam, are a feature of X-ray diffractometers. When the collimated x-rays strike the sample, constructive interference produces a diffracted x-ray beam as long as Bragg's law is met. The entering diffracted beam is recorded by a detector, which then processes and converts it into signals that may be seen on a computer or printer.

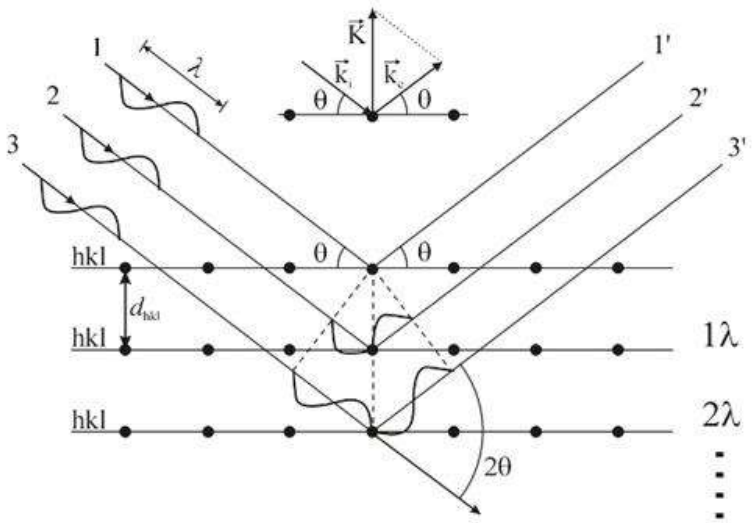


Fig. 1: The working principle of the x-ray diffraction pattern (Cullity, 1956).

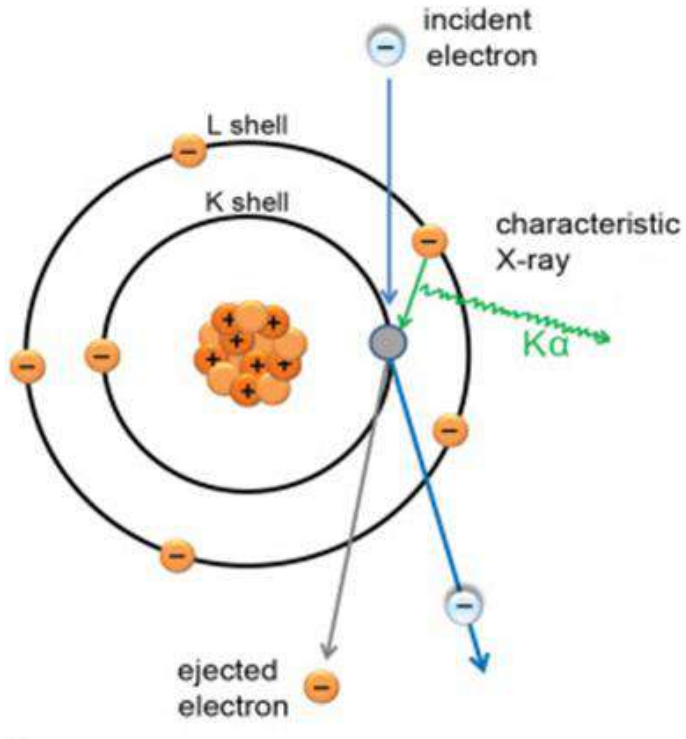


Fig. 2: Production of x-rays (Pirozzi et al., 2021).

Particle Size

When a crystal's size is less than 0.1 μm, it's referred to as "particle size" and can be determined using the Sherrer equation (Muniz et al., 2016).

$$D = \frac{57.3\,k\lambda}{\beta \cos\theta} \qquad (2)$$

λ is the wavelength of the input x-ray radiation, θ is the diffracting angle of the x-rays, and k is related to the crystallite shape. β is the broadening of the diffraction line evaluated at half its maximum intensity. According to equation 2, when

the size of a crystallite rises, the diffracted maxima's breadth (β) decreases (Alexander and Klug, 1950). The Debye-Scherrer equation is valid for the specimen with particles between 100 and 200 nm in size. It becomes difficult to determine whether the peak broadening results from crystallite size or other causes if the particle size beyond this point (Holzwarth and Gibson, 2011).

Scanning Electron Microscopy (SEM)

Using a microscope, one may discern objects that are invisible to the unaided eye. In the past, microscopes used light as the source to examine or work with the material. The resolution that is obtained is insufficient to disclose the minute details at the sub-micro and nanoscale. An electron beam is used to solve this issue since the resolution limit increases with decreasing wavelength (Hamid, 2018). Techniques like transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are developed using this concept. These advanced methods provide an image with a resolution better than a light microscope by probing the specimen with an electron beam.

SEM is used to examine the topography of the surface and provide details about the bulk material's surface, near-surface, composition, and flaws. For material and biological scientists to analyze their specimens at the nano and micro levels in a variety of industries, scanning electron microscopy (SEM) is an incredibly versatile tool.

Interaction of the Electron Beam with the Specimen

An overview of the SEM's operation and equipment is shown in Figure 3. When an electron beam with energy of 2–40 keV (primary electrons) interacts with the material, it produces three types of electrons: characteristic x-rays (c), backscattered electrons (BSE), and secondary electrons (SE) (Goodhew et al., 2000).

a) Secondary Electrons (SE)

When primary electrons collide with atomic electrons and knock them out of their orbits, inelastic collision occurs, producing SE. When SE with an energy less than 50 eV escapes from the specimen's near-surface layers, a high-resolution picture is created.

b) Backscattering Electrons (BSE)

When incident electrons approach an atom's nucleus close enough to be reflected at very broad angles, they scatter, resulting in BSE. Because BSE originates from the specimen's deeper layers and has lesser energy than SE, the resulting image has poorer resolution (Vernon-Parry, 2000).

c) X-rays

Electrons from outer shells descend by releasing energy in the form of x-rays when high-energy incident electrons knock out electrons from the inner shell to fill the holes. Their resolving power is one micrometer.

Instrumentation

An electron column, a specimen chamber, a computer control system, and three components make up a standard SEM instrument. These numerous parts are designed to carry out diverse tasks related to microscopy and microchemical analysis.

a) Electron Column

An electron cannon, electron lenses, scan coils, condenser, and objective lenses make up an electron column, which is cylindrical. The cathode and related electrodes make up the electron cannon, which is situated in the highest section of the electron column. The applied potential difference causes the electron beam, which is produced by the electron cannon, to move down the electron column. Depending on the type of investigation, tungsten filament, LaB6 emitter, Schottky field emission, and cold field emission gun are the most often utilized electron sources. The electron beam that is produced is concentrated by electromagnetic lenses composed of copper coils encased in an iron shell. The focal length of electromagnetic lenses can be adjusted by adjusting the current flowing through their coils, unlike traditional lenses. A small probe size and current on the specimen come from the electron beam spreading out and being mostly blocked by the apertures as it travels through the condenser lens. Through the objective lens, the specimen's surface is the focus of the electron beam. The specimen is closely examined by two scanning electromagnetic coils inside the objective lens bore, and a signal is produced. The detectors process this signal, which consists of both BSE and SE, and an image is displayed on the screen once it has been synchronized.

b) Specimen Chamber

Specimen Chamber is positioned at the end of the electron column. A specimen chamber comprises of specimen stage, specimen holder, optional air lock chamber, CCD camera and detectors. The specimen-containing stab is inserted into the specimen stage. To obtain better signals and realign the features in the SEM image, the stage can be tilted and rotated. In order to prevent collisions, cameras play a critical role in maintaining the proper distance between the specimen

and the objective lens.

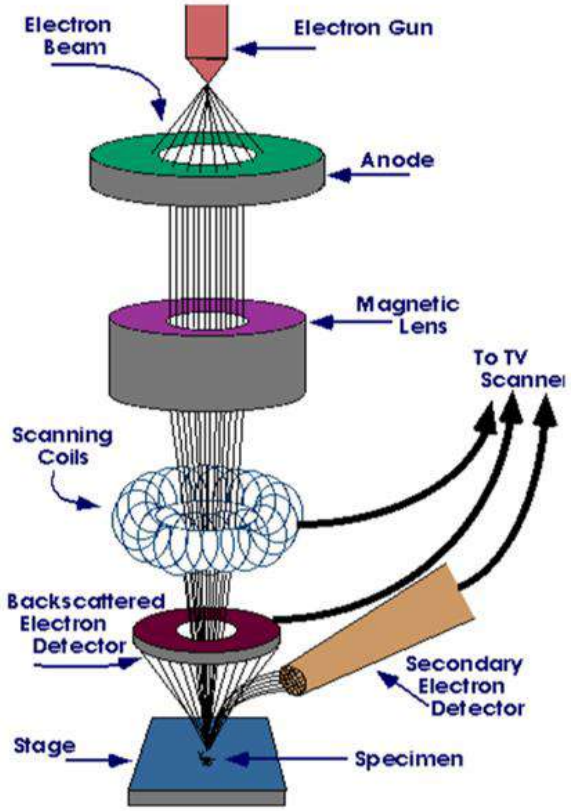


Fig. 3: The working of a scanning electron microscope (Ford et al., 2019).

c) Computer Control System

The software that comes with modern SEM devices is designed to carry out many tasks, such as data storage, networking, electron beam imaging, specimen chamber evacuation, specimen stage motions, and microchemical analysis.

Thermal Analysis (TA)

ICTAC (International Confederation for Thermal Analysis and Calorimetry) defined thermal analysis as

"Thermal analysis (TA) means the analysis of a change in a property of a sample, which is related to an imposed temperature alteration."

Thermal analysis (TA) encompasses a number of methods, including thermometry, thermomanometry, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), and thermomechanometry. Thermal examination of a sample (usually solid) causes the atoms' lattice motion to become random at a certain temperature, which might result in one of the following phenomena: a) phase change; b) melting; c) sublimation; or d) thermal decomposition (Brown, 1989). TGA and DSC are the methods most frequently employed to examine how a specimen's thermal behavior varies as a result of temperature changes (Gabbott, 2008).

Thermogravimetric Analysis (TGA)

Using the TGA technique, variations in the specimen's mass are monitored in a controlled atmosphere at a predetermined temperature as a function of time. A thermogravimetric analyzer, sometimes known as a thermobalance, is the apparatus used to carry out the complete procedure. Two separate changes in the specimen's mass can be noticed as a result of TGA (Parlouer, 2013).

a) Weight Loss

Weight loss may happen as a result of dehydration, dihydroxylation, evaporation, decomposition, desorption, pyrolysis, etc.

b) Weight Gain

Weight gain may happen due to adsorption and hydration etc.

Instrumentation

A thermobalance houses three components: a controlled environment cabinet, a furnace, and a sensitive balance module. Although there are other varieties of thermobalance, the most often used one operates on the null position

balance concept.

a) Balance Module

A torsion wire hangs the balancing assembly, and a rod with four magnets attached goes through the middle of it. The solenoid is submerged in these magnets. A photodiode measures the signal after a light is delivered by an optical detection device. The light becomes partially obscured as soon as the sample's mass changes because the balance beam is forced to move. The solenoid receives current in order to make up for this and return the balance to the null state. The compensatory current corresponds to the variation in the specimen's mass.

b) Furnace

Certain constructional measures must be in place between the balance and the furnace to shield it from the damaging effects of heat radiation and the entrance of corrosive breakdown products (Ebnesajjad, 2010). The heating elements utilized in the majority of furnaces were nickel chrome, kanthal, platinum, and tungsten. The specimen is set atop a crucible that, even at extremely high temperatures, ought to be inert. For research conducted at higher temperatures, crucibles composed of alumina, platinum, tungsten, and graphite are utilized (Parlouer, 2013). The sample should be between 5 and 20 mg in amount, and the heating rate should be adjusted so that the specimen has enough time to finish the reactions.

c) Atmosphere

Different kinds of analyses are conducted in different kinds of contexts. Depending on the experimental conditions, some investigations require an inert atmosphere, while others require an oxidative or reductive atmosphere.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is a technique for measuring heat flux (thermal power) to and from a specimen over time or temperature changes in a given environment. It entails comparing the heat flux of the reference crucible to the crucible containing the specimen (Gallagher, 1998). DSC permits the detection of phase changes that occur within the specimen during the heat treatment process. The approach falls into two groups based on its mechanism: heat flux DSC and power compensated DSC (Zhao et al., 2005).

a) Heat Flux DSC

A thermoelectric disk is used to support both an empty reference pan and a pan carrying specimens during the heat flux treatment process. The entire assembly is housed inside a single furnace, and a thermoelectric disk transfers heat to the pans. The temperature differential between the sample and reference pans is caused by the thermal events that take place in the specimen. Temperature sensors are made using area thermocouples (Gill et al., 2010). This temperature differential, or Δt, is measured, transformed into the equivalent of heat flow, and then recorded as a function of temperature or time.

b) Power Compensated DSC

The reference pan and the specimen pans in power compensated DSC are heated by two different heaters in two different furnaces. The reference pan and the specimen pan need to be maintained at the same temperature. Power compensation is performed to a specific furnace in the event that there is any apparent temperature change (Gabbott, 2008). comparing the energy input differences to the two furnaces and then recording the data as a function of temperature or time.

There would be a temperature differential between the reference and sample pans when the specimen underwent the heat treatment. If the specimen absorbs or releases excess heat in relation to the reference pan while maintaining the same temperature in both pans, the process is referred to as endothermic or exothermic, respectively (Gill et al., 2010).

The pan or crucible's composition should prevent it from reacting with the sample and solidifying its encapsulation. To prevent spills, the sample should be very small, ranging from 1 to 10 mg. Typically, an inert gas is present during the process; however, depending on the application, air or oxygen may be purged and utilized as oxidative agents. The gas flow is managed by restrictors and pressure regulators (Gabbott, 2008).

Electrochemical Analysis

The electrochemical analysis of the as-synthesized materials has been done by using following techniques

1) Cyclic Voltammetry (CV)

In the past ten years, cyclic voltammetry has emerged as the most well-known method for researching electrochemical reactions. It is a helpful technique to determine the energy levels of the analyte, electron transfer processes, and the thermodynamics of a redox reaction. It is the most effective technique in all electrochemical studies because of its broad application. Furthermore, the rate constant (k^), the number of electrons throughout an electron transfer process, and the thermodynamics and heterogeneous kinetics of the electron transfer reaction can all be inferred from the CV results. CV employs a three-electrode system, which comprises of a working electrode (WE), reference electrode (RE), and counter electrode (CE), just like all other electrochemical processes. Starting with an initial value, the voltage delivered to the WE in

relation to RE is scanned linearly vs time. After reaching a particular potential, the potential scan is reversed, and a counter electrode is used to monitor the current. A cyclic voltammogram is the plot of current and applied potential that results from this process (Isaev et al., 2018). Figure 4 provides a general representation of a voltammogram.

Categorization of Redox Processes

Cyclic voltammetry can be categorized into reversible, irreversible and quasi reversible processes. This classification is based on parameters like cathodic and anodic peak currents (I_{pc} and I_{pa}) and peak potentials (E_{pc} and E_{pa}), peak width (E_p-$E_{p/2}$), and half wave potential ($E_{½}$).

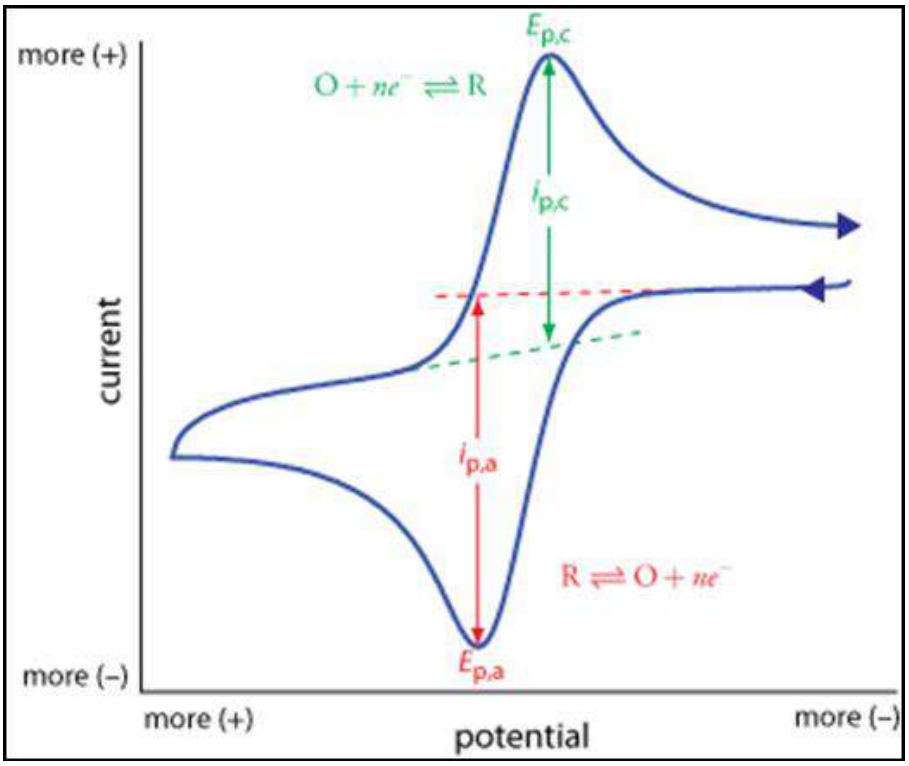


Fig. 4: Typical cyclic voltammogram featuring cathodic and anodic peaks for a reversible process (Isaev et al., 2018).

a) **Reversible Process**

The peak potential of this kind of electrochemical process is independent of the scan rate, and the forward and backward current ratio is unity. An irreversible process's peak current can be calculated using the Randles-Sevcik equation (Isaev et al., 2018). The following is the mathematical relationship:

$$I_p = (2.69 \times 10^5)\, n^{3/2}\, A\, C\, D^{1/2}\, \upsilon^{1/2} \qquad (3)$$

According to this equation I_p stands for current in amperes, n for number of electrons, A for area of the electrode in cm^2, C for concentration of the analyte in mol cm^{-3}, D for diffusion coefficient in $cm^2\ s^{-1}$ and υ for scan rate in V/s.

During a reversible process, the exchange of electrons at the electrode/electrolyte interface is often very fast. Equation 4 is used to calculate the number of electrons taking part in a chemical reaction that proceeds through a reversible process.

$$\Delta E_p = E_{pa} - E_{pc} = (0.059/n)\ V \qquad (4)$$

In reversible processes, potentials corresponding to cathodic and anodic peaks do not change with scan rate. In that situation half-wave potential ($E_{p/2}$) is used, and calculated by the following equation.

$$E_{p1/2} = E_{1/2} \pm 28/n\ (mV) \text{ at } 298\ K \qquad (5)$$

$E_{1/2}$ is that potential at which the current becomes half (I_p=0.5I_p). The positive sign signifies the oxidation process and the negative sign corresponds to the reduction process. Oxidation and reduction processes are represented by positive and negative signs, respectively. Equation 6 is used to calculate the peak potential (Isaev et al, 2018).

$$E_p = E_{1/2} - [1.109 \pm 0.002]\ RT / nF \qquad (6)$$

For a reversible process, the value of the k° is $\geq 2 \times 10^{-2}$ cm s^{-1}.

b) **Irreversible Process**

Because of the slow electron transport in an irreversible process, the peaks are widely apart, and the peak separation is always larger than 59/n mV (Zahn et al., 2012). Moreover, the scan rate affects peak potential. For this procedure, the peak current is shown as:

$$I_p = (2.99 \times 10^5)\, n^{3/2}\, \alpha^{1/2}\, A\, C\, D^{1/2}\, \upsilon^{1/2} \qquad (7)$$

The transfer coefficient, denoted by α in this equation, quantifies the energy symmetry of electron transfer and has a

value between 0 and 1. The following relationship connects peak separation to the electron count:

$$n = 4\ I_p\ RT/\ FQ\ \upsilon \qquad (8)$$

c) Quasi-reversible Process

This process sometimes referred to as the quasi-reversible process, lies between the reversible and irreversible processes. A reverse scan of this system reveals the presence of a peak. Less magnitude is seen in the forward scan, though. Peak separation in this procedure increases as the scan rate increases, and it should be greater than 60 mV. Peak potentials are widely separated in voltage micrographs.

k° values for this process ranges from 2×10^{-2} cm s^{-1} to 3×10^{-4} cm s^{-1} (Birke et al., 1981).

2) Electrochemical impedance spectroscopy (EIS)

The sum of all the resistances present in a system is collectively known as impedance. Traditional electrochemical analysis fails to fully explain the process occurring at the electrode-electrolyte interface. Impedance measurements over a wide frequency range are required for a full description of the redox reactions (Choi et al, 2020). In impedance, a small perturbed potential (V_ω) is employed to record the resulting current (I_ω). The Z_ω denotes impedance and is determined by using the following relation:

$$Z_\omega = V_\omega/I_\omega = Z_o \exp(i\phi) = Z_o(\cos\phi + i\sin\phi) \qquad (9)$$

Where ω is the angular frequency, ϕ is the phase angle, i is the imaginary unit, V_ω and I_ω are the frequency-dependent voltage and current respectively (Armstrong and Henderson, 1972 and Singh et al., 2015).

Equivalent Circuit-based Analysis

In a simple scenario, the interface can be described using an equivalence circuit, commonly known as the Randles circuit. An equivalent circuit (EC) as shown in Fig. 5 is used to fit the experimental results. Figure 5 displays that a simple EC comprises of solution resistance (R_s), double-layer capacitance (C_{dl}), charge transfer resistance (R_{ct}), and Wargburg impedance (W). Besides these, inductors are also important units of EC, there is more than one way by which these components can be arranged in an EC depending on the nature of the redox processes occurring at the electrode-electrolyte interface. The simplest of them is the Randles circuit. The difference between the experimental and simulated values should be as small as possible for a clear understanding of the processes occurring at the electrode surface (Nikoo et al., 2017).

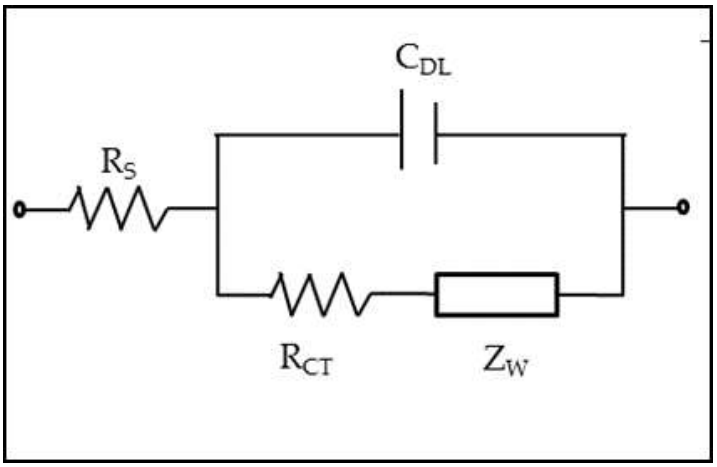


Fig. 5: Randles circuit for EIS (VanderNoot and Abrahams 1998).

The Nyquist and Bode plots are the two most convenient ways to treat impedance data.

a) Nyquist Plot

Fig. 6 shows Nyquist plot, in which imaginary component of the impedance is plotted on y-axis and real component on x- axis. In an Nquist plot, the impedance that appears at higher frequency represents solution resistance while charge transfer resistance is estimated from lower frequency region. A small value of charge transfer resistance is an indication of facile transfer of electrons (fast kinetics) at the electrode surface and vice versa.

b) Bode Plot

Bode graphs show the absolute values of impedance or phase angle vs frequency. It also delivers essentially identical information as the Nyquist plot. The Φ vs log ω in Fig. 6 indicates that the material is resistant in both high and low frequency ranges. This is confirmed with no phase shift. At intermediate frequencies, the responses grow more capacitive as the phase shift approaches 90º (Park and Yoo, 2003).

Reasons to Run EIS

Characterization of Electrochemical Systems

EIS provides extensive information about the electrical properties of electrochemical systems, assisting in the understanding of resistances, capacitances, and reaction rates.

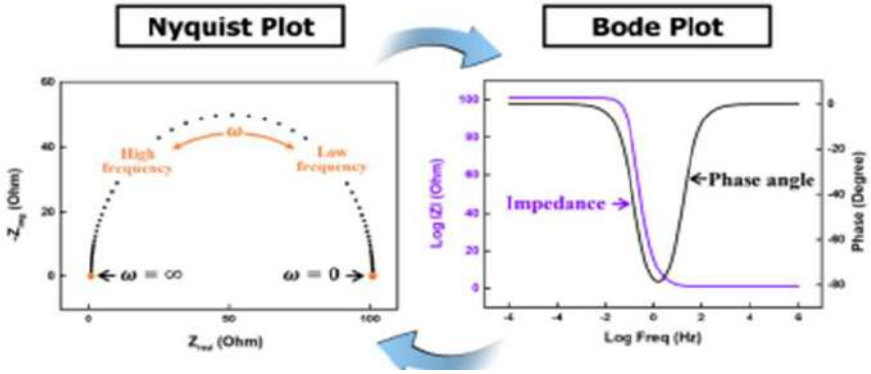


Fig. 6: Nyquist Plot and Bode plot for EIS (Birke, 1981).

Understanding Reaction Mechanisms

EIS uses impedance spectra analysis to discover and comprehend electrochemical processes such as charge transfer reactions, mass transport events, and surface changes.

Detection of Electrochemical Interfaces

EIS sensitivity allows for the detection and characterizations of events such as adsorption desorption, and corrosion at electrode interfaces.

Quality Control and Process Optimization

EIS helps to ensure consistency and dependability throughout the fabrication of electrochemical devices and coatings.

Interdisciplinary Applications

EIS has applications in a variety of domains, making it an invaluable tool for researchers and practitioners working on electrochemical problems and applications.

EIS is non-destructive and non-invasive, allowing for repeated measurements without affecting system integrity, which is advantageous for fragile or sensitive systems. EIS provides key insights required for the development of novel materials and devices in areas such as chemistry, physics, and engineering.

Conclusion:

To summarize, the characterisation of nanoparticles necessitates a multidisciplinary approach using a variety of experimental approaches. X-ray diffraction (XRD) allows for structural investigation of crystalline materials, whereas scanning electron microscopy (SEM) provides information about surface morphology and composition. Thermal analysis (TA), which includes thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), yields critical information on thermal behavior and phase transitions. Electrochemical analysis techniques like cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) provide useful information on redox processes and interfacial phenomena. By combining these techniques, researchers can gain comprehensive insights into the properties and behavior of nanoparticles materials, facilitating understanding and enabling the development of advanced applications in fields such as materials science, energy storage, and catalysis.

REFERENCES

Hanawalt, J., Rinn, H., and Frevel, L. (1938). Chemical analysis by X-ray diffraction. *Industrial and Engineering Chemistry Analytical Edition*, 10(9), 457- 512.

Alexander, L., and Klug, H. P. (1950). Determination of crystallite size with the X-Ray spectrometer. *Journal of Applied Physics*, 21(2), 137-142.

Armstrong, R. D., and Henderson, M. (1972). The impedance of transpassive chromium. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry,* 40(1), 121-131.

Birke, R. L., Kim, M. H., and Strassfeld, M. (1981). Diagnosis of reversible, quasi-reversible, and irreversible electrode processes with differential pulse polarography. *Analytical Chemistry*, 53(6), 852-856.

Brown, M. E. (1989). Introduction to thermal analysis: techniques and applications. *Mineralogical Magazine*, 53(373), 1-207.

Bunaciu, A. A., UdriŞTioiu, E. G., and Aboul-Enein, H. Y. (2015). X-ray diffraction: instrumentation and applications. *Critical Reviews in Analytical Chemistry*, 45(4), 289-299.

Choi, W., Shin, H. C., Kim, J. M., Choi, J. Y., and Yoon, W. S. (2020). Modeling and applications of electrochemical impedance spectroscopy (EIS) for lithium-ion batteries. *Journal of Electrochemical Science and Technology*, 11(1), 1-13.

Cullity, B. D. (1956). Elements of X-ray Diffraction (pp. 81-106). Addison-Wesley Publishing.

Dinnebier, R. E., and Billinge, S. J. (2008). Powder diffraction: Theory and practice (pp. 1-19). Royal Society of Chemistry.

Ebnesajjad, S. (2010). Surface and material characterization techniques. Handbook of adhesives and surface preparation: technology, applications and manufacturing (pp. 31-48). William Andrew.

Ford, B.J., Savile, B. and Joy, D. C. (2019). Scanning electron microscope. Encyclopedia Britannica. https://www.britannica.com/technology/scanning-electron-microscope.

Gabbott, P. (2008). Principles and applications of thermal analysis (pp. 1-118). Wiley Blackwell.

Gallagher, P. K. (1998). Thermogravimetry and thermomagnetometry. Handbook of thermal analysis and calorimetry (pp. 225-278). Elsevier Science BV.

Gill, P., Moghadam, T. T., and Ranjbar, B. (2010). Differential scanning calorimetry techniques: applications in biology and nanoscience. *Journal of Biomolecular Techniques*, 21(4), 167.

Goodhew, P. J., Humphreys, J., and Beanland, R. (2000). Electron microscopy and analysis (pp. 20-37). CRC press.

Holzwarth, U., and Gibson, N. (2011). The Scherrer equation versus the 'Debye-Scherrer equation'. *Nature Nanotechnology*, 6(9), 534-534.

Huang, J., Li, Z., Liaw, B. Y., and Zhang, J. (2016). Graphical analysis of electrochemical impedance spectroscopy data in Bode and Nyquist representations. *Journal of Power Sources,* 309, 82-98.

Isaev, V. A., Grishenkova, O. V., and Zaykov, Y. P. (2018). Theory of cyclic voltammetry for electrochemical nucleation and growth. *Journal of Solid State Electrochemistry*, 22(9), 2775-2778.

Jenkins, R., and Snyder, R. L. (1996). Introduction to X-ray Powder Diffractometry (pp. 1-22). NY, John Wiley and Sons, Inc.

Muniz, F. T. L., Miranda, M. A. R., Morilla dos Santos, C., and Sasaki, J. M. (2016). The Scherrer equation and the dynamical theory of X-ray diffraction. Acta Crystallographica Section A: Foundations and Advances, 72(3), 385-390.

Nikoo, M., Sadowski, Ł., and Nikoo, M. (2017). Prediction of the corrosion current density in reinforced concrete using a self-organizing feature map. *Coatings*, 7(10), 160.

Park, S. M., and Yoo, J. S. (2003). Peer reviewed: EIS for better electrochemical measurements. *Analytical Chemistry*, 75(21), 455-461.

Parlouer, P. L. (2013). Thermal analysis and calorimetry techniques for catalytic investigations. Calorimetry and thermal methods in catalysis (pp. 51-101). Springer, Berlin, Heidelberg.

Pirozzi, N. M., Kuipers, J., and Giepmans, B. N. (2021). Sample preparation for energy dispersive X-ray imaging of biological tissues. *Methods in Cell Biology*, 162, 29-114.

Singh, R. K., Devivaraprasad, R., Kar, T., Chakraborty, A., and Neergat, M. (2015). Electrochemical impedance spectroscopy of oxygen reduction reaction (ORR) in a rotating disk electrode configuration: effect of ionomer content and carbon-support. *Journal of The Electrochemical Society*, 162(6), 489-498.

Ul-Hamid, A. (2018). A beginners' guide to scanning electron microscopy (pp. 1-14). Springer.

VanderNoot, T. J., and Abrahams, I. (1998). The use of genetic algorithms in the non-linear regression of immittance data. *Journal of Electroanalytical Chemistry*, 448(1), 17-23.

Vernon-Parry, K. D. (2000). Scanning electron microscopy: an introduction. *III-Vs Review*, 13(4), 40-44.

Zahn, R., Coullerez, G., Vörös, J., and Zambelli, T. (2012). Effect of polyelectrolyte interdiffusion on electron transport in redox-active polyelectrolyte multilayers. *Journal of Materials Chemistry*, 22(22), 11073-11078.

Zhao, S., Wei, G. W., and Xiang, Y. (2005). DSC analysis of free-edged beams by an iteratively matched boundary method. *Journal of Sound and Vibration*, 284(1-2), 487-493

Chapter 26

Use of Nanoparticles against Salmonellosis in Poultry

Muhammad Abu Bakar*[1], Muhammad Fahad[1], Muhammad Saad Arshad[1], Ali Hussain[2], Abdul Ali[3], Furqan Ali[4], Ahmed Suleman[5], Zaighum Ali[1], Syed Abdullah Bukhari[1] and Aftab Shahzad[1]

[1]Faculty of Veterinary Sciences, Bahauddin Zakariya University Multan, Pakistan
[2]Facultad de Veterinaria, University of Zaragoza, CIHEAM & Autonomous University of Barcelona
[3]Department of Biosciences, COMSATS University Islamabad, Pakistan
[4]Institute of Chemistry, Faculty of Natural Sciences, University of Pécs
[5]Department Of Microbiology & Molecular Genetics, Bahauddin Zakariya University Multan, Pakistan
*Corresponding author: bakae34@gmail.com

ABSTRACT

The infections are getting harder to treat day by day due to an increase in the prevalence of drug-resistant bacteria. The primary use of nanoparticles against infections is their role as an alternative to antibiotics for preventing antibiotic resistance. Along with antibiotic resistance, the other factors involved in their usage are enhanced potency and broad-spectrum activity. Various nanoparticles have shown a potential against bacterial infections such as salmonellosis, which has considerable impacts on public health, poultry products, and economics. Many of the infections caused by *Salmonella* spp. are drug-resistant to commonly used antibiotics. One of the main reasons is the irrational use of antibiotics in both the human and animal sectors. The use of NPs has had a great impact in treating these infections. Gold, Silver, Zinc Oxide, Copper, MgO, and Selenium NPs have shown a key role in antibacterial activity against salmonellosis. The research is being done to manage their dosages and usages. However, there is a need to more widely apply the use of nanoparticles against salmonellosis in the poultry farming industry. This chapter highlights the importance of the antibacterial use of nanoparticles along with their mechanisms.

KEYWORDS
Infections, Chemical drugs, bacteria, Alternatives, Nanoparticles, Poultry

Received: 10-Jun-2024
Revised: 18-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Bakar MA, Fahad M, Arshad MS, Hussain A, Ali A, Ali F, Suleman A, Ali Z, Bukhari SA and Shahzad A, 2024. Use of nanoparticles against salmonellosis in poultry. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 227-232. https://doi.org/10.47278/book.CAM/2024.304

INTRODUCTION

With continued advancement in the poultry sector, the demand for poultry products along with its socioeconomic perspective is making a huge contribution to the food animals producing industry. The world production of fresh or chilled chicken meat increased from 120.4 million to 123.6 million tonnes from the year 2021 to 2022. The United States of America, Mainland China, and Brazil are the top three chicken meat producers. The amount of eggs produced worldwide has surged by 150 percent in the last thirty years. Asia has seen the greatest of this expansion, with production nearly tripling there (FAOSTAT, 2022). Genetic Selection has played a key role in maximizing the production of poultry meat and eggs over time (Korver, et al., 2023). Poultry meat is a rich source of protein content and amino acid balance, energy, and micronutrients while eggs contain large amounts of amino acids along with essential fatty acids and high levels of vitamins (Bohrer et al., 2017). Meanwhile, viruses, fungi, and bacteria are responsible for causing various disease outbreaks in poultry (Saif et al., 2009). For example, non-typhoidal salmonella serotypes are associated with salmonellosis in poultry. Salmonellosis has a zoonotic potential which can be due to consumption of contaminated eggs and meat. There are various routes of transmission of salmonella in poultry such as contact with carrier animals like rodents, cats, and insects. Contaminated water, litter, feed, and aerosol transmission are also involved in its transmission (Shaji et al., 2023). Meanwhile, the economic losses attributed due to salmonellosis in the United States as a foodborne disease is estimated to be 4 billion dollars. (Scharff et al., 2012)

Chemical Control of Salmonellosis in Poultry

Broad-spectrum antibiotics are recommended against salmonella infections in poultry. Chloramphenicol, Neomycin Polymyxin B, Nitrofurazone, Amoxicillin, and Tetracycline, are the drugs of choice for the treatment of salmonellosis (Tariq et al., 2022). A review study published in 2020 shows that 70.0% of the studied strains of Poultry Salmonella are sensitive to drugs of the Fluoroquinolone group (nalidixic acid, norfloxacin, ciprofloxacin, enrofloxacin) and 66.67% to the

cephalosporins (ceftazidime). 83.33% of strains were resistant to tetracycline drugs (tetracycline); 63.33% - β - lactams (ampicillin); 56.67% - aminoglycosides (gentamicin, kanamycin, streptomycin); 46.67% - sulfonamides (trimethoprim). Enrofloxacin is also used to treat salmonella in poultry. The recommended dose is 10 mg/kg of body weight per day for 5 to 10 days, added to the drinking water (Lenchenko et al., 2020).

Alternate Control Measures for the Control of Salmonellosis in Poultry

Essential oils have been found to act as environmental disinfectants along with decreasing intestinal colonization in chickens (Ebani et al., 2019). The dietary supplementation of essential oils (Khan et al., 2023) and organic acids is also helpful in reducing the salmonella load in the liver, spleen, and cecum (Hu et al., 2023). Probiotic supplementation of the feed leads to increased anti-salmonella IgA which helps boost humoral immunity against the salmonella infections in the birds (Shanmugasundaram et al, 2020). There is also a role of prebiotics such as non-digestible oligosaccharides and polysaccharides against salmonella which help the gut to lower the pH (Bogusławska-Tryk et al., 2012). While providing broiler birds with whole yeast cell prebiotic supplementation increases the proportion of Tregs and enhances the expression of the anti-inflammatory cytokine IL-10. All of these effects are known to modulate the immune response (Shanmugasundaram et al., 2012). Moreover, mineral nanoparticles have a role in reducing intestinal mineral antagonism thereby improving feed efficiency and immunity (Gopi et al., 2017).

Introduction of Nanoparticles

Nanoparticles (NPs) are a wide class of materials that include particulate substances, which have dimensions less than 100 nm at least. Depending on the overall shape these materials can be zero, one, two, or three-dimensional, i.e.; 0D, 1D, 2D, or 3D. Nanoparticles have a size range from 1 to 100 nm with a large surface area (Khan et al., 2023). They are extensively used in modern-day medicine for their unique ability to deliver the drugs in the optimum concentration resulting in improved patient care. Nanoparticles have also been used in diagnostic imaging technology and the development of the immunoassay. The main aspects of nanoparticles usage in medicine are their antimicrobial properties and the treatment of cancer (Maria et al., 2023). There are various classifications of the nanoparticles such as Carbon-based, Metal, Ceramic, Lipid-based, and Semiconductor NPs (Khan et al., 2019). In addition, there are two approaches for the preparation of the nanoparticles such as Bottom-Up Syntheses and Top-Down Syntheses (Wang and Xia, 2004).

Top-Down Syntheses of Nanoparticles Includes the following Steps;

- ➢ Mechanical milling
- ➢ Chemical etching
- ➢ Sputtering
- ➢ Laser Ablation
- ➢ Electro explosion

Bottom-up Synthesis of Nanoparticles is Summarized into the following steps;

- ➢ Spinning
- ➢ Template support synthesis
- ➢ Plasma or flame spraying synthesis
- ➢ Laser pyrolysis
- ➢ Chemical Vapor Deposition (CVD)
- ➢ Atomic or molecular condensation (Ibrahim et al., 2019)

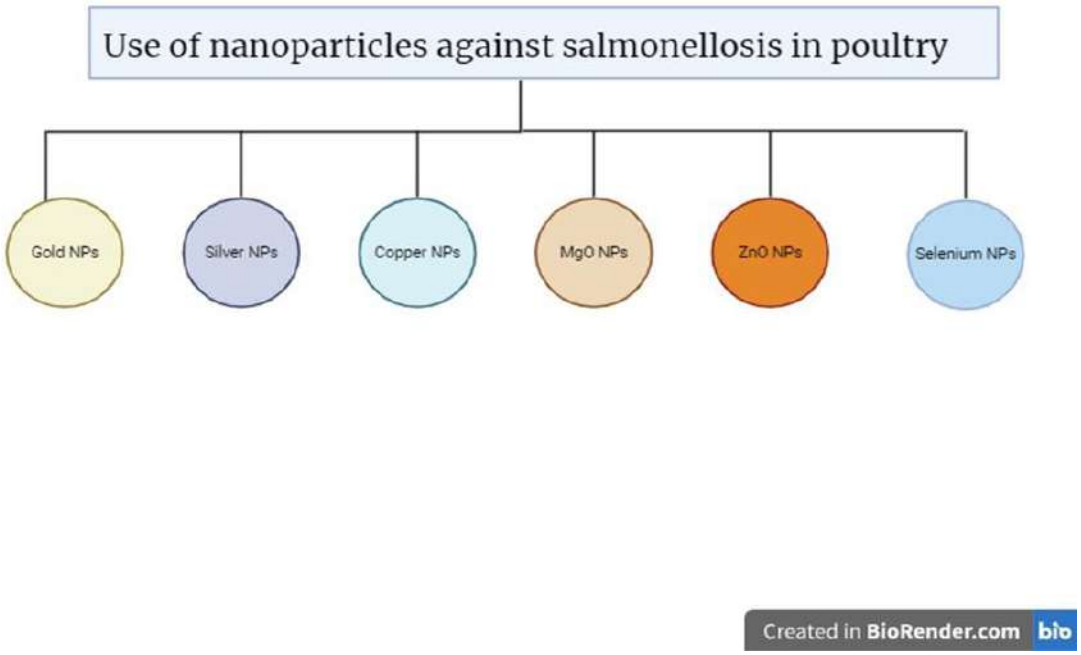


Fig. 1: Nanoparticles against Salmonella in poultry

Mechanism of Antibacterial Action of Nanoparticles

Nanoparticles (NPs) must come into contact with bacterial cells to exert their antibacterial effects. Various mechanisms can result in this contact like electrostatic attraction, receptor-ligand binding, van der Waals forces, and hydrophobic interactions. After the establishment of this contact, NPs can cross the bacterial cell membrane and accumulate along the cell's metabolic pathways and it influences the cell membrane's shape and function. This forms interaction with essential cellular components including DNA, ribosomes, lysosomes, and enzymes which results in oxidative stress, changes in membrane permeability, cellular damage, enzyme inhibition, disruption in electrolyte balance, alteration in gene expression, and protein inactivation. The antimicrobial mechanism of action of NPs is generally owes to one of the three models; metal ion release, oxidative stress induction, or non-oxidative mechanisms. Simultaneous occurrence of these three mechanisms can also be seen (Wang et al., 2017).

Table 1: Antibacterial Mechanism of Action of Some Nanoparticles

Types	Antibacterial Mechanism	References
Gold NPs	Oxidative stress due to the production of reactive free oxygen and penetration inside the cell	(Kaur et al., 2023)
Zinc Oxide NPs	Destruction of cell integrity, ROS formation, release of antimicrobial ions, mainly Zn2+ ions	(Li et al., 2011)
Silver NPs	Interferes with cell membrane and electron transport, Ag NPs work as catalysts in pollution treatment along with treatment for burns	(Li et al., 2008; Wang et al., 2017)
Titanium Oxide NPs	Releases reactive oxygen species (ROS) and damages cell membranes	(Bozdek et al., 2022)
Nitric Oxide-Releasing NPs	Produces an array of antimicrobial effector molecules acting on different targets within the microbial cell with the release of NO and reactive oxygen species	(Weller et al., 2009)

Mechanism of Nanoparticles against Salmonellosis

Nanoparticles have shown a key role against salmonellosis in poultry and the potential NPs against salmonella are discussed as follows. The biogenic silver NPs have a key role against Salmonella bacteria producing the inner membrane disruption followed by membrane dysfunction. AgNPs affect the inner membrane of bacteria without damage to the outer membrane. Moreover, the formation of antibiotic-induced reactive oxygen species (ROS) and changes in the calcium gradient also contribute to bacterial cell death (Minju et al., 2017). The antibacterial effect of Ag NPs is more pronounced at low concentrations and a study shows that Ag NPs inhibited 60–90% of *Salmonella* pathogens (Lilit G, et al., 2020). AgNPs synergized with H_2O_2 showed broad-spectrum bactericidal activity toward multi-drug-resistant *S. typhimurium* which was isolated from dairy and beef cattle (El-Gohary et al., 2020). Another study indicated that AgNPs have exhibited antimicrobial and antibiofilm activity against *S. Enteritidis*. The bacterial count decreases after using AgNPs on the biofilm as compared to the use of the sanitizer (Dias de Emery et al., 2023).

Foodborne S*almonella* pathogens are susceptible to the antibacterial activity of MgO NPs. When NPs contact bacterial cells, this interaction causes induction of oxidative stress, cell membrane leakage, and ultimately death of the cell (Yiping et

al., 2016). MgO NPs gain entry within the bacterial cells by cell membrane disruption which allows them to penetrate the cytoplasm. Once these NPs enter the cytoplasm, they can either directly damage the DNA and the enzymes, or generate the reactive oxygen species (ROS) through a light-driven catalytic process. This production of ROS on the nanoparticle surface, triggered by light, results in the induction of oxidative stress in the microbial cells and leads to the death of the cell. It causes denaturation of the proteins and causes damage to the mitochondria. Additionally, interference with cellular memory is seen and trans-tolerant electron transport is also impeded. Consequently, the inflicted damage leads to the destruction of bacterial cells, prompting the release of their organelles and eventually leading to cell death (Gatou et al., 2024).

AuNPs act as an excellent biocide to eliminate *Salmonella typhi* colonies at times as short as 90 minutes (Lima et al., 2013). AuNPs obtained from *S. plagiophyllum* extract have been found to show effective antibacterial activity for biomedical applications (Dhas et al., 2020). Gold nanoparticles have shown antimicrobial activity against MDR *Salmonella* spp. obtained from fecal samples of the ruminants suffering from mastitis, respiratory signs, and diarrhea (Abdalhamed et al., 2021). The combination therapy including an antibiotic such as cefixime and a variety of NPs including Silver, Zinc oxide, Copper, and Nickel has shown antimicrobial activity against *Salmonella* Infections (Kapadia et al., 2021).

Scientific evidence demonstrated the potential of ZnO NPs as an alternative to conventional antibiotics in livestock farming (Yausheva et al., 2018). The effects of exposure to ZnO nanoparticles on the gut microbiota have been researched in various animal models (Zhu et al., 2023). Zinc Oxide NPs enhance the production of the reactive oxygen species which leads to abnormal metabolism in food pathogens including *Salmonella*. It has also been found that the exposed cells with ZnO NPs produce a high level of malondialdehyde disintegrating the bacterial cell membrane. It would also allow the ZnO NPs to enter into the cytosol to interact with cytoplasmic proteins and enzymes, producing more reactive oxygen and leading to protein aggregation and enzyme inhibition. (Krishnamoorthy et al., 2022).

The biosynthesized Selenium NPs have also demonstrated an antibacterial potential against *Salmonella typhimurium* both in vitro and in vivo experiments (Saleh et al., 2023). Selenium NPs improve the growth performance, feed conversion ratio, and meat production through their antimicrobial activity and stimulating the thyroid glands to produce the thyroid hormones in poultry. It also improves the intestinal membrane integrity and enhances the production of beneficial intestinal bacteria. Supplementation of the Selenium NPs in the laying hen's diet improves the egg production and the egg-laying capacity of the hens (Ahmad et al., 2022).

With the size of 2-350nm and increased uptake from the GIT, the Copper NPs have inhibited the growth of *Salmonella choleraesuis*. (Scott et al, 2018). However, it is reported that CuO NPs require higher concentrations to show an antimicrobial effect against *Salmonella* as tested by MIC (Duffy et al., 2018). A recent study shows that CuO NPs synthesized via the green route by using *Cassia fistula* revealed that the peace antibacterial activity was demonstrated at 280nm through UV spectrometry against *S. typhimurium*. It produces the ROS by following the type II mechanism for the production of reactive oxygen species (Rahim et al., 2024)

Conclusion

The use of nanoparticles is increasing day by day due to the wide range of their applications in diagnosis and therapeutic areas. The discussions in our book chapter include the antibacterial action of nanoparticles against salmonellosis. These nanoparticles have potential advantages against enteric pathogens and advanced research must be done to determine the applications of nanoparticles against salmonellosis on an industrial level in poultry. Salmonellosis plays a key role in mortality and morbidity in the poultry sector all over the world. There is a need to undergo further research to understand the potential application of NPs to get adopted in poultry.

REFERENCES

Abdalhamed, A. M., Ghazy, A. A., Ibrahim, E. S., Arafa, A. A., and Zeedan, G. S. (2021). Therapeutic effect of biosynthetic gold nanoparticles on multidrug-resistant Escherichia coli and Salmonella species isolated from ruminants. *Veterinary World*, *14*(12), 3200.doi: 10.14202/vetworld.2021.3200-3210

Ahmad, I., Mashwani, Z. U. R., Raja, N. I., Kazmi, A., Wahab, A., Ali, A., and Rahimi, M. (2022). Comprehensive approaches of nanoparticles for growth performance and health benefits in poultry: An update on the current scenario. *BioMed Research International*, *2022*(1), 9539908. doi: 10.1155/2022/9539908.

Bodzek, M. (2022). Nanoparticles for water disinfection by photocatalysis: A review. *Archives of Environmental Protection*, *48*(1), 3-17.

Bogusławska-Tryk, M., Piotrowska, A., and Burlikowska, K. (2012). Dietary fructans and their potential beneficial influence on health and performance parametrs in broiler chickens. *Journal of Central European Agriculture*, *13*(2), 0-0.

Bohrer, B. M. (2017). Nutrient density and nutritional value of meat products and non-meat foods high in protein. *Trends in Food Science and Technology*, *65*, 103-112.

de Emery, B. D., Chitolina, G. Z., Qadir, M. I., Furian, T. Q., Borges, K. A., de Souza Moraes, H. L., and do Nascimento, V. P. (2023). Antimicrobial and antibiofilm activity of silver nanoparticles against Salmonella Enteritidis. *Brazilian Journal of Microbiology*, *54*(1), 285. https://doi.org/10.1007/s42770-022-00868-1

Dhas, T. S., Sowmiya, P., Kumar, V. G., Ravi, M., Suthindhiran, K., Borgio, J. F., and Kumar, C. V. (2020). Antimicrobial effect of

Sargassum plagiophyllum mediated gold nanoparticles on Escherichia coli and Salmonella typhi. *Biocatalysis and Agricultural Biotechnology*, *26*, 101627.https://doi.org/10.1016/j.bcab.2020.101627

Duffy, L. L., Osmond-McLeod, M. J., Judy, J., and King, T. (2018). Investigation into the antibacterial activity of silver, zinc oxide and copper oxide nanoparticles against poultry-relevant isolates of Salmonella and Campylobacter. *Food Control*, *92*, 293-300. https://doi.org/10.1016/j.foodcont.2018.05.008

Ebani, V. V., Nardoni, S., Bertelloni, F., Tosi, G., Massi, P., Pistelli, L., and Mancianti, F. (2019). In vitro antimicrobial activity of essential oils against Salmonella enterica serotypes Enteritidis and Typhimurium strains isolated from poultry. *Molecules*, *24*(5), 900. https://doi.org/10.3390/molecules2405090

El-Gohary, F. A., Abdel-Hafez, L. J. M., Zakaria, A. I., Shata, R. R., Tahoun, A., El-Mleeh, A., and Elmahallawy, E. K. (2020). Enhanced antibacterial activity of silver nanoparticles combined with hydrogen peroxide against multidrug-resistant pathogens isolated from dairy farms and beef slaughterhouses in Egypt. *Infection and Drug Resistance*, 3485-3499. https://doi.org/10.2147/IDR.S271261

Gabrielyan, L., Badalyan, H., Gevorgyan, V., and Trchounian, A. (2020). Comparable antibacterial effects and action mechanisms of silver and iron oxide nanoparticles on Escherichia coli and Salmonella typhimurium. *Scientific Reports*, *10*(1), 13145. https://doi.org/10.1038/s41598-020-70211-x

Gatou, M. A., Skylla, E., Dourou, P., Pippa, N., Gazouli, M., Lagopati, N., and Pavlatou, E. A. (2024). Magnesium Oxide (MgO) Nanoparticles: Synthetic Strategies and Biomedical Applications. *Crystals*, *14*(3), 215. https://doi.org/10.3390/cryst14030215

He, Y., Ingudam, S., Reed, S., Gehring, A., Strobaugh, T. P., and Irwin, P. (2016). Study on the mechanism of antibacterial action of magnesium oxide nanoparticles against foodborne pathogens. *Journal of Nanobiotechnology*, *14*, 1-9. https://doi.org/10.1186/s12951-016-0202-0

Hu, Z., Liu, L., Guo, F., Huang, J., Qiao, J., Bi, R., and Wang, Z. (2023). Dietary supplemental coated essential oils and organic acids mixture improves growth performance and gut health along with reduces Salmonella load of broiler chickens infected with Salmonella Enteritidis. *Journal of Animal Science and Biotechnology*, *14*(1), 95. https://doi.org/10.1186/s40104-023-00889-2

Kapadia, C., Alhazmi, A., Patel, N., Elesawy, B. H., Sayyed, R. Z., Lokhandwala, F., and Datta, R. (2021). Nanoparticles combined with cefixime as an effective synergistic strategy against Salmonella enterica typhi. *Saudi Journal of Biological Sciences*, *28*(8), 4164-4172. https://doi.org/10.1016/j.sjbs.2021.05.032

Kaur, H., Rauwel, P., and Rauwel, E. (2023). Antimicrobial nanoparticles: synthesis, mechanism of actions. In *Antimicrobial activity of nanoparticles* (pp. 155-202). *Elsevier*. https://doi.org/10.1016/B978-0-12-821637-8.00008-0.

Kausar, M., Saleem, Z., Azhar, R., Rukhsar, G., Ali, M., Fan, C., and Khan, A. M. A. Role Of Nanoparticles In Covid-19 Management. https://Doi.Org/10.61748/Cam.2023/010

Khan, A. M. A., Arshad, M. A., Naeem, R. F., Shafiq, M. S., Irshad, M., Shahid, D. A., and Usmani, M. W. Role Of Essential Oils And Other Alternatives To Control Ticks (Hyalomma Species) The Major Cause Of Cchf (a Threat For Humans And Livestock). https://Doi.Org/10.61748/Cam.2023/006

Khan, A. M. A., Wei, C. R., Fatima, K., Ali, A., Akram, M. S., Saeed, Z., and Ullah, H. Use Of Nanoparticles As Antioxidant Agents To Combat Bacterial Infections And Its Benefits To Intestinal Microbiota And Immune Response. https://Doi.Org/10.61748/Cam.2023/001

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931. https://doi.org/10.1016/j.arabjc.2017.05.011 .

Korver, D. R. (2023). Current challenges in poultry nutrition, health, and welfare. *Animal*, *17*, 100755.

Krishnamoorthy, R., Athinarayanan, J., Periyasamy, V. S., Alshuniaber, M. A., Alshammari, G., Hakeem, M. J., and Alshatwi, A. A. (2022). Antibacterial mechanisms of zinc oxide nanoparticle against bacterial food pathogens resistant to beta-lactam antibiotics. *Molecules*, *27*(8), 2489. https://doi.org/10.3390/molecules27082489

Lenchenko, E., Blumenkrants, D., Vatnikov, Y., Kulikov, E., Khai, V., Sachivkina, N., and Mansur, T. (2020). Poultry Salmonella Sensitivity to Antibiotics. *Systematic Reviews in Pharmacy*, *11*(2).

Li, M., Zhu, L., and Lin, D. (2011). Toxicity of ZnO nanoparticles to Escherichia coli: mechanism and the influence of medium components. *Environmental Science and Technology*, *45*(5), 1977-1983. doi: 10.1021/es102624t

Li, Q., Mahendra, S., Lyon, D. Y., Brunet, L., Liga, M. V., Li, D., and Alvarez, P. J. (2008). Antimicrobial nanomaterials for water disinfection and microbial control: potential applications and implications. *Water Research*, *42*(18), 4591-4602.doi:10.1016/j.watres.2008.08.015

Lima, E., Guerra, R., Lara, V., and Guzmán, A. (2013). Gold nanoparticles as efficient antimicrobial agents for Escherichia coli and Salmonella typhi. *Chemistry Central Journal*, *7*, 1-7. https://doi.org/10.1186/1752-153X-7-11

Marappan Gopi, M. G., Beulah Pearlin, B. P., Kumar, R. D., Muthuvel Shanmathy, M. S., & Govindasamy Prabakar, G. P. (2017). Role of nanoparticles in animal and poultry nutrition: modes of action and applications in formulating feed additives and food processing.

Rahim, M., Khan, M., Abbas, N., Khalid, M., and Hussain, M. A. (2024). Synthesis, characterization, and antimicrobial activity of Cassia fistula mediated Cobalt doped Copper oxide nanoparticle against Salmonella typhi a step toward antibacterial nanomedicine. *International Journal of Nanoelectronics and Materials (IJNeaM)*, *17*(1), 147-152. https://doi.org/10.58915/ijneam.v17i1.504

Randall, L. P., Cooles, S. W., Coldham, N. C., Stapleton, K. S., Piddock, L. J., and Woodward, M. J. (2006). Modification of enrofloxacin treatment regimens for poultry experimentally infected with Salmonella enterica serovar Typhimurium DT104 to minimize selection of resistance. *Antimicrobial agents and chemotherapy*, *50*(12), 4030-4037..https://doi.org/10.1128/aac.00525-06

Saif, Y. M. (2009). *Diseases of poultry*. John Wiley and Sons.

Saleh, A., El-Masry, T. A., Negm, W. A., Alotaibi, B., Elharty, M. E., Alotaibi, K. N., and Elekhnawy, E. (2023). Unravelling the antibacterial potential of biosynthesized selenium nanoparticles against Salmonella Typhimurium food pathogen: in vitro and in vivo investigation. *European Review for Medical and Pharmacological Sciences*, *27*(8).

Scharff, R. L. (2012). Economic burden from health losses due to foodborne illness in the United States. *Journal of Food Protection*, *75*(1), 123-131.

Scott, A., Vadalasetty, K. P., Chwalibog, A., and Sawosz, E. (2018). Copper nanoparticles as an alternative feed additive in poultry diet: a review. *Nanotechnology Reviews*, *7*(1), 69-93.. https://doi.org/10.1515/ntrev-2017-0159

Seong, M., and Lee, D. G. (2017). Silver nanoparticles against Salmonella enterica serotype typhimurium: role of inner membrane dysfunction. *Current Microbiology*, *74*, 661-670. https://doi.org/10.1007/s00284-017-1235-9

Shaji, S., Selvaraj, R. K., and Shanmugasundaram, R. (2023). Salmonella infection in poultry: a review on the pathogen and control strategies. *Microorganisms*, *11*(11), 2814. https://doi.org/10.3390/microorganisms1111281

Shanmugasundaram, R., and Selvaraj, R. K. (2012). Effect of killed whole yeast cell prebiotic supplementation on broiler performance and intestinal immune cell parameters. *Poultry Science*, *91*(1), 107-111. https://doi.org/10.3382/ps.2011-01732.

Shanmugasundaram, R., Applegate, T. J., and Selvaraj, R. K. (2020). Effect of Bacillus subtilis and Bacillus licheniformis probiotic supplementation on cecal Salmonella load in broilers challenged with salmonella. *Journal of Applied Poultry Research*, *29*(4), 808-816.https://doi.org/10.1016/j.japr.2020.07.003

Tariq, S., Samad, A., Hamza, M., Ahmer, A., Muazzam, A., Ahmad, S., and Amhabj, A. M. A. (2022). Salmonella in poultry; an overview. *International Journal of Multidisciplinary Sciences and Arts*, *1*(1), 80-84.

Van Alfen, N. K. (2014). *Encyclopedia of agriculture and food systems*. Elsevier.

Wang, L., Hu, C., and Shao, L. (2017). The antimicrobial activity of nanoparticles: present situation and prospects for the future. *International Journal of Nanomedicine*, 1227-1249. https://doi.org/10.2147/IJN.S121956

Wang, Y., and Xia, Y. (2004). Bottom-up and top-down approaches to the synthesis of monodispersed spherical colloids of low melting-point metals. *Nano Letters*, *4*(10), 2047-2050.

Weller, R. B. (2009). Nitric oxide–containing nanoparticles as an antimicrobial agent and enhancer of wound healing. *Journal of Investigative Dermatology*, *129*(10), 2335-2337.https://doi.org/10.1038/jid.2009.149.

Yausheva, E., Miroshnikov, S., and Sizova, E. (2018). Intestinal microbiome of broiler chickens after use of nanoparticles and metal salts. *Environmental Science and Pollution Research*, *25*(18), 18109-18120.

Zhu, L., Luo, M., Zhang, Y., Fang, F., Li, M., An, F., and Zhang, J. (2023). Free radical as a double-edged sword in disease: Deriving strategic opportunities for nanotherapeutics. *Coordination Chemistry Reviews*, *475*, 214875.

Chapter 27

Nanoparticle-Mediated Antimicrobial Armory: Employing Nanotechnology for Precision Control of Bacterial and Viral Infections

Muhammad Usama Javed[1], Tahreem Fatima[2], Muhammad Haseeb Amir[1], Muhammad Tayyab Naveed[1], Nida Liaqat[3], Muhammad Abdullah[1], Muhammad Abubakar Amin[1], Tayyab ur Rehman[1], Fasih Yousaf[1] and Muhammad Zeeshan Hadier Javed[3]

[1]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Mbbs, Registered Medical Practitioner, Pakistan
[3]Faculty of Food Nutrition and Home Sciences, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: drosamajaved@gmail.com

ABSTRACT

This chapter gives us details about the complex role of nanoparticles in dealing with bacteria and viruses as antimicrobial agents. Nanoparticles are tiny particles with a size of 1- 100 nm. Their properties are very unique so a lot of research is carried out on these revolutionary particles. They are present in nature and have a very ancient history. The evolution of these particles from ancient history to Michael Faraday's work is tracked which can elaborate their importance in modern medicine and industry fields. The classification of these particles into various types such as organic and inorganic nanoparticles helps us to study their antimicrobial activity in detail. Further, this chapter explores the antibacterial properties of nanoparticles. Organic nanoparticles such as liposomes and inorganic nanoparticles such as gold and silver nanoparticles destroy the cell walls of bacteria by different mechanisms of action. The importance of nanoparticles increases more because they can be an alternative to antibiotics in case of AMR which is a big threat to the world nowadays. This chapter also delves into the antiviral properties of nanoparticles. Viral infections are a big threat to society and unfortunately, they have no specific treatments but nanoparticles can be used to prepare vaccination that can be used against these viruses with more precise targeting mechanisms.

KEYWORDS
Bacteria, Viruses, Chemical drugs, Resistance, Alternative, Nanoparticles

Received: 18-Jun-2024
Revised: 14-Jul-2024
Accepted: 16-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Javed MU, Fatima T, Amir MH, Naveed MT, Liaqat N, Abdullah M, Amin MA, Rehman TU, Yousaf F and Javed MZH, 2024. Nanoparticle-mediated antimicrobial armory: employing nanotechnology for precision control of bacterial and viral infections. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 233-242. https://doi.org/10.47278/book.CAM/2024.309

INTRODUCTION

Nanoparticles are matter particles (Griffin et al., 2017), have a small size of 1-100 nanometers (Paulami et al., 2023; Tripathi et al., 2023), and can't be seen with the naked human eye or even with the compound microscope. (Diaspro et al., 2022; M. Ismail et al., 2019) The electron microscope is required to see nanoparticles (Dahy et al., 2023). They are also called ultrafine particles (Li et al., 2016; Burtscher et al., 2012). Nanoparticles are widely present in nature (Suhag et al., 2023; Niu et al., 2023). They play an important role in modern medicines (Joseph et al., 2023; Munir et al., 2020) and are present in many industrial products (Litter et al., 2023; Malik et al., 2023) like plastic (Majeed et al., 2024, Calovi et al. 2023), paints, metallic (Santos et al., 2015) and magnetic products (Zerkani and Abbodi, 2023). Their roles are very deeply studied in different sciences such as chemistry, physics, and even in medical science to treat different diseases (Zahin et al. 2020).

They are generated through a lot of naturally occurring events in the Universe (Buzea et al., 2007) e.g. volcanic eruptions (Ermulin et al., 2023; Fedotov et al., 2023), microbial processes (Milani et al., 2023), forest fires (Nim et al., 2023), etc. There is a very unique history of Nanoparticles. Artists have used nanoparticles in their crafts but they didn't know their properties since prehistory (Montanarella and Kovalenko, 2022). Many artifacts of ancient times showed that tiny metal particles were mixed with different materials to make them unique. The example of the Lycurgus Cup is perfect in which nanoparticles were used for their color-changing characteristics but at that time artists didn't know about it (Babu et al., 2023; Khatun and Predeep, 2023). The unique visual was obtained by mixing silver and gold nanoparticles in glass which interact with light and give beautiful visions (Litter and Ahmad, 2023). Similarly, Mesopotamia lusterware pottery shows a beautiful metallic shine due to metallic nanoparticles of copper and silver in the glass. (Jayalatha and Rayappan,

2015; Mirguet et al., 2015). The ancient artist manipulated things at the nano level, making remarkable achievements in their creations. (Heiligtag and Niederberger, 2013). In the 19th century, Michael Faraday gave scientific knowledge of nanoparticle-scale metal properties in his paper in 1857 (Merupa et al., 2023; Norton et al., 2023). He observed that heating mounted gold or silver thin leaves on the glass below red heat changes their properties, it changes light transmission and reflection in these metals and their electricity resistivity also increases (Stempski et al., 2019; Parveen et al., 2016). The interaction of light with nanoparticles was described by Mie in 1908 (Dorodnayy et al., 2023; Talapin and Shevchenko, 2016).

In the 1970s and 80s, proper studies started in America and Japan (Litter and Ahmad, 2023; Ma, 2022). In the beginning, they called them ultrafine particles, but by the 1990s the term nanoparticle became more common. The National Nanotechnology Initiative started in America officially in 2000 (Roco, 2023; Hashmin et al., 2022).

Nanoparticles are very useful in all science subjects but our topic is related to the use of nanoparticles in antimicrobial resistance and control. Nanoparticles are classified into different types based on physiochemical compositions (Khan, 2019; Stone et al., 2010) e.g. Organic based nanoparticles (nanocapsule, nanosphere, liposomes, dendrimers), Inorganic based nanoparticles (silver, gold, magnetic and alloy nanoparticles.), carbon-based Nps, semiconductor-based nanoparticles, etc.

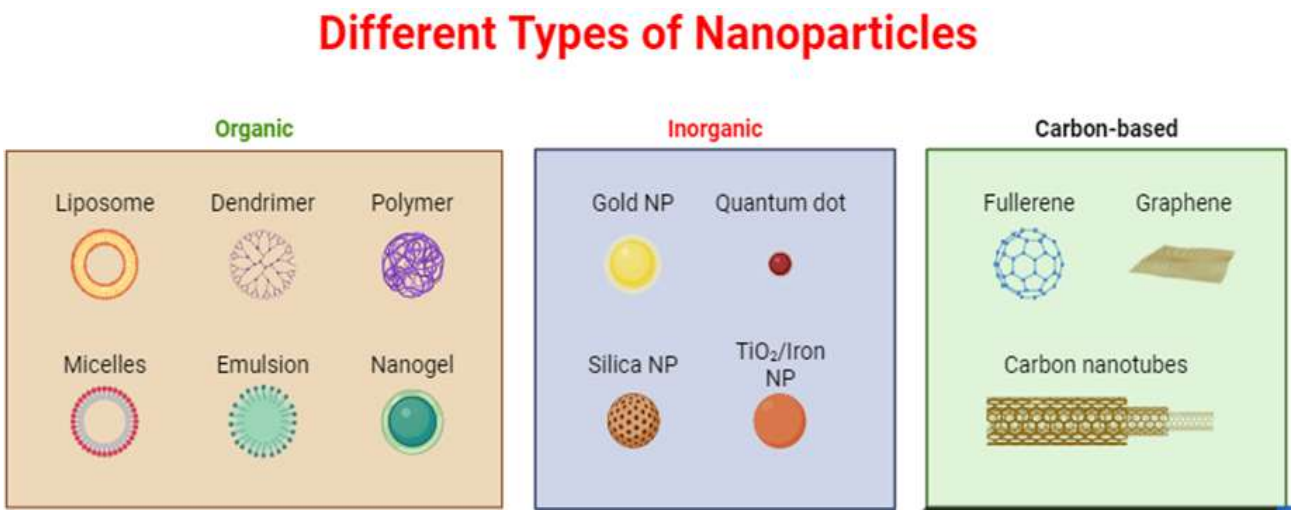
Organic Nanoparticle is the type of nanoparticle used in drug delivery systems (Natesan and Kim, 2023; Ulises and Sharma, 2023; Mitragotri et al., 2014). Following are some organic nanoparticles. Nanocapsule are hollow spheres (Vasilaki et al., 2023; Panigrahi et al., 2022) in which the drug is confined in the inner cavity with a polymer coating (Anis et al. 2023; Li et al., 2023) their size is 50-300 nm (Verma et al., 2016). They have low density but higher loading capacity (Wu et al., 2020; Geothals et al., 2013). Nanospheres are a matrix system of drug delivery in which the drug is spread uniformly (Purabisaha et al., 2021). Their size ranges from 100-200 nm (Barcelo et al., 2012). In many studies, they are used to treat influenza (Cho et al., 2015), Hepatitis B (Wen et al., 2019), and Herpes Simplex Virus (Shen et al., 2019).

Liposomes (Li et al., 2023) are a type of Organic NP that is very important. They are spherical carriers with tiny sizes of 20-30 nm (Nsairat et al., 2022). They are made up of a phospholipid bilayer that surrounds the aqueous core (Rai et al., 2014). Phospholipid bilayer gives them a very unique quality. They can mimic cell membranes and easily fuse with microbial cell membranes (Fang et al., 2015). Drugs can be mixed in the inner core for targeted drug delivery. They are non-toxic and biodegradable (Farid et al., 2020; Singh et al, 2017) Inorganic nanoparticles are smaller than organic nanoparticles but have More efficacy.

Silver nanoparticles are a Great role of nanoparticles these days in different fields but among all of the types, silver NP are a more widely used type. They are used in large quantities in the industry to make home appliances, water treatment plants, and disinfectants used in the medical field (Saifuddin et al., 2017). They are also used in biosensing and imaging technology due to their unique properties (Garg et al., 2020; Siromani and Daniel, 2011). AG NP is also very effective in treating many diseases by targeting specific cells (Franci et al., 2015) e.g. Ag NP targets the HIV-1 virus by stopping it from binding with host cells in vitro (Alarcon and Udekwu, 2015; Tsai et al., 2019)

Gold nanoparticles are synthesized in large quantities because they are used in many medical treatments e.g. treatment of PPR in ruminants (Bisht et al., 2023). They have a very important role in the medication of different infections. They are made from Tetra chloroauric acid (HAuCl4) and Trisodium citrate by a reduction process in an aqueous solution (Hammami et al., 2021). Their surface plasmon resonance properties make them suitable for imaging techniques and biomedical tools (Verma and Singh, 2014). They are used to detect DNA in a sample as a lab tracer. They can be used to detect aminoglycoside antibiotics. They are used to detect cancer stem cells which are very useful in cancer diagnosis (Hasan, 2015).

Magnetic nanoparticles are also a very important type. They are made up of metallic elements like iron, cobalt, and nickel and their oxides under an external magnetic field (Selim et al., 2023). They are used in MRI and targeted drug and gene delivery (Shen et al., 2018; Shubayev et al, 2009).



Nanoparticle: Tiny Warriors against Microbes

Nanoparticles are the modern and ting fighters that fight against microbes (Mobeen et al., 2021). They can solve many problems caused by bacterial and viral infections (Baptista et al., 2018). They can target the pathogens very accurately and kill them in different ways even if they develop resistance to antibiotics (Natan and Banin, 2017). This seems very fictional but it's reality now.

In present days, bacterial infections are treated with antibiotics which is a very useful way to overcome infections which is very good but we need these futuristic technologies. The reason behind this is microbial resistance against these antibiotics. Microbial resistance is a big threat these days (Muteeb et al., 2023; Tang et al., 2023). Many antibiotics are not useful for many bacterial infections nowadays because bacteria develop resistance against these antibiotics and they aren't able to kill these bacteria anymore (Costanzo and Roviello, 2023). Superbugs and multidrug-resistant bacteria are endemic in many parts of the world (Aslam et al., 2023; Panuli et al., 2023). This is the start of resistance as time proceeds all bacteria may develop resistance and infections become untreatable. Before this happens, we have to develop alternatives to these antibiotics. (Christaki, Marcou, and Tofarides, 2020)

Nanoparticles can easily alternate these conventional antibiotics (Kanwar et al., 2023). They can not only work against bacterial infection but also against viral infections, which is the best thing about them (Teirumnieks et al., 2023; Aguilera et al., 2021). Nanoparticles have a high surface area-to-volume ratio, tailored surface properties, and customizable composition (Schneider et al., 2021). These properties make nanoparticles act against the pathogen. Nanoparticles can also be designed to specifically target microbial cells while minimizing adverse effects on host cells (Sethu et al. 2017). They are also concerned with toxicity, scalability, and regulatory factors.

They can be used in wound dressing (Kalantari et al., 2020), coating for medical devices (Marassi et al. 2018), and as delivery systems for antimicrobial drugs (Canaparo et al., 2019). Nanoparticles play a role in water purification systems by effectively eliminating bacteria eliminating bacterial contaminants (Joseph et al., 2023). Future research aims to optimize nanoparticles for improved efficacy, biocompatibility, and scalability.

Nanoparticles as Precision Tools against Bacterial Infection

Nanoparticles have emerged as strong candidates for fighting against bacterial infections with unique properties and applications (Khan and Rasool, 2023). By functionalizing the surface of nanoparticles, scientists can design them to recognize and bind selectively to bacterial cell surfaces (Ho et al. 2004). This gives a specific targeting approach to nanoparticles. Nanoparticles have a different way of interacting with bacteria. Some penetrate bacterial cell walls (Mei et al., 2013), destroy cell wall integrity, and cause cell death. Some release antimicrobial compounds or generate reactive oxygen species which stop bacterial growth and interact with important cellular processes, making them effective antibacterial agents (Karanwal et al. 2023).

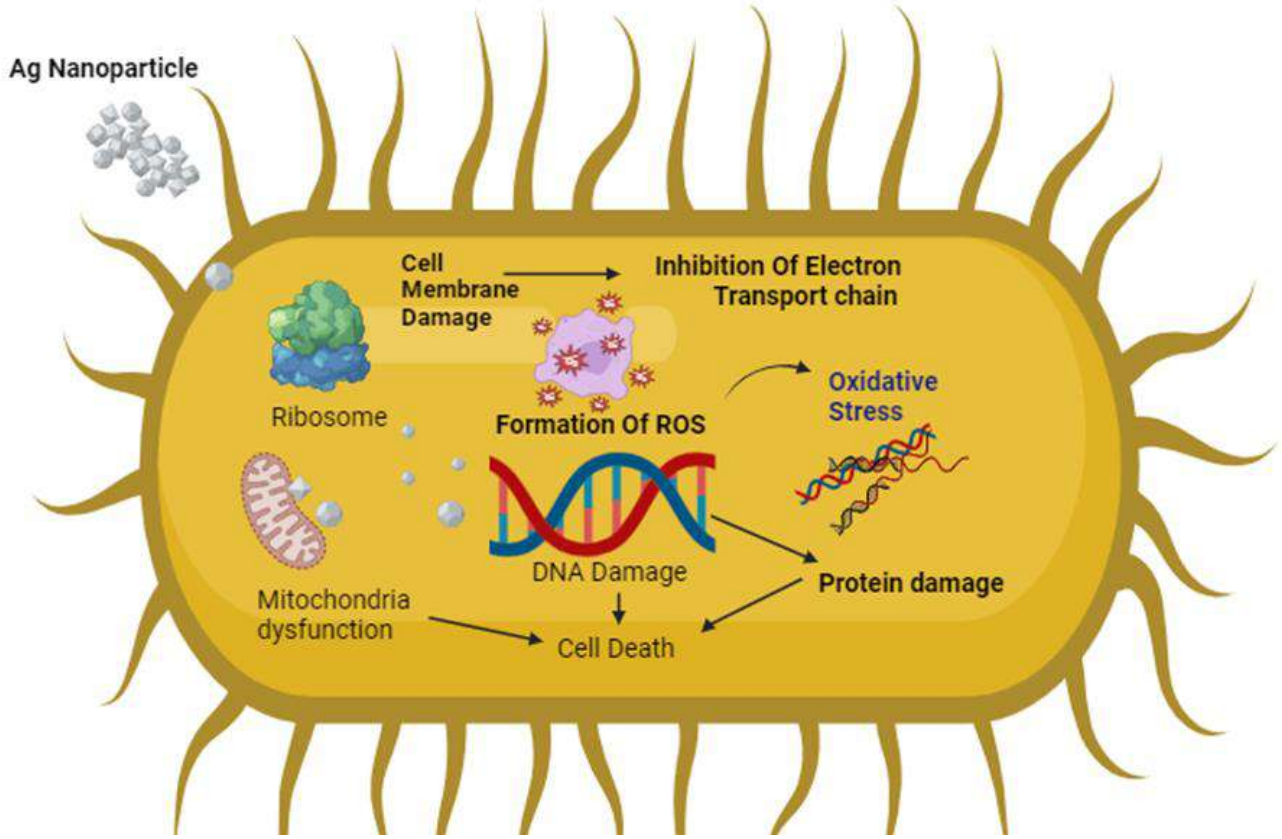
The rise of antibiotic-resistant bacteria can be treated with nanoparticle solutions. Nanoparticles can fight against resistance strains through multiple MOA making them effective against multidrug-resistant bacteria. (Cui and Zhang, 2012). In bacterial infection, vascular permeability increases due to the release of bacterial components which trigger an inflammatory response and malfunction in the body's defense system. Nanoparticles take advantage of it and enhance permeation and retention for targeted antibiotic delivery to the site of infection (Gao et al., 2014). Bacteria usually maintain a negative surface charge, nanoparticles that are positively charged are designed to bind to bacteria through electrostatic interaction and neutralize the bacteria (Tan and Onur, 2018; Wang and Shao, 2017).

Nanoparticles can be functionalized with a pathogen-binding ligand such as small molecules e.g. lectins, antibiotics, or bacteriophage proteins. These ligands help in specific binding to bacteria which increases the precision of nanoparticles to target specific pathogens (Yeh et al., 2020). Macrophages can take the nanoparticle to the targeted site through passive or ligand-mediated mechanisms which improves antibiotic therapy, particularly for intracellular bacterial infections (Gao et al., 2014). Some nanoparticle-based vaccines are also made which can treat and produce immunity against bacterial infections (Lin et al., 2018).

Nanoparticles provide us with a solution to problems faced by traditional vaccines. By conjugating antigen to the nanoparticle surface, b-cell activation is facilitated due to increased antigen delivery to antigen-presenting cells. modern fabrication methods like layer-by-layer and cellular membrane-coated nanoparticles increase antigen loading and immune modulation (Bezbaruah et al., 2022). Nanoparticles allow for the parallel delivery of antigens and adjuvants that mimic natural microbes (Gao et al., 2014). Toll-like receptor ligands can be delivered using nanoparticles that boost the immune response (Haegebaert et al., 2022).

Nanoparticles can be delivered very specifically at specific sites safely and effectively. For example, pH-responsive nanoparticles protect antigens in the stomach and release them in lower GIT for translocation across in intestinal epithelium (Gao and Zhang, 2014). Nanoparticles are also used in the detection of bacterial infections in different parts of the body (Aflakian et al., 2023). Silica nanoparticles which have various fluorescent molecules enable ultrasensitive bacterial infection at single cell level (Gao et al., 2014). Semiconductor dots are used for sensitive bacterial detection and help in identifying different strains of bacteria (Zhang et al., 2023). Iron oxide nanoparticles are used to isolate bacteria from blood samples (Al-Rawi et al., 2021). Microfluidic systems with these nanoparticles allow high-throughput bacterial detection (Zhou et al., 2019). Paramagnetic iron oxide nanoparticles help in the detection of ultra-sensitive bacteria by using an MRI system (Gao et al., 2014).

Gold nanoparticles have unique properties that help in the detection of bacterial infections aggregation of gold nanoparticles due to changes in the plasmon resonance spectrum is used to detect bacterial DNAs and proteins (Mehrabi et al, 2023).



Mechanism of Action:

Nanoparticles interact differentially with different organisms (Deng et al., 2017). The nanoparticles also have different modes of action. Some nanoparticles bind with the cell wall. Some are attached to the protein of the cell. Silver NPs damage the membrane (Duran et al., 2016), bind protein to inactive it (Banerjee and Das, 2013), and stop the replication of DNA (Abbas et al., 2019). In *E. coli*, Ag NPs accumulate the enveloped protein in the cytoplasm by disappearing the proton motive force (Rao et al., 2022). This accumulation stops the proper functioning of protein in the membrane. In Staphylococcus aureus, AG NPs elevate the formate acetyltransferase which forms an anaerobic condition and reduces recombinase A which is related to DNA repair in this species (Cui et al., 2012).

TiO2 and ZnO NPs kill bacteria by producing reactive oxygen species (hydroxyl radical and hydrogen peroxide) under exposure to UV radiation (Leung et al. 2016). Gold NPs have a very unique mode of action. They disorganize the cell membrane, attach to nucleic acid, and stop the production of protein (Cui et al., 2012). Thus, they kill bacteria. They have bactericidal properties against *E. coli* (Hameed et al. 2020; Cui et al., 2012). Gold NPs exert their antimicrobial action in two ways: one is to change the potential of the membrane and stop the production of ATP Synthase due to which synthesis of ATP stops and general metabolism decreases. The other is they stop the subunit of Ribosome from binding with tRNA. AU NPs also increase the chemotaxis in early-phase reactions (Cui and Zhang, 2012).

Nanotechnology's Role In Combating Viral Infections

Nanoparticles play an important role in fighting against viral infections (Rai et al., 2016). It helps in the detection, diagnosis, treatment, and prevention of viral infections (Yadavalli and Shukla et al., 2017). Nanoparticles can be used to detect viral infections. It helps in the development of highly sensitive and specific diagnostic tools for viral infections (Koudelka et al. 2015). Nanoparticle-based assays such as quantum dots and gold nanoparticles increase the sensitivity of PCR and immunoassay to detect viral infections easily (Banerjee et al., 2018).

Nanoparticles are an effective carrier for antiviral drugs to be delivered at targeted sites (Maus et al., 2021). Lipid-based nanoparticles, polymeric nanoparticles, and dendrimers enable controlled release and increased bioavailability of antiviral agents (Chakraverty and Vora, 2021). This targeted delivery can minimize the adverse effects of drugs and maximize the therapeutic effects against viral infections. Nanoparticles are also used in important vaccines against viral infection (Szulczewski et al., 2018). Nanoparticles are used to boost the immune system by mimicking viral agents (Li et al., 2021). Nanoparticle-based vaccines are more stable and have more efficacy against infections (Diaz-Arevalo et al., 2020). They promote immune responses and help in targeted approaches to immune cells.

Nanoparticle types	MOA	Average size	Bacterial strains	Reference
Au	Damage Cell membrane	20-30 nm	Drug-Resistant *S. aureus, k. pnueumoniae* and *E. coli*	Predeepa et al., 2016
Ag	Stop replication of DNA	12-15 nm	*S. aureus, E. coli, S. typhimurium*	Bajaj et al., 2017
Fe3O4-Ag	Increased hydrophilicity	20-25 nm	*S. aureus, E. coli*	Zomorodian et al., 2018
MnFe2O4	Inhibit the growth	17 nm	*S. aureus, E. coli*	Pu et al., 2016
Chitosan	Stop DNA replication	200 nm	Staphylococcus	Silva et al. 2015
Heparin	Inactivate thrombin	250 nm	*E. coli*	Kumar et al., 2016
PMLA	Hydrolytic Degradation	302 nm	*S. aureus, E. coli*	Arif et al., 2018
SLNs	Defuse In Cell Membrane	133 nm	*MRSA*	Kalhapure et al.,2017
PEG	Reduce protein and small molecule interaction	180 nm	*P. aeruginosa*	Yin et al., 2017
NLCS	Improve Drug Permeability	175-330 nm	S. epidermidis	Lewies et al., 2017
Dendritic MSNs	Growth Inhibition	79-160 nm	*E. coli*	Wang et al. 2016

Nanoparticles are used to design material that can stop the attachment of the virus to the host cell (Rai et al., 2016). They can also stop the entry of viruses into host cells. They can interfere with their replication process and stop them from spreading in the body (Goharshadi et al., 2020). They can neutralize viruses directly and increase the traditional antiviral treatments.

Nanotechnology contributes to the development of antiviral coating for personal protective equipment (Phuna et al., 2023), surfaces (Erkoc et al., 2021), and medical equipment. Nanomaterials with virucidal properties are designed to prevent the transmission of viral infections.

Nanoparticles are used to prepare many vaccines to treat viral infections (Kuczenski et al., 2018). The benefit of Nanovaccines is that they can deliver peptides or proteins to very specific cells which help boost the immune response and no booster dose is required (Gheibi Hayat et al., 2019). Nps also protect vaccines from enzymatic degradation, especially for mucosal vaccinations (Jin et al., 2019). They are easy to produce and have great biocompatibility and biodegradability which improve the bioavailability of antigens in vivo and influence the immune system. Memory cells are generated through these vaccines which make them successful against viral infections (Sulcuzewski, Liszbinski, Romao and Rodrigues, 2018).

AIDS is a very dangerous viral disease caused by HIV (Bekker et al., 2023). Its cure is very hard to find. Currently, in advanced medication, there are six medicine classes used to attack different stages of the virus. But these medicines are not easy to take. They have a heavy pill burden, toxicity, and other side effects. Moreover, AIDS is chronic so medication remains the whole life. So, there is a big need to develop modern technology. And nanoparticles can be used. ARV drug delivery with nanoparticles can decrease the pill's burden and toxicity of drugs. NPs can also be used to prepare vaccines against HIV (Jampilek and kralova, 2022). There are many studies conducted to evaluate the result of nanoparticles as a drug delivery system in AIDS and those studies have very good results. E.g. studies by Chioda et al (2014), Jayant et al (2015) Jaramillo-Ruiz et al (2016), and Parbossing et al (2017).

HBV is the cause of inflammation of the liver. It causes liver failure and cirrhosis, and the treatment of very high cost moreover toxicity by anti-HBV drugs is very high. To overcome these problems, many nano-therapy (interferon, pegylated IFN, lamivudine, adefovir, entecavir, telvivudine, and tenofovir) are available that have very good results. (Singh, Kruger, Maguire, Govender and Parboosing, 2017).

Virus	Nanoparticle type	Size	Mechanism Of Action
HIV-1	Silver (Ag)	1-10 nm	Interaction with gp 120
	Gold (Au)	2-20	Bind with Viral envelope glycoprotein
	Polymeric	50 nm	Inhibition of TAK-779 receptor
HSV-1	Ag	4nm	Competition for the binding of the virus to cell
	Au		
HBV	Ag	10-50 nm	Interact with DNA
Monkeypox virus	Ag	10-80 nm	Block host- virus-cell binding and penetration
Influenza Virus	Au	5-10 nm	Inhibition of virus binding to plasma membrane

REFERENCES

Anis, T., Ul Hassan, S. M., Khurshid, A., Fakhar-e-Alam, M., Shahzad, F., Ali, A., and Hossain, N. (2023). Hollow multicomponent capsules for biomedical applications: a comprehensive review. *Journal of Cluster Science*, *34*(1), 77-110.

Aguilera-Correa, J. J., Esteban, J., and Vallet-Regí, M. (2021). Inorganic and polymeric nanoparticles for human viral and bacterial infections prevention and treatment. *Nanomaterials*, *11*(1), 137.

Aslam, B., Ahmad, M., Tariq, M. U., Muzammil, S., Siddique, A. B., Khurshid, M., and Baloch, Z. (2023). Antibiotic resistance:

retrospect and prospect. In *Degradation of Antibiotics and Antibiotic-Resistant Bacteria from Various Sources* (pp. 1-37). Academic Press.

Aflakian, F., Mirzavi, F., Aiyelabegan, H. T., Soleimani, A., Gholizadeh Navashenaq, J., Karimi-Sani, I., Rafati Zomorodi, A., and Vakili-Ghartavol, R. (2023). Nanoparticles-based therapeutics for the management of bacterial infections: A special emphasis on FDA approved products and clinical trials. *European Journal of Pharmaceutical Sciences*, *188*, 106515

Al-Rawi, M., and Al-Mudallal, N. H. A. (2021). Determination of ferrous oxide nanoparticles minimum inhibitory concentration against local virulent bacterial isolates. *Archives of Razi Institute*, *76*(4), 795.

Abbas, W. S., Atwan, Z. W., Abdulhussein, Z. R., and Mahdi, M. A. (2019). Preparation of silver nanoparticles as antibacterial agents through DNA damage. *Materials Technology*, *34*(14), 867-879.

Alarcon, E. I., Griffith, M., and Udekwu, K. I. (2015). Silver nanoparticle applications. *Springer International Publishing. doi*, *10*, 978-3.

Babu, P. J., and Tirkey, A. (2023). Green synthesis of gold nanoparticles and their biomedical and healthcare applications. In *Nanotechnology and Human Health* (pp. 191-229). Elsevier.

Bezbaruah, R., Chavda, V. P., Nongrang, L., Alom, S., Deka, K., Kalita, T., Ali, F., Bhattacharjee, B., and Vora, L. (2022). Nanoparticle-Based Delivery Systems for Vaccines. *Vaccines*, *10*(11)

Banerjee, R., and Jaiswal, A. (2018). Recent advances in nanoparticle-based lateral flow immunoassay as a point-of-care diagnostic tool for infectious agents and diseases. *Analyst*, *143*(9), 1970-1996.

Burtscher, H., and Schüepp, K. (2012). The occurrence of ultrafine particles in the specific environment of children. *Paediatric Respiratory Reviews*, *13*(2), 89-94.

Barcelo, S. J., Lam, S. T., Gibson, G. A., Sheng, X., and Henze, D. (2012, March). Nanosphere lithography based technique for fabrication of large area well-ordered metal particle arrays. In *Alternative Lithographic Technologies IV* (Vol. 8323, pp. 547-553). SPIE.

Buzea, Cristina, Ivan I. Pacheco and Robbie, K. (2007). "Nanomaterials and nanoparticles: sources and toxicity." *Biointerphases* 2, no. 4 (2007): MR17-MR71.

Bisht, D., Sajjanar, B. K., Saxena, S., Kakodia, B., Dighe, V., Thakuria, D., and Kumar, S. (2023). Identification and characterization of phage display-selected peptides having affinity to Peste des petits ruminants virus. *Journal of Immunological Methods*, *515*, 113455.

Calovi, M., Coroneo, V., Palanti, S., and Rossi, S. (2023). Colloidal silver as innovative multifunctional pigment: The effect of Ag concentration on the durability and biocidal activity of wood paints. *Progress in Organic Coatings*, *175*, 107354.

Cho, H. J., Jang, J. W., Ko, S. Y., Choi, S. H., Lim, C. S., and An, S. S. A. (2015). Evaluation and verification of the nanosphere Verigene RV+ assay for detection of influenza A/B and H1/H3 subtyping. *Journal of Medical Virology*, *87*(1), 18-24.

Costanzo, V., and Roviello, G. N. (2023). The Potential Role of Vaccines in Preventing Antimicrobial Resistance (AMR): An Update and Future Perspectives. *Vaccines*, *11*(2), 333.

Chakravarty, M., and Vora, A. (2021). Nanotechnology-based antiviral therapeutics. *Drug Delivery and Translational Research*, *11*, 748-787.

Christaki, E., Marcou, M., and Tofarides, A. (2020). Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence. *Journal of Molecular Evolution*, *88*, 26-40

Canaparo, R., Foglietta, F., Giuntini, F., Della Pepa, C., Dosio, F., and Serpe, L. (2019). Recent developments in antibacterial therapy: Focus on stimuli-responsive drug-delivery systems and therapeutic nanoparticles. *Molecules*, *24*(10), 1991.

Cui, Y., Zhao, Y., Tian, Y., Zhang, W., Lü, X., and Jiang, X. (2012). The molecular mechanism of action of bactericidal gold nanoparticles on Escherichia coli. *Biomaterials*, *33*(7), 2327-2333.

Chiodo, F., Marradi, M., Calvo, J., et al. (2014). Glycosystems in nanotechnology: gold glyconanoparticles as carrier for anti-HIV prodrugs. *Beilstein Journal Org Chemistry,* 10: 1339–1346.

Diaz-Arévalo, D., and Zeng, M. (2020). Nanoparticle-based vaccines: opportunities and limitations. In *Nanopharmaceuticals* (pp. 135-150). Elsevier.

Deng, R., Lin, D., Zhu, L., Majumdar, S., White, J. C., Gardea-Torresdey, J. L., and Xing, B. (2017). Nanoparticle interactions with co-existing contaminants: joint toxicity, bioaccumulation and risk. *Nanotoxicology*, *11*(5), 591-612.

Durán, N., Durán, M., De Jesus, M. B., Seabra, A. B., Fávaro, W. J., and Nakazato, G. (2016). Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. *Nanomedicine: Nanotechnology, Biology and Medicine*, *12*(3), 789-799.

Dorodnyy, A., Smajic, J., and Leuthold, J. (2023). Mie Scattering for Photonic Devices. *Laser and Photonics Reviews*, *17*(9), 2300055.

Dahy, G., Soliman, M. M., Alshater, H., Slowik, A., and Hassanien, A. E. (2023). Optimized deep networks for the classification of nanoparticles in scanning electron microscopy imaging. *Computational Materials Science*, *223*, 112135.

Diaspro, A. (2022). *Expedition Into the Nanoworld: An Exciting Voyage from Optical Microscopy to Nanoscopy*. Springer Nature.

Erkoc, P., and Ulucan-Karnak, F. (2021). Nanotechnology-based antimicrobial and antiviral surface coating strategies. *Prosthesis*, *3*(1), 25-52.

Franci, G., Falanga, A., Galdiero, S., Palomba, L., Rai, M., Morelli, G., and Galdiero, M. (2015). Silver nanoparticles as potential antibacterial agents. *Molecules*, *20*(5), 8856-8874.

Fang, R. H., Luk, B. T., Hu, C. J., and Zhang, L. (2015). Engineered nanoparticles mimicking cell membranes for toxin

neutralization. *Advanced Drug Delivery Reviews*, *90*, 69-80.

Farid, M., Faber, T., Dietrich, D., and Lamprecht, A. (2020). Cell membrane fusing liposomes for cytoplasmic delivery in brain endothelial cells. *Colloids and Surfaces B: Biointerfaces*, *194*, 111193.

Fedotov, P. S., Ermolin, M. S., and Ivaneev, A. I. (2023). Study of Elemental Composition and Properties of Volcanic Ash and Urban Dust Nanoparticles. In *Advances in Geochemistry, Analytical Chemistry, and Planetary Sciences: 75th Anniversary of the Vernadsky Institute of the Russian Academy of Sciences* (pp. 133-143). Cham: Springer International Publishing.

Sharoon, G., Masood, M.I., Nasim, M. J., Sarfraz, M., Ebokaiwe, A. P., Schäfer, K. H., Keck, C. M., and Jacob, C., (2017). "Natural nanoparticles: a particular matter inspired by nature." *Antioxidants* 7, no. 1 (2017): 3.

Goethals, E. C., Elbaz, A., Lopata, A. L., Bhargava, S. K., and Bansal, V. (2013). Decoupling the effects of the size, wall thickness, and porosity of curcumin-loaded chitosan nanocapsules on their anticancer efficacy: size is the winner. *Langmuir*, *29*(2), 658-666.

Garg, D., Sarkar, A., Chand, P., Bansal, P., Gola, D., Sharma, S., and Bharti, R. K. (2020). Synthesis of silver nanoparticles utilizing various biological systems: mechanisms and applications—a review. *Progress in Biomaterials*, *9*, 81-95.

Gao, W., Thamphiwatana, S., Angsantikul, P., and Zhang, L. (2014). Nanoparticle Approaches against Bacterial Infections. *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology*, *6*(6), 532.

Goharshadi, E. K., Goharshadi, K., and Moghayedi, M. (2022). The use of nanotechnology in the fight against viruses: A critical review. *Coordination Chemistry Reviews*, *464*, 214559.

Gheibi Hayat, S. M., and Darroudi, M. (2019). Nanovaccine: A novel approach in immunization. *Journal of Cellular Physiology*, *234*(8), 12530-12536.

Hammami, I., Alabdallah, N. M., Jomaa, A. A., and Kamoun, M. (2021). Gold nanoparticles: Synthesis properties and applications. *Journal of King Saud University - Science*, *33*(7), 101560.

Selim, M. M., El-Safty, S., Tounsi, A., and Shenashen, M. (2023). Review of the impact of the external magnetic field on the characteristics of magnetic nanofluids. *Alexandria Engineering Journal*, *76*, 75-89.

Hasan, S. (2015). A review on nanoparticles: their synthesis and types. *Research Journal Recent Science*, *2277*, 2502.

Heiligtag, F. J., and Niederberger, M. (2013). The fascinating world of nanoparticle research. *Materials Today*, *16*(7-8), 262-271.

Hameed, S., Wang, Y., Zhao, L., Xie, L., and Ying, Y. (2020). Shape-dependent significant physical mutilation and antibacterial mechanisms of gold nanoparticles against foodborne bacterial pathogens (Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus) at lower concentrations. *Materials Science and Engineering: C*, *108*, 110338.

Haegebaert, R. M., Kempers, M., Ceelen, W., Lentacker, I., and Remaut, K. (2022). Nanoparticle mediated targeting of toll-like receptors to treat colorectal cancer. *European Journal of Pharmaceutics and Biopharmaceutics*, *172*, 16-30.

Ho, K. C., Tsai, P. J., Lin, Y. S., and Chen, Y. C. (2004). Using biofunctionalized nanoparticles to probe pathogenic bacteria. *Analytical Chemistry*, *76*(24), 7162-7168.

Hasmin, N. A., Matmin, J., and Basir, S. A. (2022). National Nanotechnology Policies in Malaysia, European Union and United States: A Comparative Analysis. *Quantum Journal of Social Sciences and Humanities*, *3*(3), 72-92.

Ismail, M., Khan, M. I., Akhtar, K., Seo, J., Khan, M. A., Asiri, A. M., and Khan, S. B. (2019). Phytosynthesis of silver nanoparticles; naked eye cellulose filter paper dual mechanism sensor for mercury ions and ammonia in aqueous solution. *Journal of Materials Science: Materials in Electronics*, *30*, 7367-7383.

Joseph, T. M., Kar Mahapatra, D., Esmaeili, A., Piszczyk, Ł., Hasanin, M. S., Kattali, M., and Thomas, S. (2023). Nanoparticles: Taking a unique position in medicine. *Nanomaterials*, *13*(3), 574.

Jayant, R.D., Atluri, V.S.R., Agudelo, M., et al. (2015). Sustained-release nanoART formulation for the treatment of neuroAIDS. *International Journal Nanomedicine,* 10: 1077–1093.

Jaramillo-Ruiz, D., De La, Mata F.J., Gómez, R., et al. (2016). Nanotechnology as a new therapeutic approach to prevent the HIV infection of Treg cells. *PLoS ONE,* 11: e0145760.

Jampílek, J., and Kráľová, K. (2022). Nanotechnology: New frontiers in anti-HIV therapy. In *Nanotechnological Applications in Virology* (pp. 129-171). Academic Press.

Jayalatha, A., and Rayappan, J. B. B. (2015). Light on Theoretical Path to Nanoparticles—A Review. *Reviews in Theoretical Science*, *3*(3), 245-256.

Jin, Z., Gao, S., Cui, X., Sun, D., and Zhao, K. (2019). Adjuvants and delivery systems based on polymeric nanoparticles for mucosal vaccines. *International Journal of Pharmaceutics*, *572*, 118731.

Khatun, E., and Pradeep, T. (2023). Alloy nanoclusters. In *Atomically Precise Metal Nanoclusters* (pp. 393-426). Elsevier.

Kanwar, A., Virmani, M., Lal, S., Chaudhary, K., Kumar, S., Magotra, A., and Pandey, A. K. (2023). Silver nanoparticle as an alternate to antibiotics in cattle semen during cryopreservation. *Animal Reproduction*, *20*, e20220030.

Karnwal, A., Kumar, G., Pant, G., Hossain, K., Ahmad, A., and Alshammari, M. B. (2023). Perspectives on Usage of Functional Nanomaterials in Antimicrobial Therapy for Antibiotic-Resistant Bacterial Infections. *ACS Omega*, *8*(15), 13492-13508.

Kalantari, K., Mostafavi, E., Afifi, A. M., Izadiyan, Z., Jahangirian, H., Rafiee-Moghaddam, R., and Webster, T. J. (2020). Wound dressings functionalized with silver nanoparticles: Promises and pitfalls. *Nanoscale*, *12*(4), 2268-2291.

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931.

Koudelka, K. J., Pitek, A. S., Manchester, M., and Steinmetz, N. F. (2015). Virus-based nanoparticles as versatile

nanomachines. *Annual Review of Virology*, *2*, 379-401.
Li, Y., Ji, T., Torre, M., Shao, R., Zheng, Y., Wang, D., and Kohane, D. S. (2023). Aromatized liposomes for sustained drug delivery. *Nature Communications*, *14*(1), 6659.
Li, Z., Xu, K., Qin, L., Zhao, D., Yang, N., Wang, D., and Yang, Y. (2023). Hollow Nanomaterials in Advanced Drug Delivery Systems: From Single-to Multiple Shells. *Advanced Materials*, *35*(12), 2203890.
Litter, M. I., and Ahmad, A. (2023). The world of nanotechnology. In *Industrial applications of nanoparticles* (pp. 1-15). CRC Press.
Litter, M. I., and Ahmad, A. (2023). *Industrial Applications of Nanoparticles: A Prospective Overview*. CRC Press
Leung, Y. H., Xu, X., Ma, A. P., Liu, F., Ng, A. M., Shen, Z., and Leung, F. C. (2016). Toxicity of ZnO and TiO2 to Escherichia coli cells. *Scientific Reports*, *6*(1), 35243.
Lin, L. C. W., Chattopadhyay, S., Lin, J. C., and Hu, C. M. J. (2018). Advances and opportunities in nanoparticle-and nanomaterial-based vaccines against bacterial infections. *Advanced Healthcare Materials*, *7*(13), 1701395.
Li, N., Georas, S., Alexis, N., Fritz, P., Xia, T., Williams, M. A., and Nel, A. (2016). A work group report on ultrafine particles (AAAAI) why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in humans. *The Journal of Allergy and Clinical Immunology*, *138*(2), 386.
Majeed, H., Iftikhar, T., and Abid, R. (2024). Green synthesis of zinc nanoparticles with plant material and their potential application in bulk industrial production of mosquito-repellent antibacterial paint formulations. *Reaction Chemistry and Engineering*.
Malik, S., Muhammad, K., and Waheed, Y. (2023). Nanotechnology: A revolution in modern industry. *Molecules*, *28*(2), 661.
Merupo, V., Zarate, J. C., Abramova, A., Arjona, N., Herrera-Celis, J., and Arriaga, L. G. (2023). Inorganic Nanoparticles. *Nanochemistry: Synthesis, Characterization and Applications*, 33.
Milani, M., Curia, R., Shevlyagina, N. V., and Tatti, F. (2023). Staphylococcus aureus Staphylococcus aureus Scouts the Nanoworld: A Neverending Story Nano world. In *Bacterial Degradation of Organic and Inorganic Materials: Staphylococcus aureus Meets the Nanoworld* (pp. 57-76). Cham: Springer International Publishing.
Muteeb, G., Rehman, M. T., Shahwan, M., and Aatif, M. (2023). Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. *Pharmaceuticals*, *16*(11), 1615.
Mehrabi, M. R., Soltani, M., Chiani, M., Raahemifar, K., and Farhangi, A. (2023). Nanomedicine: New Frontiers in Fighting Microbial Infections. *Nanomaterials*, *13*(3)
Mubeen, B., Ansar, A. N., Rasool, R., Ullah, I., Imam, S. S., Alshehri, S., and Kazmi, I. (2021). Nanotechnology as a novel approach in combating microbes providing an alternative to antibiotics. *Antibiotics*, *10*(12), 1473.
Munir, M., Hussain, S., Anwar, R., Waqas, M., and Ali, J. (2020). The Role of Nanoparticles in the Diagnosis and Treatment of Diseases. *Scientific Inquiry and Review*, *4*(3), 14-26.
Ma, Y. (2022). New progress in international nanotechnology research in the past ten years–visual analysis based on CitesSpace. *Journal of Computational Methods in Sciences and Engineering*, *22*(1), 265-277.
Mitragotri, S., and Stayton, P. (2014). Organic nanoparticles for drug delivery and imaging. *Mrs Bulletin*, *39*(3), 219-223.
Marassi, V., Di Cristo, L., Smith, S. G., Ortelli, S., Blosi, M., Costa, A. L., and Prina-Mello, A. (2018). Silver nanoparticles as a medical device in healthcare settings: A five-step approach for candidate screening of coating agents. *Royal Society Open Science*, *5*(1), 171113.
Mei, L., Lu, Z., Zhang, W., Wu, Z., Zhang, X., Wang, Y., and Jia, Y. (2013). Bioconjugated nanoparticles for attachment and penetration into pathogenic bacteria. *Biomaterials*, *34*(38), 10328-10337.
Maus, A., Strait, L., and Zhu, D. (2021). Nanoparticles as delivery vehicles for antiviral therapeutic drugs. *Engineered Regeneration*, *2*, 31-46.
Sulczewski, F. B., Liszbinski, R. B., Romão, P. R., and Rodrigues Junior, L. C. (2018). Nanoparticle vaccines against viral infections. *Archives of Virology*, *163*, 2313-2325.
Montanarella, F., and Kovalenko, M. V. (2022). Three millennia of nanocrystals. *ACS Nano*, *16*(4), 5085-5102.
Mirguet, C., Fredrickx §, P., Sciau, P., and Colomban, P. (2008). Origin of the self-organisation of Cu/Ag nanoparticles in ancient lustre pottery. A TEM study. *Phase Transitions*, *81*(2-3), 253-266.
Natesan, V., and Kim, S. J. (2023). The Trend of Organic Based Nanoparticles in the Treatment of Diabetes and Its Perspectives. *Biomolecules and Therapeutics*, *31*(1), 16.
Nsairat, H., Khater, D., Sayed, U., Odeh, F., Bawab, A. A., and Alshaer, W. (2022). Liposomes: Structure, composition, types, and clinical applications. *Heliyon*, *8*(5).
Norton, M. G. (2023). There's Still Plenty of Room at the Bottom. In *A Modern History of Materials: From Stability to Sustainability* (pp. 81-100). Cham: Springer International Publishing.
Phuna, Z. X., Panda, B. P., Hawala Shivashekaregowda, N. K., and Madhavan, P. (2023). Nanoprotection from SARS-COV-2: would nanotechnology help in Personal Protection Equipment (PPE) to control the transmission of Suhag, D., Thakur, P., and Thakur, A. (2023). Introduction to nanotechnology. In *Integrated Nanomaterials and their Applications* (pp. 1-17). Singapore: Springer Nature Singapore.
COVID-19?. *International Journal of Environmental Health Research*, *33*(7), 670-699
Natan, M., and Banin, E. (2017). From Nano to Micro: using nanotechnology to combat microorganisms and their multidrug resistance. *FEMS Microbiology Reviews*, *41*(3), 302-322.

Nim, N., Morris, J., Tekasakul, P., and Dejchanchaiwong, R. (2023). Fine and ultrafine particle emission factors and new diagnostic ratios of PAHs for peat swamp forest fires. *Environmental Pollution*, *335*, 122237.

Paulami, D. A. M., Paret, M. L., Mondal, R., and Mandal, A. K. (2023). Advancement of noble metallic nanoparticles in agriculture: a promising future. *Pedosphere*, *33*(1), 116-128.

Parboosing R, Chonco L, De La, Mata FJ, et al. (2017). Potential inhibition of HIV-1 encapsidation by oligoribonucleotide–dendrimer nanoparticle complexes. *International Journal Nanomedicine,* 12: 317–325.

Parveen, K., Banse, V., and Ledwani, L. (2016). Green synthesis of nanoparticles: Their advantages and disadvantages. In *AIP Conference Proceedings* (Vol. 1724, No. 1). AIP Publishing.

Rao, S. Q., Zhang, R. Y., Chen, R., Gao, Y. J., Gao, L., and Yang, Z. Q. (2022). Nanoarchitectonics for enhanced antibacterial activity with Lactobacillus buchneri S-layer proteins-coated silver nanoparticles. *Journal of Hazardous Materials*, *426*, 128029.

Rai, M., Deshmukh, S. D., Ingle, A. P., Gupta, I. R., Galdiero, M., and Galdiero, S. (2016). Metal nanoparticles: The protective nanoshield against virus infection. *Critical Reviews in Microbiology*, *42*(1), 46-56.

Santos, C. S., Gabriel, B., Blanchy, M., Menes, O., García, D., Blanco, M., and Neto, V. (2015). Industrial applications of nanoparticles–a prospective overview. *Materials Today: Proceedings*, *2*(1), 456-465.

Stempski, B., and Grodzicki, G. (2019). Production of surface agents for limiting the growth of bacteria and fung based on silver nano and microparticles made by electrochemical methods on an industrial scale. In *Smart Cities International Conference (SCIC) Proceedings* (Vol. 7, pp. 225-233).

Stone, V., Nowack, B., Baun, A., van den Brink, N., von der Kammer, F., Dusinska, M., and Fernandes, T. F. (2010). Nanomaterials for environmental studies: classification, reference material issues, and strategies for physico-chemical characterization. *Science of the Total Environment*, *408*(7), 1745-1754.

Shen, M. X., Ma, N., Li, M. K., Liu, Y. Y., Chen, T., Wei, F., and Yang, Z. Q. (2019). Antiviral properties of R. tanguticum nanoparticles on herpes simplex virus type I in vitro and in vivo. *Frontiers in Pharmacology*, *10*, 959.

Syafiuddin, A., Salmiati, Salim, M. R., Beng Hong Kueh, A., Hadibarata, T., and Nur, H. (2017). A review of silver nanoparticles: research trends, global consumption, synthesis, properties, and future challenges. *Journal of the Chinese Chemical Society*, *64*(7), 732-756.

Sironmani, A., and Daniel, K. (2011). Silver nanoparticles–universal multifunctional nanoparticles for bio sensing, imaging for diagnostics, and targeted drug delivery for therapeutic applications. *Drug Discovery and Development–present and Future*, 463-84.

Shen, L., Li, B., and Qiao, Y. (2018). Fe3O4 nanoparticles in targeted drug/gene delivery systems. *Materials*, *11*(2), 324.

Schneider, R., Facure, M. H., Chagas, P. A., Andre, R. S., dos Santos, D. M., and Correa, D. S. (2021). Tailoring the surface properties of micro/nanofibers using 0d, 1d, 2d, and 3d nanostructures: a review on post-modification methods. *Advanced Materials Interfaces*, *8*(13), 2100430.

Sethu, S. N., Namashivayam, S., Devendran, S., Nagarajan, S., Tsai, W. B., Narashiman, S., and Ambigapathi, M. (2017). Nanoceramics on osteoblast proliferation and differentiation in bone tissue engineering. *International Journal of Biological Macromolecules*, *98*, 67-74.

Shubayev, V. I., Pisanic II, T. R., and Jin, S. (2009). Magnetic nanoparticles for theragnostics. *Advanced Drug Delivery Reviews*, *61*(6), 467-477.

Sulczewski, F. B., Liszbinski, R. B., Romão, P. R., and Rodrigues Junior, L. C. (2018). Nanoparticle vaccines against viral infections. *Archives of Virology*, *163*, 2313-2325.

Singh, L., Kruger, H. G., Maguire, E. M., Govender, T., and Parboosing, R. (2017). The role of nanotechnology in the treatment of viral infections. *Therapeutic Advances in Infectious Disease*. https://doi.org/10.1177/2049936117713593

Talapin, D. V., and Shevchenko, E. V. (2016). Introduction: nanoparticle chemistry. *Chemical Reviews*, *116*(18), 10343-10345.

Tan, G., and Onur, M. A. (2018). Cellular localization and biological effects of 20nm-gold nanoparticles. *Journal of Biomedical Materials Research Part A*, *106*(6), 1708-1721.

Teirumnieks, E., Balchev, I., Ghalot, R. S., and Lazov, L. (2020). Antibacterial and anti-viral effects of silver nanoparticles in medicine against COVID-19—a review. *Laser Physics*, *31*(1), 013001.

Tsai, C. H., Whiteley, C. G., and Lee, D. J. (2019). Interactions between HIV-1 protease, silver nanoparticles, and specific peptides. *Journal of the Taiwan Institute of Chemical Engineers*, *103*, 20-32.

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., and Clancy, C. J. (2023). Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clinical Infectious Diseases*, ciad428.

Tang, K. W. K., Millar, B. C., and Moore, J. E. (2023). Antimicrobial resistance (AMR). *British Journal of Biomedical Science*, *80*, 11387.

Ulises, A., and Sharma, A. (2023). Drug-delivery using Inorganic and Organic Nanoparticles. *Nanochemistry: Synthesis, Characterization and Applications*, 194.

Verma, H. N., Singh, P., and Chavan, R. M. (2014). Gold nanoparticle: synthesis and characterization. *Veterinary World*, *7*(2), 72.

Vasilaki, E., Gaj, G., Wróbel, S., Karchilakis, G., Pietrasik, J., and Vamvakaki, M. (2023). Non-cross-linked hollow polymer nanocapsules of controlled size and shell thickness. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*,

661, 130928.

Verma, G., Rajagopalan, M. D., Valluru, R., and Sridhar, K. A. (2016). Nanoparticles: A Novel Approach to Target Tumors. *Nano- and Microscale Drug Delivery Systems*, 113-129.

Verma, P., and Maheshwari, S. K. (2019). Applications of Silver nanoparticles in diverse sectors. *International Journal of Nano Dimension*, *10*(1), 18-36.

Wu, B., Yang, C., Li, B., Feng, L., Hai, M., Zhao, C. X., and Weitz, D. A. (2020). Active encapsulation in biocompatible nanocapsules. *Small*, *16*(30), 2002716.

Wilczewska, A. Z., Niemirowicz, K., Markiewicz, K. H., and Car, H. (2012). Nanoparticles as drug delivery systems. *Pharmacological Reports*, *64*(5), 1020-1037.

Wang, L., Hu, C., and Shao, L. (2017). The antimicrobial activity of nanoparticles: Present situation and prospects for the future. *International Journal of Nanomedicine*, *12*, 1227-1249.

Yeh, C., Huang, H., Yang, C., Chen, C., and Fang, Y. (2020). Nano-Based Drug Delivery or Targeting to Eradicate Bacteria for Infection Mitigation: A Review of Recent Advances. *Frontiers in Chemistry*, *8*.

Yadavalli, T., and Shukla, D. (2017). Role of metal and metal oxide nanoparticles as diagnostic and therapeutic tools for highly prevalent viral infections. *Nanomedicine: Nanotechnology, Biology and Medicine*, *13*(1), 219-230.

Zhang, J., Zhou, M., Li, X., Fan, Y., Li, J., Lu, K., and Ren, J. (2023). Recent advances of fluorescent sensors for bacteria detection-A review. *Talanta*, *254*, 124133.

Zhou, W., Le, J., Chen, Y., Cai, Y., Hong, Z., and Chai, Y. (2019). Recent advances in microfluidic devices for bacteria and fungus research. *TrAC Trends in Analytical Chemistry*, *112*, 175-195.

Zerkani, A., and Abboodi, S. A. (2023). *Heat transfer enhancement using ferro-nanofluid with megnatic field in tube having inserted twisted tube* (Master's thesis, Altınbaş Üniversitesi/Lisansüstü Eğitim Enstitüsü).

Zahin, N., Anwar, R., Tewari, D., Kabir, M. T., Sajid, A., Mathew, B., and Abdel-Daim, M. M. (2020). Nanoparticles and its biomedical applications in health and diseases: special focus on drug delivery. *Environmental Science and Pollution Research*, *27*, 19151-19168

Chapter 28

Role of Nanoparticles in Biofertilizers

Javeria Arshad*[1]

[1]Department of Chemistry, Government College Women University, Sialkot, Pakistan
*Corresponding author: javeriaarshad777@gmail.com

ABSTRACT

Modern cropping systems mostly rely on synthetic or chemical fertilizers to improve yields; however, persistent, long-term use of these fertilizers can have negative impacts on soil fertility, soil biota, and the environment. These problems highlight the need for extremely economical, highly effective fertilizers that can raise yields and have the least amount of harm to the environment. To maintain bio-safety in agriculture, bio- and nano-fertilizers are chosen over synthetic (chemical) fertilizers since they are non-toxic and environmentally benign. Regarding this, Nanotechnology has become a potentially game-changing invention in the twenty-first century. In light of population growth, this chapter focuses on the coupling of nanoparticles with biofertilizers to act as nano-biofertilizers (NBFs), which could guarantee global food security. When plants are injected with NBFs, their growth and stress tolerance are enhanced. NBFs that are based on microorganisms and metallic nanoparticles get over the restrictions of traditional chemical fertilizers. While the NBF application is still in its early stages, it appears to have greater potential than other methods for transforming traditional farming into high-tech, "smart" farming. This chapter examines the innovative application of nanotechnology in agriculture, which leverages the special properties of materials at the nanoscale to solve pressing issues including crop protection, nutrient delivery, and sustainable agricultural practices. Future directions and recent advancements in field farming with NBF formulations are also discussed.

KEYWORDS
Nanozymes, Nanotechnology, Chemical fertilizers, Nanoparticles, Biofertilizers, Sustainable Agriculture, Ecofriendly

Received: 29-June-2024
Revised: 02-July-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Arshad J, 2024. Role of nanoparticles in biofertilizers. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 243-253. https://doi.org/10.47278/book.CAM/2024.310

INTRODUCTION

The global economy has been built on agriculture, which is under great stress and cries for new answers to sustainable development. Food production must be increased by around 70% while conserving the environment in order to meet the requirements of an increasing population, projected to hit nine billion by the year 2050 (Godfray et al., 2010). Worse still, climate change affects crop yields negatively leading to reduced food security and a depreciating soil quality. Additionally, these challenges are again made worse by resource depletion with poor water quality, soil erosion and loss of arable land as a result of unsustainable agricultural practices. Chemicals from pesticides and synthetics fertilizers degrade soil health, reduce fertility and contaminate food with hazardous residues. This means that, for sure, we have to address socio-economic inequalities by dealing with rural poverty, limited resources, and bad infrastructures to make sure we achieve sustainable agriculture (Kopittke et al., 2019).

Sustainable agriculture pays main attention to biodiversity and maintenance of the ecosystem. Approaches like crop rotation, agroforestry, and integrated pest control not only guarantee soil fertility and biodiversity but also decrease dependence upon external inputs. Climate-resilient techniques—the use of drought-tolerant crops and water-efficient irrigation systems, in particular would help in limiting the consequences related to climate change while conserving the resources. It enhances soil health and ecosystem services through practices like cover cropping and reduced tillage, by improving fertility, carbon sequestration, and water retention. Organic farming, apart from producing better food with less synthetic chemicals, also protects biodiversity by minimizing environmental pollution (Thrupp et al., 2000). In rural areas it is important to invest in infrastructure reforms that will support farmers at small scale level or subsistence farming. This includes resource access fairness among others that help improve economic stability in rural communities towards a more food-secure region.

Agricultural practices have been transformed by conventional chemical fertilizers through increasing yields and food security. Growth and development can be enhanced through the instant release of nutrients that correct crop deficiencies. The use of chemical fertilizers in poor countries, mainly during the Green Revolution has led to increased agricultural output. They work towards precision agriculture through efficient utilization of resources as well as endorsing prevailing trends such as highly dense planting and modern irrigation systems (Pahalvi et al., 2021). Improved fertilizer formulation is

aimed at enhancing efficiency while minimizing environmental pollution; however, misuse of this product leads to water pollution, soil degradation, and disarray in microbial community within soils. Mitigating these concerns involves accurate nutrient management strategies, sustainable farming methods and innovative technologies with biological and nanotechnology alternatives pointing to positive approaches for escalating agricultural adaptability and ecological conservationism.

Biofertilizers: Exploiting the Potential of Nature

Biofertilizers are the living microorganisms that contain natural compounds which improve development by increasing the provision or accessibility of essential nutrients to the host plant upon application to seeds, plants, or soil. Biofertilizers consist of different types of useful microorganisms such as nitrogen-fixing bacteria, phosphate-solubilizing microbes and growth promoting agents like enzymes and hormones. This rich composition promotes symbiotic connections between bacteria and plants, which improves soil fertility and nutrient uptake. Biofertilizers improve the quality of the soil by improving its texture, porosity, and soil moisture-holding capacity. They also enhance the formation of soil aggregates, promote organic matter decomposition, and foster improvement in soil fertility and plant growth. Besides, biofertilizers are environmentally friendly because they decompose and break down to non-toxic materials, leaving no harmful residues (Brahmaprakash and Sahu, 2012).

Mechanisms of Biofertilizers

Biofertilizers promote plant and soil health through several processes. They form associations like the Rhizobium-legume association, which are symbiotic in nature and enhance nutrient uptake and soil fertility. Auxins and other growth hormones like cytokinins secreted by microorganisms in the biofertilizers lead to root development and hence overall plant health. Apart from this, these biofertilizers excrete bioactive compounds that exert influence on plant development and microbial populations, hence enhancing the fertility of the soil and health of the plants, as reported by Hofmann et al. (2023). In addition to this, the products strengthen the constitutive immunity of the plants, rendering them resistant to infection by the induction of defense-related proteins and chemicals through a process called induced systemic resistance (Kannojia et al., 2019).

Furthermore, biofertilizers purify heavy metals through biosorption and chelation done by some bacteria and fungi to ensure overall soil health and safety of crops. They are capable of degrading certain pollutants in an effort to use plants for remediation; this is able to enhance the capacity of plants to absorb harmful substances.

According to Anli et al. (2020), biofertilizers produce osmoprotectants that help the plants to balance the cells under dry and saline conditions, hence improving the stress tolerance. Through all these mechanisms, biofertilizers contribute to sustainable agriculture by improving soil fertility, promoting healthy crops, and creating a clean environment.

Application of Biofertilizers

In the present methodology, various modes of application may be involved in enriching the fertility of the soil and promoting plant growth by using biofertilizers. (Anand and Kamaraj, 2017).

a) Seed treatment: The seed treatment with bio-fertilizers will enhance faster colonisation of beneficial microorganisms which helps in developing healthy seedlings. Soil application: The inoculation of bio-fertilizers into the soil during the preparation of the field enriches microbial diversity and availability of nutrients resulting in enriched soil quality.

a) Exposing the roots in bio-fertilizer solutions prior to planting can stimulate microbial colonization, reduce transplanting shock and can enhance root growth. The foliar application promotes nutrition absorption through leaves by misting the moisture content on the plants that enhances nutrition uptake and also systematic disease resistance.

c) Drip irrigation of fertilizers economizes water while dispensing the fertilizers to the root zone in exactly the required quantity.

Inoculation of biofertilizers combined with irrigation as a method of application, namely fertigation, improves nutrient availability and enhances microbes' activity, resulting in enhanced plant growth and higher yield.

The environment-friendly nature of the biofertilizers is followed by the disadvantages such as slow release, variable quality feed due to environmental factors, special storage conditions, high upfront investment, contamination, narrow nutritional spectrum, and skill requirement make them less attractive for general use.

Nanozyme-based biofertilizers are far better than their traditional counterparts. Nanozymes act as enzyme mimics and provide the formulation of biofertilizers with enhanced activity and stability but do not compromise the good microbes. Therefore, such formulations ensure a controlled and slow release of nutrients, thereby increasing their uptake by plants, encouraging plant growth, and raising their resistance to the environment. Besides, nanozymes enhance nutrient delivery and absorption at the cellular level, thereby increasing the crop yield with less extra fertilizer application. This method is eco-friendly because it reduces the requirements of chemical fertilizers by not allowing them to runoff and promotes efficient use of the natural resource, hence fit for sustainable agriculture.

Nanozyme Coupled Biofertilizers

Such nanozymes, which can be considered as nanomaterials endowed with catalytic properties similar to enzymes, have been in the limelight for several applications, including agricultural. Among the most important characteristics that

make nanozymes highly applicable in agriculture are their size-dependent catalytic activity, tunable surface functionalities, and biocompatibility. In comparison with natural enzymes, nanozymes exhibit enhanced stability, catalytic efficiency, and adaptability and can replicate a number of enzymatic functions involved in agricultural applications. It includes the functions of these genes in the areas of soil remediation, nitrogen management, pest control, improvement of the plant growth, and stress tolerance (Manjunatha et al., 2016).

Characteristics of Nanozymes

These nanozymes will offer a number of properties that make them act as active catalysts in many biological processes, mimicking the activities of peroxidase, catalase, and superoxide dismutase. They are more stable to the harsh conditions like a wide pH range or high temperatures, and thus can be used for longer (Ma et al., 2023). One way through which the adaptability of nanozymes can be understood is that changes in their composition, variations in size, surface functionalization, and structure can fine-tune their catalytic activities so that they are efficient and selective for certain processes (Ali et al., 2021). In this context, many types of nanozymes have been compatible with biological systems or degradable after use, making them very suitable for biomedical applications where low cytotoxicity and minimal environmental impact are desired. These dimensional modifications can, in turn, modulate the size-dependent activities of these catalysts.

Also, they are substrate-specific and selective and may be adjusted in composition or structure, making them more adapted for the process of catalysis (Huang et al., 2019). Nanozymes are also robust to stand up to shoals in drastic conditions, be stable in catalyzing across pH and thermally stable in high temperature (Zhao et al., 2022). Hence, owing to their stability and reprocessability, they make very good materials for long-term operation in a wide range of applications, from the development of biomimetic systems to bio-inspired technology (Jiang et al., 2019). If it were possible to functionalize their surfaces to interact differently with substrates or a target system, then their value in biological and medical applications would be correspondingly increased (Liu and Liu, 2017).

Classification of Nanozymes

These nanozymes differ in composition and functionalities, hence portray their ability to be versatile in acting as different catalysts.

A) Metal-based nanozymes, including AuNPs, AgNPs, and FeNPs, have different capabilities as enzymes because they have different surface topographies and catalytic abilities. These get the same things done as peroxidase, catalase or oxidase that's why they are called the mimetic enzymes (Liu et al., 2021). Hence the reason why their resistance and flexible catalytic properties have fascinated people from medicine to ecology to industry (Huang et al., 2019).

B) Based on Zhu et al. (2022), carbon-based nanozymes like CNTs and graphene-based structures act in a similar manner as natural enzymes. Thus the electron transfer based on redox reactions can occur using these compounds that resemble oxidoreductases, peroxidases and hydrolases therefore useful for biosensing, drug delivery systems and environmental remediation (Lee and Kamruzzaman, 2023).Polymeric nanozymes made out of organic polymers or polymer based nanoparticles take advantage of their forms and surfaces to mimic enzymatic activities. Dendrimers such as polymer-coated nanoparticles suggest certain features of catalytic activities exhibited by proteases or even by peroxidases acts catalytically like *polymer coated NPs* which means it works like any other enzyme in human bodies. In such fields as biomedicine, sensing, and therapy, these materials have a lot of potential due to their biocompatibility, ease of production, and variable catalytic properties (Huang et al., 2023).

C) Quantum dot nanozymes (QDs) demonstrate peroxidase and catalase functions mimicking enzymes. These semiconducting nanoparticles have flexible dimensions for light-induced degradation resistant with effective catalytic capabilities enabling them to detect biological materials, visualize structure and deliver targeted drugs (Devi et al., 2021).

D) Liposomes and lipid-coated nanoparticles are structurally similar to cell membranes which are the same as enzymes such as lipases, phosphatases, esterases. Their bio-compatibility features and simplicity in terms of functionalization make them appropriate for drug delivery systems (Wang et al., 2023).

E) Nanozymes made from proteins resemble natural enzymes and they enable one to regulate catalytic processes with precision through their adjustable activity levels. There is an application of protein folding principles in nanomedicine as well as biotechnology and synthetic biology inspired nanostructures (Wang et al., 2023).

F) DNAzymes are artificial DNA sequences with different types of enzyme activities like nuclease or ligase that can include peroxidase.Their programmability, chemical resistance, and potential for biosensing, diagnostics, and nanotechnology-based treatments make them versatile tools in biomedical research and analytical chemistry (Zhou et al., 2023).

Nanozyme Mechanisms

Nanozymes work like redox catalysts through the imitation of peroxidases, catalases, and oxidases that help in breaking down reactive oxygen species (ROS) as well as promoting oxidation-reduction reactions. Some nanozymes also have hydrolytic properties and can break chemical bonds like hydrolases (Huang et al., 2019). This size dependence arises from quantum confinement effects (quantum size control); the changes in electronic states with sizes govern their distinctive intrinsic catalytic activity. An increased surface area to volume ratios leads to more active sites for catalytic activity relative solid-state of the materials. Some metallic nanozymes show LSPR (Localized Surface Plasmon Resonance)

because the migration of unbound electrons increases catalytic activity due to the concentration of electromagnetic fields and facilitation of electron transfer processes (Wang et al., 2023). Bimetallic nanozymes exhibit synergistic interactions between the two metals that make up the system, which leads to increased catalytic capabilities or substrate selectivities (Zhou et al., 2023). Additionally, under different environmental conditions, the structure of nanozyme surfaces can undergo changes, which can positively impact catalytic activity by altering the surface (Pietrzak and Ivanova, 2021). When placed in external magnetic fields, magnetic nanozymes display modified catalytic behaviors, allowing for remote-controlled or magnet-directed catalysis (Afzal et al., 2021). The catalytic activity heavily depends on surface characteristics like shape and size, which strongly influence adsorption and reaction kinetics, especially near edges and corners (Dong et al., 2022). By incorporating nanozymes, it can overcome the limitation of heterogeneous nutrient release and poor absorption of the biofertilizer by encapsulating/modifying its components to ensure highly accurate nutrient release at a target point. A controlled release system reduces leaching and volatilization of the nutrients, thereby improving nutrient uptake and reducing environmental pollution. The nanozymes act as catalyzers, much like enzymes, breaking down complex organic compounds to simple ones, increasing nutrient availability in the biofertilizer. They are also known to stabilize the components of the biofertilizer, in effect acting as preservatives that maintain the effectiveness till use (Attia and Saad, 2001). Coupled nanozymes with biofertilizers thus can make farming much more ecofriendly, reducing environmental pollution, providing easier nutrient uptake, improving soil fertility, and promoting eco-friendly agriculture (Al-Mamun et al., 2021).

Synergistic Approach: Nanozymes with Biofertilizers

Such a combination of nanozymes and biofertilizers can exert a synergistic effect; that is, the digestion of organic molecules by nanozymes can increase the bioavailability of nutrients for the beneficial microorganisms in the biofertilizer. Therefore, this collaborative effect helps further strengthen the cycling of elements to create the most favorable soil environment for the growth and activities of microorganisms, hence enhancing nutrient uptake by plants. Nanozymes accelerate the conversion of complex chemical molecules into simpler forms that can be easily absorbed by the plants. Application of biofertilizers containing potent microorganisms could enhance nutrient mobilization and uptake in improving plant growth and yield. The combination of nanozymes and biofertilizers is a green strategy over conventional agrochemicals, and offers a solution to environmental pollution and soil degradation. High technology in sustainable agriculture supports the preservation of fertility and biodiversity in soils while reducing the negative impacts related to synthetic inputs on ecosystems.

Applications of Nanozyme-Coupled Biofertilizers

The Catalytic Potential of Nanoenzymes

Because of their gigantic catalytic properties, nanozymes can improve the efficiency of applied biofertilizers. For instance, nanozymes synthesized from metal NPs such as iron or copper oxides will take on the activity of enzymes and increase the speed at which important nutrients are available to plants in growth. Such nanomaterials increase the decomposition of organic matter, increasing the release of nutrients into the soil, therefore releasing more significant amounts of crucial elements such as nitrogen, phosphorus, and potassium. (Patel et al., 2023). Having an extremely high catalytic efficiency, these nanomaterials facilitate enzymatic reactions in the soil, stimulate microbial activity, and finally create a nutrient-rich environment that helps promote plant well-being.

Controlled Release Systems

On association with biofertilizers, nanozymes develop intricate mechanisms of controlled release. Nanozymes involve the trapping of the bioactive substances, enzymes, or growth regulators within the nanostructures with tunable features that enable controlled release over a longer period of time. For instance, the silica-based nanozymes loaded with plant growth-promoting substances, upon mixing with biofertilizers, release the growth stimulants into the soil in a steady and sustained manner. This will ensure that the plants grow steadily and progressively for a longer period of time (Vejan et al., 2021).

Manipulation of Soil Microbiota

The combination of nanozymes with biofertilizers alters the soil microbiome for the better, and this has a positive effect on plant health. Nanostructures, mainly composed of carbon-based nanotubes or graphene oxide in biofertilizers, influence microbial activity and diversity. According to Sambangi et al. (2022), these nanomaterials enhance the interaction between bacteria and root exudates, thus showing their positive effect on microbial populations. They can enhance the multiplication of microorganisms that are beneficial in enhancing the sharing of nutrients within the soil, improving soil structure, and increasing resistance to plant diseases by colonizing the rhizosphere.

Improved Resilience to Stress

The nanozymes' embedding into the biofertilizer is a very effective way to improve plants' resistance to stressful conditions. These nanoparticles contain antioxidants capable of reducing oxidative stress induced by a number of environmental factors such as drought, salinity, or metal ions. For instance, selenium or ceria nanozymes, when

incorporated into bio-fertilizers, can function as antioxidants by clearing reactive oxygen species and alleviating stress-induced harm in plants (Husen et al., 2021)

Environmental Sustainability

Such combined applications of nanozymes and biofertilizers lower chemical dependencies, environmental contaminations, and promote sustainable practices of farming for better soil quality and productivity. Interactions of nanozymes and biofertilizers decrease the burden of applying synthetic fertilizers and agrochemicals, thereby solving environmental pollution, soil erosion, and other connected ecological risks. This is an integrated approach toward viable soil management, as it changes the structure of the soil, nutrient cycling, and the diversity of microbes. This reduces the quantity of chemicals used, hence their adverse effects on the health of the general ecosystem, and preserves the fertility of the soil in the long term (Zulfiqar et al., 2019).

Sustainable Precision Agriculture

In case of biofertilizers, nanozymes represent a more environment-friendly and it involves a very accurate form of farming called precision farming. It makes use of nanotechnology's precision and catalytic features to ensure efficiency in resource use, hence not overdosing on nutrients. This might make it possible for nanozyme-based biofertilizers to deliver in a tailored way, ecological footprint reduction, and sustainable agriculture with crop production balanced against environmental conservation. This new technique is part of the changing times of farming. It provides accurate, efficient, and environmentally sensitive solutions to the current challenges facing agriculture.

Sequential Synthesis of Nanozyme-Coupled Biofertilizers

Nanozymes and Biofertilizer Matrix Selection

The integration of nanotechnology with agronomic research is implemented in formulating

nanozyme conjugated biofertilizers through approaches that combine nanostructures with biofertilizer supports. Those nanozymes, as metal nanoparticles and carbon-based nanostructures, are chosen for their ability to replicate the essential enzymatic catalytic mechanisms that occur in nutrient transformation. The surface is then modified superbly towards enhancing stability by mimicking enzymes and corresponds to the carrier of biofertilizers. The matrix, usually composed of biopolymers or natural substrates, is formulated to favor the efficient incorporation of the nanozymes, which in turn assures that they perform in the best way possible in agricultural settings.

Synthesis and Modification of Nanozymes

By utilizing techniques of encapsulation, such as emulsion, co-precipitation, or layer-by-layer, the nanozymes assembly process with the carrier matrix is a crucial task. These methods ensure homogeneous dispersion and long-term entrapment of nanostructures within the biofertilizer matrix. Strategic optimization at this stage can guarantee precise control over it. This would further regulate the nanozymes' release rate and prevent possible inadvertent loss or aggregation (Sarkar et al., 2023).

Characterization and Quality Control

After synthesis, detailed investigation using advanced spectroscopic and imaging methods—including transmission electron microscopy, scanning electron microscopy, Fourier-transform infrared spectroscopy, and so on— enables one to obtain all the detailed information about physical and chemical characteristics, distribution, and interaction kinetics of obtained compounds, which are products of the interaction of nanozymes and biofertilizers. Strict control at all stages of their production ensures uniformity and structural soundness, which is required to be a batch of effectiveness and upscaling potential for the formulation.

After performing a reduction reaction detailed assessment at this stage with the aid of state-of-the-art spectroscopic and imaging tools including TEM, SEM, and FTIR will be possible which allows us to explore their interaction with the biofertilizers and their physical-chemical features.

Nanozyme complexes will require an extensive QC program that will prove consistency, uniformity, and structural integrity for each batch. This factor is key to the securing of stability and scalability of a formulation.

Expansion and Implementation

Compatibility tests indicate that nanozymes retain their catalytic activity throughout the biofertilizer matrix and are resistant to some type of environmental stress. In addition, stability studies in different conditions will answer how robust the formulation is in terms of agricultural longevity. Therefore, field trials are so important to evaluate the real efficiency of enzyme-enhanced biofertilizers. These trials assess their effect on crop yields, soil health, and environmental sustainability to refine formulations for best performance across multiple sites.

Working of NBF Application, and Its Uptake and Translocation in Plants

NBFs can be applied by seed priming, foliar spraying, or soil (Sharma et al., 2023). Applying NBFs to the soil can increase plant growth and replenish soil fertility. Heterogeneous aggregation between NPs and soil particles substantially

limits the activity, mobility, and bioavailability of NBF in soil. Foliar spraying NBF would be a more effective way to enable NPs to enter plant tissues quickly (Bairwa et al., 2023). A pre-planting technique called "seed priming" entails soaking seeds in NBFs to hasten seed germination, increase seedling growth, and use less fertilizer. Stress resistance genes are upregulated, and chemicals that reduce reactive oxygen species and promote plant development are stimulated (Nile et al., 2022).

After coming into touch with the surfaces of seeds, roots, and leaves, nanoparticles cling to plant surfaces by hydrophobic, electrostatic, and Vander Waals forces (Bashir et al., 2022). NPs are mostly absorbed by roots through physiologically active lateral roots and root hairs, as opposed to the leaf, where they enter largely through stomata but also through trichomes. After entering roots and leaves, NPs move upward through the xylem (apoplastic transport) and downward through phloem tissues (symplastic transport). NPs enter plant cells and travel between cells by a variety of pathways, including plasmodesmata, endocytosis, ion transporters, and cell wall pores (Rani et al., 2023). The processes that control NPs' entry and migration into plant cells are greatly influenced by their chemical makeup, size, shape, and aggregation state. Since different plants have different receptors, it also depends on the species of plant. A plant can act as an accumulator for some types of NP and as an excluder for others (Masarovicova and Kralova 2013).

Significance of NBFs

To throw a light on the significance of NBFs in the agrochemical systems, following are the three case studies that carried out in three different region of the world on three different plants. These studies reveal that plants show a better growth when they are exposed to NBFs.

Peanut *(Arachis hypogea L.)*

Peanut *(Arachis hypogea L.)* is an essential and inexpensive crop with high oil, protein-based content as well carbohydrate in its multiple grown tropical subtropical regions of the world (Shahid et al. 2010). Plants need Boron (B) and Calcium (Ca) from peg emergence to pod fill, since B is necessary for protein synthesis, and meristematic tissue growth/cell elongation/maturity. Ca and B deficiencies result in a high rate of aborted seeds and underfilled pods, greatly lowering yields and shelling percentages (Walker, 1975; Yang et al., 2020). Abdelghani et al. (2022) investigated the effect of B and Ca nanoparticles (NPs) and biofertilizers on nutrient uptake in 2020 and 2021. The study assessed the impact of these treatments on nitrogen, phosphorous and potassium (NPK) uptake from sandy soil along with peanut seed oil and protein yield. Mycorrhiza and combination of nano-B with mycorrhiza had the highest percentage of nitrogen (3.9%) and phosphorus (1.4%), respectively as shown in Table 1, for two seasons. In the first season, mycorrhiza and nano-Ca or phosphorine and nano-Ca had the highest potassium concentration (0.3%), followed by mycorrhiza and nano-B in the second season (0.4%). In the first season, phosphorine and foliar nano Ca+B yielded the maximum oil content (45.6%), followed by mycorrhiza and nano-B in the second season (48.9%). Mycorrhiza and nano-B produced the highest protein content in both seasons (25.1% and 25.2%), respectively. Mycorrhizal distribution enhances plant growth and nutrient absorption. (Moradi et al., 2020).

Table 1: Effects of interaction between biofertilizer and nanoparticle treatments on peanut seed biochemical traits across season 2021(Abdelghani et al., 2022).

Bio	Nano	Nitrogen		Phosphorous		Potassium		Oil		Protein	
fertilizers	Particles	2020	2021	2020	2021	2020	2021	2020	2021	2020	2021
	Control	2.2^{e}	2.6^{d}	1.1^{d}	1.1^{f}	0.1^{cde}	0.1^{c}	29.1^{d}	29.1^{f}	18.3^{f}	18.3^{f}
Control	Ca	2.2^{e}	3.4^{abc}	1.2^{bcd}	1.2^{def}	0.1^{cde}	0.1^{bc}	33.6^{c}	32.6^{ef}	20.6^{def}	19.4^{f}
	B	2.6^{de}	3.7^{ab}	1.1^{d}	1.1^{ef}	0.3^{a}	0.2^{c}	Cd	38.6^{cd}	19.3^{ef}	20.5^{cdef}
	Ca+B	2.3^{e}	3.5^{abc}	1.3^{ab}	1.3^{abc}	0.1^{cde}	0.1^{c}	32.4^{cd}	32.4^{ef}	21.6^{cde}	19.9^{def}
	Control	3.0^{cd}	3.0^{cd}	1.1^{cd}	1.1^{f}	0.1^{fg}	0.1^{c}	35.1^{c}	35.1^{de}	20.9^{de}	20.3^{cdef}
Mychorrihza	Ca	3.2^{bcd}	3.2^{bc}	1.3^{ab}	1.2^{def}	0.3^{a}	0.3^{a}	39.8^{b}	41.5^{bc}	22.2^{bcd}	24.1^{ab}
	B	3.9^{a}	3.9^{a}	1.4^{a}	1.4^{ab}	0.1^{def}	0.4^{a}	39.2^{b}	48.9^{a}	25.1^{a}	25.1^{a}
	Ca+B	3.7^{ab}	3.6^{abc}	1.4^{a}	1.4^{a}	0.1^{c}	0.1^{c}	44.9^{a}	47.2^{a}	23.6^{abc}	23.0^{abc}
	Control	3.5^{abc}	3.0^{cd}	1.1^{d}	1.1^{f}	0.1^{cd}	0.1^{c}	32.9^{cd}	32.9^{ef}	19.3^{ef}	19.3^{ef}
Phosphorine	Ca	3.2^{bcd}	3.2^{bcd}	1.3^{ab}	1.3^{bcd}	0.3^{b}	0.3^{ab}	33.9^{c}	33.6^{e}	21.0^{de}	21.4^{de}
	B	3.8^{a}	3.8^{a}	1.1^{d}	1.2^{def}	0.1^{efg}	0.1^{c}	39.6^{b}	39.6^{c}	24.3^{ab}	24.3^{ab}
	Ca+B	3.5^{abc}	3.5^{abc}	1.3^{bc}	1.2^{cde}	0.1^{g}	0.1^{c}	45.6^{a}	45.6^{ab}	22.7^{bcd}	22.7^{abcd}

Different lowercase letters on error bars indicate statistically significant differences between treatments ($p \leq 0.05$), as performed by the least significant difference (Fisher's LSD) test.

Cotton (*GossypiumhirsutumL.*)

Plant-eating insects are major global threats to world crop production, *Spodoptera littoralis* one among them feeds on cotton and other crops substantially. Metwally et al. (2022) explored the combination of *Beauvaria bassiana* silicon nanoparticles (Si NPs), arbuscular mycorrhizal (AM) fungus as novel approaches to enhance defense in cotton against *S.*

littoralis. Table 2 shows how *S. littoralis* infestation affected cotton plant growth parameters. Under regulated conditions, AM cotton plants had a considerably greater shoot fresh weight (Fwt) (4.9 g/plant) than non-AM plants (3.6 g/plant). Cotton plants infected with *S. littoralis* were treated with AM fungi and either *B. bassiana* Si NPs or Chlorpyrifos insecticide, resulting in an increase in both shoot Fwt and root dry weight. This revealed that AM fungi would improve immunity when challenged with pests by triggering the nitrogen uptake and boosting immunological responses in comparison to non-AM plants (Abdelhameed et al., 2021). On the other side, phenotypic traits of cotton plants treated with Chlorpyrifos manifested as a slight decrease suggesting stress and also changes in cellular activity The edible residues for male *C. medinalis* are according to FAO from 0-2 days (summer) or >1 day (winter). These data indicated that AM fungi potentially promoted the development of cotton and resistance against insect, which magnified their application in IPM.

Table 2: Fresh (Fwt) and dry weights (Dwt) of *mycorrhizal* (AM) and non-mycorrhizal shoots and roots of cotton plants reared with (+) or without (−) S. littoralis under different treatments (Metwally et al., 2022)

	Fwt (g/plant)			Dwt (g/plant)			MD%
Treatments	Shoot	Root	Total	Shoot	Root	Total	
-S. littoralis	3.638^{bc}	0.539^{ab}	4.178^{bc}	1.044^{ab}	0.145^{b}	1.189^{ab}	23.07^{c}
-S. littoralis + AM	4.906^{a}	0.674^{a}	5.581^{a}	1.342^{a}	0.204^{ab}	1.546^{a}	
+S. littoralis	3.020^{c}	0.520^{ab}	3.540^{c}	0.710^{bc}	0.113^{b}	0.823^{bc}	24.48^{b}
+S. littoralis + AM	4.501^{ab}	0.591^{ab}	5.092^{ab}	0.950^{abc}	0.140^{b}	1.090^{abc}	
+S. littoralis + B. bassiana Si NPs	2.953^{c}	0.360^{b}	3.313^{c}	0.675^{bc}	0.072^{b}	0.747^{bc}	34.50^{a}
+S. littoralis +B. bassiana Si NPs +AM	4.43^{ab}	0.413^{b}	4.843^{ab}	0.700^{bc}	0.440^{a}	1.140^{abc}	
+S. littoralis + Chlorpyrifos	2.961^{c}	0.450^{ab}	3.411^{c}	0.590^{c}	0.104^{b}	0.694^{c}	22.31^{d}
+S. littoralis + Chlorpyrifos+ AM	4.303^{ab}	0.492^{ab}	4.795^{ab}	0.651^{bc}	0.243^{a}b	0.894^{bc}	

Wheat (*Triticum aestivum L.*)

Drought stress in plants causes lower grain yield and oxidative damage from reactive oxygen species (ROS). Sharifi *et al.* used a combination of nanofertilizers (nano zinc oxide, nano iron oxide, and nano Zn-Fe oxide at 1.5 g L^{-1}) and biofertilizers (*Azotobacter*, *Azosperilium*, and *Pseudomonas*) on wheat (*Triticum aestivum* L.) at different irrigation levels to offset these impacts. Table 3 reveals that under extreme water constraints, *Azotobacter* with nano Zn-Fe oxide boosted grain production by 88%. Normal watering produced the maximum yield (331.7 g/m^{-2}). *Azotobacter* inoculation and nano Zn-Fe oxide resulted in the lowest yield (98.5 g m^{-2}) under severe water scarcity without fertilizer. The applications of oxide nanoparticles in plants raised peroxidase activity by 27%. Under normal irrigation, the supplementation of azotobacter and nano Zn-Fe oxide results in the highest level of chlorophyll, 4.59 mg g −1 FW, while the lowest under severe water scarcity conditions, 1.43 mg g −1 FW, in the absence of fertilizers. This mixture increases ROS scavenging and improves plants' tolerance to stress.

Table 3: Effects of irrigation, biofertilizer, and nanooxide on grain yield, chlorophyll and peroxidase production. (Sharifi *et al.*, 2020)

Treatment			Grain Yield (gm^{-2})			Chlorophyll				Peroxidase			
I	B	N_o	N_1	N_2	N_3	N_o	N_1	N_2	N_3	N_o	N_1	N_2	N_3
I_1	F_o	158.33^{no}	205.41^{ghi}	194.16^{g-k}	225^{ef}	2.05^{pq}	2.65^{jkl}	2.91^{hi}	3.21^{efg}	2.36^{w}	2.43^{vw}	2.55^{uvw}	2.76^{t-w}
	F_1	230.41^{de}	285.41^{b}	256.66^{c}	331.66^{a}	3.52^{d}	3.80^{c}	4.30^{b}	4.59^{a}	3.18^{q-t}	3.42^{n-s}	4.25^{ijk}	4.56^{i}
	F_2	204.16^{ghi}	246.25^{cd}	210.00^{fg}	288.33^{b}	3.23^{efg}	3.50^{d}	3.78^{c}	3.90^{c}	3.12^{rst}	3.06^{stu}	3.68^{i-q}	3.79^{k-p}
	F_3	162.91^{no}	244.16^{cd}	199.16^{g-j}	279.16^{b}	2.61^{jkl}	3.15^{fgh}	3.43^{de}	3.42^{de}	3.31^{o-s}	2.94^{s-v}	3.82^{k-o}	4.14^{i-l}
I_2	F_o	127.08^{stu}	155.83^{nop}	146.66^{opq}	172.50^{lmn}	1.77^{Rst}	1.91^{Rq}	2.31^{no}	2.58^{klm}	3.13^{rst}	3.30^{p-s}	4.27^{ijk}	4.00^{j-m}
	F_1	186.25^{jkl}	210.00^{fg}	209.16^{fgh}	243.75^{cd}	2.57^{klm}	2.83^{lj}	3.11^{gh}	3.37^{def}	5.22^{g}	5.19^{g}	6.18^{de}	6.27^{de}
	F_2	166.66^{mn}	192.08^{h-k}	190.41^{ijk}	225.00^{ef}	2.34^{mn}	2.50^{Lmn}	2.81^{ijk}	2.83^{ij}	4.61^{Hi}	5.09^{Gh}	5.34^{g}	5.98^{ef}
	F_3	147.91^{opq}	181.25^{klm}	155.83^{nop}	199.58^{g-j}	2.08^{opq}	2.20^{nop}	$2.43l^{mn}$	2.79^{ijk}	3.91^{k-n}	4.44^{lj}	4.56^{l}	3.87^{k-n}
I_3	F_o	98.95^{w}	109.89^{uvw}	104.79^{vw}	119.37^{tuv}	1.43^{u}	1.50^{u}	1.49^{u}	1.63^{stu}	3.62^{m-q}	3.79^{k-p}	3.20^{df}	6.04^{ef}
	F_1	140.00^{p-s}	182.91^{j-m}	146.25^{o-r}	186.25^{jkl}	2.35^{mn}	$2.50l^{mn}$	3.13^{fgh}	3.33^{d-g}	6.92^{c}	7.00^{bc}	7.50^{b}	8.89^{a}
	F_2	121.66^{tuv}	132.91^{q-t}	129.16^{rst}	170.83^{lmn}	1.86^{Qrs}	2.02^{q}	2.32^{no}	2.85^{ij}	6.62^{cd}	6.84^{c}	6.85^{c}	7.06^{bc}
	F_3	109.58^{vw}	128.75^{st}	120.83^{tuv}	161.25^{no}	1.50^{stu}	1.61^{tu}	2.06^{pq}	2.57^{klm}	5.53^{fg}	5.99^{ef}	6.67^{cd}	6.67^{cd}

I_1, I_2, and I_3 are normal irrigation, moderate water limitation, and severe water limitation respectively. F_0, F_1, F_2 and F_3 indicate noninoculation, inoculation with *Azotobacter, Azosperilium, Pseudomonas* respectively. N_0: without nanofertilizer (as control), N_1: nano Fe oxide; N_2: nano Zn oxide; N_3: nano Zn-Fe oxide. Means followed by different alphabets indicate significant difference between treatments at $P \leq 0.05$ by using the Least Significant Difference test.

Potential Risks Associated with NBFs in Agriculture

The persistent nature of nanomaterials and their potential to accumulate in soil and water system makes them a concern for ecological sustainability. Thus, they can change soil microbial composition and impair plant growth and

development, therefore altering ecological equilibrium. Hence, their long-term environmental distribution and bioaccumulation and potential toxicity need to be thoroughly investigated. Moreover, humans could be exposed to such materials during synthesis, application, or food chains ingestion, leading to potential health problems after inhalation or skin contact due to cutaneous sensitivity or respiratory problems. Finally, the production of ROS and non-selective cellular death that occasionally results in apoptosis, exhibited by nanomaterials may be harmful to plant growth aspect. Therefore, they need to be assessed for dosage reaction and their effects if mortality mechanisms in biological systems are not comprehended. Several dosage metrics can reduce the adverse reactions of such nanoparticles, e.g. particle charge, concentration, and surface area and dimension size and toxicity. Furthermore, some nanoparticles may alter the optimal configuration of beneficial soil bacteria. Some of these nanoparticles, such as AgNPs, will impair the viability of essential soil bacteria at lower doses, directly affecting plant growth. Therefore, to prevent environmental degradation when using nanoparticles as biofertilizers, compatibility is among the key selection criterions.

Although ecotoxicological aspects of various biofertilizers can be studied using post-nano formulations, there is significant potential for these technologies in agriculture, from processing to final delivery.

Nanotechnology is addressing environmental challenges with innovative solutions. Despite recent advances in nanotechnology improving biomedical diagnostics and treatments, understanding plant interactions with nanomaterials is still emerging. Research on developing environmentally friendly biofertilizers is limited. Further investigation into key parameters will enable biofertilizers to support sustainable agriculture and become a cutting-edge tool for promoting agricultural development.

Future Perspective

Nanotechnology presents immense potential to revolutionize agriculture but necessitates a cautious approach due to inherent risks. Rigorous risk assessment, standardized monitoring protocols, robust regulations, and ongoing research are paramount to harness the benefits of nanomaterials while mitigating potential environmental and health risks associated with their use in agriculture. A balanced approach, involving collaboration among researchers, policymakers, industry, and the public, is crucial to ensure the responsible and sustainable integration of nanotechnology into agricultural practices. Following are some points through which the potential of nanotechnology in agrochemical system can be enhanced.

i. A versatile NBF appropriate for a variety of crops must be developed.

ii. Cutting-edge technology, protocols, machine learning, and artificial intelligence (AI) must be combined to produce NBF that is of the highest quality, has a longer shelf life, is inexpensive, and is easy to use.

iv. NBF needs to be carefully investigated to ascertain how they affect human health and the environment.

v. Further research is needed to determine how NBF affects the physicochemical, biochemical, and molecular systems of plants at the cellular and molecular levels in both ambient and stressful environments.

vi. Research is required to determine how NBFs affect the agricultural ecology over the course of their long life cycle.

vii. Farmers need to be informed about the disadvantages of chemical fertilizers and the ways in which NBFs can save expenses and yield long-term gains.

Table 4: Comparison of Nanofertilizers and Conventional Fertilizers Applications (Nagula and Usha, 2016)

	Properties	Nano fertilizers	Conventional fertilizers
1	Solubility and dispersion of 'mineral micronutrients	Reduce soil absorption and fixation, increase soil bioavailability, and improve the solubility and dispersion of insoluble nutrients.	Reduced solubility and big particle size resulting in decreased bioavailability for plants
2	Nutrient uptake efficiency	Might improve the absorption ratio of soil nutrients and fertiliser efficiency in crop production while conserving fertiliser resources.	For roots, bulk composite is unavailable and reduces efficiency.
3	Controlled-release modes	Encapsulating water soluble fertilizers in envelope forms allows for fine control over the release pattern and rate of nutrients.	Overuse of fertilizers can lead to toxicity and upset the soil's natural equilibrium.
4	Effective duration of nutrient release	The effective time that fertilizers give nutrients to the soil can be increased with nanofertilizers.	Utilised by the plants at the time of delivery, the remainder is transformed by the soil into insoluble salts.
5	Loss rate of fertilizer nutrients	Lower the rate at which fertilizers nutrients seep or drain into the soil.	High rate of loss due to drift, rain, and leaching.

Conclusion

Nanotechnology is unique because of its new ways to solve agriculture problems. Because they show enhanced plant growth, targeted nutrient delivery in soils and a strong systemic resistance compared to NPs or biofertilizers alone, these crop sustainability effects may make an NBF open up new possibilities. NBFs have a lot to offer agriculture; hence it is imperative that they be manufactured industrially using stable formulas and eco-friendly methods. The green synthesis of NBFs is an intriguing endeavor since a lot of work is being done to use natural resources and biological synthesis

processes, which have several established advantages including being easy to scale up, affordable, and ecologically beneficial. However, we really do not understand how plants sense and interact with nanoparticles. Nanobiofertilizer Formulations could also be a solution to make agriculture sustainable. These also are non-toxic nanocarriers for efficient nano biofertilizer formulations. Still, further research is required to know the effect of NMs on the growth meantime need for strength and rationality in nanotechnology that could be used better fertilizers for maximum agricultural production. Although NMs have a lot of positive effects on plants, phytotoxicity is one major problem. Further investigations of NMs' functions in both normal and stressed plant environments are required to provide a better understanding because they can modulate the cellular and molecular levels on plants. Even though the exact process that NMs interact with plants is not known, it can be helpful for future studying in this area. A fruitful and necessary enhancement of interdisciplinary collaboration strategies will fill the gap of knowledge on NMs applications in agriculture, especially for plant science-related issues. Ilotan and Regep are key NBFs because they could help usher in a thriving agro-economy through better output, efficient resource savings, increased safety of the environment from pollutants (which is an ongoing challenge) as well deal with unpredictable weather due to climate change.

REFERENCES

Abdelghani, A. M., El-Banna, A. A., Salama, E. A., Ali, M. M., Al-Huqail, A. A., Ali, H. M., and Lamlom, S. F. (2022). The individual and combined effect of nanoparticles and biofertilizers on growth, yield, and biochemical attributes of peanuts (*Arachis hypogea L.*). *Agronomy*, *12*(2), 398.

Abdelhameed, R. E., Abu-Elsaad, N. I., Abdel Latef, A. A. H., and Metwally, R. A. (2021). Tracking of zinc ferrite nanoparticle effects on pea (*Pisum sativum L.*) plant growth, pigments, mineral content and arbuscular mycorrhizal colonization. *Plants*, *10*(3), 583.

Afzal, I., Saleem, S., Skalicky, M., Javed, T., Bakhtavar, M. A., ul Haq, Z., and EL Sabagh, A. (2021). Magnetic field treatments improves sunflower yield by inducing physiological and biochemical modulations in seeds. *Molecules*, *26*(7), 2022.

Ali, S. S., Al-Tohamy, R., Koutra, E., Moawad, M. S., Kornaros, M., Mustafa, A. M., and Sun, J. (2021). Nanobiotechnological advancements in agriculture and food industry: Applications, nanotoxicity, and future perspectives. *Science Total Environment*, *792*, 148359.

Al-Mamun, M. R., Hasan, M. R., Ahommed, M. S., Bacchu, M. S., Ali, M. R., and Khan, M. Z. H. (2021). Nanofertilizers towards sustainable agriculture and environment. *Environment Technology Innovation*, *23*, 101658.

Anand, S., and Kamaraj, A. (2017). Effect of pre sowing biofertilizer seed treatment on morphological and physiological seed quality in rice (*Oryza Sativa L.*). *Plant Archieve*, *17*(2), 1444-1446.

Anli, M., Baslam, M., Tahiri, A., Raklami, A., Symanczik, S., Boutasknit, A., and Meddich, A. (2020). Biofertilizers as strategies to improve photosynthetic apparatus, growth, and drought stress tolerance in the date palm. *Frontier Plant Science, 11*, 516818.

Attia, F., and Saad, O. A. O. (2001). Biofertilizers as partial alternative of chemical fertilizer for Catharanthus roseus G. Don. *International Journal Plant Prodroction*, *26*(11), 7193-7208.

Bahrulolum, H. Nooraei, S., Javanshir, N., Tarrahimofrad, H., Mirbagheri, V.S., Easton A. J., and Ahmadian, G., 2021. Green synthesis of metal nanoparticles using microorganisms and their application in the agrifood sector. *Journal Nanobiotechnology*, *19(1),* 1-26.

Bairwa, P., Kumar, N., Devra, V., and Abd-Elsalam, K. A. (2023). Nano-Biofertilizers Synthesis and Applications in Agroecosystems. *Agrochemicals*, *2*(1), 118-134.

Bashir, S. M., Ahmed Rather, G., Patrício, A., Haq, Z., Sheikh, A. A., Shah, M. Z. U. H., and Fonte, P. (2022). Chitosan nanoparticles: a versatile platform for biomedical applications. *Materials*, *15*(19), 6521.

Devi, M., Das, P., Boruah, P. K., Deka, M. J., Duarah, R., Gogoi, A., and Das, M. R. (2021). Fluorescent graphitic carbon nitride and graphene oxide quantum dots as efficient nanozymes: Colorimetric detection of fluoride ion in water by graphitic carbon nitride quantum dots. *Journal Environment Chemistry Eng*, *9*(1), 104803.

Dong, K., Xu, C., Ren, J., and Qu, X. (2022). Chiral nanozymes for enantioselective biological catalysis. *Angew Chemistry, International Ed. Engl*, *61*(43), e202208757.

Godfray, H. C. J., Beddington, J. R., Crute, I. R., Haddad, L., Lawrence, D., Muir, J. F., ... and Toulmin, C. (2010). Food security: the challenge of feeding 9 billion people. *Science*, *327*(5967), 812-818.

Hofmann, D., Thiele, B., Siebers, M., Rahmati, M., Schütz, V., Jeong, S., and Schulz, M. (2023). Implications of Below-Ground Allelopathic Interactions of Camelina sativa and Microorganisms for Phosphate Availability and Habitat Maintenance. *Plants*, *12*(15), 2815.

Huang, L., Sun, D. W., Pu, H., Zhang, C., and Zhang, D. (2023). Nanocellulose-based polymeric nanozyme as bioinspired spray coating for fruit preservation. *Food Hydrocoll*, *135*, 108138.

Huang, Y., Ren, J., and Qu, X. (2019). Nanozymes: classification, catalytic mechanisms, activity regulation, and applications. *Chemistry Review, 119*(6), 4357-4412.

Husen, A. (2021). The Harsh Environment and Resilient Plants. *Harsh Environment and Plant Resilience*. Springer, Cham.

Iavicoli, I., Leso, V., Beezhold, D. H., and Shvedova, A. A. (2017). Nanotechnology in agriculture: Opportunities, toxicological implications, and occupational risks. *Toxicology and Applied Pharmacology*, *329*, 96-111.

Jiang, D., Ni, D., Rosenkrans, Z. T., Huang, P., Yan, X., and Cai, W. (2019). Nanozyme: new horizons for responsive biomedical applications. *Chemistry Society Review*, *48*(14), 3683-3704.

Kannojia, P., Choudhary, K. K., Srivastava, A. K., and Singh, A. K. (2019). PGPR bioelicitors: induced systemic resistance (ISR) and proteomic perspective on biocontrol. *PGPR amelioration in sustainable agriculture* (pp. 67-84). Woodhead Publishing.

Kopittke, P. M., Menzies, N. W., Wang, P., McKenna, B. A., and Lombi, E. (2019). Soil and the intensification of agriculture for global food security. *Environment International*, *132*, 105078.

Kumar, N., Samota, S. R., Venkatesh, K., and Tripathi, S. C. (2023). Global trends in use of nano-fertilizers for crop production: Advantages and constraints–A review. *Soil Tillage Research*, *228*, 105645.

Lee, D. H., and Kamruzzaman, M. (2023). Organic compound-based nanozymes for agricultural herbicide detection. *Nanoscale*, *15*(31), 12954-12960.

Liu, B., and Liu, J. (2017). Surface modification of nanozymes. *Nano Research*, *10*, 1125-1148.

Liu, Q., Zhang, A., Wang, R., Zhang, Q., and Cui, D. (2021). A review on metal-and metal oxide-based nanozymes: properties, mechanisms, and applications. *Nanomicro Letter*, *13*, 1-53.

Ma, T., Huang, K., and Cheng, N. (2023). Recent Advances in Nanozyme-Mediated Strategies for Pathogen Detection and Control. *International Journal Molecular Science, 24*(17), 13342.

Mahapatra, D. M., Satapathy, K. C., and Panda, B. (2022). Biofertilizers and nanofertilizers for sustainable agriculture: Phycoprospects and challenges. *Science Total Environment*, *803*, 149990.

Manjunatha, S. B., Biradar, D. P., and Aladakatti, Y. R. (2016). Nanotechnology and its applications in agriculture: A review. *Journal Farm Science*, *29*(1), 1-13.

Masarovicova, E., and Kráľová, K. (2013). Metal nanoparticles and plants/nanocząstki metaliczne I rośliny. *Ecological Chemistry and Engineering S*, *20*(1), 9-22.

Metwally, R. A., Azab, H. S., Al-Shannaf, H. M., and Rabie, G. H. (2022). Prospective of mycorrhiza and Beauvaria bassiana silica nanoparticles on Gossypium hirsutum L. plants as biocontrol agent against cotton leafworm, Spodoptera littoralis. *BMC Plant Biology*, *22*(1), 409.

Moradi, T. Z., Iranbakhsh, A., Mehregan, I., and Ahmadvand, R. (2020).Impact of arbuscular mycorrhizal fungi (AMF) on gene expression of some cell wall and membrane elements of wheat (Triticum aestivum L.) under water deficit using transcriptome analysis. *Physiology Molecular Biology*, *26*, 143-162.

Nagula, S. A. I. N. A. T. H., and Usha, P. B. (2016). Application of nanotechnology in soil and plant system with special reference to nanofertilizers. *Advance Life Science*, *1*(14), 5544-5548.

Nile, S. H., Thiruvengadam, M., Wang, Y., Samynathan, R., Shariati, M. A., Rebezov, M., and Kai, G. (2022). Nano-priming as emerging seed priming technology for sustainable agriculture recent developments and future perspectives. *Journal Nanobiotechnology*, *20*(1), 1-31.

Pahalvi, H. N., Rafiya, L., Rashid, S., Nisar, B., and Kamili, A. N. (2021). Chemical fertilizers and their impact on soil health. *Microbiota and Biofertilizers, Vol 2: Ecofriendly Tools for Reclamation of Degraded Soil Environs*. (pp 1-20). Springer

Patel, C., Singh, J., Karunakaran, A., and Ramakrishna, W. (2023). Evolution of Nano-Biofertilizer as a Green Technology for Agriculture. *Agriculture*, *13*(10), 1865.

Pietrzak, M., and Ivanova, P. (2021). Bimetallic and multimetallic nanoparticles as nanozymes. *Sens. Actuators B Chemistry*, *336*, 129736.

Rai, S., and Shukla, N. (2020). Biofertilizer: An alternative of synthetic fertilizers. *Plant Archieve*, *20*(2), 1374-1379.

Rani, S., Kumari, N., and Sharma, V. (2023). Uptake, translocation, transformation and physiological effects of nanoparticles in plants. *Archiev Agronomy Soil Science*, *69*(9), 1579-1599.

Sambangi, P., Gopalakrishnan, S., Pebam, M., and Rengan, A. K. (2022). Nano-biofertilizers on soil health, chemistry, and microbial community: benefits and risks. *Procces Indian National Science Acadamic*, *88*(3), 357-368.

Sarkar, A., and Ahmed, I. A. (2023). Design and operation of new microbial product bioprocessing system. *Microbial Products for Future Industrialization (*pp. 23-55). Springer Nature.

Seyed Sharifi, R., Khalilzadeh, R., Pirzad, A., and Anwar, S. (2020). Effects of biofertilizers and nano zinc-iron oxide on yield and physicochemical properties of wheat under water deficit conditions. *Communication Soil Science Plant Analysis*, *51*(19), 2511-2524.

Shahid, L. A., Saeed, M. A., and Amjad, N. (2010). Present status and future prospects of mechanized production of oilseed crops in Pakistan-a review. *Pakistan Journal of Agricultural Research*, *23*(1-2).

Sharma, B., Tiwari, S., Kumawat, K. C., and Cardinale, M. (2023). Nano-biofertilizers as bio-emerging strategies for sustainable agriculture development: Potentiality and their limitations. *Science of the Total Environment*, *860*, 160476, Elsevier.

Tevini, M., and Teramura, A. H. (1989). UV-B effects on terrestrial plants. *Photochemistry and Photobiology*, *50*(4), 479-487.

Thrupp, L. A. (2000). Linking agricultural biodiversity and food security: the valuable role of agrobiodiversity for sustainable agriculture. *International Aff.*, *76*(2), 265-281.

Vejan, P., Khadiran, T., Abdullah, R., and Ahmad, N. (2021). Controlled release fertilizer: A review on developments, applications and potential in agriculture. *JCR*, *339*, 321-334.

Walker, M. E. (1975). Calcium requirements for peanuts. *Commun. Soil Science Plant Analysis*, *6*(3), 299-313.

Wang, Y., Jia, X., An, S., Yin, W., Huang, J., and Jiang, X. (2023). Nanozyme-Based Regulation of Cellular Metabolism and their Applications. *Advance Mater*, 2301810.

Yang, S., Wang, J., Tang, Z., Guo, F., Zhang, Y., Zhang, J., and Li, X. (2020). Transcriptome of peanut kernel and shell reveals the mechanism of calcium on peanut pod development. *Science Reproduction*, *10*(1), 15723.

Zhao, L., Bai, T., Wei, H., Gardea-T. J. L., Keller, A., and White, J. C. (2022). Nanobiotechnology-based strategies for enhanced crop stress resilience. *National Food*, *3*(10), 829-836.

Zhou, J., Liu, Y., Du, X., Gui, Y., He, J., Xie, F., and Cai, J. (2023). Recent Advances in Design and Application of Nanomaterials-Based Colorimetric Biosensors for Agri-food Safety Analysis. *ACS Omega 8*(49), 46346-46361.

Zhu, L., Chen, L., Gu, J., Ma, H., and Wu, H. (2022). Carbon-based nanomaterials for sustainable agriculture: their application as light converters, nanosensors, and delivery tools. *Plants*, *11*(4), 511.

Zulfiqar, F., Navarro, M., Ashraf, M., Akram, N. A., and Munné-Bosch, S. (2019). Nanofertilizer use for sustainable agriculture: Advantages and limitations. *Plant Science, 289*, 110270

Chapter 29

Synthesis Techniques and Applications of Diverse Nanoparticles

Muhammad Adil[1], Farrah Deeba[1], Bushra Mumtaz[2], Marwa Abbas[2], Sayeda Nimra Jabeen[3*], Hassan Raza[4], Rabia Ali[2], Saba Imtiaz[4], Saifuddin[2] and Maham Naseer[5]

[1]Department of Clinical Medicine & Surgery, University of Agriculture, Faisalabad, Pakistan
[2]Institute of Microbiology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[3]Department of Chemistry, Government College Women University, Faisalabad, Pakistan
[4]Department of Chemistry, University of Agriculture, Faisalabad, Pakistan
[5] National Institute of Food Science & Technology, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: syedanimrajabeen@gmail.com

ABSTRACT

Nanotechnology involves the creation of nanomaterials, including nanoparticles, which exhibit unique properties because of their nanoscale size (1-100nm). These particles differ significantly from bulk materials in their chemical, optical, physical, and electrical characteristics, primarily because of their large surface area-to-volume ratio and quantum mechanical effects. Nanoparticles can be synthesized using various techniques, including chemical methods (sol-gel, hydrothermal, solvothermal, vapor synthesis), biological methods (microbial, plant-based synthesis), mechanical methods (milling, mechanical alloying), and both top-down and bottom-up approaches. The characterization of nanoparticles deals with determining their morphology, structure optics, and physiochemical properties by means such as electron microscopy, X-ray diffraction spectroscopy (XRD) BET(Brunner-Emmet-Teller) surface area analysis to calculate particle size, shape crystalline structure, and elemental composition. From cancer therapy to drug delivery, environmental cleanup, and even energy devices, nanoparticles have a wide scope of uses because of their unique characteristics and ability to be manipulated. Nanoparticles also have some benefits and threats to health and the environment, which can be overcome by using the techniques of green synthesis that include non-toxic eco-friendly reagents. Nanoparticles are classified, synthesized, and characterized and their application in various fields along with prospects have been included in this chapter.

KEYWORDS
Nanoparticle, Microscopic, Biological, Chemical, Mechanical, Metallic

Received: 29-Jun-2024
Revised: 02-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Adil M, Deeba F, Mumtaz B, Abbas M, Jabeen SN, Raza H, Ali R, Imtiaz S, Saifuddin and Naseer M, 2024. Synthesis techniques and applications of diverse nanoparticles. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 254-260. https://doi.org/10.47278/book.CAM/2024.237

INTRODUCTION

Nanotechnology is the creation and formation of nanomaterials that are functionalized in less than or equal to 100nm range (Adil et al., 2023). Because of their small size, between one and a hundred nanometers (nm) in diameter, these particles have unique chemical, optical, physical, and electrical properties (Bhattacharjee and Bose, 2021). Nanoparticles themselves are synthesized and developed by nanotechnology. Nanoparticles mainly consist of a core that is encapsulated by several layers of nanomaterials and, as a result, shell form with an exterior surface that is commonly functionalized (Bolokang et al., 2015). Nanoparticles are substantially different from bulk materials in terms of their surface-area-to-volume ratio, interfacial layer, solubility into the solvent phase, type of coating quantum mechanical effects, diffusion rate, and last modifiers such as metal ions (Bhoi et al., 2016). Surfactants act as modifiers for nanoparticle properties for all kinds of applications (Fanhoefer et al., 2004).

Synthesis Techniques of Nanoparticles

Chemical Methods

Nanoparticles can be synthesized through different chemical methods, such as sol-gel, precipitation, hydrothermal, thermal breakdown, solvothermal, and vapor synthesis methods (Rane et al., 2018). The sol-gel technique is very fundamental in creating nanostructures. Here, the precursors are dissolved in a solvent to solve with characteristics like a gel. It is then heated to produce nanoparticles, and the solvent is also evaporated through gelation (Bokov et al., 2021). The wet chemical precipitation technique is still another method that one can use; it is quite fast and efficient. High

pressure and temperature, especially in aqueous solvents such as water, led to heterogeneous treatment known as hydrothermal treatment. The nanoparticle properties can therefore be controlled by the pressure, pH, and temperature that are used to synthesize the nanoparticles (Darr et al., 2017). These nanoparticles are hydrophilic and, therefore, appropriate for the biotechnological field. Thermal breakdown involves the heating of a solid material until it melts, that is the release of binding forces, the formation of molecules, and a gaseous effect. Solvothermal synthesis involves the utilization of solvents with medium to high pressure to create materials like metals, semiconductors, and polymers (Sasikala et al., 2017). The solvothermal method comparatively works at controlled temperature, leading to the formation of stable nanoparticles. Different surfactant stabilizers enhance nanodot formation from cationic precursor kinds (Li et al., 2021). Zinc oxide, zinc selenide, and cadmium selenide obtained by this process are used in biotech and magnetic corporations (Balakrishnan and Kadam, 2021). In vapor synthesis, the gaseous state of the material carries out a chemical reaction and forms a phase that condenses to induce particle growth, and, in this phase, the temperature has a direct influence on the process. The methods of condensing inert gases, vaporizing supersaturated material by using a pulsed laser, sputtering by unreactive gaseous ions, spark discharge, and chemical methods including Chemical Vapor Deposition, Photothermal Method, Flame Synthesis, and Spray Pyrolysis are some ways which can cause homogeneous nucleation (Danielson et al., 2020). Titania, carbon, and silica nanoparticles can be produced using this method, although the process can be time-consuming. Flame synthesis is applied in the commercial synthesis of silica, carbon black, optical fibers, and titania. While it may be possible to obtain agglomerated particles, the ones derived from the conversion of gases in the furnace reactors or hot walls are rather clean (Zhao et al., 2024).

Biological Methods

Biological nanoparticle synthesis using microorganisms represents a clean, uncontaminated, and environmentally sustainable method (Samrot et al., 2021). This approach has produced various nanoparticles, particularly oxides that include ferrous, silver, nickel, copper, and zinc (Ezealigo et al., 2021). The synthesis site depends on whether the production occurs extracellularly or intracellularly (Chan et al., 2022). For intracellular nanoparticle synthesis, the ions are transported into microbial cells through the action of enzymes and the nanoparticles are synthesized within the cells (Rana et al., 2020). Extracellular fungi with large secretion glands located outside the cell wall are used in this method. Microorganisms such as bacteria and fungi are highly effective in the synthesis of nanomaterials due to their cost effectiveness, non-toxicity, and ability as scavengers. Plant-based nanoparticles suitable for biological systems make use of abundant and stable natural resources by excluding the use of toxic synthetic agents (George et al., 2021). The pH variations affect the geometric aspects of plants, binding capability, and the concentration of metal ions for biosynthesis. The sources, synthesis methods, and applications of nanoparticles are shown in Fig. 1 (Jamkhande et al., 2019). Generating nanoparticles by using Biogenic methods such as utilizing microorganisms and waste materials is both eco-friendly and cost-effective (Mughal et al., 2021).

Mechanical Methods

Mechanical techniques are used for making nanoparticles, such as mechanical alloying, milling, and mechanochemical processes (Yadav et al., 2012). When contacting for a chemical reaction, the milled sample should be improved, and this should especially apply to cases where the milling was done at low temperatures. Using continuous welding processes to help select milling materials and minimize occurrences of agglomerations here will again use mechanochemical methods. The source material stoichiometry, thermal treatment conditions, reaction mechanism, and milling parameters should be optimally controlled for high production. Mechanical techniques are used to make oxide, iron, nickel, silver, and cobalt nanoparticles (Iqbal et al., 2016).

Top-Down Approach

The top-down method of preparing nanoparticles comprises the fission of large particles and converting them into particles of the required size (Priyadarshana et al., 2016). It is detrimental and uses enhanced breakdown techniques like Physical Vapor Deposition (PVD), grinding, and Chemical Vapor Deposition (CVD) (Abid et al., 2022). Milling was also engrossed to extract the nanoparticles from coconut resemblance shells and the crystallite size was decreased with time. This process is used to synthesize nanoparticles of cobalt (III) oxide, carbon, iron oxide, and dichalcogenides (Harish et al., 2022).

Bottom-up Approach

The bottom-up approach involves the assemblage of nanoparticles from fundamental elements, and this procedure is slow. This technique is quite accurate, inexpensive, relatively safe for humans and the bio of insects, and safe for the environment (Modan and Plăișu, 2020). The methods comprise spin coat-ting, green synthesis, biochemical synthesis, sol-gel synthesis, and other reduction and sedimentation methods. Through this approach, titanium dioxide, gold, and bismuth nanoparticles are synthesized (Ambre et al., 2023).

Nanoparticle synthesis can also involve biological or chemical procedures. Chemical synthesis processes consist of microwave methods, wet chemical synthesis, sol-gel, hydrothermal methods, and thermal decomposition (Hachem et al., 2022). Conversely, biological methods utilize enzymes, microbes, plant extracts, and fungi.

Characterization Methods for Nanoparticles

Thorough characterization of nanoparticles is essential to determine their shape, size, surface morphology, crystalline nature, light absorption, and other properties (Cuenya, 2010). *Some of the methods used to characterize nanoparticles include:*

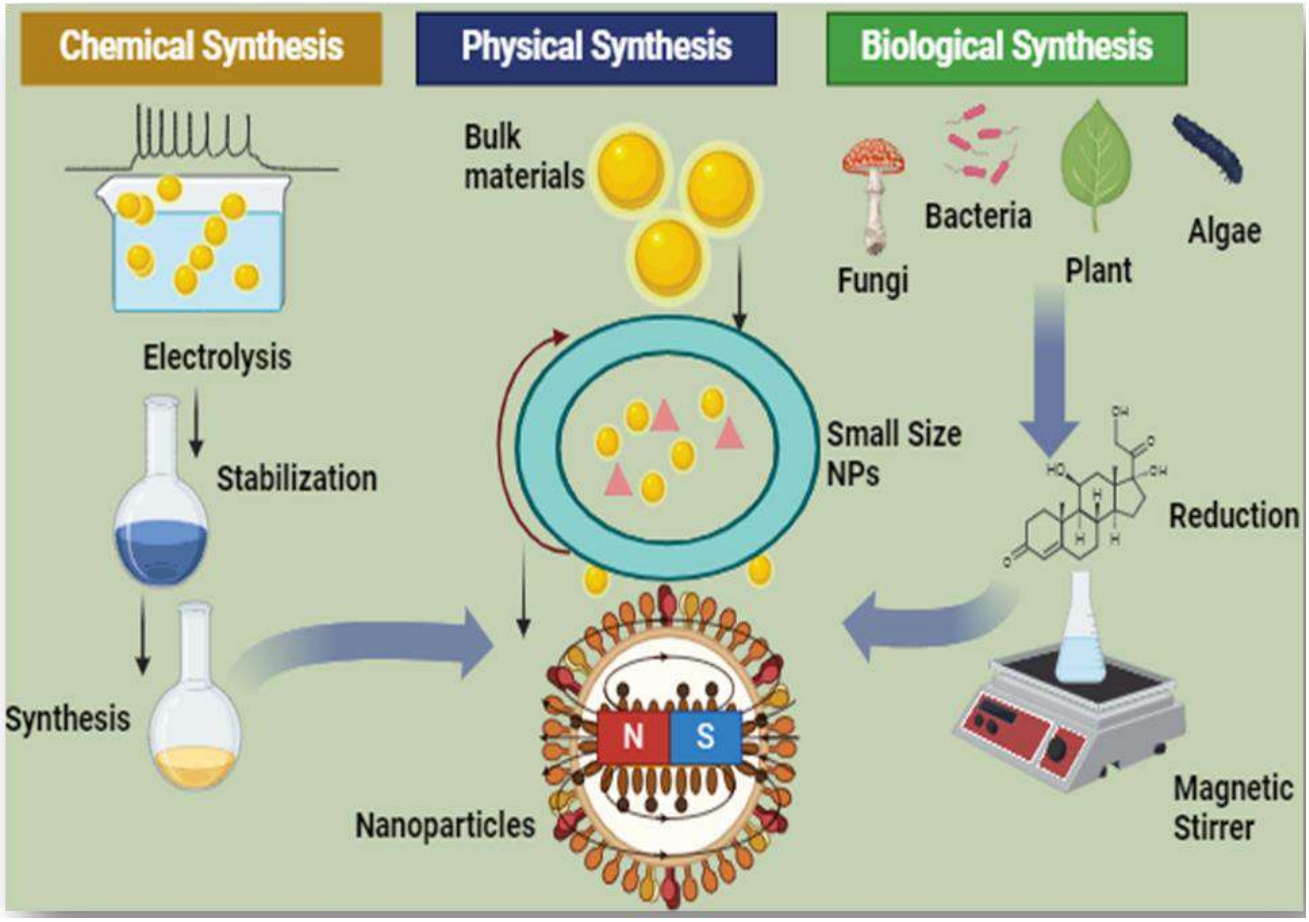


Fig. 1: Methods of Synthesis of Nanoparticles

Morphological Features

An important factor influencing the characteristics that nanoparticles exhibit is their shape. Particularly scanning probes or electron microscopy are used on nanoparticles (Ngoi et al., 2021). The dispersion and shape of nanoparticles can be studied at the nanoscale and surface using a scanning electron microscope (SEM) (Tang et al., 2020). Measurements of individual particles are made using destructive microscopy techniques. Utilizing electron transmittance, transmission electron microscopy (TEM) may obtain large amounts of data at both high and low magnifications (Zhang et al., 2020). Because nanoparticles are smaller than the limit of light diffraction, the optical microscopic approach does not apply to them. Combining electron microscopes and spectroscopic methods would be possible for elemental studies (Taghavi Fardood et al., 2020).

Optical Studies

Optical methods are innovative techniques used to characterize the photochemical, luminescence, transmittance, and reflectance characteristics of nanoparticles that unmask these properties. Spectroscopy is a method that apprises the density of nanoparticles and their size and shape by monitoring how they react to electromagnetic waves or light (Gudkov et al., 2023). Nanoparticle spectroscopies are more prominent as IR, UV–VIS, NIR, and PL DRS (photoluminescence) than MRI (Mmelesi et al., 2024). The band gap energy can be achieved by using the method of DRS (diffuse reflectance spectroscopy) and this could only be done via specialized, high-sensitivity instrumentation. PL studies show that the excitability of photons, half-life and charge results produced by recombination work differently due to emissivity and absorptivity. The size-mobilized optical properties and application aspects of nanoparticles incorporated into bioimaging tools (Wang et al., 2020).

Structural Analysis

In this technique, the nanoparticles are directly linked through the type of inter-atomic bond and this crystal structure

projects, onto a nanoscale level within bulk material so that distinctive qualities of bulk are shown. Through this technique characterization of nanoparticles like the composition and structure of the synthesized selenium nanoparticles was done by X-ray diffraction (XRD), infrared (IR) spectroscopy, Brunauer-Emmett-Teller (BET) surface area measurements, and other electron microscopy imaging techniques. Findings on the phases, size, and type of nanoparticles will be characterized by powdered crystal X-ray diffractograms (Khan et al., 2020).

Elemental Studies

The elemental composition of nanoparticle techniques for characterization are Energy dispersive X-ray (EDX), Raman Spectroscopy, and Fourier transform infrared (FT-IR) spectroscopy, are included. This technique provides information about the nanoparticles present in the powder form (Patil et al., 2022). The exact composition of elemental particles can be studied with their proper ratios. In this regard, X-ray photoelectron spectroscopy (XPS) is the most sensitive method for finding out all dimensional characterizations. The vibrational effect of Raman and FTIR, respectively, shows the functionalization of those peaks and provides particle information (Castro and Zuazo, 2024).

Size Estimation

Scanning Electron Microscopes, X-ray diffraction instruments, Transmission Electron Microscopy, Atomic Force Microscopes, and so on can be used to measure the sizes of the nanoparticles (Selvan et al., 2021). Sizing distribution curves are employed in the process of measuring the sizes of particles, and the value of such magnitudes becomes correct when they are merged with the digital models. Adsorption and desorption processes are the procedures making use of BET to characterize the surface area, which has been pointed out by (Hou et al., 2020).

Physiochemical Characteristics

The physicochemical features of nanoparticles that make them appropriate for industrial applications include their mechanical character flexibility and their optical activity to absorb sunlight. While lighting, electrons on the surface of nanoparticles become much free. Therefore, their motion is very active, and they can lose congregation (Kishore et al., 2023). Magnets are characterized by magnetism at the nanoscale because crystalline planes of the materials where NPs have a random orientation. This orientation is regulated by the synthesis method used. They are abundant in catalytic machines, biomedicine, and nucleotide resonance imaging (Roostaee and Sheikhshoaie, 2020). The mechanical properties of nanoparticles, including stress, adhesiveness, friction, hardness, strain, and surface coatings, are crucial for understanding their behavior and significantly affect surface quality (Mehmood et al., 2023). Nanoparticles, especially those on their surfaces, demonstrate superior thermal conduction.

Application Areas of Nanoparticles

Because of their unique properties, nanoparticles are used in a variety of fields, including cancer treatments, vaccines, disease management, cancer detection, mechanical industries, electronics, optical devices, energy harvesting, manufacturing, cell imaging, and delivery systems (Aghebati-Maleki et al., 2020). They also play a role in environmental protection by helping to remove toxins from water during purification (Pooja et al., 2020).
The application areas of nanoparticles have been given in Table 1 (Singh et al., 2021).

Table 1: Application areas of some nanoparticles.

Nanoparticles	*Application areas*
Silver	Fitness centers, medicine, electronics, automotive, agriculture, food packaging, textile industries, clothing
Gold	Medicine, food, environmental products, cosmetics
Carbon nanotubes	Cosmetics, construction, medicine, electronic components, textiles, integrated circuits.
Titanium dioxide	Skin coatings, H_2O purifiers, paints
Zinc oxide	Food, cosmetics, agriculture, automotive, home appliances
Cerium oxide	Applying in biomedical equipment, electronic and energy devices
Nickel oxide	Gas sensing devices, water treatment and catalytic systems, supercapacitors, dye-sensitized solar cells, batteries
Iron (Fe^{++})	Applying in optics instruments, H_2O purifiers
Calcium (Ca^{++})	Applying in agronomy, automotive, and nutrition

Although nanoparticles (NPs) are extensively used, their introduction into the body through various pathways or their release into the environment can cause toxic and adverse effects. Furthermore, organic compounds can interact with nanoparticles, resulting in their agglomeration. Using green synthesis techniques can reduce the toxic affects of NP synthesis, particularly when creating nanoparticles of gold, silver, iron, and copper, among other metals *(Dikshit et al., 2021).* Green synthesis uses a variety of capping materials, including polysaccharides and biomolecules. Utilizing reagents such as sugars, polymers, vitamins, and plant extracts, green procedures are non-toxic, eco-friendly, and compatible with biological systems *(Ahmed et al., 2022).* Due to their low cost, simplicity, ease of replication, and high stability, plant-based extracts such as latex, leaves, seeds, roots, or stems are better suited for bioprocesses. By calculating the rates at which the

particles nucleate, models can be created to reduce the challenges related to dispersing the particle size and NP formation *(Shrestha et al., 2020)*.

Classification of Nanoparticles

Nanoparticles can be categorized into artificial, engineered, metallic, non-metallic, organic, or inorganic types. Non-metallic nanoparticles encompass materials such as silica and carbon nanotubes, whereas nanoparticles that are metallic in nature include elements like copper, magnesium, zinc, gold, titanium, and silver (Khan et al., 2022). Anthropogenic nanoparticles arise as by-products from industrial processes, while engineered nanoparticles are specifically produced through manufacturing techniques (Barhoum et al., 2022). Table 2 provides a summary of various nanoparticles and their characteristics (Khan et al., 2019; Khan and Hossain, 2022).

Table 1: Nanoparticles and their implications

Nanoparticles	*Features*
Silver	Extremely potent, excellent antibacterial activity, wide use
Gold	Effective for diagnosing cancer and other microorganisms, good at detecting protein interactions, helpful in tracking fingerprints, and able to detect antibiotics and malignant cells.
Iron	Suitable for medication administration, gene analysis, cancer treatment, and stem cell sorting, biocompatible
Quantum dot	less than 10 nm in diameter, semiconducting, and size-dependent
Carbon nanotubes	Strong electron bonds, excellent electrical conductivity, sp2 hybridized carbon atoms, and effective catalysts.
Copper	Good-quality nanoparticles are produced by a broad absorption spectrum and unique optical characteristics.
Ceramics	Inorganic amorphous solids are widely used in photocatalysis, imaging devices, and other fields. They can be polycrystalline, porous, amorphous, or dense.
Semiconductor	Excellent for electronic equipment and water splitting due to its large and adjustable band gap nature.
Polymeric	Mostly organic materials that can readily be operational.
Fat-type	Include components like fat and employ surface-active agents as central stables.

Conclusion and Future Perspective

Researchers are actively working on developing nanoparticles in response to the growing need for eco-friendly or green materials that can be simultaneously utilized in biological systems. At the nanoscale, nanoparticles are prevalent due to their potential as stable, eco-friendly materials that can integrate harmoniously with biological systems. This chapter commences by detailing the classification, advantages, and limitations of nanoparticles, followed by an overview of synthesis and characterization methods. Numerous cost-effective and efficient techniques for synthesizing nanoparticles exist, including chemical and biological synthesis, top-down and bottom-up approaches, as well as mechanical methods. Multiple approaches for characterizing nanoparticles are developed to extract information about their shape, structure, optical characteristics, mechanical properties, and physiochemical properties. The most important aspects of nanoparticles depend on the synthesis and characterization techniques used. In the areas of medicine, drug delivery, cosmetics, optics, electronics, and solar energy devices, nanoparticles prove to be beneficial specifically.

REFERENCES

Abid, N., Khan, A. M., Shujait, S., Chaudhary, K., Ikram, M., Imran, M., and Maqbool, M. (2022). Synthesis of nanomaterials using various top-down and bottom-up approaches, influencing factors, advantages, and disadvantages: A review. *Advances in Colloid and Interface Science*, *300*, 102597.

Adil, M., Murtaza, G., Sajid, M., Zaidi, B., and Jan, S. (2023). Unveiling the Marvels and Mysteries of Nanomedicine. *Biological Times*, *2*(9), 3-4.

Aghebati-Maleki, A., Dolati, S., Ahmadi, M., Baghbanzhadeh, A., Asadi, M., Fotouhi, A., and Aghebati-Maleki, L. (2020). Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *Journal of Cellular Physiology*, *235*(3), 1962-1972.

Ahmed, S. F., Mofijur, M., Rafa, N., Chowdhury, A. T., Chowdhury, S., Nahrin, M., and Ong, H. C. (2022). Green approaches in synthesizing nanomaterials for environmental nanobioremediation: Technological advancements, applications, benefits and challenges. *Environmental Research*, *204*, 111967.

Ambre, S. K., Patil, S. S., Bhat, T. S., and Patil, P. S. (2023). Bi2S3-sensitized TiO2 nanorods by bottom-up approach for photoelectrochemical solar cell. *Journal of Solid State Electrochemistry*, *27*(2), 337-343.

Balakrishnan, R. M., and Kadam, V. V. (2021). Biological synthesis of metal selenide nanoparticles and their applications. *Environmental Technologies to Treat Selenium Pollution; Lens, PNL, Pakshirajan, K., Eds*, 323-351.

Barhoum, A., García-Betancourt, M. L., Jeevanandam, J., Hussien, E. A., Mekkawy, S. A., Mostafa, M., and Bechelany, M. (2022). Review on natural, incidental, bioinspired, and engineered nanomaterials: history, definitions, classifications,

synthesis, properties, market, toxicities, risks, and regulations. *Nanomaterials*, *12*(2), 177.

Bhattacharjee, Y., and Bose, S. (2021). Core-shell nanomaterials for microwave absorption and electromagnetic interference shielding: A review. *ACS Applied Nano Materials*, *4*(2), 949-972.

Bokov, D., Turki Jalil, A., Chupradit, S., Suksatan, W., Javed Ansari, M., Shewael, I. H., and Kianfar, E. (2021). Nanomaterial by sol-gel method: synthesis and application. *Advances in Materials Science and Engineering*, *2021*, 1-21.

Bolokang, A. S., Cummings, F. R., Dhonge, B. P., Abdallah, H. M. I., Moyo, T., Swart, H. C., and Motaung, D. E. (2015). Characteristics of the mechanical milling on the room temperature ferromagnetism and sensing properties of TiO2 nanoparticles. *Applied Surface Science*, *331*, 362-372.

Castro, G. R., and Zuazo, J. R. (2024). Hard X-ray photoelectron spectroscopy and X-ray diffraction techniques: non-destructive compositional, electronic, chemical and structural in-depth characterization in the tens-of-nanometer scale. In *Non-Destructive Material Characterization Methods* (pp. 417-486). Elsevier.

Chan, S. S., Low, S. S., Chew, K. W., Ling, T. C., Rinklebe, J., Juan, J. C., and Show, P. L. (2022). Prospects and environmental sustainability of phyconanotechnology: A review on algae-mediated metal nanoparticles synthesis and mechanism. *Environmental Research*, *212*, 113140.

Cuenya, B. R. (2010). Synthesis and catalytic properties of metal nanoparticles: Size, shape, support, composition, and oxidation state effects. *Thin Solid Films*, *518*(12), 3127-3150.

Danielson, E., Sontakke, V. A., Porkovich, A. J., Wang, Z., Kumar, P., Ziadi, Z., and Sowwan, M. (2020). Graphene based field-effect transistor biosensors functionalized using gas-phase synthesized gold nanoparticles. *Sensors and Actuators B: Chemical*, *320*, 128432.

Darr, J. A., Zhang, J., Makwana, N. M., and Weng, X. (2017). Continuous hydrothermal synthesis of inorganic nanoparticles: applications and future directions. *Chemical Reviews*, *117*(17), 11125-11238.

Dikshit, P. K., Kumar, J., Das, A. K., Sadhu, S., Sharma, S., Singh, S., and Kim, B. S. (2021). Green synthesis of metallic nanoparticles: Applications and limitations. *Catalysts*, *11*(8), 902.

Ezealigo, U. S., Ezealigo, B. N., Aisida, S. O., and Ezema, F. I. (2021). Iron oxide nanoparticles in biological systems: Antibacterial and toxicology perspective. *JCIS Open*, *4*, 100027.

George, J. A., Sundar, S., and Paari, K. A. (2021). A Review on Metal Nanoparticles from Medicinal Plants: Synthesis, Characterization and Applications. *Nanoscience and Nanotechnology-Asia*, *11*(5), 77-98.

Gudkov, S. V., Matveeva, T. A., Sarimov, R. M., Simakin, A. V., Stepanova, E. V., Moskovskiy, M. N., and Izmailov, A. Y. (2023). Optical Methods for the Detection of Plant Pathogens and Diseases. *Agriengineering*, *5*(4), 1789-1812.

Hachem, K., Ansari, M. J., Saleh, R. O., Kzar, H. H., Al-Gazally, M. E., Altimari, U. S., and Kianfar, E. (2022). Methods of chemical synthesis in the synthesis of nanomaterial and nanoparticles by the chemical deposition method: A review. *BioNanoScience*, *12*(3), 1032-1057.

Harish, V., Ansari, M. M., Tewari, D., Gaur, M., Yadav, A. B., García-Betancourt, M.-L., and Barhoum, A. (2022). Nanoparticle and nanostructure synthesis and controlled growth methods. *Nanomaterials*, *12*(18), 3226.

Hou, L., Liang, Q., and Wang, F. (2020). Mechanisms that control the adsorption–desorption behavior of phosphate on magnetite nanoparticles: the role of particle size and surface chemistry characteristics. *RSC Advances*, *10*(4), 2378-2388.

Iqbal, T., Hassan, A., and Ghazal, S. (2016). Synthesis of iron oxide, cobalt oxide and silver nanoparticles by different techniques: a review. *International Journal Science Eng. Research*, *7*, 1178-1221.

Jamkhande, P. G., Ghule, N. W., Bamer, A. H., and Kalaskar, M. G. (2019). Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. *Journal of Drug Delivery Science and Technology*, *53*, 101174.

John, A. T., and Tricoli, A. (2022). Flame assisted synthesis of nanostructures for device applications. *Advances in Physics: X*, *7*(1), 1997153.

Khan, H., Yerramilli, A. S., D'Oliveira, A., Alford, T. L., Boffito, D. C., and Patience, G. S. (2020). Experimental methods in chemical engineering: X-ray diffraction spectroscopy—XRD. *The Canadian Journal of Chemical Engineering*, *98*(6), 1255-1266.

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908-931.

Khan, S., and Hossain, M. K. (2022). Classification and properties of nanoparticles. In *Nanoparticle-based Polymer Composites* (pp. 15-54). Elsevier.

Khan, Y., Sadia, H., Ali Shah, S. Z., Khan, M. N., Shah, A. A., Ullah, N., and Khedher, N. B. (2022). Classification, synthetic, and characterization approaches to nanoparticles, and their applications in various fields of nanotechnology: A review. *Catalysts*, *12*(11), 1386.

Kishore, K., Pandey, A., Wagri, N. K., Saxena, A., Patel, J., and Al-Fakih, A. (2023). Technological challenges in nanoparticle-modified geopolymer concrete: A comprehensive review on nanomaterial dispersion, characterization techniques and its mechanical properties. *Case Studies in Construction Materials*, e02265.

Li, C., Yang, W., He, W., Zhang, X., and Zhu, J. (2021). Multifunctional surfactants for synthesizing high-performance energy storage materials. *Energy Storage Materials*, *43*, 1-19.

Mehdaoui, B., Meffre, A., Carrey, J., Lachaize, S., Lacroix, L. M., Gougeon, M., and Respaud, M. (2011). Optimal size of

nanoparticles for magnetic hyperthermia: a combined theoretical and experimental study. *Advanced Functional Materials*, *21*(23), 4573-4581.

Mehmood, U., Yasmeen, S., Nazar, R., and Tiwari, S. K. (2023). Metallic Nanoparticles: Status and Prospect. In *Nanoparticles Reinforced Metal Nanocomposites: Mechanical Performance and Durability* (pp. 127-159). Springer.

Mmelesi, O. K., Ammar-Merah, S., Nkambule, T. T. I., Nkosi, B., Liu, X., Kefeni, K. K., and Kuvarega, A. T. (2024). The photodegradation of naproxen in an aqueous solution employing a cobalt ferrite-carbon quantum dots (CF/N-CQDs) nanocomposite, synthesized via microwave approach. *Journal of Water Process Engineering*, *59*, 104968.

Modan, E. M., and PlĂIaŞU, A. G. (2020). Advantages and disadvantages of chemical methods in the elaboration of nanomaterials. *The Annals of "Dunarea de Jos" University of Galati. Fascicle IX, Metallurgy and Materials Science*, *43*(1), 53-60.

Mughal, B., Zaidi, S. Z. J., Zhang, X., and Hassan, S. U. (2021). Biogenic nanoparticles: Synthesis, characterisation and applications. *Applied Sciences*, *11*(6), 2598.

Ngoi, K. H., Wong, J. C., Chiu, W. S., Chia, C. H., Jin, K. S., Kim, H.-J., and Ree, M. (2021). Morphological structure details, size distributions and magnetic properties of iron oxide nanoparticles. *Journal of Industrial and Engineering Chemistry*, *95*, 37-50.

Patil, R. M., Deshpande, P. P., Aalhate, M., Gananadhamu, S., and Singh, P. K. (2022). An update on sophisticated and advanced analytical tools for surface characterization of nanoparticles. *Surfaces and Interfaces*, 102165.

Pooja, D., Kumar, P., Singh, P., and Patil, S. (2020). *Sensors in water pollutants monitoring: role of material*. Springer.

Priyadarshana, G., Kottegoda, N., Senaratne, A., Alwis, A. d., and Karunaratne, V. (2016). Synthesis of magnetite nanoparticles by top-down approach from a high purity ore. *Journal of Nanomaterials*, *16*(1), 317-317.

Rana, A., Yadav, K., and Jagadevan, S. (2020). A comprehensive review on green synthesis of nature-inspired metal nanoparticles: Mechanism, application and toxicity. *Journal of Cleaner Production*, *272*, 122880.

Rane, A. V., Kanny, K., Abitha, V. K., and Thomas, S. (2018). Methods for synthesis of nanoparticles and fabrication of nanocomposites. In *Synthesis of Inorganic Nanomaterials* (pp. 121-139). Elsevier.

Roostaee, M., and Sheikhshoaie, I. (2020). Magnetic nanoparticles; synthesis, properties and electrochemical application: a review. *Current Biochemical Engineering*, *6*(2), 91-102.

Samrot, A. V., Sahithya, C. S., Selvarani, J., Purayil, S. K., and Ponnaiah, P. (2021). A review on synthesis, characterization and potential biological applications of superparamagnetic iron oxide nanoparticles. *Current Research in Green and Sustainable Chemistry*, *4*, 100042.

Sasikala, S. P., Poulin, P., and Aymonier, C. (2017). Advances in subcritical hydro-/solvothermal processing of graphene materials. *Advanced Materials*, *29*(22), 1605473.

Selvan, G. A., Rachel, S., and Gajendran, T. (2021). Several assorted characterization methods of nanoparticles. In *Nanomaterials* (pp. 301-308). Elsevier.

Shrestha, S., Wang, B., and Dutta, P. (2020). Nanoparticle processing: Understanding and controlling aggregation. *Advances in Colloid and Interface Science*, *279*, 102162.

Singh, V., Yadav, S. S., Chauhan, V., Shukla, S., and Vishnolia, K. K. (2021). Applications of Nanoparticles in Various Fields. *Diagnostic Applications of Health Intelligence and Surveillance Systems*, 221-236.

Taghavi Fardood, S., Moradnia, F., Ghalaichi, A. H., Danesh Pajouh, S., and Heidari, M. (2020). Facile green synthesis and characterization of zinc oxide nanoparticles using tragacanth gel: investigation of their photocatalytic performance for dye degradation under visible light irradiation. *Nanochemistry Research*, *5*(1), 69-76.

Tang, M., Yuan, W., Ou, Y., Li, G., You, R., Li, S., and Wang, Y. (2020). Recent progresses on structural reconstruction of nanosized metal catalysts via controlled-atmosphere transmission electron microscopy: a review. *ACS Catalysis*, *10*(24), 14419-14450.

Wang, L., Hasanzadeh Kafshgari, M., and Meunier, M. (2020). Optical properties and applications of plasmonic-metal nanoparticles. *Advanced Functional Materials*, *30*(51), 2005400.

Yadav, T. P., Yadav, R. M., and Singh, D. P. (2012). Mechanical milling: a top down approach for the synthesis of nanomaterials and nanocomposites. *Nanoscience and Nanotechnology*, *2*(3), 22-48.

Zhang, W., Dong, Z., Zhu, L., Hou, Y., and Qiu, Y. (2020). Direct observation of the release of nanoplastics from commercially recycled plastics with correlative Raman imaging and scanning electron microscopy. *Acs Nano*, *14*(7), 7920-7926.

Zhao, J., Korba, D., Mishra, A., Klausner, J., Randhir, K., AuYeung, N., and Li, L. (2024). Particle-based high-temperature thermochemical energy storage reactors. *Progress in Energy and Combustion Science*, *102*, 101143.

Chapter 30

Effectiveness of Intra Articular Steroid Injection in Osteoarthritic Patients

Abdur Rehman[1], Maida Ilyas[2], Hamid Mushtaq[3], Hamza Zahid[4], Faiza zubair[5], Naila Riaz[6], Muhammad Danial Musa[7] and Tasawar Iqbal[8*]

[1]Department of Epidemiology and Public Health, University of Agriculture Faisalabad, Pakistan
[2]Department of Knowledge Unit of Health Sciences –DPT, University of Management and Technology, Sialkot, Pakistan
[3]Department of Epidemiology and Public Health, University of Agriculture Faisalabad, Pakistan
[4]Department of Knowledge Unit of Health Sciences –DPT, University of Management and Technology, Sialkot, Pakistan
[5]Department of Zoology, University of Sargodha, Pakistan
[6]Department of Zoology, University of Sargodha, Pakistan
[7]Department of Knowledge Unit of Health Sciences –DPT, University of Management and Technology, Sialkot, Pakistan
[8]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
*Corresponding Author: tasawariqbal177@gmail.com

ABSTRACT

Osteoarthritis is a chronic and long-lasting disease that puts a heavy burden on healthcare providers, individuals, and society at large. This kind of arthritis is more frequent among the elderly age people and mostly affects them. Mono- or oligo osteoarthritis may develop in those affected with this degenerative condition, it is described by the dynamic damage to articular cartilage. Injections of intra-articular corticosteroids are among the most well-known pharmacological treatment used to decrease inflammation, stop pain, and further develop and improved function. Such injections are becoming the preferred technique of local medication administration because to their many benefits, including greater bioavailability, lower systemic exposure, and reduced chances of adverse responses. There are a variety of intra-articular therapies that may alleviate osteoarthritis symptoms, and there are also new disease-modifying medicines (DMOADs) that are making headway in phase 3 clinical studies.

KEYWORDS
Osteoarthritis, Corticosteroids, Intra articular injections

Received: 19-Jun-2024
Revised: 05-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Rehman A, Ilyas M, Mushtaq H, Zahid H, zubair F, Riaz N, Musa MD and Iqbal T, 2024. Effectiveness of intra articular steroid injection in osteoarthritic patients. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 261-268. https://doi.org/10.47278/book.CAM/2024.379

INTRODUCTION

Definition of Osteoarthritis (OA)

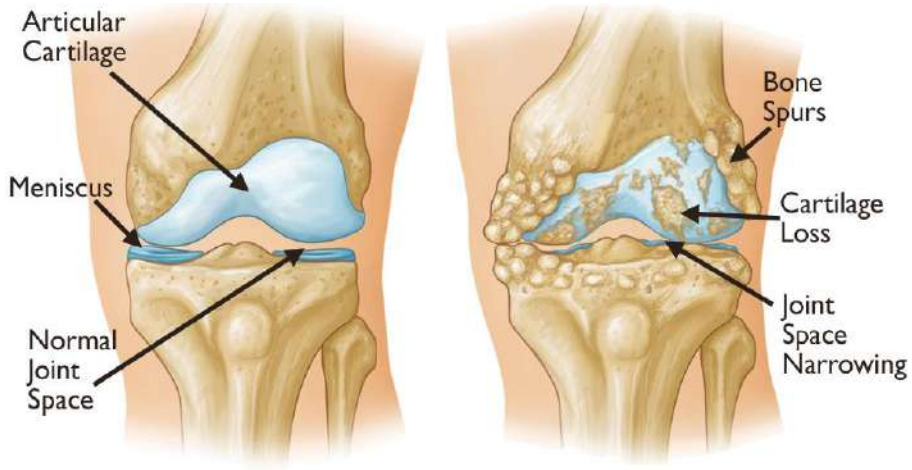
Osteoarthritis, a degenerative joint condition defined by the degradation of articular cartilage, promotes inflammation in the surrounding soft tissues. It is the most prevalent kind of arthritis, and it mostly affects those who are 65 and older. This chronic illness commonly causes discomfort and stiffness in the joints, particularly during or after activity, caused by persistent irritation of the cartilage. Osteoarthritis is a severe health burden, with considerable effect on individuals, communities, and health care systems. Its prevalence, affecting 10-15% of adults over the age of 60, highlights its position as a widespread and chronic illness. Joint inflammation, cartilage deterioration, and bone remodeling synergistically lead to the expression of persistent pain, restricted mobility, and functional restrictions. As a prominent cause of joint pain globally, the incidence of osteoarthritis continues to grow, paralleling increases in life expectancy and risk factors such as obesity. Related pain and disability incredibly trouble communities and medical care frameworks, with osteoarthritis of the hip and knee arising as a critical supporter of overall handicap (Allen, 2022).

Osteoarthritis occurs as a condition defined by a mix of degraded and degenerative changes inside the articular cartilage, accompanied by alterations in the subchondral bone, modest osteophyte development, and low-grade inflammation and irritation. This state commonly affects the hips, knees, spine and interphalangeal joints, osteoarthritis generally manifests clinically in a monoarticular or oligoarticular fashion, with severity and location noticed with time (Kudashev et al., 2023).

Osteoarthritis (OA) stands apart as the most regular and dynamic musculoskeletal disease or infection, influencing generally 10% of men and 13% of ladies beyond 60 years. This disorder exerts a tremendous pressure on health, well-being and the economy. Until to date, conservative therapies have demonstrated little efficacy in lowering symptoms, with no existing medication able to restore cartilage degradation or alter the normal development of the condition. Knee joints

are commonly affected by OA, and intra-articular drugs, for example, glucocorticoids are generally used in its treatment. Although these medicines are regularly used to improve function and diminish pain, their safety and efficacy keep on being addressed. Safety concerns have been raised throughout development, with certain studies revealing undesirable results, including rapid progression of osteoarthritis and quick joint degradation, involving bone loss, perhaps pre-existing osteonecrosis increases (Wittenauer et al., 2013)Osteoarthritis stands as an essential and widespread joint infection, which offers a substantial difficulty and hurdle in the Western world. It creates as an ongoing, chronic, and degenerative problem that influences the entire joint, causing damage to both bone and cartilage. Osteoarthritis affects more than 10% of the worldwide population owing to variable inflammation and structural abnormalities in subchondral bone as well as damage to the protecting articular cartilage. In particular, women between the ages of 50 and 60 are significantly impacted. It stands as a primary cause of impairment in people over the age of 65, with the incidence of joint pain and persistent symptoms rising with age. osteoarthritis arises in two basic forms, each with its own specific features and consequences:

Idiopathic, some of the times named fundamental or essential osteoarthritis, which might be associated with lifestyles factors or age. Secondary osteoarthritis, which may occur from a number of pathological situations, including developmental or metabolic problems, illnesses, or joint infections. Although osteoarthritis may potentially affect any joint. Joints that are regularly engaged in weight-bearing activities, such as the knee, are more vulnerable (Maqbool et al., 2021).



A. Normal knee joint. B. Osteoarthritic knee joint

{Allen, 2022 #58}

Prevalence and Impact on Patients

Osteoarthritis (OA), the most prevalent type of joint pain or arthritis, stands out as a key contributor to functional restrictions and reduced mobility in adults. Among people or groups whose age are above 50- 65years are mostly affected. osteoarthritis of the knees and hips are rated as the two essential drivers of pain and physical disability. Additionally, symptomatic hand osteoarthritis is a prevalent disorder in the elderly, considerably impairing hand function, usually owing to discomfort. As with other chronic illnesses, the etiology of osteoarthritis is complicated, with several local and systemic risk factors recognized. Discrepancies in the frequency of osteoarthritis may be due to a mix of genetic predisposition and lifestyle factors. Osteoarthritis affects roughly 25% of the wilder population, with a growing incidence in the elderly population osteoarthritis affects women more than males, particularly those under the age of 50. However, beyond the age of 50, women are more affected by osteoarthritis than males (Cui et al., 2020).

In Pakistan, osteoarthritis affects approximately 3.6% of the rural population and 4.6% of those residing in northern areas {Ghaznavi, 2017 #59}. With no treatment availability, the worldwide burden of osteoarthritis is on the increase, with an estimated 28% of the adult population (aged over 60) afflicted by the osteoarthritis. As indicated by the 2017 Worldwide Weight of Sickness (GBD) review, hip and knee osteoarthritis appraised as the eleventh most prominent reason for inability universally and the 23rd most significant commitment to incapacity changed life years (DALYs) Steinmetz, 2023 #60}.

Further researches and studies show that with increased life expectancy and an older population, osteoarthritis will become the fourth largest cause of disability by 2023. There has already been a considerable rise in DALYs due to osteoarthritis since 2007.estimated prevalence of osteoarthritis worldwide has varied, ranging from a low of 14.6 per osteoarthritis correspondence and republish demands of increasing in osteoarthritis {Safiri, 2020 #61}.

According to Osteoarthritis and cartilage (2020), the normality of osteoarthritis increases from 10.0 to 40.5 per 1000 man lives in Canada and the UK, independently. Although three countries have archived developing patterns in the frequency of osteoarthritis, none have given detailed pattern of information. In Sweden, age-normalized hospitalization rates because of hip and knee osteoarthritis rose from 1998 to 2014. Basically, in Canada, gathered rate rates created from 11.8 to 14.2 per 1000 man-years in men a while in folks and from 15.7 to 18.5 per 1000 man-years a while in women from 2000 to 2008. Be that as it may, a UK research utilizing the Clinical Practice Exploration Datalink (CPRD) uncovered no

adjustment of examples of doctor analyzed osteoarthritis from 1992 to 2013. Meeting data from seven years till 2010 showed that over 8.75 million individuals in the UK have searched therapy for osteoarthritis at any clinical benefits establishment. By 2035, it is guessed that 8.3 million people grown-ups in the UK having age 45 years or above could have suggestive knee osteoarthritis (Cui et al., 2020; Felson et al., 2000).

The investigation assessed around the world, nearby, and public event, disability, and years lived with illness for 354 disorders and wounds across 195 nations and areas from 1990 to 2017. effective assessment of the Worldwide Weight of Infection Study 2017 (Breedveld, 2004).

Osteoarthritis is the most prevalent kind of joint pain, with around 25% of persons aged over 65 globally having pain and impairment linked with this illness, according to the World Health Organization. While osteoarthritis influences people of any age, its recurrence perceptibly ascends past the age of 50 in males and 40 in females. In 1997, somewhere in the range of 1.3 and 1.7 million people in England and Grains were burdened with osteoarthritis, while in France in the mid-1990s, 6 million new cases were recorded yearly. These figures are probably going to climb attributable to an extending old populace. The assembled countries extends that the portion of the western European populace matured north of 65 will develop from 20% in 1995 to 25% in 2010 (Swain et al., 2020).

Social and Economic Impact of Osteoarthritis

The social and economic consequences of osteoarthritis is enormous. As the most frequent kind of arthritis, osteoarthritis is among the primary causes of physical impairment in the old age population outside of institutional settings. While the condition typically presents as physical symptoms, it may also lead to despair or anxiety. A research done in 1998 explored the association between knee pain and its influence on depression, anxiety, and physical function among osteoarthritis patients. It discovered that knee discomfort was substantially linked with reduced quadriceps strength, radiographic abnormalities, and depression. Disability was also connected with diminished quadriceps strength and depression, but not with radiographic scores. One more exploration in the US researched the wellbeing related personal satisfaction of osteoarthritis patients utilizing an overall personal satisfaction measure. The findings revealed that the quality of life of these individuals was poorer compared to a community-matched sample and was comparable to ratings reported in patients with depression or advanced disease. The monetary effect of osteoarthritis incorporates both direct consumptions associated with drugs, clinical therapy, facilities, and exploration, as well as aberrant costs, for example, lost efficiency attributable to chronic and short term disability. While treatment might ease side effects and may limit the social impact and certain aberrant expenses of the condition, the consumptions associated with treatment and the consideration of conceivable unfriendly medication reactions can be extensive. A few investigations have assessed the expense viability of pharmacological treatments for osteoarthritis, including standard non-steroidal calming meds (NSAIDs) and specific cyclooxygenase (COX)- 2 inhibitors. Although, irregularities in the cost appraisal techniques and little information on asset used in specific exploration make it hard to reach clear determinations in regards to the most practical treatments. Moreover, an Australian exploration demonstrated that people having osteoarthritis experience high private uses related to treatment. More established females with osteoarthritis burned through 25% more on local area administrations contrasted with more young age females with the disease. Higher sickness related spending was connected with bigger torment levels, lower social and mental working, and longer illness term (Swain et al., 2020).

Background of Intra-Articular Steroid Injections

Corticosteroids are phenomenally convincing medications. Intra-articular injections of corticosteroids have been used for almost fifty years the symptomatic treatment of osteoarthritis. An examination done among rheumatologists in the US showed that over 95% of them use this medicine in certain conditions, with over half utilizing it frequently. Moreover, intra-articular corticosteroids are proposed in the continuous ideas from the American School of Rheumatology for the treatment of serious knee infection in individuals with osteoarthritis. Corticosteroids apply their calming activities by altering the incendiary and immunological fountain at a few phases, including (Williams, 2018).Corticosteroids decrease antigen opsonization, stop the adhesion and migration of inflammatory cells across the vascular endothelium, disrupt cell-cell communication by changing cytokine production, or antagonize cytokines such as interleukin-1, leukotrienes, and prostaglandins. Disrupts synthesis, metalloproxes, inhibits metal processes, superlute processes. activator (plasminogen activator), and reduces immunoglobulin production. Past examinations have uncovered that corticosteroid infusions might diminish cartilage proteoglycan creation, harm ligament, or even produce degenerative changes in sound cartilage. In later distributions, utilizing creature models of osteoarthritis (bunny and guinea pig), different agents have shown that low-portion intra-articular corticosteroids (adequate to restrict catabolism) reestablish cartilage proteoglycan creation. more, significantly bring down the recurrence and seriousness of cartilage corruption, osteophyte advancement (Chacon Arenas, 2020).

Treatment options for knee osteoarthritis differ based on the severity of the condition. In mild situations, modest pain management measures and lifestyle adjustments may serve to reduce symptoms. However, in chronic stages of the condition, knee substitution medical procedure is a safe and practical treatment for decreasing pain and reestablishing actual disability. For knee discomfort associated with moderate osteoarthritis, intra-articular injections might be targeted. Steroid-based injections, typically mixed with local anesthetics, are routinely used to control acute flare-ups of the condition. Their usefulness originates from their significant anti-inflammatorycharacteristics, which help ease pain produced by synovitis, a typical occurrence in osteoarthritis. Lately, viscosupplementation has created as a treatment procedure for tending to knee osteoarthritis. This therapy includes injecting hyaluronic acid (HA) into the joint, based on its

physiological qualities inside the synovial joint (Williams, 2018).

Rationale for use in Osteoarthritic Patients

While certain individuals arise with generalized osteoarthritis, which is thought to be altogether influenced by hereditary factors, most osteoarthritis influencing weight-bearing joints is instigated by distorted mechanical powers. Osteoarthritis, in contrast to numerous different problems, is delicate to both local intra-articular treatment and systematic treatment. Although most endeavors have focused on making systematic drugs, these methodologies incorporate more serious dangers of systemic adverse effects, like cardiovascular occasions and gastrointestinal unfavorable impacts, contrasted with most non-steroidal joint pain medicines. Related with mitigating medications and cyclooxygenase-2 inhibitors. Given the persistent idea of the infection, the need to deliver drugs fitting for long systematic therapy with most reduced unfavorable impacts is an intense endeavor. The utilization of local medications, for example, infusing drugs straightforwardly into the impacted joints, is a procedure for the treatment of osteoarthritis that is currently consistently utilized and brings the ability to provide the ideal profile. In the outline, the improvement and movement of knee osteoarthritis is driven by local factors, including aggravation of the synovial film, chondrocyte actuation, and bone rebuilding. Consequently, it looks reasonable to pick an intra-articular strategy to the treatment of knee (as well as hip) osteoarthritis (Allen et al., 2022; Wang et al., 2022).

Table 1: Information About Intra-Articular Injection of Corticosteroids

Agent	Anti-Inflammatory Potency	Action Time	Dose: From Small Joint to Large Joint	Serum Half-Life	Fluorinated	References
Hydrocortisone acetate	I	S	10–25 (mg)	2h	No	{Zhang, 2020 #62}
Triamcinolone acetate	5	I	2.5–15 (mg)	88min	Yes	{Conaghan, 2018 #63}
Triamcinolone hexacetonide	5	I	2–20 (mg)	88min	YES	{Rubin, 2022 #64}
Methyl prednisone acetate	5	I	4–80 (mg)	18–26h	No	{Zhang, 2020 #65}
Dexamethasone	25	L	0.8–4 (mg)	36–54h	Yes	{Najm, 2021 #66}
Betamethasone acetate	25	L	0.25–2 (mL)	6.5h	Yes	{Liu, 2018 #67}

Abbreviations: S, short = 8–12h biologic half-life; I, intermediate = 12–36h biologic half-life; L, long = 36–72h biologic half-life.

Evidence Supporting Intra-Articular Steroid Injections

Regardless of the fact that intra-articular corticosteroid injections are routinely and broadly used in the management of osteoarthritis of the knee, and having brief advantages. Moreover, Tenoxicam is additionally utilized as an intra-articular treatment which is a helpful choice to reduce the gastrointestinal adverse effects related with NSAIDs when taken orally. Clinically it's proved and recommended that the synchronous utilization of NSAIDs and corticosteroids is synergistic, especially in conditions like retinal edema after cataract procedure in ophthalmology. Accordingly, the reason for this study is to recognize whether the blend of intra-articular steroid and tenoxicam is more successful than tenoxicam alone or steroid injections in the treatment of osteoarthritis (Primorac et al., 2021).

Meta-analyses and Systematic Reviews

40 randomized controlled preliminaries (RCTs) evaluated, 38 gave satisfactory information to be remembered for the meta-analysis. In examinations where intra-articular saline was utilized, it cut down knee pain in 32 assessments influencing 1705 people (SMD = - 0.68; 95% CI: - 0.78 to - 0.57; $p < 0.001$; I2 = 50). On a very basic level dealt with short term span%). Basically, 19 assessments wrapping 1445 patients (SMD = - 0.61; 95% CI: - 0.76 to - 0.45; $p < 0.001$) showed a huge reduction in long span knee pain after intra-articular saline mixture, however an outstandingly serious degree of irregularity. (I2 = 74%).the included investigations, 29 have reported side effects none of which distinguished any serious treatment-related unfavorable conditions after intra-articular saline infusion. Examination of meta-analyses comparing intra-articular hyaluronic acid treatment with other intra-articular therapies and oral NSAIDs found that hyaluronic acid is a potential therapeutic option for knee osteoarthritis. It was shown to cause benefits in pain and function that lasted up to 26 weeks, with a positive safety profile (Wang et al., 2022).

Comparison with other Treatment Modalities

Intra-articular medication dispersion gives various benefits over systematic organization. Nonetheless, over the course of recent years, restorative and management choices for knee osteoarthritis have been compelled to analgesics, glucocorticoids, hyaluronic corrosive (HA) and few trial alternative medications. Despite the fact that HA and glucocorticoids might convey clinically significant enhancements to numerous patients, new exploration uncovers that their efficacy is generally affected by attributes, for example, a placebo treatment. Biologic medications focusing on provocative pathways have been fruitful in the administration of rheumatoid joint pain yet have not been as powerful in osteoarthritis. A shortage of facts and high level information and strategic limitations block how we might interpret "stem" cell treatments. Despite the fact that intra-articular cell medicines, for example, platelet-rich plasma and bone marrow suction concentrate are regularly utilized off-mark, high quality evidence and top notch clinical information are essential before these treatments might be given or advised. A few potential intra-articular medicines are under observation and in clinical improvement in the US, including unassuming synthetic and organic treatments, gadgets and quality treatments.

although the possibility of new nonsurgical treatment for osteoarthritis is tempting, the advantages of these new medications should be painstakingly evaluated against their cost and potential risks (Su et al., 2018).

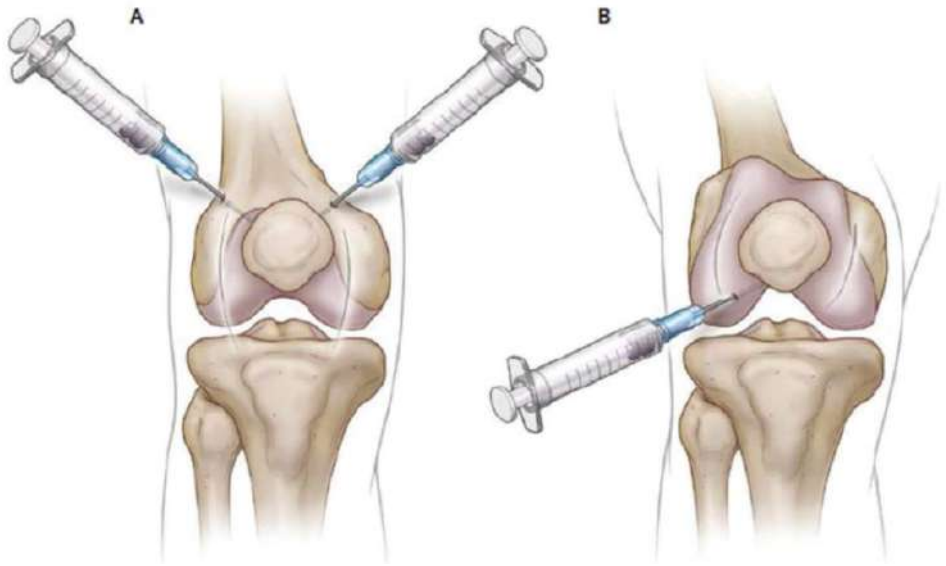
Mechanisms of Action

Intra-articular corticosteroids have been already consistently used in the treatment of osteoarthritis of the knee for fifty years. The aim behind its usage is to minimize joint inflammation and discomfort by local administration of a powerful anti-inflammatory drug. Triamcinolone preparations are frequently used and authorized by the US FDA and in Europe as crystalline suspensions. However, important limitations of intra-articular corticosteroids include their short duration of action and safety issues that restrict their frequent usage. Knee intra-articular steroid infusions are helpful for short-to medium-term the board of joint infection. By lessening aggrecans and collagenases, specialists/modulators of proinflammatory middle people and mononuclear cells, corticosteroids decrease synovial irritation (Stone et al., 2021).

Table 2: Indications, Contraindications and Adverse Reactions of the Intra-Articular Injection of Corticosteroid, and the Methods to Reduce the Incidence of Adverse Reactions

Indications	Contraindications	Adverse Reactions	References
Osteoarthritis.	Intra-articular or osteochondral fracture at the injection site	Injection site pain and local swelling	{Zhang, 2020 #68}
Rheumatoid arthritis	Uncontrolled coagulopathy	Atrophic changes of skin	{Compagnoni, 2024 #69}
Traumatic arthritis	Severe joint destruction (e.g., Charcot joint) and skin breakdown	Septic arthritis	{Testa, 2021 #70}
Shoulder perarthritis	Local infection: septic arthritis, periarticular sepsis and bacteremia	Chondrotoxicity	{Zhang, 2020 #71}
Crystalline arthropathies reactions	Hypersensitivity to the injection	Anaphylactic reactions	{Mandell, #73}
Seronegative arthropathies	Osteomyelitis	Soft tissue calcinosis	{Al Khayyat, 2023 #74}
Mixed connective tissue disease	Joint prosthesis	Crystal-induced erythema	{Zhang, 2020 #75}

{Testa, 2021 #76}



Injection Sites and routes which are commonly used in clinical practice. Panel A shows the super medial and superolateral injection sites. These injections are performed with the knee extended. Panel B shows the lateral joint line injection site, with the right knee flexed 90 degrees. {Testa, 2021 #76}.

Anti-inflammatory Effects

Recent investigations have suggested that corticosteroids may produce a substantially more dramatic loss in cartilage volume than intra-articular saline. A systematic study of the effects of corticosteroids on articular cartilage demonstrated that at high dosages and during extended therapy, intra-articular corticosteroids were related with chondrotoxicity. As a consequence, many doctors restrict the use of corticosteroids to 3-4 intra-articular injections per year in any particular joint. It has been proposed that corticosteroids may be more beneficial in particular patient subpopulations, such as those with joint effusion or patients who are resting rather than ambulatory. However, there is no clinical agreement on these results or the safety of corticosteroids for these instances. Further meta-analyses have demonstrated short-term relief in osteoarthritis symptoms using intra-articular corticosteroids. However, little data is available for long-term benefits

(greater than 4 weeks after injection). Additionally, concerns have been expressed that continuous exposure to intra-articular corticosteroids may have a deleterious impact on articular cartilage and hasten the onset of osteoarthritis. In a recent research, corticosteroids induced a substantially more dramatic loss in cartilage volume than intra-articular saline (Jones et al., 2019).

Analgesic Properties

Intra-articular corticosteroid injections are regularly used in the treatment of tireless osteoarthritis of the knee and stay standard practice among a huge number. These injections are primarily aimed to relieve pain and inflammation in arthritic knee joints. However, there is substantial variety among health care personnel about the procedures utilized to execute the treatment, including the injection location, medications administered, and degree of sterility.

Steroid injections have been demonstrated to be useful in lowering arthritic knee pain for a short span of time. They give relief from discomfort and help decline irritation, accordingly working on joint capability. Different particles used to treat the signs and side effects of osteoarthritis incorporate hyaluronic corrosive (HA) and platelet-rich plasma (PRP). Corticosteroids act by decreasing aggrecans and collagenases, which are specialists/modulators of proinflammatory arbiters and mononuclear cells. This prompts a decrease in synovial irritation. The instrument of activity is perplexing and includes diminished synovial blood stream, exhaustion of leukocytes, and concealment of provocative middle people (Allen et al., 2022)

Impact on Joint Structure and Function

In osteoarthritis, inflammation inside the knee joint is associated with increasing cartilage deterioration.Intra-articular injections may help delay the duration of the infection. There are different corticosteroid infusions commonly available, including triamcinolone acetonide (Canalog), dexamethasone (Decadron) LA, betamethasone (Celestone), and methylprednisolone acetic acid derivation (Depomedrol). The most generally used injection are methylprednisolone acetic acid derivation (Depomedrol) and triamcinolone acetonide (Cenalog). Minor side effects of intra-articular injection include local discomfort and edema at the injection site. However, other findings reveal the existence of minor atrophic lesions, subcutaneous tissue atrophy, and peri-articular or intra-articular calcification during follow-up of >18 months following intra-articular steroid injection. About forty percent of patients reports flushing following intra-articular steroid injection, whereas fifteen percent experience severe flushing. It normally appears approximately 19 hours after injection, lasts up to 36 hours, and is more prevalent in women and more severe in those who have taken a greater dosage. If intra-articular injections are administered too often, problems such as temporary hyperglycemia and cushionoid appearance may arise. Furthermore, up to 25% of patients might experience a fleeting effect on the hypothalamic-pituitary-adrenal (HPA) hub following intra-articular corticosteroid infusion, driving in a decrease in blood cortisol levels, which is by and large yet recuperates to standard inside 1-4 month (Clynes et al., 2019).

Safety and Adverse Effects

Intra-articular corticosteroid injections are regularly used in the treatment of essential and optional osteoarthritis in patients who having chronic pain that isn't successfully eased by regular analgesics. This therapy method is validated by several studies indicating that single steroid injections considerably decrease pain and enhance function, particularly in the short term. These injections are commonly used in more severe forms of osteoarthritis, including "end-stage" osteoarthritis, particularly in joints that exhibit clinical symptoms of inflammation such as effusion, before surgical intervention is contemplated. If the injection effectively cures the pain but the symptoms increase over time, the injection may be repeated, although generally no more than four times a year for a specific joint. An inflammatory component is considered to be involved in the development of osteoarthritis. Therefore, one of the aims of intra-articular injection is to minimize inflammation and prevent articular injury (Allen et al., 2022).

Impact on Cartilage Integrity

It was previously assumed that intra-articular injections would have a good impact on cartilage health and integrity. In any case, new and creating research shows that continuous injections might reduce cartilage volume. In clinical practice, irregular intra-articular infusions are usually used to ease patients' side effects. To address the viability and wellbeing of various intra-articular infusions for osteoarthritis conditions an orderly survey was finished to dissect the writing. Two main clinically relevant issues were addressed: Are numerous intra-articular injections beneficial for osteoarthritis pain and are they safe? Accelerated advancement, rapid progressive osteoarthritis (RPOA), commonly known as acute osteoarthritis, has been researched by several authors. Type 1 RPOA is described by speedy loss of joint space on radiographs, at a surprisingly extraordinary rate. This strategy was described in clinical trials in which nerve growth factor inhibitors, potent analgesics, are regularly provided by subcutaneous injection. Early examinations uncovered that a minority of patients created sped up OA, requiring joint substitution sooner than anticipated. The particular meaning of RPOA type 1 is dubious, albeit a few distributions say that joint space misfortune more prominent than 2 mm north of a year time span is demonstrative of quick joint space restricting. Joint space loss on radiographs often reflects cartilage loss or meniscal tears and effusions, as revealed on MRI scans. Notwithstanding, unobtrusive changes in quiet situation during radiography could prompt changes in joint space estimations without genuine primary changes, requesting thorough examination for span changes.

Discoveries associated with RPOA type 1, distinguished radiographically, may incorporate joint combination, synovitis, encompassing delicate tissue adjustments, and subosseous changes, for example, significant bone marrow edema and sore like changes on following X-ray checks (Bricca et al., 2019).

Factors Influencing Effectiveness

Patient Selection

Today, doctors and health care professionals generally reassure patients that even if an intra-articular injection does not give symptomatic relief, there is no risk. However, based on clinical findings, this may not be true for other people. Short-term consequences may include joint discomfort, edema, and stiffness along the needle route, as well as injury to intra-articular and peri-articular structures. There are other possible long-term consequences of which patients should be warned, which might be straightforwardly associated with the genuine intra-articular infusion. These results incorporate rapidly moderate osteoarthritis type 1 and quickly moderate osteoarthritis type 2, which may lead to fast joint destruction with subchondral insufficiency fractures, articular collapse, osteonecrosis, and bone loss is single institution findings implying that such occurrences may occur in up to 10% of patients having hip and knee injections. It is not always obvious whether these outcomes were noticeable before or after the injection. Therefore, in addition to describing these possible dangers throughout the informed consent process, it is crucial to tell patients that if they suffer increasing joint pain following intra-articular injection, they should seek emergency medical assistance should get attention and perhaps undergo follow-up imaging. Osteoarthritis is a prominent source of impairment, with the knee being the most usually afflicted joint. Key treatment techniques for osteoarthritis of the knee often involve illness information, exercise therapy, weight reduction, and pain medicines. Among these medications, intra-articular glucocorticoid infusions are normally used and have been demonstrated in clinical examinations to effectively assuage moderate to serious knee torment temporarily. A few expert proposals support the utilization of intra-articular glucocorticoid infusions for people with osteoarthritis of the knee who have not answered oral or skin torment treatment. Be that as it may, there is rising worry among specialists in regards to the security of infusing glucocorticoids into the knee. A 2-year randomized clinical trial showed that intra-articular glucocorticoid infusion brought about extensively higher ligament debasement. Also, while phenomenal, intra-articular infusions are connected with an expanded gamble of septic joint pain and postoperative joint disease. Hence, a time frame least 3 months is proposed among infusions and extra medical procedures. Another hurdle to the deployment of intra-articular injections is that general practitioners (GPs) in primary care may not feel able to conduct the process of placing the needle into the knee joint (Wang et al., 2022)

Controversies and Limitations

Repeated intra-articular injections may enhance possible harmful effects, according to some studies. However, cohort data fail to clarify confounding factors, including the likelihood to obtain more injections for those with severe or resistant symptoms, perhaps contributing to rapid progression to joint replacement. Further work is expected to assess the underlying trustworthiness and adequacy of rehashed intra-articular infusions gave in clinical work on as per individual prerequisites as opposed to at foreordained spans paying little heed to side effect force. Suggestions propose a tailored and varied injection schedule, with a prudent restriction of no more than four injections per year for individuals receiving considerable alleviation after first therapy. Intra-articular medication delivery has various benefits over systemic administration, notably in the therapy of knee osteoarthritis during the last two decades. Traditional therapy strategies have concentrated on analgesics, glucocorticoids, hyaluronic acid, and a number of dubious alternatives. Although hyaluronic acid and glucocorticoids generate substantial benefits for many patients, growing data underscores the relevance of placebo effects in their perceived effectiveness. Biologic medications focusing on the provocative pathway have showed guarantee in the treatment of rheumatoid joint pain yet have not yet demonstrated identical outcomes in that frame of mind of osteoarthritis. The effectiveness of the suggested 'stem' cell treatment is unknown, needing convincing clinical evidence before general acceptance. Despite continuous research in the United States on novel intra-articular medicines, including small compounds, biologics, devices, and gene therapies, the adoption of such therapies must be prudently balanced against the associated costs and possible dangers (Guermazi et al., 2020).

Future Directions and Research Needs

Given the shortfall of compelling and okay pain relieving treatment for osteoarthritis (OA), upgrading the adequacy of intra-articular corticosteroid (IACS) infusions while restricting conceivable harm is significant. There are numerous serious problems about this frequently utilized therapy: What is the genuine effectiveness of IACS injections? What is the best frequency and duration of administration? What patient variables impact treatment efficacy? What are the related dangers of IACS injection, and how probable are they? Who is most prone to bad events? Can pre-injection imaging or radiography assist lessen risk? Are there additional strategies to diminish risk, for example, upgrading joint biomechanics or limiting weight-bearing following treatment? Are there extra potential perils connected with intra-articular infusions? What are the dangers implied with customary strategies of joint relief from discomfort? Future research will need large-scale long-term examinations to resolve these problems. Extensive clinical experience with repeated intra-articular injections in certain joints does not show a preponderance of acute structural adverse effects, nor is quick worsening of symptoms usually noted {Kompel, 2019 #77}.

Conclusion

As osteoarthritis (OA) continues to develop worldwide, the cost on the health care system is rising, compounded by the lack of disease-modifying osteoarthritis medications (DMOADs) that minimize the risk of joint destruction having the power to arrest or reverse cartilage deterioration. Intra-articular therapies provide an innovative therapy strategy, seeking to avoid systemic side effects while benefitting from local treatment advantages. Intra articular injections provide the best local treatment for osteoarthritis which reduces the adverse effects and improve therapeutic effects and functions. Given the unknown etiopathogenesis of OA and the broad variety of symptoms it presents, identification of the appropriate patient group for effective intra-articular treatment with minimum side effects is crucial. Therefore, thorough research, cost-effectiveness analysis, and accurate reporting of side-effect profiles are necessary.

Intra-articular therapies have potential for avoiding undesirable systemic responses as well as having significant local therapeutic benefits, especially with certain regenerative medicine agents. This minimally invasive method provides an effective and promising way of controlling patient pain, warranting further investigation and advancement.

Notwithstanding, careful assessments incorporate randomized controlled trials (RCTs) that use repeated intra-articular corticosteroid (IACS) infusions, utilize fluctuated steroid regimens and target different joint areas, ordinarily with every infusion. Diagnosed with occasional pain just before technique precludes conclusive conclusions concerning the effectiveness of recurrent IACS injections in real-world clinical settings.

REFERENCES

Allen, K., Thoma, L., and Golightly, Y. (2022). Epidemiology of osteoarthritis. *Osteoarthritis and Cartilage, 30*(2), 184-195.

Breedveld, F. (2004). Osteoarthritis—the impact of a serious disease. *Rheumatology, 43*(suppl_1), i4-i8.

Bricca, A., Juhl, C. B., Steultjens, M., Wirth, W., and Roos, E. M. (2019). Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. *British Journal of Sports Medicine, 53*(15), 940-947.

Chacon Arenas, D. F. (2020). *Comparison of the Frequency and Intensity of the Systemic Inflammatory Response in Patients Undergoing Cardiac Muscle Revascularization Surgery With And Without The Use Of Extracorporeal Blood Flow*. University of Split. School of Medicine. Anesthesiology and intensive medicine,

Clynes, M. A., Jameson, K. A., Edwards, M. H., Cooper, C., and Dennison, E. M. (2019). Impact of osteoarthritis on activities of daily living: does joint site matter? *Aging Clinical and Experimental Research, 31*, 1049-1056.

Corti, M. C., and Rigon, C. (2003). Epidemiology of osteoarthritis: prevalence, risk factors and functional impact. *Aging Clinical and Experimental Research, 15*, 359-363.

Cui, A., Li, H., Wang, D., Zhong, J., Chen, Y., and Lu, H. (2020). Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine, 29*.

Felson, D. T., Lawrence, R. C., Dieppe, P. A., Hirsch, R., Helmick, C. G., Jordan, J. M., and Zhang, Y. (2000). Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Annals of Internal Medicine, 133*(8), 635-646.

Guermazi, A., Neogi, T., Katz, J. N., Kwoh, C. K., Conaghan, P. G., Felson, D. T., and Roemer, F. W. (2020). Intra-articular corticosteroid injections for the treatment of hip and knee osteoarthritis-related pain: considerations and controversies with a focus on imaging—Radiology scientific expert panel. *Radiology, 297*(3), 503-512.

Jones, I. A., Togashi, R., Wilson, M. L., Heckmann, N., and Vangsness Jr, C. T. (2019). Intra-articular treatment options for knee osteoarthritis. *Nature Reviews Rheumatology, 15*(2), 77-90.

Kudashev, D., Kotelnikov, G., Lartsev, Y., Zuev-Ratnikov, S., Asatryan, V., and Shcherbatov, N. (2023). Pathogenetic and clinical aspects of osteoarthritis and osteoarthritis-associated defects of the cartilage of the knee joint from the standpoint of understanding the role of the subchondral bone. *NN Priorov Journal of Traumatology and Orthopedics*.

Maqbool, M., Fekadu, G., Jiang, X., Bekele, F., Tolossa, T., Turi, E., and Fanta, K. (2021). An up to date on clinical prospects and management of osteoarthritis. *Annals of Medicine and Surgery, 72*, 103077.

Oo, W. M., Yu, S. P.-C., Daniel, M. S., and Hunter, D. J. (2018). Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. *Expert Opinion on Emerging Drugs, 23*(4), 331-347.

Primorac, D., Molnar, V., Matišić, V., Hudetz, D., Jeleč, Ž., Rod, E., and Dobričić, B. (2021). Comprehensive review of knee osteoarthritis pharmacological treatment and the latest professional societies' guidelines. *Pharmaceuticals, 14*(3), 205.

Stone, S., Malanga, G. A., and Capella, T. (2021). Corticosteroids: review of the history, the effectiveness, and adverse effects in the treatment of joint pain. *Pain Physician, 24*(S1), S233.

Su, K., Bai, Y., Wang, J., Zhang, H., Liu, H., and Ma, S. (2018). Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. *Clinical Rheumatology, 37*, 1341-1350.

Swain, S., Sarmanova, A., Mallen, C., Kuo, C. F., Coupland, C., Doherty, M., and Zhang, W. (2020). Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). *Osteoarthritis and Cartilage, 28*(6), 792-801.

Wang, Q., Mol, M. F., Bos, P. K., Dorleijn, D. M., Vis, M., Gussekloo, J., and Bierma-Zeinstra, S. M. (2022). Effect of intramuscular vs intra-articular glucocorticoid injection on pain among adults with knee osteoarthritis: The KIS randomized clinical trial. *JAMA Network Open, 5*(4), e224852-e224852.

Williams, D. M. (2018). Clinical pharmacology of corticosteroids. *Respiratory Care, 63*(6), 655-670.

Wittenauer, R., Smith, L., and Aden, K. (2013). Background paper 6.12 osteoarthritis. *World Health Organisation*.

Chapter 31

Hydrogel Based Nanoparticles for Enhanced Wound Healing

Awn Abbas[1], Sadia[2], Sameera Naseer[1], Dongbo Li[1], Chao Li[1], Nanxin Li[1], Yifan Zhang[1], Lian Chen[1], Shaungcai Qi[1] and Hualin Fu*

[1]College of Veterinary Medicine, Sichuan Agricultural University, Chengdu, China
[2]College of Animal Science and Technology, Sichuan Agricultural University, Chengdu, China
*Corresponding author: fuhl.sicau@163.com

ABSTRACT

Advanced wound healing techniques have shown considerable potential for hydrogel-based nanoparticles. Hydrogels, due to their substantial water content and ability to interact well with living organisms, are highly suitable for administering medicinal substances. Drug loading, mechanical strength, and stability are improved by nanoparticles in hydrogel matrices. These nanoparticles can be engineered to systematically release bioactive compounds, such as growth factors, antibacterial agents, and anti-inflammatory medications, in a regulated manner. This controlled release method can effectively target different stages of the wound healing process. Moreover, the adjustable properties of hydrogels enable accurate manipulation of the rate at which enclosed medicines are released. The integration of hydrogel matrices and nanoparticles fosters a milieu that enhances cellular proliferation, migration, and tissue regeneration. Incorporating stimuli-responsive features allows for the controlled release of drugs in response to certain physiological signals, enhancing the therapeutic efficacy. In summary, hydrogel-based nanoparticles provide an adaptable platform for creating advanced wound healing treatments that have enhanced effectiveness and accuracy.

KEYWORDS
Hydrogel, Nanoparticles, Wound healing

Received: 17-Jun-2024
Revised: 02-Jul-2024
Accepted: 11-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Abbas A, Sadia, Naseer S, Li D, Li C, Li N, Zhang Y, Chen L, Qi S and Fu H, 2024. Hydrogel based nanoparticles for enhanced wound healing. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 269-275. https://doi.org/10.47278/book.CAM/2024.479

INTRODUCTION

Hydrogel nanoparticles are vital in the fields of biomedical engineering and materials science, specifically in improving the process of wound healing. This novel method utilizes the distinct characteristics of hydrogels, which are composed of polymer networks that are highly hydrated and three-dimensional, and nanoparticles, which are minuscule particles with dimensions on the nanometer scale (Chakraborty et al., 2021). By amalgamating these two components, a potent synergy is produced, promoting effective and enhanced wound healing.

Wound healing is a key physiological process after tissue injury. This process involves a sequence of intricate biochemical events, such as hemostasis, inflammation, proliferation, and remodeling (Rodrigues et al., 2019). Historically, wound care techniques mostly involved simple bandages, stitches, and antibacterial substances. Nevertheless, these methods frequently demonstrate insufficiency in effectively handling intricate wounds such as diabetic ulcers, burns, and vast surgical sites. Fortunately, the advancement of hydrogel-based nanoparticles has arisen as an innovative answer. These nanoparticles are designed to overcome the limitations of traditional therapies by improving effectiveness, shortening recovery periods, and limiting the formation of scars.

Hydrogels are very suitable for wound healing applications due to their abundant water content, which closely mimics normal tissue (Ho et al., 2022). They provide a humid environment that promotes the movement and growth of cells, which is essential for the process of healing. Moreover, hydrogels can be precisely customized to fit the tissue at the wound site by adjusting their physical characteristics such as porosity and mechanical strength (Vedadghavami et al., 2017). This customization not only enhances the structural integrity of the wound but also allows for the regulated release of medicinal drugs. Integrating nanoparticles into hydrogels results in a distinct enhancement of functionality (Jiang et al., 2020). To improve the administration and effectiveness of medications, growth factors, and other bioactive compounds directly at the site of a wound, these particles can tightly interact with biological molecules due to their minute size (Rajendran et al., 2018). This allows the particles to improve the transport of these substances. This feature enables the use of precise therapy, where therapeutic substances are supplied in a regulated manner, minimizing general side effects and focusing treatment on the specific areas that require it the most. The utilization of nanocomposite hydrogels demonstrates the capacity to combine hydrogels with nanoparticles. These polymers serve as both carriers of drugs and reinforce the

hydrogel matrix (Lavrador et al., 2021). By integrating silver nanoparticles, the hydrogel can obtain antibacterial characteristics, which are crucial for preventing infections in exposed wounds (Pangli et al., 2021). Moreover, bioactive nanoparticles can be utilized for the purpose of administering targeted growth factors, hence facilitating tissue regeneration and assisting in the process of healing. The synthesis of hydrogel-based nanoparticles is an intricate procedure that guarantees the durability, compatibility with organisms, and effectiveness of the result. Hydrogels are typically formed via different methods, including ionic cross-linking, covalent bonding, and freeze-thaw cycles (Hassan and Peppas, 2000). Nanoparticles can be included by either in situ polymerization or physical mixing (Li et al., 2017). It is imperative to carefully regulate these processes to create a composite that is not only safe for medical use but also efficient in delivering therapeutic outcomes. When it comes to the field of clinical applications, nanoparticles based on hydrogel have demonstrated promising results in the treatment of a variety of wounds. Regarding diabetic ulcers, which have poor healing, these composites can efficiently administer insulin or growth hormones to reinstate the normal healing process (Duarte et al., 2024). In burn instances, hydrogel-nanoparticle systems are utilized to provide cooling agents, pain-relieving drugs, and facilitate tissue regeneration (Mishra et al., 2017).

In addition to treating wounds, nanoparticles based on hydrogel have the potential to perform additional functions. These devices can be specifically engineered to incorporate sensors that observe various characteristics of the wound environment, such as the pH level and temperature (Dong and Guo, 2021). These sensors offer crucial data regarding the advancement of the healing process or the existence of an infection. The incorporation of diagnostic capabilities into a treatment matrix signifies a notable progress in personalized medicine for wound care. Nevertheless, despite the multitude of benefits and encouraging studies, there are obstacles and factors that must be dealt with as these materials go from the experimental stage to practical application in medical settings. Important considerations include the biocompatibility and biodegradability of materials used in the body, as they should not elicit negative immunological reactions or leave behind toxic substances after fulfilling their intended function. Furthermore, it is crucial to consider the potential to expand production and achieve cost efficiency to guarantee universal acceptance in clinical settings.

Section 1: Fundamentals of Wound Healing

Phases of Wound Healing

Wound healing is a complex and ever-changing process that takes place in multiple stages, including hemostasis, inflammation, proliferation, and remodeling (Rodrigues et al., 2019). Every stage is essential in the process of healing injured tissue and regaining its functionality. The procedure commences with hemostasis, which promptly takes place following the occurrence of skin injury. During this stage, the body's main objective is to stop the flow of blood. Blood arteries undergo vasoconstriction to decrease the volume of blood flowing through them, while platelets aggregate at the site of injury to form a clot (Hickman et al., 2018). This blood clot not only ceases additional blood loss but also serves as a temporary barrier against infection.

The inflammatory phase, which usually lasts for a few days, follows hemostasis. Pain, redness, and swelling at the location of the wound are the characteristics that define this phase. Neutrophils and macrophages, which are types of white blood cells, travel to the wound site to eliminate waste, bacteria, and injured tissue. These immune cells secrete many cytokines and growth factors that are crucial for the process of healing, thereby preparing for the subsequent phase (Matar et al., 2023).

The proliferation phase is the period during which the wound initiates the process of regenerating new tissue, typically commencing within a few days of the damage and enduring for several weeks. During this phase, important processes include angiogenesis, which is the development of new blood vessels, the generation of collagen and extracellular matrix by fibroblasts, and the growth of new epithelial tissue to cover the wound (Reinke and Sorg, 2012). The appearance of pink or red granulation tissue suggests a healthy healing process.

Ultimately, the remodeling phase can endure for a significant duration, ranging from several months to even years. During this phase, the recently developed tissue undergoes a gradual process of maturation and recovers its strength. Collagen fibers, which were originally deposited in a disorganized manner, undergo reorganization and cross-linking to enhance the skin's ability to withstand tension (Beldon, 2010). Consequently, the scar eventually becomes more even and less conspicuous, but it usually maintains a distinct texture and quality compared to the surrounding skin. These stages of wound healing collectively allow the efficient recovery of the skin from injury. Nevertheless, the efficacy and success of the treatment may differ based on factors such as the severity of the damage, the individual's overall health, and the quality of wound care provided.

Challenges in Wound Healing

Wound healing can be complicated by several circumstances, one of which is that of infection. Infections have the potential to extend the duration of the inflammatory phase and give rise to consequences, such as sepsis (Delano and Ward, 2016). Chronic diseases such as diabetes and vascular disorders can hinder the flow of blood, which is crucial for supplying the necessary oxygen and nutrients for tissue regeneration (Baltzis et al., 2014). Furthermore, inadequate nourishment can lead to insufficiencies in essential vitamins and proteins necessary for cellular regeneration, hence exacerbating the challenges of healing. Addressing wounds in elderly people is a notable difficulty due to their skin's diminished flexibility and cellular activity, which hampers the rate of healing. Inadequate wound care, including insufficient

cleansing and dressing, might introduce or exacerbate issues. This underscores the significance of adequate medical supervision and patient instruction in the management of wounds.

Section 2: Overview of Hydrogels and Nanoparticles

Overview of Hydrogels

The ability of hydrogels, a versatile form of polymeric material, to retain considerable volumes of water within their three-dimensional networks is one of the most recognized characteristics of hydrogels. Consisting primarily of hydrophilic polymer chains, these gels can soak up water and retain a significant amount of fluid relative to their weight when dry, which makes them extremely absorbent (Guo et al., 2020). Hydrogels are created by either physically or chemically connecting molecules together, resulting in a structure that is stable and yet retains a soft and flexible nature, resembling natural tissue (Khandan et al., 2017). The distinctive amalgamation of these characteristics has resulted in a diverse array of uses in various domains, including biomedical engineering, drug delivery systems, tissue engineering, and agricultural goods. Moreover, their ability to interact harmoniously with living organisms and their ability to react to changes in their surroundings make them well-suited for developing highly sensitive and adaptable materials for a wide range of scientific and industrial applications.

Overview of Nanoparticles

The size of a nanoparticle is measured in nanometers, or billionths of a meter. Nanoparticles, which are usually between 1 and 100 nanometers in size, have distinct physical and chemical characteristics that significantly deviate from those of bigger materials (Tsuzuki, 2013). An example of a characteristic possessed by these entities is their heightened surface area to volume ratio, which amplifies their reactivity and strength. These characteristics make nanoparticles beneficial in health, electronics, and the environment (Singh et al., 2021). Nanoparticles are utilized in medicine for the purpose of delivering drugs to specific targets and for diagnostic imaging (Parveen et al., 2017). When it comes to environmental applications, nanoparticles help in the control of pollution and the purification of water (Pinto et al., 2020). In the field of electronics, they contribute to the creation of more efficient6 batteries and enhanced display technologies (Abdin et al., 2013). Scientific research is currently focused on manipulating and integrating nanoparticles into goods and processes. The aim is to utilize their potential while also addressing safety and environmental concerns.

Hydrogel nanoparticles, which are gaining popularity in biomedical fields like drug delivery, tissue engineering, and bio-sensing, exhibit distinct characteristics. Among these characteristics are a high-water content, biocompatibility, and environmental stimuli response capability. These nanoparticles can be synthesized using a range of materials, each possessing distinct benefits and difficulties. The main materials utilized comprise both organic and artificial polymers.

Section 3: Hydrogel based Nanoparticles in Wound Healing

Table 1: Composition and types of hydrogels forming polymers

Polymers	Types	Source	Properties	Applications	References
Natural Polymers	Alginate,	Extracted from brown seaweed	Highly biocompatible, gel-forming ability through ionic cross-linking with calcium ions.	Ideal for encapsulating proteins, cells, and drugs due to its mild gelation conditions.	(Tavakoli et al., 2023)
Natural Polymers	Chitosan	Derived from Chitin	Positively charged, biodegradable, and has antimicrobial properties	Its cationic nature allows it to form hydrogels through interactions with negatively charged molecules and polymers, useful in mucosal drug delivery.	(Tavakoli et al., 2023)
Synthetic Polymers	Polyethylene Glycol (PEG)		Non-toxic, non-immunogenic, and hydrophilic, which helps in evading the immune system	Often used as a hydrogel matrix or coating to enhance biocompatibility and reduce protein adsorption and cell adhesion.	(Xu et al., 2023)
Synthetic Polymers	Polylactic-co-glycolic Acid (PLGA):		It is biodegradable and the degradation rate can be adjusted by varying the ratio of PLA to PGA	Widely used in drug delivery systems due to its FDA-approved status and ability to degrade into lactic and glycolic acids, which are naturally metabolized by the body	(Xu et al., 2023)

a) Natural polymer, in general being more biocompatible than synthetic ones, can still change in composition and goods due to their natural origins (Bhatia and Bhatia, 2016).

b) Manipulation of Properties: Synthetic polymers provide greater precision in controlling the characteristics of nanoparticles, such as their degradation rates and mechanical strength. This control is essential for particular applications (Bhatia and Bhatia, 2016).

c) Immunogenicity and Toxicity: Synthetic polymers, particularly those that are not precisely engineered, may elicit an immunological reaction or exhibit hazardous effects. Conversely, natural polymers often have a reduced likelihood of causing an immune response (Bhatia and Bhatia, 2016).
d) Functionalization: Both types of polymers can be chemically modified to incorporate functional groups that can be used for targeting, imaging, or therapeutic applications.
The application and the features that are wanted are two of the most important factors to consider when choosing materials for nanoparticles based on hydrogel. Natural polymers are well-suited for applications that require sensitivity to biological systems, whereas synthetic polymers offer variety and durability for applications centered on engineering (Bhatia and Bhatia, 2016).

Mechanism of Action

Hydrogel nanoparticles have demonstrated significant potential around wound healing because of their distinct characteristics and mode of operation. The nanoparticles are predominantly composed of hydrophilic polymers that could absorb and hold substantial quantities of water, thereby generating an optimal moist environment for the healing of wounds (Stoica et al., 2020). The presence of moisture in this environment not only aids in maintaining cleanliness of the wound, but also facilitates the natural healing processes, such as the movement and growth of cells. The method by which hydrogel-based nanoparticles promote wound healing is complex and includes multiple factors. Firstly, they create a defensive barrier that covers the wound, protecting it from outside pollutants while yet allowing for the flow of gases, which is essential for cellular respiration and metabolism. Furthermore, these nanoparticles can be designed specifically to gradually release therapeutic medicines at the location of the wound (Choudhury et al., 2020). The controlled release mechanism can incorporate antibiotics to prevent infection, growth factors to facilitate tissue regeneration, or anti-inflammatory agents to diminish swelling and pain. Additionally, hydrogel-based nanoparticles possess the ability to react to environmental stimuli, such as variations in pH or temperature, thereby augmenting their efficacy (Lavrador et al., 2021). Inflamed wounds with decreased pH can cause nanoparticles to release more medication. This approach customizes the treatment to address the precise requirements of the wound, eliminating the need for any external interference. Finally, the physical characteristics of hydrogels enable them to conform to the wound surface, guaranteeing a uniform dispersion of the therapeutic substances. This adaptability also helps in absorbing wound exudate, which has a high concentration of proteolytic enzymes that might hinder the healing process. Hydrogel-based nanoparticles expedite and enhance the healing process by absorbing surplus fluids and inhibiting enzyme activity. Hydrogel-based nanoparticles greatly improve the healing process, making them a vital tool in advanced wound care management.

Section 4: Applications of Hydrogels Nanoparticles

Drug Delivery

Hydrogel nanoparticles offer an advanced method to wound management by enhancing the healing process by precise administration of medication. The nanoparticles are composed of polymeric networks that swell in water and enclose different medicinal substances, such as antibiotics, anti-inflammatory medicines, and analgesics. The hydrogel's structure is beneficial for wound healing because of its high concentration of water. It creates a damp environment which encourages tissue regeneration and minimizes scar formation. When administered to a wound, these nanoparticles slowly release their payload in reaction to stimuli at the wound site, such as changes in pH, fluctuations in temperature, or enzymes generated by bacteria during infections. The focused administration of this release optimizes the therapeutic impact of the medications while reducing overall contact and any adverse reactions (Divyashri et al., 2022). Hydrogel-based delivery of antibiotics efficiently targets and eliminates infection-causing bacteria at the location of the wound, hence facilitating the healing process. The local swelling and irritation that are caused by anti-inflammatory medications are reduced, which allows for stronger tissue repair. In addition, analgesic drugs can be targeted to the specific wounded location, offering both instant and long-lasting pain relief as the wound undergoes healing. This approach not only boosts the effectiveness of drug administration but also improves patient comfort and treatment results.

Growth Factor Delivery

Growth factors are vital for tissue regeneration. They facilitate the growth, specialization, and movement of cells, all of which are crucial for the restoration of injured tissues. These proteins function as signaling molecules that selectively attach to certain receptors on the surfaces of cells. This interaction triggers a series of biological reactions, ultimately resulting in the restoration and renewal of the tissue. The utilization of nanoparticles for the delivery of growth factors represents a notable breakthrough in the field of wound healing treatments. These nanoparticles can be manipulated to systematically release growth factors in a regulated manner. This guarantees the sustained presence of growth factors at the wound site for a longer duration. This targeted delivery system not only optimizes the utilization of growth factors but also mitigates their systemic exposure, thereby minimizing potential adverse effects (Gainza et al., 2015). Furthermore, nanoparticles can be engineered to safeguard growth ingredients against deterioration prior to reaching their intended destination. This enhances the overall therapeutic results. The use of nanoparticles facilitates the expedited distribution of growth factors, hence enhancing the process of wound healing. Consequently, it exhibits significant potential in the realm of regenerative medicine and tissue engineering.

Gene Therapy

Hydrogel-based nanoparticles show great potential in the field of gene therapy, specifically in improving wound healing processes by accurately managing gene expression. These nanoparticles are ideal for this purpose since they are biocompatible, have a high-water content, and can imitate the natural extracellular matrix. These conditions create an optimal environment for cellular contact and tissue integration. Hydrogel-based nanoparticles are designed to encapsulate different gene vectors, such as DNA, siRNA, or mRNA (Mo et al., 2021). Targeting genes that promote tissue regeneration, angiogenesis, and inflammation with these vectors is possible.

Section 5: Current Research and Case Studies

Recent Innovations

Hydrogel nanoparticles have made notable progress in wound healing because of their distinctive characteristics, which facilitate effective administration of drugs and regeneration of tissue. Recent investigations illustrate these materials' adaptability and efficacy. Aldakheel et al. (2023) formulated a hydrogel containing silver nanoparticles, which exhibited antibacterial characteristics and enhanced rates of wound closure. The study demonstrated that the hydrogel not only inhibited infection but also facilitated collagen deposition, a crucial process for tissue regeneration. (Liu et al., 2022) proposed a novel methodology employing temperature-responsive hydrogels. These hydrogels are designed to release therapeutic chemicals when exposed to the body's natural heat at the wound site, which helps improve the effectiveness of the healing process. The hydrogels demonstrated the ability to conform to the wound environment, retaining moisture and promoting expedited tissue regeneration. Furthermore, studies on hydrogels with dual functionality have demonstrated encouraging outcomes in diminishing inflammation and improving the healing process in persistent wounds. The hydrogels could provide growth factors and anti-inflammatory medicines at the same time. In summary, these improvements showcase the capacity of hydrogel-based nanoparticles to transform wound treatment. Their therapeutic options are focused, adaptable, and versatile.

Case Studies

Nanoparticles have been extensively studied for their ability to promote wound healing. They exhibit distinctive characteristics that enable the precise release of medications, safeguarding of active components, and focused administration. For example, silver nanoparticles have well-established antimicrobial properties that play a crucial role in preventing infections and facilitating the healing process. A study conducted by Paladini and Pollini in 2019 showed that dressings containing silver nanoparticles effectively decreased the presence of bacteria in chronic wounds. As a result, this resulted in accelerated wound healing and reduced healing durations in comparison to conventional dressings. Chitosan nanoparticles have been researched for their capacity to enhance blood clotting and support crucial cellular processes involved in wound healing. According to Yang et al.'s research from 2020, chitosan nanoparticles loaded with growth factors could boost the proliferation of fibroblasts and facilitate the deposition of collagen. Consequently, this results in accelerated healing of diabetic ulcers. Furthermore, the potential anti-inflammatory capabilities of gold nanoparticles have been investigated in the context of wound healing. (Leu et al., 2012) documented that the combination of gold nanoparticles with peptides promotes the polarization of macrophages towards a regenerative phenotype, which is essential for healing without scarring. This study also emphasized that these nanoparticles effectively decrease inflammation and promote tissue regeneration in acute wounds.

These case studies demonstrate the therapeutic efficacy of nanoparticles in the treatment of different types of wounds. They provide cutting-edge remedies by utilizing their antibacterial, anti-inflammatory, and regenerative characteristics. The safety profiles documented in these trials demonstrate little adverse responses, affirming that they are appropriate for usage in clinical settings. Every category of nanoparticle has demonstrated the ability to accelerate the healing process and enhance the quality of the recovered tissue. These factors indicate a positive outlook for the advancement of wound care management.

Section 6: Challenges and Future Perspectives

Biocompatibility and Toxicity

The introduction of nanoparticles into clinical applications poses substantial obstacles in terms of biocompatibility and potential toxicity, which might severely limit their practical utilization in the field of medicine. Nanoparticles, owing to their little size and substantial surface area in proportion to their volume, have the capacity to engage with biological systems in complicated manners that remain incompletely comprehended. These interactions can lead to unforeseen toxicological consequences, such as oxidative stress, inflammation, and even genotoxicity. Specifically, some metal oxide nanoparticles could generate reactive oxygen species, which can cause damage to biological structures, DNA, and proteins.

Additionally, because of their small size, nanoparticles can cross biological barriers including the placental and blood-brain barriers. The propensity of these substances to traverse barriers raises concerns over their potential systemic dissemination and accumulation in non-target tissues, hence emphasizing concerns about long-term toxicity. Another obstacle arises from the fluctuation in the physical and chemical characteristics of nanoparticles, encompassing dimensions, morphology, electrostatic charge, and surface covering. These characteristics can influence the biocompatibility of nanoparticles. Furthermore, a significant number of nanoparticles tend to clump or interact with serum

proteins, resulting in modifications in their intended function and distribution within the body. Hence, it is imperative to conduct meticulous evaluations of the safety characteristics of nanoparticles via extensive preclinical investigations prior to considering them appropriate for clinical use. The requirement for customized toxicity assessment techniques adds extra complexity to the process of incorporating nanoparticles into clinical practice, highlighting the intricacies required in utilizing their promise in medicine.

Future Prospect

Hydrogel nanoparticles exhibit significant potential in the field of medicine, particularly in targeted drug administration, regenerative medicine, and biosensing. However, in order to maximize their potential, future research should prioritize enhancing the accuracy and regulation of drug release mechanisms. The advancement of stimuli-responsive hydrogels capable of reacting to specific biological signals has the potential to enhance the effectiveness of treatment while minimizing adverse reactions. Furthermore, it is imperative to improve the biocompatibility and biodegradability of hydrogel nanoparticles to guarantee their secure incorporation into the body. Another potential avenue is the incorporation of hydrogel nanoparticles into medical imaging systems, allowing for the live monitoring of drug administration and tissue regeneration procedures. Research should also investigate the scalability of the production process to enable the transfer from laboratory research to clinical and commercial applications. Understanding the interactions between hydrogel nanoparticles and the immune system has the potential to enable the development of nanoparticles that can either avoid being detected by the immune system or regulate immunological responses for therapeutic applications. The exploration of these research lines has the potential to greatly broaden the range of uses for hydrogel-based nanoparticles in the field of medicine, resulting in the development of more advanced therapies for various diseases.

Conclusion

Hydrogel-based nanoparticles hold significant potential in the field of enhanced wound healing technology. These nanocomposites combine hydrogels' biocompatibility, moisture retention, and mechanical support with nanoparticles' targeted drug delivery, antibacterial activity, and increased cellular interactions. Preclinical investigations have shown that advanced formulations have a considerable capacity to stimulate angiogenesis, regulate inflammatory responses, and improve cellular proliferation and migration. It has proven possible to produce significant improvements in wound closure rates, decreased infection risks, and quicker tissue regeneration with the incorporation of bioactive molecules into these matrices. Furthermore, the hydrogel-nanoparticle systems could be customized, enabling the creation of specific therapeutic strategies for various types and levels of wound severity. Future research should prioritize the optimization of these systems for clinical application, assuring scalability, and undertaking comprehensive in vivo investigations to evaluate their usefulness and safety. This novel strategy has the potential to revolutionize wound care and improve patient outcomes, and it has a great deal of promise in this department.

REFERENCES

Abdin, Z., Alim, M. A., Saidur, R., Islam, M. R., Rashmi, W., Mekhilef, S., and Wadi, A. (2013). Solar energy harvesting with the application of nanotechnology. *Renewable and Sustainable Energy Reviews*, *26*, 837-852.

Aldakheel, F. M., Mohsen, D., El Sayed, M. M., Alawam, K. A., Binshaya, A. S., and Alduraywish, S. A. (2023). Silver nanoparticles loaded on chitosan-g-PVA hydrogel for the wound-healing applications. *Molecules*, *28*(7), 3241.

Baltzis, D., Eleftheriadou, I., and Veves, A. (2014). Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Advances in Therapy*, *31*, 817-836.

Beldon, P. (2010). Basic science of wound healing. *Surgery (Oxford)*, *28*(9), 409-412.

Bhatia, S., and Bhatia, S. (2016). Natural polymers vs synthetic polymer. *Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae*, 95-118.

Chakraborty, A., Roy, A., Ravi, S. P., and Paul, A. (2021). Exploiting the role of nanoparticles for use in hydrogel-based bioprinting applications: Concept, design, and recent advances. *Biomaterials Science*, *9*(19), 6337-6354.

Choudhury, H., Pandey, M., Lim, Y. Q., Low, C. Y., Lee, C. T., Marilyn, T. C. L., Loh, H. S., Lim, Y. P., Lee, C. F., and Bhattamishra, S. K. (2020). Silver nanoparticles: Advanced and promising technology in diabetic wound therapy. *Materials Science and Engineering: C*, *112*, 110925.

Delano, M. J., and Ward, P. A. (2016). The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunological Reviews*, *274*(1), 330-353.

Divyashri, G., Badhe, R. V., Sadanandan, B., Vijayalakshmi, V., Kumari, M., Ashrit, P., Bijukumar, D., Mathew, M. T., Shetty, K., and Raghu, A. V. (2022). Applications of hydrogel-based delivery systems in wound care and treatment: an up-to-date review. *Polymers for Advanced Technologies*, *33*(7), 2025-2043.

Dong, R., and Guo, B. (2021). Smart wound dressings for wound healing. *Nano Today*, *41*, 101290.

Duarte, J., Mascarenhas-Melo, F., Pires, P. C., Veiga, F., and Paiva-Santos, A. C. (2024). Multifunctional hydrogels-based therapies for chronic diabetic wound healing. *European Polymer Journal*, 113026.

Gainza, G., Villullas, S., Pedraz, J. L., Hernandez, R. M., and Igartua, M. (2015). Advances in drug delivery systems (DDSs) to

release growth factors for wound healing and skin regeneration. *Nanomedicine: Nanotechnology, Biology and Medicine*, *11*(6), 1551-1573.

Guo, Y., Bae, J., Fang, Z., Li, P., Zhao, F., and Yu, G. (2020). Hydrogels and hydrogel-derived materials for energy and water sustainability. *Chemical Reviews*, *120*(15), 7642-7707.

Hassan, C. M., and Peppas, N. A. (2000). Structure and applications of poly (vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods. *Biopolymers· PVA Hydrogels, Anionic Polymerisation Nanocomposites*, 37-65.

Hickman, D. A., Pawlowski, C. L., Sekhon, U. D., Marks, J., and Gupta, A. S. (2018). Biomaterials and advanced technologies for hemostatic management of bleeding. *Advanced Materials*, *30*(4), 1700859.

Ho, T.-C., Chang, C.-C., Chan, H.-P., Chung, T.-W., Shu, C.-W., Chuang, K.-P., Duh, T.-H., Yang, M.-H., and Tyan, Y.-C. (2022). Hydrogels: Properties and applications in biomedicine. *Molecules*, *27*(9), 2902.

Jiang, Y., Krishnan, N., Heo, J., Fang, R. H., and Zhang, L. (2020). Nanoparticle–hydrogel superstructures for biomedical applications. *Journal of Controlled Release*, *324*, 505-521.

Khandan, A., Jazayeri, H., Fahmy, M. D., and Razavi, M. (2017). Hydrogels: Types, structure, properties, and applications. *Biomat Tiss Eng*, *4*(27), 143-169.

Lavrador, P., Esteves, M. R., Gaspar, V. M., and Mano, J. F. (2021). Stimuli-responsive nanocomposite hydrogels for biomedical applications. *Advanced Functional Materials*, *31*(8), 2005941.

Leu, J.-G., Chen, S.-A., Chen, H.-M., Wu, W.-M., Hung, C.-F., Yao, Y.-D., Tu, C.-S., and Liang, Y.-J. (2012). The effects of gold nanoparticles in wound healing with antioxidant epigallocatechin gallate and α-lipoic acid. *Nanomedicine: Nanotechnology, Biology and Medicine*, *8*(5), 767-775.

Li, X., Sotto, A., Li, J., and Van der Bruggen, B. (2017). Progress and perspectives for synthesis of sustainable antifouling composite membranes containing in situ generated nanoparticles. *Journal of Membrane Science*, *524*, 502-528.

Liu, H., Du, C., Liao, L., Zhang, H., Zhou, H., Zhou, W., Ren, T., Sun, Z., Lu, Y., and Nie, Z. (2022). Approaching intrinsic dynamics of MXenes hybrid hydrogel for 3D printed multimodal intelligent devices with ultrahigh superelasticity and temperature sensitivity. *Nature Communications*, *13*(1), 3420.

Matar, D. Y., Ng, B., Darwish, O., Wu, M., Orgill, D. P., and Panayi, A. C. (2023). Skin inflammation with a focus on wound healing. *Advances in Wound Care*, *12*(5), 269-287.

Mishra, B., Upadhyay, M., Reddy Adena, S., Vasant, B., and Muthu, M. (2017). Hydrogels: an introduction to a controlled drug delivery device, synthesis and application in drug delivery and tissue engineering. *Austin Journal Biomedicine Eng*, *4*(1), 1037-1049.

Mo, F., Jiang, K., Zhao, D., Wang, Y., Song, J., and Tan, W. (2021). DNA hydrogel-based gene editing and drug delivery systems. *Advanced Drug Delivery Reviews*, *168*, 79-98.

Paladini, F., and Pollini, M. (2019). Antimicrobial silver nanoparticles for wound healing application: progress and future trends. *Materials*, *12*(16), 2540.

Pangli, H., Vatanpour, S., Hortamani, S., Jalili, R., and Ghahary, A. (2021). Incorporation of silver nanoparticles in hydrogel matrices for controlling wound infection. *Journal of Burn Care and Research*, *42*(4), 785-793.

Parveen, S., Misra, R., and Sahoo, S. K. (2017). Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomedicine in Cancer*, 47-98.

Pinto, M., Ramalho, P., Moreira, N., Gonçalves, A., Nunes, O., Pereira, M., and Soares, O. (2020). Application of magnetic nanoparticles for water purification. *Environmental Advances*, *2*, 100010.

Rajendran, N. K., Kumar, S. S. D., Houreld, N. N., and Abrahamse, H. (2018). A review on nanoparticle based treatment for wound healing. *Journal of Drug Delivery Science and Technology*, *44*, 421-430.

Reinke, J., and Sorg, H. (2012). Wound repair and regeneration. *European Surgical Research*, *49*(1), 35-43.

Rodrigues, M., Kosaric, N., Bonham, C. A., and Gurtner, G. C. (2019). Wound healing: a cellular perspective. *Physiological Reviews*, *99*(1), 665-706.

Singh, V., Yadav, S. S., Chauhan, V., Shukla, S., and Vishnolia, K. K. (2021). Applications of nanoparticles in various fields. *Diagnostic Applications of Health Intelligence and Surveillance Systems*, 221-236.

Stoica, A. E., Chircov, C., and Grumezescu, A. M. (2020). Nanomaterials for wound dressings: an up-to-date overview. *Molecules*, *25*(11), 2699.

Tavakoli, M., Labbaf, S., Mirhaj, M., Salehi, S., Seifalian, A. M., and Firuzeh, M. (2023). Natural polymers in wound healing: From academic studies to commercial products. *Journal of Applied Polymer Science*, *140*(22), e53910.

Tsuzuki, T. (2013). Properties of Nanoparticulate Materials. *Nanotechnology Commercialization*, 1.

Vedadghavami, A., Minooei, F., Mohammadi, M. H., Khetani, S., Kolahchi, A. R., Mashayekhan, S., and Sanati-Nezhad, A. (2017). Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications. *Acta Biomaterialia*, *62*, 42-63.

Xu, R., Fang, Y., Zhang, Z., Cao, Y., Yan, Y., Gan, L., Xu, J., and Zhou, G. (2023). Recent advances in biodegradable and biocompatible synthetic polymers used in skin wound healing. *Materials*, *16*(15), 5459.

Yang, S., Li, X., Liu, P., Zhang, M., Wang, C., and Zhang, B. (2020). Multifunctional chitosan/polycaprolactone nanofiber scaffolds with varied dual-drug release for wound-healing applications. *ACS Biomaterials Science and Engineering*, *6*(8), 4666-4676

Chapter 32

Nanoparticles: An Alternative Strategy against Antibiotic-Resistant Mastitogens

Asma Ayoob[1], Ammara Khaliq[1], Sundas Mehboob[1], Ahmad Murtaza[2], Muhammad Aafaq Khan[3], Muhammad Ibraheem Ijaz[3] and Muhammad Arif Zafar[1*]

[1]Department of Clinical Studies
[3]Department of Livestock Production and Management, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
[2]Department of Animal Nutrition, Faculty of Veterinary Sciences, Riphah College of Veterinary Sciences, 54000, Lahore-Pakistan
*Corresponding author: dr.mazafar@uaar.edu.pk

ABSTRACT

The emergence of antibiotic-resistant mastitogens exacerbates the serious problems being faced by dairy industry from mastitis, an inflammatory illness of the mammary glands. This chapter offers an in-depth analysis of mastitis, covering its etiology, pathophysiology, prevalence, and the difficulties involved in using traditional therapeutic approaches. Alternative therapeutic techniques are essential considering the ever-present problem of antibiotic resistance because traditional treatments are becoming less and less effective against these pathogens. In the fight against antibiotic resistance in mastitis, nanoparticles have shown promising results. The potential of nanoparticles to defeat antibiotic-resistant mastitogens is thoroughly reviewed in this chapter. The chapter delves into the intriguing possibilities of using nanoparticles to treat mastitis, explaining how their antibacterial, drug-delivery, and immunomodulatory properties work. It highlights the value of interdisciplinary cooperation and technological innovation in efficiently treating mastitis through a synthesis of recent research findings and prospective viewpoints. Nanoparticles offer a step-up in mastitis therapy, overcoming the shortcomings of traditional antibiotics by destroying biofilms and improving medication efficacy. This chapter offers insightful data on the changing mastitis control scenario and emphasizes the need for preventative actions to protect animal welfare and the sustainability of the dairy business from antibiotic-resistant mastitogens.

KEYWORDS
Mastitis, Antibiotic-resistant mastitogens, Prevalence, Alternative therapeutics, Nanoparticles

Received: 30-Jun-2024
Revised: 21-Jul-2024
Accepted: 31-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Ayoob A, Khaliq A, Mehboob S, Murtaza A, Khan MA, Ijaz MI and Zafar MA, 2024. Nanoparticles: an alternative strategy against antibiotic-resistant mastitogens. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 276-283. https://doi.org/10.47278/book.CAM/2024.377

INTRODUCTION

Mastitis is an inflammatory disorder of the mammary gland that continues to pose a major issue in veterinary and human medicine, resulting in substantial global health and economic burdens (Paramasivam et al., 2023). Even with the significant efforts made to treat mastitis, the effectiveness of traditional antibiotic therapy has been weakened by the appearance and dissemination of antibiotic-resistant mastitogens (Abdi et al., 2021). The emergence of nanotechnology presents a viable approach to overcome antibiotic resistance and augment the effectiveness of mastitis treatment (He et al., 2017).

Mastitogens' increasing incidence of antibiotic resistance presents a serious danger to livestock production systems and public health (Banza, 2020). Various reasons, including genetic mutations, horizontal gene transfer, and indiscriminate antibiotic usage, have contributed to the spread of resistant strains and the inefficacy of conventional antibiotic treatments (Mbindyo et al., 2021). Furthermore, since biofilms give improved resistance to antibiotics and host immunological defense (Guliy et al., 2023), the persistence of biofilm-associated mastitogens further complicates therapeutic methods.

Nanoparticles have become effective tools in the fight against antibiotic-resistant mastitogens due to their distinct physicochemical characteristics and high surface-to-volume ratio (Jampilek and Kralova, 2022). Nanoparticles provide a versatile strategy to treating mastitis by targeting resistant bacterial populations and avoiding conventional resistance mechanisms by taking advantage of their innate antibacterial activity (Jamil, Bokhari, and Imran, 2017). Furthermore, because of the design flexibility of nanoparticles, customized formulations optimized for particular antimicrobial

applications are possible, encompassing anything from wound dressings and diagnostic imaging agents to drug delivery systems (Paladini and Pollini, 2019).

In this chapter a thorough review of the mechanisms of action, kinds, applications, difficulties, and potential uses of nanoparticles in combating antibiotic-resistant mastitogens is given (Paramasivam et al., 2023). By synthesizing recent research findings and upcoming trends, we hope to shed light on the potential of nanoparticles as a game-changing weapon against antibiotic-resistant mastitis and develop long-term plans for preserving both animal and human health (Algharib, Dawood, and Xie, 2020).

Etiology of Mastitis

Bacterial Pathogens

The primary cause of mastitis in dairy cattle is the invasion of mammary gland tissue by bacterial infections. The pathogens in concern can be broadly classified into two groups: infectious and environmental bacteria. The environment surrounding cows is frequently home to environmental infections including *Streptococcus uberis* and *Staphylococcus aureus*, which can enter the udder through damage to the teat or through the teat canal during milking. *Mycoplasma* species and *Staphylococcus aureus* are two examples of contagious diseases that are commonly spread from diseased cows to healthy ones by milking or contaminated milking equipment. For effective management and treatment, it is imperative to comprehend the wide range of bacterial pathogens involved in mastitis (Schunig et al., 2024).

Non-Bacterial Causes

In addition to the main cause of mastitis, other variables could play a role in its development. The non-bacterial reasons include immune-mediated reactions, physical trauma to the udder and chemical irritants. Harsh teat disinfectants and incorrect intramammary antibiotic use are examples of chemical irritants that can harm the mammary gland's sensitive tissues, making the cow more susceptible to infection. Physical trauma such as cuts sustained during hard handling or by using incorrect milking methods can increase inflammation and provide bacterial entry routes. Moreover, inflammation and tissue damage within the udder can result from immune-mediated reactions, such as those observed in allergic reactions or autoimmune illnesses. Non-bacterial causes of mastitis are less frequent than bacterial infections however, they still emphasize the significance of thorough management techniques for the illness' prevention and treatment (Hogeveen, Huijps, and Lam, 2011).

Prevalence of Mastitis

Epidemiological Studies

Epidemiological studies plays an important role in understanding the efficacy of mastitis management and the prevalence as well as spatial distribution of mastitis in dairy cattle herds, identifying risk factors linked to the onset of the disease (De Jong, 2024). Epidemiologists can detect patterns across time, evaluate how management strategies affect illness outcomes, and develop evidence-based interventions to lessen the burden of mastitis by gathering and evaluating data on mastitis incidence, prevalence, and etiology. To precisely identify mastitis cases and the organisms causing them, these studies use a variety of designs and methodologies, including cross-sectional and longitudinal approaches, and diagnostic tools such bacteriological culture, genetic techniques, and somatic cell count (SCC) analysis (Kabui et al., 2024). The prevalence of mastitis varies significantly amongst different geographic regions, herd sizes, and management approaches, according to epidemiological data. Mastitis risk has been found to be significantly influenced by a number of factors, including living conditions, hygiene standards for milking, and cleanliness of milking equipment. Furthermore, herd-level variables that affect disease prevalence and transmission dynamics include herd size, breed mix, and production system. Epidemiological investigations have additionally emphasized the significance of particular bacterial pathogens in the etiology of mastitis, with prevalent causal agents being identified as Staphylococcus aureus, Streptococcus agalactiae, and Escherichia coli. The prevalence of mastitis varies significantly amongst different geographic regions, herd sizes and management approaches, according to epidemiological data (Jesse, Bitrus, Peter, Chung, and Tukiran, 2023).

Economic Impact

Mastitis not only affects the health and welfare of animals but also causes significant financial losses for the dairy sector. These losses are the result of decreased milk yield, lower milk quality (i.e., due to elevated somatic cell counts), higher veterinary expenses, and the culling of afflicted animals. The financial impact of mastitis on dairy farms has been quantified using economic modeling studies, emphasizing the necessity of putting in place affordable mastitis control measures to lessen these losses (Hogeveen et al., 2011).

Pathogenesis of Mastitis

Infection and Inflammation

The pathophysiology of mastitis is caused by pathogenic bacteria invading the tissue of the mammary gland triggering off a cascade of inflammatory and immunological reactions. Bacteria adhere themselves and then penetrate mammary epithelial cells upon entering the udder, where they multiply and release poisons. The cow's immune system is triggered by this invasion, which causes neutrophils and other immune cells to be drawn to the infection site. These

immune cells cause tissue damage by increasing the inflammatory response and releasing pro-inflammatory cytokines and chemokines. As the inflammatory process worsens, the udder may swell, turn red, hurt, and may produce a decrease in milk production. Necrosis or the formation of an abscess may result from severe tissue injury. For effective treatment and control mastitis, one must comprehend the intricate interactions between bacterial infections and the animal immune system (Meng et al., 2022).

Biofilm Formation

Bacterial ailments linked to mastitis possess a propensity of producing biofilms, which are intricate bacterial populations wrapped in an extracellular polymeric material matrix. Biofilms are a major cause of the chronicity and recurrence of mastitis because they offer defense against both host immune responses and antimicrobial therapies. Bacteria can grow into biofilms on the surface of the mammary epithelial cells or inside the ducts within the mammary gland, producing infection reservoirs that are challenging to clear up. Furthermore, biofilms can let bacteria exchange genetic material, which can propagate genes that confer resistance to antibiotics. Improving the results of mastitis requires methods to prevent biofilm development and increase the effectiveness of antimicrobial therapies (Nourbakhsh, Nasrollahzadeh, Tajani, Soheili, and Hadizadeh, 2022).

Antibiotic Resistance in Mastitis

Antibiotics have been the mainstay of care for mastitis affected animals since a long time. They are essential in reducing symptoms and managing bacterial infections in the mammary gland. Antibiotic-resistant mastitogens have emerged as a result of the indiscriminate and frequently overuse of antibiotics in both agricultural and medical settings (Abdi et al., 2021). For the purpose of developing efficient treatment plans and preventing the spread of resistant strains, it is essential to comprehend the mechanisms behind antibiotic resistance in mastitis.

Emergence of Antibiotic Resistance

Antibiotic resistance is a growing concern in the management of mastitis, posing significant challenges to treatment efficacy and animal welfare. The widespread use of antibiotics in both human medicine and agriculture has contributed to the emergence and spread of antibiotic-resistant bacteria, including those associated with mastitis. Over time, bacteria can develop various mechanisms to evade the effects of antibiotics, such as the production of antibiotic-degrading enzymes, efflux pumps to expel antibiotics from the cell, and mutations in target sites to prevent antibiotic binding. This evolution of resistance is accelerated by factors such as inappropriate antibiotic use, suboptimal dosing regimens, and the use of broad-spectrum antibiotics, which exert selective pressure on bacterial populations. As a result, antibiotic-resistant mastitis pathogens have become increasingly prevalent in dairy herds, complicating treatment decisions and necessitating alternative therapeutic approaches (Bradley, 2002).

Causes of Antibiotic Resistance

Overuse and Misuse of Antibiotics

Antibiotics have been used for mastitis treatment for a long time and substantially, which has put selection pressure on bacterial populations and encouraged the emergence of resistance (Banza, 2020). Concerns about antibiotic resistance are becoming more widespread in the management of mastitis, which presents serious obstacles to both animal welfare and therapeutic effectiveness. Antibiotic-resistant bacteria, such as those linked to mastitis, have emerged and proliferated as a result of the extensive use of antibiotics in both human health and agriculture. Bacteria can produce enzymes that degrade drugs, efflux pumps that remove medications from the cell, and target site mutations that stop antibiotic binding are just a few of the ways they can evolve resistance to antibiotics over time. Inappropriate use of antibiotics, inadequate dosage schedules, and the use of broad-spectrum antibiotics, which place selective pressure on bacterial populations, all contribute to the acceleration of this evolution of resistance. Antibiotic-resistant mastitis bacteria have therefore proliferated in dairy herds, making treatment choices more difficult and requiring the use of other therapeutic modalities (Bradley, 2002).

Horizontal Gene Transfer

The transmission of resistance traits within microbial communities is accelerated by the horizontal transfer of resistance genes between bacterial strains, which promotes the spread of antibiotic resistance (Mbindyo et al., 2021).

Genetic Mutations

Antibiotic-resistant bacteria can survive and proliferate in the presence of antimicrobial drugs due to spontaneous mutations in their genomes (Jamil et al., 2017).

Consequences of Antibiotic Resistance

Treatment Failure

Antibiotic-resistant mastitogens frequently resist standard antibiotic treatments, which leads to treatment failure and an extended course of the illness (Paramasivam et al., 2023). Treatment results and clinical response can be significantly

influenced by the presence of antibiotic-resistant bacteria in mastitis infections. Treatment failure, prolonged infection, and illness recurrence can result from resistant microorganisms that do not react to conventional antibiotic therapy. This raises the danger of transmission to other members of the herd and the spread of resistance within the farm environment, in addition to lengthening the illness's duration in the affected animals. In severe circumstances, systemic disease, septicemia and even death can result from untreated or inadequately managed mastitis. Furthermore, milk from treated animals may include antibiotic residues, which could jeopardize the safety and quality of the milk and raise concerns from consumers and regulatory bodies. Thus, the development of alternative treatment techniques and responsible antibiotic therapeutic practices are required in light of the enormous threat that the establishment of antibiotic resistance in mastitis poses to public health and the economy (Yang et al., 2023).

Increased Morbidity and Mortality

Antibiotic-resistant mastitogens infection are associated to increased rates of morbidity and mortality, presenting significant health risks to cattle and afflicted humans (Algharib et al., 2020).

Economic Impact

Antibiotic-resistant mastitis leads to significant financial losses due to reduced milk yield, medical costs and the costs of culling affected animals (Paramasivam et al., 2023).

Mechanisms of Resistance

Antibiotic resistance is exhibited by mastitis pathogens via a range of genetic and molecular mechanisms that confer resistance to certain antibiotic classes. A few examples of these techniques include the activation of efflux pumps to remove medications from the bacterial cell, chromosomal mutations that change the targets or metabolic pathways of antibiotics, and the horizontal gene transfer acquisition of resistance genes. Antibiotic-resistant bacteria are additionally provided with a safe haven by bacterial biofilms, which are often associated with recurrent and chronic mastitis infections. This allows the bacteria to evade the host's immune system and antibiotic therapies. Understanding the processes of antibiotic resistance in mastitis pathogens is essential for antimicrobial stewardship programs and focused therapeutic approaches that maintain the efficacy of current medications and curb the spread of resistance (Seixas et al., 2014).

Current Challenges in Mastitis Treatment

Limited Treatment Options

Alternative treatment modalities must be devised due to the decreasing supply of antibiotics that are effective against antibiotic-resistant mastitogens (Abdi et al., 2021).

Biofilm-Mediated Resistance

Biofilm formation by mastitogenic bacteria confers enhanced resistance to antibiotics, reducing the effectiveness of antibiotics and complicating treatment approaches (Paramasivam et al., 2023).

One Health Perspective

A comprehensive One Health approach encompassing animal medicine, human health, agriculture, and environmental stewardship is necessary to address antibiotic resistance in mastitis (Paramasivam et al., 2023).

Nanoparticles: An Emerging Approach

Nanoparticles have become a viable strategy against antibiotic-resistant mastitogens with certain advantages over conventional antibiotic treatments. This section examines the properties of nanoparticles, their function in medicine, and possible uses in the management of mastitis.

Introduction to Nanoparticles

Nanoparticles are particles with dimensions have sizes from 1 to 100 nanometers, exhibiting distinct physicochemical properties compared to their bulk counterparts (Ali et al., 2021). High surface area-to-volume ratio, configurable surface chemistry, and size-dependent behavior are some of the characteristics that enable nanoparticles' multiple application in a wide range of industries, including biomedicine.

Properties of Nanoparticles

(a). Antimicrobial Activity

The inherent antibacterial properties of nanoparticles began from their capacity to rupture bacterial membranes, impede cellular functions, and trigger oxidative stress (Jampilek and Kralova, 2022).

(b). Biocompatibility

Biomedical applications such as medication administration and tissue engineering may advance with using of biocompatible nanoparticles due to their minimal cytotoxicity and immunogenicity (Paladini and Pollini, 2019).

(c). Surface Modification

By precisely modifying the characteristics of nanoparticles through surface functionalization, one may attain targeted delivery, increased stability, and a decrease in nonspecific interactions in biological contexts (Song et al., 2024).

Role of Nanoparticles in Medicine

By providing cutting-edge methods for illness diagnosis, treatment, and monitoring, nanoparticles have completely transformed the medical industry. the confines of medicine, nanoparticles serve a key role in;

(a). Drug Delivery System

By means of nanoparticles, therapeutic medications are carried to certain regions of infection or inflammation, which also allow for enhanced bioavailability, controlled release, and targeted administration (Jampilek and Kralova, 2022).

(b). Diagnostic Imaging Agents

Nanoparticle-based contrast agents make high-resolution imaging modalities attainable, including computed tomography (CT), magnetic resonance imaging (MRI), and fluorescence imaging, which helps with early disease identification and monitoring (Paladini and Pollini, 2019).

Advantages of Nanoparticles over Traditional Antibiotics

(a). Overcoming Antibiotic Resistance

With a goal to cure mastitis, nanoparticles impart an versatile approach that can target resistant bacterial populations and get beyond traditional resistance mechanisms (Jamil et al., 2017).

(b). Enhanced Bioavailability

By improving an antimicrobial agent's solubility, stability, and residence frequency in biological systems, nanoparticles enhanced the pharmacokinetic profile of the drug and increase its therapeutic efficacy (Jampilek and Kralova, 2022).

(c). Versatility and Customization

Nanoparticles' adaptable nature allows for customized formulations that have the greatest potential for certain antimicrobial applications, such as drug delivery systems, wound dressings, and diagnostic imaging agents (Song et al., 2024).

Applications of Nanoparticles in Mastitis Treatment

(a). Nanoparticles as Antimicrobial Agents

Nanoparticles have appeared as prospective antibacterial agents for the treatment of mastitis, in light of their distinctive physicochemical characteristics along with their ability to interact with bacterial cells. Many kinds of nanoparticles have shown strong antibacterial action against mastitis pathogens (Rai et al., 2016), including metal nanoparticles (such as silver, copper), metal oxide nanoparticles (such as zinc oxide, titanium dioxide), and polymer-based nanoparticles. These particles have the ability to damage bacterial cell membranes, obstruct vital enzyme routes, and cause oxidative stress, all of which can result in the death of bacterial cells. Moreover, nanoparticles have the ability to break through bacterial biofilms, eliminating resistance mechanisms and boosting the effectiveness of antibiotic therapies. In addition, it is possible to create nanoparticles to specifically target virulence factors or particular species of bacteria, hence reducing off-target effects and maintaining the host microbiota (Shariatinia and Zahraee, 2017).

(b). Drug Delivery Systems

Nanoparticles impart additional advantages as methods to deliver drugs for the treatment of mastitis and by enabling the targeted and regulated release of antimicrobial drugs directly to the site of infection (Liew et al., 2022). Antimicrobial medication encapsulation in nanoparticle carriers can increase the medication's bioavailability, prevent it from degrading, and extend its duration in the mammary gland (Ranch et al., 2021). Furthermore, antimicrobial medications with a higher therapeutic index can have fewer systemic side effects and lessen the emergence of antibiotic resistance when delivered via nanoparticle-based drug delivery systems. Moreover, site-specific drug delivery and regulated release kinetics can be achieved by functionalizing nanoparticles with stimuli-responsive moieties or targeting ligands (Lee et al., 2012). This maximizes therapeutic benefits while reducing side effects.

(c). Immunomodulatory Effects

Moreover, nanoparticles have been demonstrated to have immunomodulatory effects, which strengthen the host immune response against mastitis infection (Amiri, Alavi, Taran, and Kahrizi, 2022). Enhancement in phagocytosis, cytokine generation, and antigen presentation can result from the modulation of immune cell function by some nanoparticles, such as liposomal and gold nanoparticles, which can affect neutrophils, dendritic cells, and macrophages. In the afflicted mammary gland, this immunostimulatory impact can mitigate inflammation, expedite the removal of bacterial infections,

and encourage tissue regeneration. Furthermore, immunomodulatory drugs, including cytokines or immunomodulatory peptides, can be delivered directly to the infection site via tailored nanoparticles, boosting mastitis clearance and strengthening the host immune response (Dobrovolskaia and McNeil, 2007).

(d). Biofilm Disruption

Bacterial biofilms present a substantial problem in the treatment of mastitis since they are more resistant to antimicrobial drugs and immunological clearance systems (Flemming et al., 2016). Nanoparticles present intriguing strategies for the eradication of biofilms due to their capacity to infiltrate biofilm matrix, sever bacterial adhesion, and prevent biofilm formation. (Meeker et al., 2016). By interfering with quorum sensing pathways, preventing the formation of extracellular matrix, and encouraging the dispersal of biofilms, metal nanoparticles in particular have demonstrated potent antibiofilm activity. Moreover, the combination of nanoparticle-based tactics, like photothermal therapy and sonochemical treatment, might improve antimicrobial efficiency and biofilm breakup, offering new ways to treat biofilm-associated mastitis infections (Khatun, Bonala, Pogu, and Rengan, 2022).

Challenges and Future Perspectives

Notwithstanding the intriguing potential of nanoparticles in the management of mastitis, a number of obstacles need to be overcome before these developments may be implemented in clinical settings. The use of nanoparticles in the treatment of mastitis is discussed in this section along with its present and potential future applications.

(a). Resistance and Adaptation

Antibiotic-resistant mastitis bacteria present serious obstacles to animal welfare and treatment effectiveness (Bradley, 2002). Antibiotic resistance restricts the therapeutic options for treating mastitis, which might result in treatment failures, longer illness, and higher medical expenses. Antibiotic resistance in mastitis calls for a multimodal response that includes prudent antibiotic usage, alternate treatment plans, and efficient infection prevention and control methods (Hogeveen et al., 2011). Moreover, it is imperative that scientists, veterinarians, dairy farmers, and legislators work together to prevent antibiotic resistance and maintain the effectiveness of antimicrobial treatments for mastitis (Yang et al., 2023).

(b). Biofilm Formation

A significant barrier to the effective treatment of mastitis is the presence of bacterial biofilms, which can lead to treatment failure, recurrence of the disease, and persistent infections (Flemming et al., 2016). Pathogens linked to biofilm-associated mastitis are more resistant to antimicrobial treatments and host immunological responses, which makes them challenging to eliminate. Improving biofilm susceptibility to antibiotic treatments and preventing biofilm development are essential goals for bettering mastitis outcomes. Research endeavors aimed at comprehending the molecular mechanisms underlying biofilm formation, pinpointing unique antibiofilm agents, and creating inventive treatment approaches like photodynamic therapy and quorum sensing inhibitors exhibit potential in surmounting biofilm-related obstacles in the management of mastitis (Meeker et al., 2016).

(c). One Health Approach

Mastitis is a multifaceted disease with a complex etiology that affects human and animal health in significant ways (Erkyihun and Alemayehu, 2022). Addressing the issues raised by mastitis requires a One Health strategy that acknowledges the connections between animal, human, and environmental health. To address common health challenges, such as antimicrobial resistance and zoonotic infections, this multidisciplinary approach prioritizes collaboration and coordination amongst veterinary medicine, human medicine, environmental science, and public health disciplines (Queenan, Häsler, and Rushton, 2016). Through the integration of knowledge and skills from several sectors, the One Health approach may safeguard the health and well-being of humans, animals, and ecosystems, promote sustainable agriculture practices, and inform evidence-based solutions.

(d). Technological Advances

Innovation and technological advancements offer novel opportunities to enhance mastitis prevention, diagnosis, and treatment (Redding et al., 2013). Novel technology, like early identification of mastitis, real-time udder health monitoring, wearable sensors, and precision farming technologies, allow for targeted therapies, and point-of-care diagnostic tools. Furthermore, breakthroughs in immunology, genetics, and nanotechnology offer fresh perspectives on how to create vaccines, antimicrobial drugs, and diagnostic instruments that are specific to mastitis bacteria and host immune responses (Lee et al., 2012). Leveraging these technical advancements can help dairy production systems remain sustainable in the face of changing difficulties, improve disease management methods, and maximize treatment outcomes. Innovative methods for prevention, diagnosis, and treatment of antibiotic-resistant mastitis can be addressed through the potential use of nanoparticles. This chapter summarizes the main conclusions and offers some insights into the potential future directions of nanoparticle-based mastitis treatment medicines.

Summary of Key Findings

(a). Antimicrobial Efficacy

Enhanced antibacterial activity of nanoparticles against mastitogenic bacteria provides a versatile strategy to counteract antibiotic resistance and prevent the production of biofilms.

(b). Diagnostic Imaging

Contrast agents based on nanoparticles allow for high-resolution imaging of lesions linked to mastitis, which helps with early diagnosis and treatment monitoring.

(c). Wound Healing

Nanoparticle-loaded wound care dressings provide a multipurpose method of treating wounds related to mastitis by accelerating wound healing and tissue regeneration.

(d). Targeted Drug Delivery

Antimicrobial medicines can be specifically delivered to mastitis-affected mammary glands using nanoparticles, reducing systemic adverse effects and increasing therapeutic efficacy.

(e). Challenges and Future Perspectives

For nanoparticle-based therapeutics for mastitis to reach their full potential, several obstacles must be overcome, including regulatory barriers, biocompatibility issues, resistance development, and translation to clinical practice.

Conclusion

There is a critical need for novel strategies to combat dairy cattle mastitis because of the financial costs and increasing incidence of antibiotic resistance associated with mastitis. The chapter focused on a number of mastitis-related aspects, such as the etiology, frequency, and therapeutic potential of nanoparticles. It drew attention to the drawbacks of traditional antibiotic treatments and emphasized the significance of implementing substitute tactics, like treatments based on nanoparticles. It also emphasized on how important it is to work together and incorporate cutting-edge technologies in order to effectively prevent mastitis. Although mastitis poses significant obstacles, yet the investigation of nanoparticle-based treatments gives encouraging opportunities for transforming mastitis management and enhancing the general health of dairy herds.

REFERENCES

Abdi, R. D., Gillespie, B. E., Ivey, S., Pighetti, G. M., Almeida, R. A., and Kerro Dego, O. (2021). Antimicrobial resistance of major bacterial pathogens from dairy cows with high somatic cell count and clinical mastitis. *Animals, 11*(1), 131.

Algharib, S. A., Dawood, A., and Xie, S. (2020). Nanoparticles for treatment of bovine Staphylococcus aureus mastitis. *Drug Delivery, 27*(1), 292-308.

Ali, S. S., Moawad, M. S., Hussein, M. A., Azab, M., Abdelkarim, E. A., Badr, A., and Khalil, M. (2021). Efficacy of metal oxide nanoparticles as novel antimicrobial agents against multi-drug and multi-virulent Staphylococcus aureus isolates from retail raw chicken meat and giblets. *International Journal of Food Microbiology, 344*, 109116.

Amiri, M. R., Alavi, M., Taran, M., and Kahrizi, D. (2022). Antibacterial, antifungal, antiviral, and photocatalytic activities of TiO2 nanoparticles, nanocomposites, and bio-nanocomposites: Recent advances and challenges. *Journal of Public Health Research, 11*(2), 22799036221104151.

Banza, J. L. (2020). *Milk Quality and Prevalence of Mastitis Pathogens in Infected Bovine Mammary Glands and Their Sensitivity to Local Plant Extracts.*

Bradley, A. J. (2002). Bovine mastitis: an evolving disease. *The Veterinary Journal, 164*(2), 116-128.

De Jong, E. (2024). Enhancing Antimicrobial Stewardship On Dairy Farms With A Focus On Selective Treatment Of Clinical Mastitis.

Dobrovolskaia, M. A., and McNeil, S. E. (2007). Immunological properties of engineered nanomaterials. *Nature Nanotechnology, 2*(8), 469-478.

Erkyihun, G. A., and Alemayehu, M. B. (2022). One Health approach for the control of zoonotic diseases. *Zoonoses, 2*(1), 963.

Flemming, H.-C., Wingender, J., Szewzyk, U., Steinberg, P., Rice, S. A., and Kjelleberg, S. (2016). Biofilms: an emergent form of bacterial life. *Nature Reviews Microbiology, 14*(9), 563-575.

Guliy, O. I., Evstigneeva, S. S., Bunin, V. D., and Fedonenko, Y. P. (2023). The role of biofilms and multidrug resistance in wound infections. In *Bioengineered Nanomaterials for Wound Healing and Infection Control* (pp. 57-114): Elsevier.

He, Z.-Y., Wei, X.-W., and Wei, Y.-Q. (2017). Recent advances of nanostructures in antimicrobial therapy. *Antimicrobial Nanoarchitectonics*, 167-194.

Hogeveen, H., Huijps, K., and Lam, T. (2011). Economic aspects of mastitis: new developments. *New Zealand Veterinary Journal, 59*(1), 16-23.

Jamil, B., Bokhari, H., and Imran, M. (2017). Mechanism of action: how nano-antimicrobials act? *Current Drug Targets, 18*(3),

363-373.

Jesse, F., Bitrus, A., Peter, I., Chung, E., and Tukiran, N. (2023). Clinical and Subclinical Mastitis in Ruminants: A Review of Etiological Agents, Diagnosis, Clinical Management and Risk Factors. *Journal Research Veterinary Science, 1*, 51-65.

Kabui, S., Kimani, J., Ngugi, C., and Kagira, J. (2024). Prevalence and antimicrobial resistance profiles of mastitis causing bacteria isolated from dairy goats in Mukurweini Sub-County, Nyeri County, Kenya. *Veterinary Medicine and Science, 10*(3), e1420.

Khatun, S., Bonala, S., Pogu, S. V., and Rengan, A. K. (2022). Functional Biomaterials: Drug Delivery and Biomedical Applications Polymeric Micelle in Drug Delivery Applications. In *Functional Biomaterials: Drug Delivery and Biomedical Applications* (pp. 1-36): Springer.

Lee, D.-E., Koo, H., Sun, I.-C., Ryu, J. H., Kim, K., and Kwon, I. C. (2012). Multifunctional nanoparticles for multimodal imaging and theragnosis. *Chemical Society Reviews, 41*(7), 2656-2672.

Liew, K. B., Janakiraman, A. K., Sundarapandian, R., Khalid, S. H., Razzaq, F. A., Ming, L. C., and Ng, P. W. (2022). A review and revisit of nanoparticles for antimicrobial drug delivery. *Journal of Medicine and Life, 15*(3), 328.

Mbindyo, C. M., Gitao, G. C., Plummer, P. J., Kulohoma, B. W., Mulei, C. M., and Bett, R. (2021). Antimicrobial resistance profiles and genes of Staphylococci isolated from mastitic cow's milk in Kenya. *Antibiotics, 10*(7), 772.

Meeker, D. G., Jenkins, S. V., Miller, E. K., Beenken, K. E., Loughran, A. J., Powless, A., and Smeltzer, M. S. (2016). Synergistic photothermal and antibiotic killing of biofilm-associated Staphylococcus aureus using targeted antibiotic-loaded gold nanoconstructs. *ACS Infectious Diseases, 2*(4), 241-250.

Meng, Y., Chen, L., Chen, Y., Shi, J., Zhang, Z., Wang, Y., and Zhang, L. (2022). Reactive metal boride nanoparticles trap lipopolysaccharide and peptidoglycan for bacteria-infected wound healing. *Nature Communications, 13*(1), 7353.

Nourbakhsh, F., Nasrollahzadeh, M. S., Tajani, A. S., Soheili, V., and Hadizadeh, F. (2022). Bacterial biofilms and their resistance mechanisms: a brief look at treatment with natural agents. *Folia Microbiologica, 67*(4), 535-554.

Paramasivam, R., Gopal, D. R., Dhandapani, R., Subbarayalu, R., Elangovan, M. P., Prabhu, B., and Muthupandian, S. (2023). Is AMR in dairy products a threat to human health? An updated review on the origin, prevention, treatment, and economic impacts of subclinical mastitis. *Infection and Drug Resistance*, 155-178.

Queenan, K., Häsler, B., and Rushton, J. (2016). A One Health approach to antimicrobial resistance surveillance: is there a business case for it? *International Journal of Antimicrobial Agents, 48*(4), 422-427.

Rai, M., Deshmukh, S. D., Ingle, A. P., Gupta, I. R., Galdiero, M., and Galdiero, S. (2016). Metal nanoparticles: The protective nanoshield against virus infection. *Critical Reviews in Microbiology, 42*(1), 46-56.

Ranch, K. M., Maulvi, F. A., Koli, A. R., Desai, D. T., Parikh, R. K., and Shah, D. O. (2021). Tailored doxycycline hyclate loaded in situ gel for the treatment of periodontitis: Optimization, in vitro characterization, and antimicrobial studies. *AAPS PharmSciTech, 22*, 1-11.

Redding, L., Barg, F., Smith, G., Galligan, D., Levy, M., and Hennessy, S. (2013). The role of veterinarians and feed-store vendors in the prescription and use of antibiotics on small dairy farms in rural Peru. *Journal of Dairy Science, 96*(11), 7349-7354.

Schunig, R., Busanello, M., Nogara, K. F., and Zopollatto, M. (2024). Cow-level risk factors associated with the increase in somatic cell count and the occurrence of subclinical mastitis in Brazilian Holstein and Jersey dairy cows. *Preventive Veterinary Medicine*, 106208.

Seixas, R., Santos, J., Bexiga, R., Vilela, C., and Oliveira, M. (2014). Antimicrobial resistance and virulence characterization of methicillin-resistant staphylococci isolates from bovine mastitis cases in Portugal. *Journal of Dairy Science, 97*(1), 340-344.

Shariatinia, Z., and Zahraee, Z. (2017). Controlled release of metformin from chitosan–based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel drug delivery systems. *Journal of Colloid and Interface Science, 501*, 60-76.

Song, X., Wang, Y., Bai, R., Pei, X., Xu, H., Zhu, K., and Wu, C. (2024). Antimicrobial resistance profiles of common mastitis pathogens on large Chinese dairy farms. *JDS Communications, 5*(3), 185-189.

Yang, F., Shi, W., Meng, N., Zhao, Y., Ding, X., and Li, Q. (2023). Antimicrobial resistance and virulence profiles of staphylococci isolated from clinical bovine mastitis. *Frontiers in Microbiology, 14*, 1190790.

Chapter 33

Nanotechnological Approaches to Immune Enhancement: A Novel Strategy

Saima Somal[1], Shujaat Hussain[1], Muhammad Kamran Rafique[2], Zeeshan Nawaz[3], Imtiaz Hussain[4], Lieza Iftikhar[5], Hammad Ahmed Hashmi[1], Muhammad Arif Zafar[1] and Muhammad Zishan Ahmad[6*]

[1]Department of Clinical Studies, [6]Department of Veterinary Pathology, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
[2]Department of Pathobiology, University of Veterinary and Animal Sciences, Lahore, Sub-Campus Jhang-Pakistan.
[3]Institute of Microbiology, Government College University, Faisalabad-Pakistan.
[4]Department of Animal Sciences, College of Agriculture, University of Sargodha, Sargodha-Pakistan.
[5]Department of Rehabilitation Sciences, The University of Faisalabad, Sargodha Road, Faisalabad-Pakistan.
*Corresponding author: jeelani.zishan@uaar.edu.pk

ABSTRACT

The immune system is the body's defense system that protects it from any foreign pathogen. This defense system has two main components; the innate immunity which is the first line of defense and the adaptive immunity which retains the memory of all the past infections. With time and evolving microbes, the immune system has also developed mechanisms to control and combat a wide array of pathogens using body's both lines of defenses. Many people believe in using traditional immune boosting methods by consuming herbs and spices that include garlic, mushroom, ginger etc. but all of these methods are not really backed by strong scientific evidence. Nanotechnology is a promising new approach for targeted and enhanced immune responses. It has introduced improved and better ways to make immune system stronger. Use of nanotechnology in improved vaccine delivery and efficacy can be seen through the example of nano vaccine created by Novavax®. On the other hand, nanotechnology in cancer immunotherapy is also being recognized as a valuable tool for drug delivery in cancer treatments. Moreover, use of nanomaterials have also given hope to the researchers as a promising tool for managing various autoimmune diseases and allergic reactions as well.

KEYWORDS
Nanotechnology, Nanocarriers, Targeted drug delivery, Immune enhancement, Immunomodulation

Received: 18-Jun-2024
Revised: 19-Jul-2024
Accepted: 20-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Somal S, Hussain S, Rafique MK, Nawaz Z, Hussain I, Iftikhar L, Hashmi HA, Zafar MA and Ahmad MZ, 2024. Nanotechnological approaches to immune enhancement: a novel strategy. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 284-291. https://doi.org/10.47278/book.CAM/2024.380

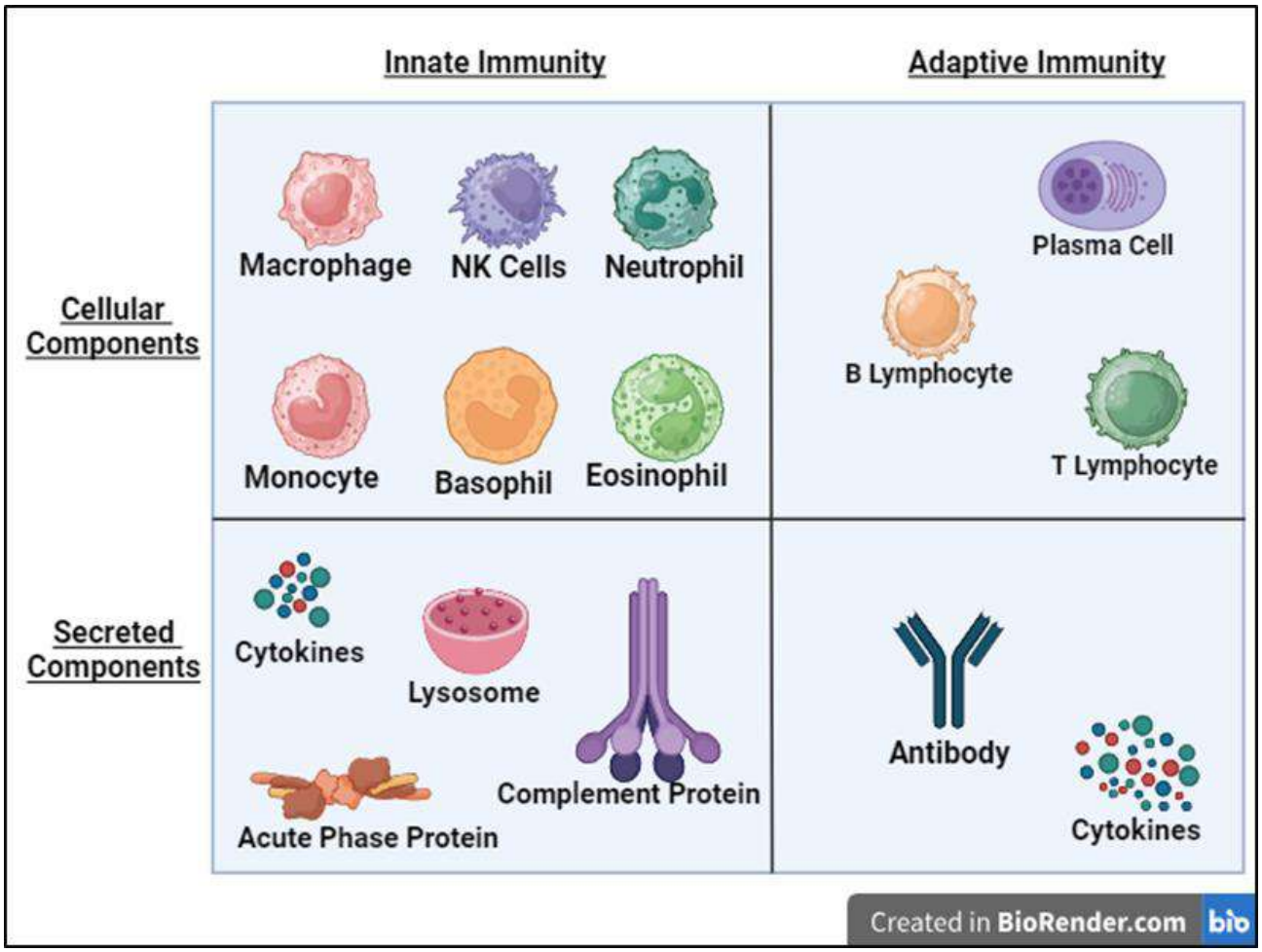
INTRODUCTION

The body has its unique and specialized system through which it protects itself against the harmful invaders. This is known as immune system of the body. It can be thought as a team made up of different components which includes organs, specialized cells, proteins and even chemicals, all of which work together to protect the body. This defense team has two main components that unite against the invaders to protect the body: Innate immunity and adaptive immunity. Innate immunity is body's first line of defense and guards the body against all the pathogens without remembering the specific threats and responds right away. On the other hand, the adaptive immunity is like body's special force which takes some time to respond but since remembers the past encounters, the response by adaptive immunity is more precise and targeted (Marshal et al., 2018). The immune system provides the body the necessary protection against a lot of dangers that range from harmful substances to all those microorganisms that may cause a disease. One of the main job is to protect the body against germs and foreign invaders, and prevent from the illness that they might bring. Moreover, the immune system monitors the body constantly for any changes inside the cells that could lead to illness. When and if something goes wrong and the body gets sick, the immune system steps in to helps the body heal and feel better (Marshal et al., 2018). The immune system has some special cells that include white blood cells, antibodies, complement proteins, and interferon etc. that act as frontline soldiers and play an important role in the body's defense and in maintaining the overall health by fighting any infections away.

Recognition and Response to Pathogens

When a pathogen invades the body, the immune system starts the response by first identifying the pathogen and

then it initiates a response against the invaders by initiating a complex set of actions to neutralize them. One of the important role of the immune system is its ability to differentiate and distinguish between body's own self and foreign/ non-self-entities in order to start a targeted defense mechanism against allergens, or any infectious agent. This ability to differentiate between self and non-self-entities is important for the immune system to ensure that it provides an accurate, efficient, and timely defense against foreign threats. The cells, proteins and chemicals in innate immunity and adaptive immunity work together as a team to detect and remove the infections. Antibodies also have an important role in finding and labeling the antigens by identifying and recognizing the microbes, hence making it easier for the immune system to destroy them (Chaplin, 2010).



On the other hand, pathogens have evolved and have developed various strategies to bypass the body's defense responses, including techniques that allow them to evade detection and elimination by the body. *Mycobacterium tuberculosis* is an example where we see that the bacteria have developed a complex cell wall resistance for the digestive enzymes of macrophages, which makes its eradication challenging for the immune system (Betts et al., 2013). The immune system has developed mechanisms to control and combat a wide array of pathogens using the body's both line of defenses, innate and adaptive, to detect and eliminate pathogenic threats effectively. (Betts et al, 2013 and Chaplin 2010).

Moreover, the immune system has a significant feature to retain the memory of past infections which, upon reinfection, enables it to generate a targeted response. This immune memory, along with the vaccination process, plays a vital role in providing a long-term protection and helps strengthen the ability of the immune system's to prevent pathogens without causing harm to self-tissues (Nicholson, 2016).

Common Traditionally Used Immune - Boosting Methods and Their Effectiveness

Many people are interested in traditional immune-boosting techniques that improve the immune system's memory-based reaction to antigens. Consumption of herbs such as garlic, mushrooms, ginger, soups, etc. that are traditionally thought to have immune-boosting qualities, is one of the popular strategies. But it should be kept in mind that the effectiveness of all these herbs and spices etc. is only backed by low quality evidence and traditional medicine, and not primarily based on medical advice (Cassa et al., 2019 and Wagner et al., 2020). Vitamin C is another traditional and common method which is used and believed to enhance one's immunity and prevent the body from infections. Vaccination, on the other hand, is one of the most effective methods and which is scientifically proven to develop antibodies against specific pathogens boosting up the immunity (Cassa et al., 2019 and Wagner et al., 2020). Scientific

evidence favors and supports vaccination, unlike traditional methods, and is considered a gold standard to prevent infections and enhance immunity in the long run (Wagner et al., 2020 and Cassa et al., 2019).

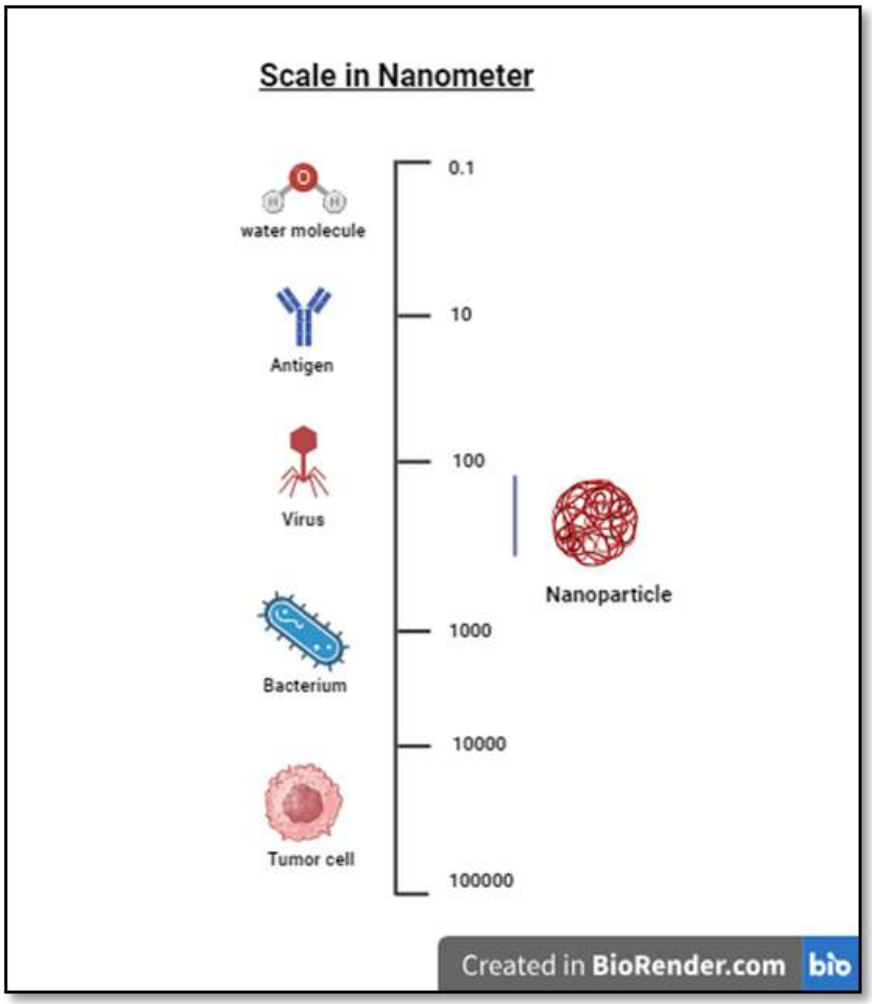
Multiple strategies and dietary modifications, including lifestyle improvements, are generally included in traditional treatments for boosting immunity and have even shown effectiveness in strengthening of the immune responses. It is important to establish an antioxidant balance in the immune cells to help them remain functional and protect them from oxidative stress, also making it sure that they receive enough nutrients for their sustenance (Mitra et al., 2022).

It has been proved through studies that when nutritional deficiencies are rectified through dietary adjustments and supplementations, the immune system might get the required strength to help the body fight off the disease. Moreover, vitamin like substances like coenzyme Q, choline, carnitine and inositol have been proved to play a huge role in regulating immune responses resulting in enhanced immunity. Additionally, experimental studies provide evidence that favors the effectiveness of vitamins and minerals in boosting immune functions and strengthening of the immune system (Mitra et al., 2022). Furthermore, immunity is significantly enhanced by physical activity. Exercise on a daily basis improves circulation and increases immune cell mobility, which allows them to actively reach for dangers and develop more robust and effective defenses (the guardian, 2016).

Introduction to Nanotechnology as a Promising New Approach for Targeted and Enhanced Immune Responses

Nanotechnology and its Scope in Immunology

Nanotechnology has expanded and opened new paths in the field of immunology. It has introduced improved and better ways to make our immune system stronger and create treatments that are specific to the problem. These nanoparticles filled with the right blend of cytokines and antigens not just give the body a quick boost against the diseases but also help it fight off the illness. Nanotechnology, through passive immunity, delivers immunoglobulin genes through nanoparticles which strengthen the immune system by making target specific antibodies without the body having to do much. These nanoparticles have different shapes, sizes, charge and other properties, and can be used to generate customized immune responses in unprecedented ways. This could not only help the body to prevent infections but also helps the body to fight off the disease before it occurs (Smith et al., 2013). Moreover, the science of nanotechnology helps the scientists to design and make synthetic materials that are proficient in delivering the drugs and biological treatments to the targeted immune cells, enhancing the effectiveness of gene and drug delivery, making the treatment work better. (Chuang et al., 2022)



Nanotechnology and Improved Targeted Immune Responses

Emergence of nanotechnology has revolutionized the field of immunology in multiple ways by offering creative approaches to strengthen the immune system. Nanogels, cationic liposomes and other nanoparticles act as carriers for the antigens and a guide for innate and adaptive immune responses to fight off the illness. (Smith et al., 2013 and Chehelgerdi et al., 2023). These nanoparticles, when acting as carriers, have the special ability to affect the immune responses, in a dose-dependent way, to activate the complement system, enhance antigen presentation and stimulate the toll-like receptor (Chehelgerdi et al., 2023). Moreover, the arrangement of antigens on the nanoparticle's surface can also encourage B-cell activation leading to efficient antibody production. (Smith et al., 2013 and Chehelgerdi et al., 2023). Additionally, these nanoparticles, by antigen cross presentation and signaling toll-like receptors, can also boost and influence the innate immune system positively. Nanoparticles also have the ability to release mediating substances like cytokines and chemokines and other immunomodulation substances to enhance the cytotoxic activity of T lymphocytes (Smith et al., 2013).

Nanotechnology, through these methods show a significant potential in areas like cancer immunotherapy, vaccine design, targeted drug delivery etc. opening new opportunities for fine-tuning the immune system and developing effective treatment plans (Chehelgerdi et al., 2023).

Nano Immunology - Interaction between Nanomaterials and Immune System

The interaction between nanoparticles and our immune cells depends highly upon their physicochemical properties like size, shape, charge, hydrophobicity etc. These factors play a pivotal role in deciding how nanoparticles will interact with different immune cells. This interaction sometimes may lead to immune toxicity which makes it important for the researchers to study how exactly these nanoparticles work in the body. This understanding will make sure they are safe for medical use minimizing the undesirable reactions. Moreover, nanoparticles can also interact with the immune system's soluble components like complement components further emphasize the complex relationship between nanoparticles and immune responses. Engineered nanoparticles have the ability to interact with different types of immune cells like monocytes/macrophages, neutrophils, granulocytes, dendritic cells etc. which sometimes may result into direct cytotoxicity or modulation of immune responses (Boraschi et al., 2017). Moreover, nanoparticles can also sometimes suppress some of the immune effector cells while activating the immune regulatory cells highlighting their effects on immune system. This might prove to be useful for vaccine delivery and increasing the efficacies of anti-inflammatory, antiviral and anticancer treatments (Dobrovolskaia et al., 2016).

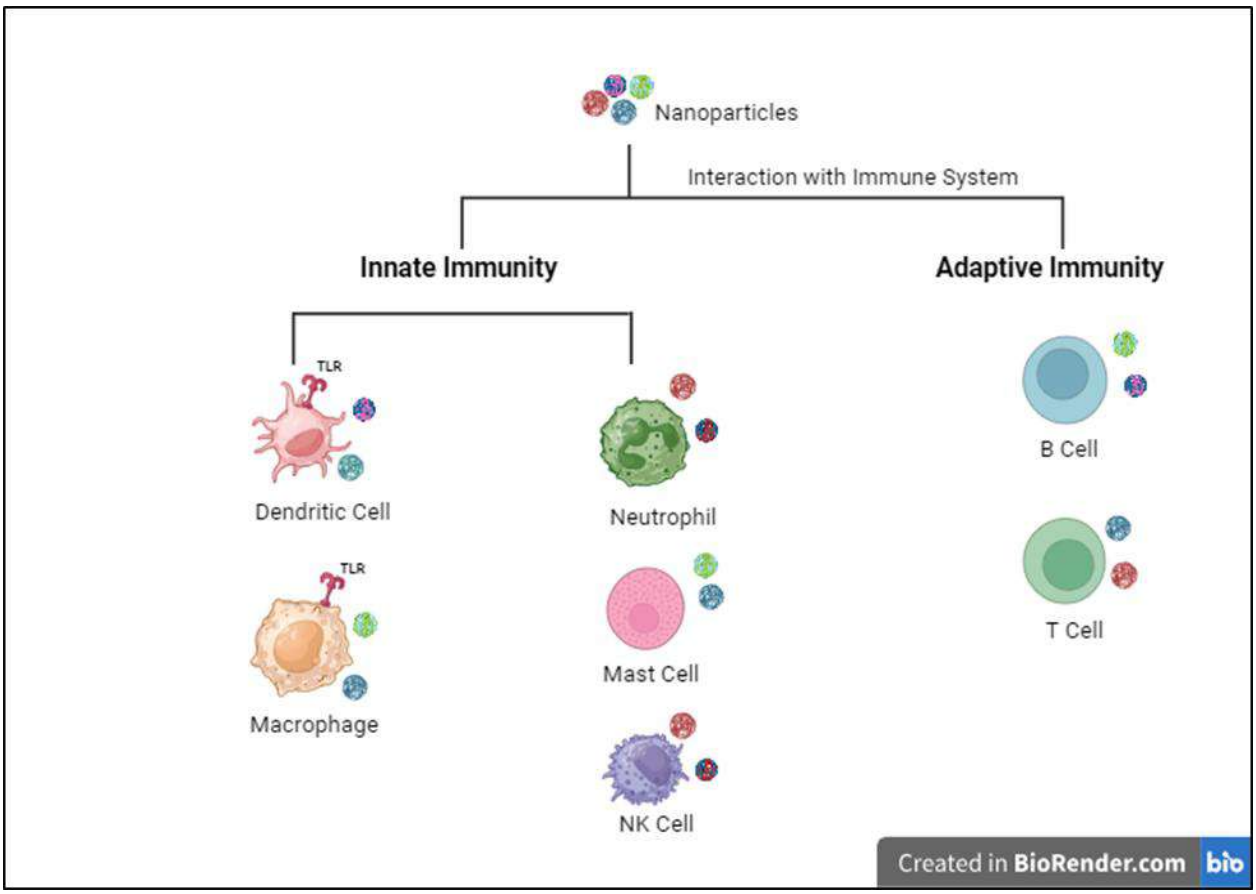


Fig. 1: Generic illustration of Nanomaterials multicolored circles, depicting their interaction with different cells in the Immune system. The image was generated by BioRender.

Nanotechnology and Immune Boosting Methods

Vaccine Development

Nanoparticles and Improved Vaccine Delivery

Nanoparticles are tiny but mighty tools that have distinct properties and capabilities, and bring opportunities for improving the vaccination process. They are custom-made miniature delivery vehicles specifically designed to carry the vaccine, so small and mirroring the structure of the pathogen, without causing any harm to the body. The nanoparticles can be tweaked to include the adjuvants that make the vaccines more effective resulting in better immunity. This customization allows controlled delivery and release of antigens, helping the immune system do its job in a better fashion. Nanoparticles also have the special ability to enter the cell and deliver the antigens to APCs which results in enhanced insusceptibility to disease (Panda, 2012).

Role of Nanomaterials in Vaccine Efficacy

Scientists and researchers use nanoparticles as special tools to make the vaccines work more effectively and efficiently. Researchers, with the help of nanotechnology, are learning more and more about the immune system and the way it responds to vaccines, making innovations for prevention and treatment of diseases. This is not only focused on just creating and developing new vaccines but also about making those vaccines that we already have, much better and effective. Nanoparticles like virus-like particles and protein nano-cages etc. mimic the look and apparent functioning of the pathogens, efficiently delivering the vaccine without causing any harm to the body. These nanoparticles also interact closely with the body's defense system helping it build a stronger immunity against diseases (Smith et al., 2013). Taking the example of nano vaccine created by Novavax®, it uses the spike protein of SARS-Cov-2. This vaccine has demonstrated effectiveness in triggering a strong immune response, showing the potential of nano vaccines in strengthening the body's ability to build immunity.

Nanotechnology and Cancer Immunotherapy

Utilization of Nanoparticles in Cancer Immunotherapy

Nanoparticles are now being recognized as valuable tools in cancer treatments. These tiny particles act as superheroes with special abilities and features that could bring about a significant change in ways cancer is treated. These super small materials are designed in a way that makes cancer treatment more effective along with reduction in side effects (Shams et al., 2022 and Dang et al., 2024). Nanoparticles play a very important role in cancer therapy by transporting the therapeutic agents directly to the targeted cells. This target delivery helps in the distribution and release of immune components at tumor location, eventually enhancing the effectiveness of treatment while reinforcing the immune system to fight off the cancer (Dang et al., 2024 and Shams et al., 2022). Besides all that, the transport of adjuvants and antigens to the antigen presenting cells is greatly enhanced by the nanoparticles, which in turn induce the specific immune response that is needed to fight off cancer (Shams et al., 2022). In this regard, cancer immunotherapy that is based on nanotechnology, not only just increases the treatment efficacy but also makes it more effectiveness (Dang et al., 2024). Furthermore, these nanoparticles can also pass through the body's natural defense barriers and get into the tumor environment, thus helping and allowing the treatment to go directly right where it is needed without being accumulated in any other parts of the body (Dang et al., 2024). Thus, nanoparticles can be considered as a multifunctional tool in cancer immunotherapy which includes their ability to transport the immunotherapeutic agents, act as immune-modulators and even help the vaccines to strengthen up the body's immune system against cancer etc, ultimately making them extremely useful in increasing the treatment efficacy in cancer (Debele et al., 2020).

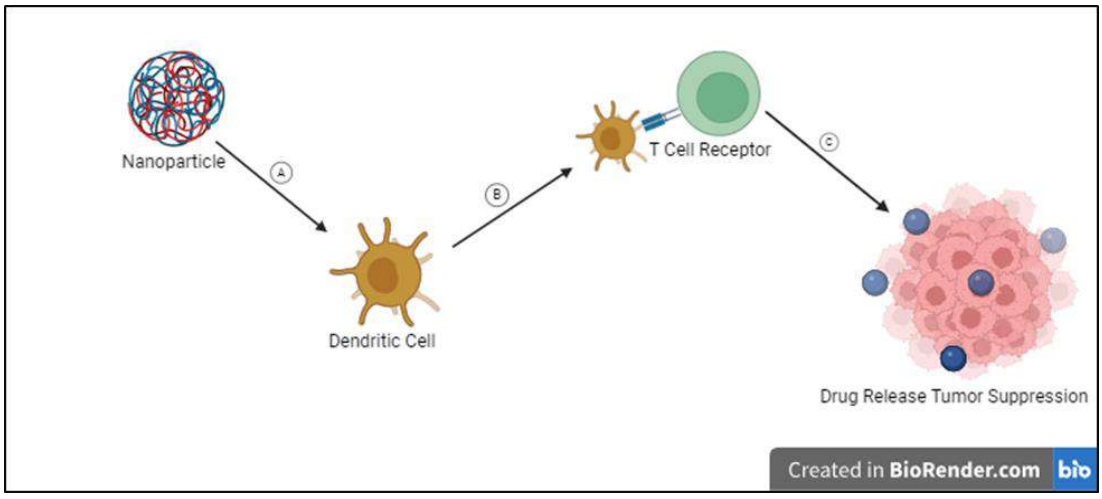


Fig. 2: Schematic illustration of nanoparticles interacting with Immune system A) Immunostimulation of dendritic cells through nanoparticles B) Priming of T cells by dendritic cells C) Release of drug into the tumor cells

Nanotechnology based Drug Delivery System and Immunotherapy

Nanoparticles and Delivery of Immunotherapeutic agents

Nanoparticles are emerging as an important and popular tool for delivering immunotherapeutic treatments and offer ways to make the treatments work better. These nanoparticles, after radiation or chemotherapy, grab the antigens shed by tumors and carry molecules, either immune stimulant or immune modulant in nature, to enhance the immune response. Moreover, vaccines that are based on nanoparticles are crafted in a way to trigger a strong response from T cells by delivering the adjuvants and antigens together, activating the dendritic cells and ensure that antigens are released constantly (NCI, 2023). Another method is the combined treatment of immunotherapy and phototherapy, done by putting the photo-dermal substances and immunotherapy drugs together inside the nanoparticle (Zhao et al., 2022). Furthermore, nanoparticles can be customized to target the specific cells and molecules within the tumor, bringing change in immunosuppressive conditions, to improve the treatment outcomes. The abilities of nanoparticles have a huge potential to make cancer treatment better by efficient drug delivery and enhanced immune responses. However, further studies are still needed necessarily to completely understand the actual effectiveness of using such method for the transportation and delivery of immunotherapeutic agents could be (Wu et al., 2022).

Targeted Drug Delivery and Advantages of using Nanocarriers in Immunotherapy

Nanocarriers serve as delivery vehicles that carry the drugs to the diseased cells with fewer side effects and offer a lot of advantages and effectiveness in drug delivery in immunotherapy (Kumbhar et al., 2023):

1. Nanocarriers can be custom designed to respond to the specific conditions of tumors, making sure that the drugs delivered are right where they are needed and enhancing the treatment efficacy at shrinking the tumor.
2. The encapsulation of antigens and adjuvants together inside the nanocarriers helps to create a long lasting immune response by activating the antigen presenting cells (APCs) effectively.
3. Specific cells like dendritic cells (DCs) etc. can be targeted by using customized nanocarriers resulting in enhanced antigen presentation and improved immune response (Kumbhar et al., 2023).
4. These nanocarriers, through special pH sensitive methods, can even cause lysosomes to rupture and trigger the production of reactive oxygen species (ROS) in dendritic cells. This results in boosting proteasome activity, making the immune system stronger.
5. Nanocarriers that are loaded with CD80 antibodies, bind to receptors on dendritic cells which further enhance the immune response (Kumbhar et al., 2023).
6. The use of nanocarriers in immunotherapy not only just delivers the drugs but also helps to target the blood vessels that are present around the tumor. This plays a role to overcome the resistance to the treatment. (NCI, 2023 and Wu et al., 2022).
7. Nanocarriers can even possess the ability to shift the cell-behavior in tumor from supporting the tumor growth to fighting against it (from pro-tumor to anti-tumor) (Kumbhar et al., 2023).

Nanotechnology and Autoimmune Diseases

Nanotechnology and Modulation of Immune Responses in Autoimmune Diseases

Researchers are hopeful that using nanotechnology they could be able to change or modulate how our immune system behaves in diseases like autoimmune disorders. The special abilities and features of nanotherapeutics, scientists can aim and stop the harmful immune reactions that occur in autoimmune diseases, leading to new and creative ways to deal and treat these conditions. Nanotechnology also helps us understand more about the working of the immune system in such diseases which is essential to find ways from their prevention and treatment (Smith et al., 2013). Also, nanomaterials have shown that they have the ability to either boost up or calm down the body's defense system which could be highly helpful for treating the diseases in which the immune system mistakenly attacks healthy tissues. Additionally, these particles can also serve as delivery vehicles and effectively carry the medicines directly to the problem causing cells that are involved in autoimmunity, thus, making the treatment more effective. Gold nanoparticles especially, have given hope to the researchers as a promising tool for managing various diseases like joint inflammation and nerve damage, indicating that this technology could be a huge help in treating such conditions (Chountoulesi and Demetzos, 2020). Furthermore, the intricate relations of the characteristics of nanoparticles, for example their size, shape, composition, surface properties etc, is what determines how they influence the immune system in autoimmune diseases. This also shows how essential it is to know what these factors are in order to effectively control the immune response (Mitarotonda et al., 2022).

Nanoscale Strategies to Target Autoimmune Cells and Induction of Immune Tolerance

In today's time and age, where autoimmune diseases are on rise, the use of nanotechnology has been a source of hope to many. Through the development of smart nano devices, researchers could be able to attain targeted drug delivery to those specific cells that cause the autoimmune inflammation, through which a more personalized treatment approach will be possible. Nanotechnology hold the potential to change the way how autoimmune diseases are managed by introducing new and improved therapeutic methods that are not only effective but also less invasive at the same time (Zhu et al., 2022).

The ability of nanoparticles to act as helpers by protecting, stabilizing and displaying antigens to APCs is significant for

inducing immune tolerance. The release of antigens into the bloodstream and surrounding tissues in a regulated manner, these nanoparticles can organize a targeted and effective immune response making them valuable in autoimmune treatments. However, it should also be kept in mind that these nanoparticles having all these unique properties to stimulate immunity could also, possibly, lead to their elimination or rejection by the body's defenses (Mobeen et al., 2022).

Nanotechnology and Allergic Diseases

Nanotechnology and Diagnosis and Treatment of Allergic Diseases

Nanotechnology has a great potential to change the ways practitioners deal with allergies. Scientists are now using nanoparticles to aim at the cells causing allergic reactions. This could mean there can be more accurate ways through which we can now figure out the allergies and treat them effectively (Paris et al., 2021). For example, nanoparticles made up of polymers when combined with CpG ODNs show that they can help in treating allergic reactions that are triggered by house dust mites. This is done by bringing and activating more dendritic cells to the airways resulting in a helpful and positive response to fight off the allergies (Johnson et al., 2020). Moreover, nanoparticles that contain protein or peptide antigens are more likely to stop and counteract the harmful immune reactions in allergies, which might be considered a new way to treat allergies. One of the major advantages of using nanotechnology in the management of allergic diseases is their ability to create immune tolerance that is antigen specific. This means it can help and control the way our immune system reacts and responds to the unwanted reactions that are commonly noticed in current treatments (Johnson et al., 2020). Also, when we use delivery systems based on nanotechnology, it helps make food allergens more available in the body and delivers them right where they're needed. This makes allergy diagnosis and treatment more effective because it targets the delivery exactly where it's needed (Rai et al., 2023).

Nanoparticles and Prevention from Allergic Reactions through Immunomodulation

Nanoparticles possess the ability to prevent allergies by changing how the immune system works through immunomodulation. The size of these antigen loaded nanoparticles, being so small and minute, helps to increase their permeability hence they are able to enter the tissue, facilitating the delivery to the target areas like blood vessels and lymph nodes. Some nanoparticles made up of amorphous silica have been noted to be even more efficient at penetration through skin and localized lymph nodes. Research has also shown that nanoparticles can boost up the potential of immunomodulation. For example, amorphous silicon dioxide nanoparticles when delivered through the skin in an allergy model help control the immune system way better. Hence, we can easily say that they are effective in preventing allergic reactions through immunomodulation. The physicochemical properties of nanoparticles, including their composition, size, charge etc. actually makes them useful for treating the allergies. They have the ability to activate and differentiate T-cells which makes them better to fight off the allergies. Nanoparticles also strengthen the immune system for the allergen uptake of allergens responsible to trigger allergies.

Conclusion

Incorporating the traditional immune-boosting methods with the improvements in nanotechnology presents a new approach to enhancing immune responses and effective management of immune-related diseases. The target specific abilities of nanotechnology, mostly in drug delivery and immune modulation is a huge step in the field of medical science. These improvements are impactful mainly in the fields of cancer immunotherapy and management of autoimmune and allergic conditions. These are the areas where targeted treatments can improve outcomes to a great extent and where precise modulation of the immune system is important. As nanotechnology makes progress, deep understanding of the complex interactions between nanomaterials and the immune system is necessary. This understanding of interactions will allow us to use this technology to great extent while also ensure that it remains safe and effective. Combining these advanced technologies with traditional methods may transform the approaches for addressing immune-related health challenges, laying foundations for more effective and personalized treatments in the future.

REFERENCES

Betts, J. G., Young, K. A., Wise, J. A., Johnson, E., Poe, B., Kruse, D. H., Korol, O., Johnson, J. E., Womble, M., and DeSaix, P. (2013). 21.5 The Immune Response against Pathogens - Anatomy and Physiology

Boraschi, D., Italiani, P., Palomba, R., Decuzzi, P., Duschl, A., Fadeel, B., and Moghimi, S. M. (2017, December). Nanoparticles and innate immunity: new perspectives on host defense. In Seminars in immunology (Vol. 34, pp. 33-51). Academic Press.

Cassa Macedo, A., Oliveira Vilela de Faria, A., and Ghezzi, P. (2019). Boosting the immune system, from science to myth: analysis the infosphere with Google. *Frontiers in Medicine*, *6*, 165.

Chaplin, D. D. (2010). Overview of the immune response. *Journal of Allergy and Clinical Immunology*, *125*(2), S3-S23.

Chehelgerdi, M., Chehelgerdi, M., Allela, O. Q. B., Pecho, R. D. C., Jayasankar, N., Rao, D. P., and Akhavan-Sigari, R. (2023). Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. *Molecular Cancer*, *22*(1), 169.

Chountoulesi, M., and Demetzos, C. (2020). Promising nanotechnology approaches in treatment of autoimmune diseases

of central nervous system. *Brain Sciences*, *10*(6), 338.

Chuang, S. T., Conklin, B., Stein, J. B., Pan, G., and Lee, K. B. (2022). Nanotechnology-enabled immunoengineering approaches to advance therapeutic applications. *Nano Convergence*, *9*(1), 19.

Dang, B. T. N., Kwon, T. K., Lee, S., Jeong, J. H., and Yook, S. (2024). Nanoparticle-based immunoengineering strategies for enhancing cancer immunotherapy. *Journal of Controlled Release*, *365*, 773-800.

Debele, T. A., Yeh, C. F., and Su, W. P. (2020). Cancer immunotherapy and application of nanoparticles in cancers immunotherapy as the delivery of immunotherapeutic agents and as the immunomodulators. *Cancers*, *12*(12), 3773.

Dobrovolskaia, M. A., Shurin, M., and Shvedova, A. A. (2016). Current understanding of interactions between nanoparticles and the immune system. *Toxicology and Applied Pharmacology*, 299, 78-89.

Firestein, G.S., and Stanford, S.M. (2020). Mechanisms of inflammation and tissue repair. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Philadelphia, PA: Elsevier; 2020: chap 42.

Johnson, L., Duschl, A., and Himly, M. (2020). Nanotechnology-based vaccines for allergen-specific immunotherapy: Potentials and challenges of conventional and novel adjuvants under research. *Vaccines*, *8*(2), 237.

Kumbhar, P. R., Kumar, P., Lasure, A., Velayutham, R., and Mandal, D. (2023). An updated landscape on nanotechnology-based drug delivery, immunotherapy, vaccinations, imaging, and biomarker detections for cancers: recent trends and future directions with clinical success. *Discover Nano*, *18*(1), 156.

Mitarotonda, R., Giorgi, E., Eufrasio-da-Silva, T., Dolatshahi-Pirouz, A., Mishra, Y. K., Khademhosseini, A., and Orive, G. (2022). Immunotherapeutic nanoparticles: From autoimmune disease control to the development of vaccines. *Biomaterials Advances*, *135*, 212726.

Mitra, S., Paul, S., Roy, S., Sutradhar, H., Bin Emran, T., Nainu, F., and Mubarak, M. S. (2022). Exploring the immune-boosting functions of vitamins and minerals as nutritional food bioactive compounds: A comprehensive review. *Molecules*, *27*(2), 555.

Mobeen, H., Safdar, M., Fatima, A., Afzal, S., Zaman, H., and Mehdi, Z. (2022). Emerging applications of nanotechnology in context to immunology: A comprehensive review. *Frontiers in Bioengineering and Biotechnology*, *10*, 1024871.

Nanotechnology cancer therapy and treatment. (2023, September 30). National Cancer Institute. https://www.cancer.gov/nano/cancer-nanotechnology/treatment

Nicholson, L. B. (2016). The immune system. *Essays in Biochemistry*, *60*(3), 275-301.

Panda, A. K. (2012). Nanotechnology in vaccine development. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, *82*, 13-27.

Paris, J. L., de la Torre, P., and Flores, A. I. (2021). New therapeutic approaches for allergy: A review of cell therapy and bio- or nano-material-based strategies. *Pharmaceutics*, *13*(12), 2149.

Rai, M., Ingle, A. P., Yadav, A., Golińska, P., Trzcińska-Wencel, J., Rathod, S., and Bonde, S. (2023). Nanotechnology as a promising approach for detection, diagnosis and treatment of food allergens. *Current Nanoscience*, *19*(1), 90-102.

Shams, F., Golchin, A., Azari, A., Mohammadi Amirabad, L., Zarein, F., Khosravi, A., and Ardeshirylajimi, A. (2022). Nanotechnology-based products for cancer immunotherapy. *Molecular Biology Reports*, 1-24.

Smith, D. M., Simon, J. K., and Baker Jr, J. R. (2013). Applications of nanotechnology for immunology. *Nature Reviews Immunology*, *13*(8), 592-605.

Wagner, D. N., Marcon, A. R., and Caulfield, T. (2020). "Immune Boosting" in the time of COVID: selling immunity on Instagram. *Allergy, Asthma and Clinical Immunology*, *16*(1), 76.

Wu, P., Han, J., Gong, Y., Liu, C., Yu, H., and Xie, N. (2022). Nanoparticle-based drug delivery systems targeting tumor microenvironment for cancer immunotherapy resistance: current advances and applications. *Pharmaceutics*, *14*(10), 1990.

Zhao, B., Li, X., Kong, Y., Wang, W., Wen, T., Zhang, Y., and Zheng, X. (2022). Recent advances in nano-drug delivery systems for synergistic antitumor immunotherapy. *Frontiers in Bioengineering and Biotechnology*, *10*, 1010724.

Zhu, J., Chen, W., Sun, Y., Huang, X., Chu, R., Wang, R., and Ye, S. (2022). Recent advances on drug delivery nanoplatforms for the treatment of autoimmune inflammatory diseases. *Materials Advances*, 3(21), 7687-7708.

Chapter 34

Nano-Particles: The New Frontiers in Drug Delivery Systems

Farah Ijaz[1]*, Abdul Mateen[1], Muhammad Farhan Rahim[2], Sayyed Aun Muhammad[1], Muhammad Abid Hayat[3] Adnan Hassan Tahir[2], Shokat Ali[4] and Abdul Rauf[1]

[1]Department of Clinical Sciences, College of Veterinary and Animal Sciences, Jhang
[2]Department of Clinical Studies, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
[3]Jiangsu Key Laboratory of Medical Science and Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang 212013, China
[4]Department of Animal Genetics Breeding and Reproduction, College of animal Science and Technology Huazhong Agriculture university, Hongshan,430070, Wuhan, Hubei, China
*Corresponding author: farah.ijaz@uvas.edu.pk

ABSTRACT

In this modern technological era, it is becoming a hot topic of interest, and it is exciting to see new applications of nanoscience and technology in medical practice. NPs hold a tremendous ability as an effective drug delivery system because of their unaccountable properties. In this chapter, we have tried to overcome recent developments in nanotechnology and their use in medicine. It also presents the concepts and philosophy of precise medicine distribution. It goes on to explain and explore recent studies on nanoparticles and their materials in practice and how different therapeutic amalgams can be encapsulated to develop effective drug delivery systems.). It is important to understand how nanomaterials intermingle with the target cell-surface receptors and biological environment, release drugs, maintain therapeutic agent stability, administer multiple medicines, and comprehend the molecular mechanisms of cell signaling involved in the pathobiology of the disease under consideration.

KEYWORDS
Nano Technology, Drug delivery system, Nanoparticles and medicine

Received: 19-Jun-2024
Revised: 25-Jul-2024
Accepted: 18-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Ijaz F, Mateen A, Rahim MF, Muhammad SA, Hayat MA, Tahir AH, Ali S and Rauf A, 2024. Nano-particles: the new frontiers in drug delivery systems. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and AlternativeMedicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 292-301. https://doi.org/10.47278/book.CAM/2024.375

INTRODUCTION

The first big innovation that would lead to a momentous shift in the future of medicine was made more than 150 years ago by Michael Faraday, who formed gold particles on a nanoscale. Eventually, scientists combined these colloidal gold particles with antibodies to create an immune-gold mark, a target-specific staining technique. This can be seen as the forerunner of the more modern use of nanotechnology in drug delivery. Although liposomes and polymer micelles were initially created in the 1960s, the term "nanoparticle" (NP) did not appear until 2000. Dendrimers and NPs were initially introduced in the 1970s. In 1980, it was stated that micelles had been successfully developed as a drug delivery system (DDS). Block copolymers of polyethylene glycol (PEG), known as PEG-Polylysine, were developed in the 1990s. The United States National Nanotechnology project is the foundation of the submission of nanotechnology in the delivery of drugs in the current era. The optimal NP medication distribution strategy should maintain patient devotion, diminution side effects, increase competence, and lower inclusive costs through tailored delivery.

Drugs located on the inside of the nano-carriers include traditional chemotherapy agents and nucleic acids, indicating that they can play a role in both cytotoxic and gene therapy (Chen, 2015)

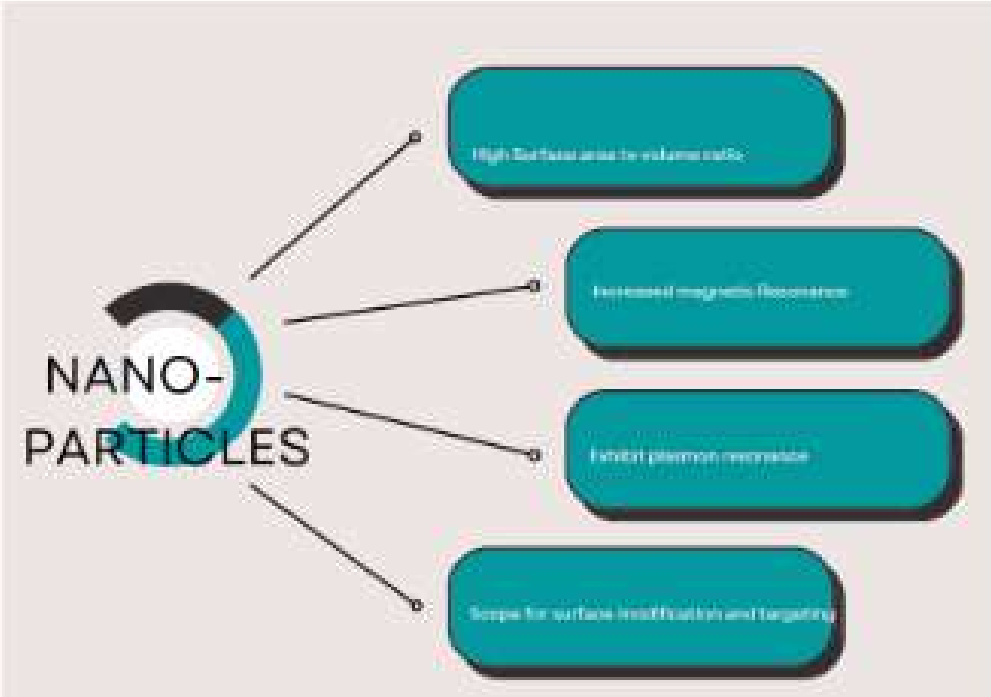
Nanoparticles are defined as edifices with at least one dimension and sizes ranging from 1 to 100 nm by the National Nanotechnology Ingenuity. However, for particles up to several hundred nanometers in size, the prefix "nano" is frequently active. Because they are more spontaneously absorbed by cells than bigger molecules, nanocarriers with ideal biophysical and biological properties can be efficiently employed as delivery systems for formerly accessible bioactive substances.(Wilczewska et al., 2012).

"Pharmaceutical nanotechnology," the rapidly growing field in pharmaceutical sciences, eventually offers innovative gadgets, predictions, and an extensive variety of uses that are projected to have a diagnosis of disease and their treatment(Bhatia, 2016). Recently, Nanopharmaceuticals have shown massive capacity for drug delivery systems, because

they act as a vehicle for the progressive and spatial supply of bioactive substances along with medicine and it is also effective for diagnostics. For this, it also shows a great concern for the supply of intelligent materials for tissue engineering. Through the practice of its nanoengineered gadgets, this field has become reputable for medication administration, finding, prognosis, and handling of diseases(Wagner et al., 2006). Therapeutic nanotechnology is the use of nanoscale items that can be improved in a variety of ways to boost their possessions.

The distinctive belongings that medicines with nanoscale modifications offer include extended circulation, better drug localization, increased medication efficacy, etc. Drug delivery and the entire medical services system have undergone revolutionary changes thanks to a variety of pharmacological nanotechnology classifications that are also recognized as nanopharmaceuticals. These systems have yielded polymeric nanoparticles, liposomes, magnetic nanoparticles, quantum dots, dendrimers, carbon nanotubes, metallic nanoparticles, and polymeric nanoparticles.

Pharmacological nanotechnology can significantly impact infection treatment and open new visions in the treatment of diseases at the molecular level through the use of nanopharmaceuticals (Wagner et al., 2006).



Nevertheless, recent discoveries on healthiness jeopardize their use in the therapeutic profession. Researchers can determine numerous disquieting matters, with safety, bioethical anxieties, noxiousness fears, and functional and pharmacologic encounters. There is still a shortage of evidences and approvals for the harmless submission of these materials and skills based on nanotechnology amid investigators nowadays. Subsequently, the field of therapeutic nanotechnology is in the beginning. The types of nanopharmaceuticals with their maximum substantial claims and the acquaintance presently accessible on the health risks connected with nanoparticles are abridged in this chapter.

Manufacturing of Nanoparticles

There are many methods to create nanoparticles which can be produced chemically or biologically.

Chemical synthesis procedures have presented some undesirable influences because sometimes they include destructive elements that are adsorbed onto their surface. Biologically justifiable alternates for chemical and physical processes in the manufacture of nanoparticles (Konishi et al., 2007) Include biological methods that employ microbes, enzymes, fungi, plants, or plant extracts(Ahmad et al., 2011) . The construction of these ecologically adequate techniques for the synthesis of nanoparticles is becoming an important area of nanotechnology, especially for the formation of Silver nanoparticles (Dubchak et al., 2010).

There are 3 widely used methods for synthesis of Nano Particles.

Physical

Various techniques, such as gas-phase statement, electron ray lithography, pulsed laser excision, laser-induced pyrolysis, precipitate ball grinding, and aerosol, all are the part of physical process (Rane et al., 2018). In laser ablation synthesis, a commanding laser beam attacks the target material to produce nanomaterials. The preliminary material or precursor vaporizes and crops nanoparticles because of the intense irradiation of the laser during the ablation process of the laser. Abundant nanomaterials, such as oxide amalgams, metal nanoparticles, carbon nanomaterials, and ceramics, can be formed using this method (Zhang et al., 2017). One method for manufacturing nanoscale gadgets at low cost from huge particles to

smaller ones is machine-driven grinding. It is an operative way to associate different phases and a good technique for producing nanocomposites at a big scale in less time (Zhuang et al., 2016). Another important skill in this regard is Lithography. It uses electrons/ focused light to generate nanoarchitectures. Lithography is further divided into two types i.e., maskless and mask-based lithography. The technique of masked nanolithography distributes nanopatterns over a large surface area by using an encoded mask or template. Techniques included in this are photolithography, soft lithography, and nanoimprint lithography (Xu and Chen, 2020).

Another special kind of nanomaterial manufacturing method is Ball-milled carbon nanoparticles that are related to the utilization of energy that can be applied to energy adaptation, energy storage, and environmental cleaning (Lyu et al., 2017). Electrospinning is one of the most central methods for producing nanostructured materials this method is widely utilized to create nanofibers from a diversity of different materials and most frequently from polymers. The method of electrospinning has been used to create hollow polymers and core-shell, organic, inorganic, and hybrid compounds (P. S. Kumar et al., 2014). Miniature atom clusters are materially homeless during splattering statements because the goal surface is inundated with strong ions of gas (Son et al., 2017). The splattering method is additional attractive and reasonable than electron-beam lithography because it produces nanomaterials with a prearrangement closer to the targeted element and fewer impurities (Nie et al., 2009).

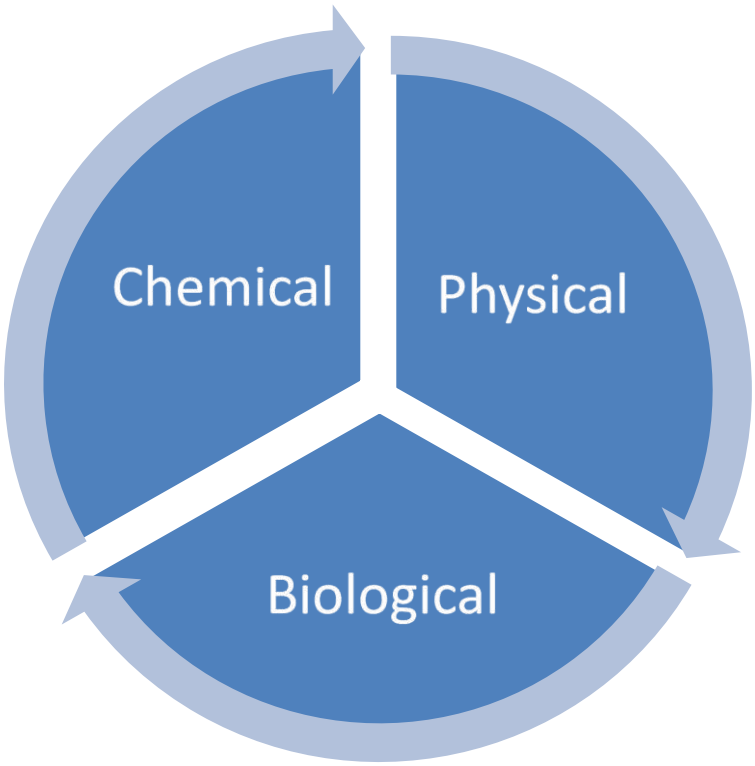


Fig: Methods For synthesis of Nano Particles

Chemical

In therapeutic imaging applications, magnetic nanoparticles are shaped using a variety of chemical processes, such as micro-level emulsions, sol-gel amalgamations, sonochemical reactions, hydrothermal reactions, precursor hydrolysis and thermolysis, flow injection syntheses, and electrospray blends (Elfeky et al., 2020). Chemical vapor deposition techniques are essential in the synthesis of carbon-based nanomaterials. A precursor is considered excellent for chemical vapor deposition if it has a long shelf life, low cost, strong evaporation stability, high chemical purity, and no hazards. Moreover, no pollutants should be left behind after it break down (Malandrino, 2009). Several techniques are used in the chemical pathway, such as thermal breakdown, coprecipitation, microemulsion, hydrothermal, electrochemical deposition, and sonochemical (Ijaz et al., 2020). Using the organic cloud deposition method, two types of graphene are produced one is formed from Ni and Co catalysts called complex graphene catalysts, and the other is formed from Cu catalysts called monolayer graphene.

One mutual wet chemical practice used in the growth of nanomaterials is the sol-gel system. A big range of superior nanomaterials which are based on metal-oxides are formed using this method. In addition to its many benefits, the sol-gel process is quite inexpensive. It produces homogenous material, requires moderate dispensation temperatures, and offers a straightforward method for creating complex nanostructures and composites(Parashar et al., 2020). One popular method for creating two-dimensional nanomaterials is the chemical vapor statement, which is also a useful technique for creating high-quality nanomaterials in general (Wu et al., 2016). Recently, there has been a lot of interest in engineering nanomaterials in which the hydrothermal technique, which is microwave-assisted, is used to associate the advantages of both microwave and hydrothermal developments (Nie et al., 2009). The utilization of the reverse micelle technique to create magnetic-based lipase-immobilized used Nanoparticles is highlighted by the NPs that are produced, which are incredibly small and

monodispersed in nature (Yi et al., 2017). It is possible to modify the diameters of the pores of nanoporous materials by adding more pore-expanding agents or varying the length of the carbon chain in the surfactant. Many nanostructured materials, including mesoporous polymers, carbonaceous nanospheres, porous alumina, single-crystal nanorods, and mesoporous N-doped graphene, can be created using the soft template technique (Baig et al., 2021) It is intriguing and useful to use solvothermal and hydrothermal techniques to make a lot of nano-geometries of ingredients, including nanowires, and nanorods. Nanospheres and nanosheets (Dong et al., 2020)..

Biosynthesis

He biological or Biosynthesis process incorporates several elements, such as fungus-, algae-, bacteria-, yeast-, and yeast-mediated processes (Saravanan et al., 2021). Microorganisms can biosynthesize nanoparticles is a biologically generous technology. These microorganisms consist of algae, fungi, bacteria, and Actinomycetes. Depending on where the nanoparticles are located, the creation of the particles might be either extracellular or intracellular..(Hulkoti and Taranath, 2014).

In several ways, biogenic enzymatic nanoparticles are vastly superior to chemically produced nanoparticles (Iqbal et al., 2020).). The latter techniques, while capable of producing large amounts of nanoparticles (NPs) with a specified shape and size in a short period, are complex, antiquated, costly, and ineffective. They also produce potentially dangerous toxic wastes that are bad for human health as well as the environment (S. Khan et al., 2021).

The formation of biological nanoparticles is further divided according to the use of microorganisms.

Synthesis of Nanoparticles using Fungi

The majority of germs are called fungi, and they are employed in many fields of study, including bioremediation, the synthesis of enzymes, nanotechnology, and more (Mohmed et al., 2017). Due to their many advantages over bacteria in the formation of nanoparticles, fungi have a lot of attractiveness and attention in producing nanoparticles made up of metal (Shaheen et al., 2021). Significant advantages include the ease of downstream processing and scaling up, the viability from an economic standpoint, and the presence of mycelia, which offers a greater surface area (Mohmed et al., 2017). Fungal-based NP is produced by a biomineralization mechanism that includes the reduction of different ions of metal by internal and external enzymes and biomolecules. Fungi generate a vast number of nanoparticles in comparison to bacteria. More proteins are secreted by fungi, which increases the formation of nanoparticles (Danaraj et al., 2022).

Synthesis of Nanoparticles using Yeast

Yeast cell mass extracellular synthesis of nanoparticles may be advantageous for simple downstream processing and large-scale manufacture. Significant changes in size, particle location, monodispersity, and features are produced by distinct methods that yeast strains of various genera adopt to generate nanoparticles (Sivaraj et al., 2020). In most of the yeast species under investigation, these molecules stabilize the complexes and define the mechanism underlying the production of nanoparticles. The capability of a yeast cell to transform ingested metallic ions into intricate polymer molecules that are not harmful to the cell is known as resistance (Shu et al., 2020).

Synthesis of Nanoparticles using Bacteria

Bacteria are suited for study because they are more abundant in the environment and can cope with adversative circumstances. They can also grow quickly, are reasonable to raise, and require little management. It is simple to control growth parameters including temperature, oxygenation, and incubation period. It is also known that bacteria can generate many inorganic compounds both within and outside of cells. For instance, the bioreduction technique is used to create Ag-NPs utilizing microorganisms (Marooufpour et al., 2019). By using the bioreduction process, bacteria are therefore potentially used as a biological workshop for creating NPs such as different metallic nanoparticles like silver, gold, zirconium, titanium oxide, cadmium, magnetite, selenium, palladium, platinum, magnetite, titanium dioxide, and other metal NPs (Hashem et al., 2021) .

Synthesis of Nanoparticles using Actinomycetes

As minor metabolites, these Actinomycetes are very capable of producing antibiotics and work against different gems (Jagannathan et al., 2021) .). It has been discovered that Actinomycetes play a major part in the synthesis of metal nanoparticles((Hassan et al., 2019) . It has been discovered that Actinomycetes play a major part in the synthesis of metal nanoparticles (Gupta et al., 2019) . Actinomycetes generate stable, well-polydisperse nanoparticles that have strong antimicrobial effectiveness in contradiction of a lot of illnesses (Mabrouk et al., 2021).

- Synthesis of nanoparticles using the plant.

Successful nanoparticle synthesis has been achieved using plant materials such as flowers, leaves, shoots, roots stems, barks, seeds, and their metabolites (Sibuyi et al., 2021). Highly intelligent and helpful to human needs are low-cost, environmentally friendly plants.

Types of Nano-Particles

The form, size, and chemical properties of nanoparticles (NPs) determine their classification into multiple classes.

According to their physical and chemical characteristics, the most well-known and widely used kinds of nanoparticles are described in this literature (I. Khan et al., 2019).

NPs derived from carbon. The two primary classes of carbon-based NPs are carbon nanotubes (CNTs) and fullerenes. Round carbon molecules known as fullerenes (C60) are made up of carbon atoms joined via sp2 hybridization. About 28 to 1500 carbon atoms are used to make the spherical structure, and the diameters of single layers range from 8.2 nm to 4–36 nm for multi-layered fullerenes (I. Khan et al., 2019). Fullerenes contain many nanomaterials made of round void cages, including allotropic shapes of carbon. Commercial concentration has been piqued by their electrical permeability, high strength, framework, electron attraction, and flexibility (Mallikarjunaiah et al., 2020).

Nanotubes of carbon (CNT)

Carbon nanotubes (CNTs) are as tiny as 0.7 nm but only for single-layered CNTs and for more than 100 nm for complicated/multi-layered CNTs. Their lengths mostly vary between a few microns to several millimeters. CNTs are created from graphene foil with a honeycomb-like structure of atoms that are divided into muffled coils. These look like a graphite coat developing on top of itself in structure (Song et al., 2018) . The rolled pieces are called single-walled (SWNTs), double-walled (DWNTs), or multi-walled carbon nanotubes (MWNTs) since they can have one, two, or more walls. To synthesize them, carbon precursors—especially the atomic ones—are frequently deposited. Using an electric arch or laser, carbons are evaporated from graphite and placed on metallic particles. They have recently been made by the chemical vapor deposition (CVD) technique (Mohamed and Mohamed, 2020).

Metal Nanoparticles

Metals are converted into nanometric scales to create metal-based nanoparticles by either constructive or destructive methods. It is possible to produce nanoparticles from almost any metal. For the synthesis of nanoparticles, cadmium, aluminum, copper, cobalt, gold, lead, iron, silver, and zinc are frequently utilized (Ijaz et al., 2020). The scope variety of 10 to 100 nm, as well as surface features such as hole size, it's high superficial-to-capacity ratio, their superficial charge with thickness, sparkling assemblies, spherical forms, color, reactivity, and sensitivity, are some of the unique characteristics of nanoparticles (Kankala et al., 2020).). Metal NPs are synthesized using metal precursors. These Nano Particles have distinct optoelectrical goods unpaid to restricted surface plasmon resonance (SPR)(Fouda et al., 2018) . Cu, Au, and Ag are examples of noble metal and alkali NPs that display a discernible fascination band in the solar electromagnetic spectrum.

Metal Oxide Nanoparticles Synthesis

In extremely small amounts, metals like Copper and silver, for instance, can be extremely toxic to microorganisms (Martínez-Alcalá and Bernal, 2020). Metals have been widely used as antimicrobial agents in a diversity of contexts in industry, medical services, and agribusiness in general because of their biocidal effect.

Metals can be utilized as additions because, in contrast to other antibacterial agents, they remain viable under current manufacturing settings(Karim et al., 2020). These days, these metal-based additions originate in a diversity of forms, for example, salts, particles, and ions exchanged or absorbed in different carriers, hybrid structures, and more (Silbernagel et al., 2020). Numerous metallic oxide nanoparticles have been investigated for the electrochemical identification of biomolecules, including ZnO, NiO, MnO_2, TiO_2, Fe_2O_3, and Co_3O_4 (Immanuel et al., 2019) .

Due to their special qualities, CuO-NPs are valuable in an extensive range of submissions, such as compounds, antibacterial materials, sensors, and extremely strong materials. Can also come into contact and interface with other nanoparticles because of the high external area-to-volume ratio (Hasanin et al., 2022).). It was recently discovered that CuO-NPs outperformed Ag-NPs in their antibacterial activity against B subtilis and E. coli. Because CuO-NPs are polymer-coated, they are frequently used as antibacterial agents in paints and textiles (Wang et al., 2015). Owing to their photolytic properties, ZnO and TiO_2 are frequently utilized. MoO_3, Bi_2O_3, $LiCoO_2$, CeO_2, and CrO_2 are the bases for more intriguing metal-oxide nanoparticles.

Diesel fuels are increasingly using CeO_2 as the combustion catalyst to improve the quality of the emissions (Farré and Barceló, 2012).). For iron oxide nanoparticles (IO-NPs) to provide high magnetization values, repeatable quality, and acceptable biocompatibility in biological settings, they need to be extremely crystalline, monodisperse, and soluble in water (Wallyn et al., 2019) The two forms of superparamagnetic IONP-based nanoparticles are superparamagnetic iron oxide (SPIO) nanoparticles with a usual crystal dimension ranging from 50–100 nm and ultra-small superparamagnetic iron oxide (USPIO) nanoparticles with a size below 50 nm. The medical community has given these two families of IO-NPs a lot of attention, particularly since they could represent the subsequent generation of MRI contrast managers. They are also being investigated as potential vectors for gene and drug delivery (Frantellizzi et al., 2020). The biodistribution of these nanoparticles can be transformed by applying an outside magnetic field. When SPIO-NPs with the right surface chemistry are used in vivo, they can be used for drug administration, tissue regeneration, immunoassay, biological fluid detoxification, hyperthermia, MRI contrast enhancement, and cell departure. For all of these biomedical claims, nanoparticles with high magnetic induction values sizes less than 100 nm, and thin particle diameter distributions are necessary (Elkhenany et al., 2020) . Generally, SPIONs are composed of two structural configurations: (i) a biocompatible polymer coated around a core of magnetic particles (maghemite, γ-Fe_2O_3), or (ii) SPIO-NPs placed inside the holes of a permeable biocompatible polymer (Chen et al., 2020).

Ceramic Nanoparticles

Nonmetallic inorganic solids, or ceramic NPs, are produced by heating and cooling.

They are dense, formless, porous, polycrystalline, and hollow, among other sizes and forms. Scholars are showing more interest in nanoparticles of this kind because of their usage in the process of photo-degradation of different dyes, catalysis, imaging implications, and photocatalysis (Ayode Otitoju et al., 2020).

NPs in Semiconductors

Semiconductor materials are widely used in the literature due to their characteristics, which lie in between those of metals and nonmetals (Terna et al., 2021). Semiconductor NPs have large bandgaps, hence bandgap tuning significantly altered their characteristics. They are therefore essential to electronic devices, photocatalysis, and photo optics. Numerous semiconductor nanoparticles (NPs) are especially effective in water-piercing claims because of their ideal bandgap and band-edge placements (Abdullah, 2022).

Polymeric Nanoparticles

In the literature, these are known as polymer nanoparticles (PNPs) and are often based on organic materials (Madkour, 2019). Their forms are usually either nano-spherical or nano-capular. The other molecules are adsorbed at the external edge of the round superficial, while the earlier are overall solid mass containing matrix particles. In the latter instance, the unit comprises an entirely dense mass (Saifullah et al., 2019). PNPs have several applications in the literature because they are easy to functionalize. There is another specialist field named Lipid nanotechnology that deals with the creation and production of sterol nanoparticles for many uses, including cancer treatment delivery and RNA release (Husen, 2020).

Alloy: Compared to their bulk samples, alloy nanoparticles display distinct structural characteristics. Ag flakes are most frequently employed because Sliver has the best electrical conductivity of all metallic fillers and, in contrast to many other metallic substances, their also oxides have comparatively greater conductivity. The features of bimetallic alloy nanoparticles are impacted by both metals and biological organisms and they have more benefits than regular metallic NPs.(Mohl et al., 2011)

Drug Distribution and the Role of Nanotechnology

Conventional DDS distribute medications to bodily cells in an indifferent manner, potentially resulting in detrimental outcomes such as adverse reactions, drug resistance, and decreased drug concentration at the intended site. By regulating the rate, duration, and location of a drug's release in the body, DDS enhances efficiency and safety when medicinal chemicals are introduced into the body, according to the definition provided by the National Institute of Health in the United States. The shortcomings of conventional DDSs are numerous and include low therapeutic effectiveness, side effects, low drug loading capacity, plasma drug level fluctuations, poor bioavailability, and lack of target delivery.

For illustration, the traditional method of delivering drugs to the tumor cells may have adverse effects on healthy tissues, such as nephrotoxicity, neurotoxicity, and cardiotoxicity this all is explained when while treating cancer. These shortcomings have stimulated scientists to learn more about novel Drug Delivery Systems. A brief note about the fact that how nanotechnology can resolve these problems can be initiated in the way that medicines are brought into use and nanoparticles (NP). The use of the medication or therapeutic product; the release of the medication's active ingredient; and the transportation of the active ingredient across the biological membrane to the intended site of action comprise the three primary divisions of the drug delivery process.

Utilizing NPs to help deliver and target medicinal, therapeutic, and diagnostic substances to the cells is one way that nanotechnology is used in DDS. Drug delivery to the target site should be possible with the drug-NP combination without causing gastrointestinal tract degradation or lowering drug activity. Second, it should decrease side effects and attack the targeted cells without harming other cells.

Why does NPS Enhance Medication Delivery?

Because of their unique chemical and physical characteristics, NPs are effective drug delivery systems (DDSs) with the potential to enhance the bioavailability of drugs, drug-carrying capacity, drug stability inside the organism, controlled absorption, and specialized administration (Grady, 2005).

Because nanoparticles have unique absorption mechanisms including absorptive endocytosis and can withstand breakdown in the gastrointestinal tract, they boost the bioavailability of medicines. Biological membranes allow the medication included in the NP to diffuse readily. Drug permeability, hydrophobicity, and solubility are all altered by drug-polymer attachment. Reducing solubility, boosting ionic interactions between the drug and matrix, and optimizing drug load absorption can all increase the drug loading capacity.

Moreover, the NPs have a lengthy half-life in the blood. Because the drug-attached NP has a particle surface covered in hydrophilic, biodegradable copolymers, the immune system cannot assault it. Surface decoration commonly uses poly-lactic acid (PLA), poly-glycolic acid (PGA), and related co-polymers (Stylios et al., 2005).

The self-regulating mechanism of medication release contributes to lessening adverse effects and plasma fluctuation. Polymers, which are biodegradable and can break down in a controlled manner to release drugs at the site, are one method for controlling the release of pharmaceuticals in specific areas. 2) The pores of the polymer can be changed to control how

quickly or slowly drugs diffuse; 3) The surface area and fusion distance of the NPs can be altered by adjusting their size. Smaller sizes have a larger surface area and faster drug release and dissolution.

Using swelling, diffusion, degradation, or erosion, the medicines are free by the matrix. Mechanical pumping, osmotic pressure, and electrokinetic transportation all regulate the drug's release.

Drugs are delivered to particular sites by DDS, which is based on nanotechnology, through ligand attraction. Ligands can be added to the NP surface, and through biorecognition, these ligands can bind to specific areas on the surface of the targeted cell. Through receptor-mediated endocytosis, the NPs penetrate the target cells. NPs grow into endosomes inside the cell. Subsequently, endosomes combine to generate big endosomes, also known as lysosomes. Lastly, by breaking down the polymeric NP shell, medicinal medications can be dispensed in a controlled manner in reaction to enzymes or an acidic pH

In the end, NPs in DDS improve patient comfort by enabling the use of extremely harmful, poorly soluble, unstable medications.

Conclusion

Abundant research on the use of NPs as a food crop has been shown, and these educations significantly assist in our understanding of the NPs' pathway, predominantly with affection to safety anxieties and possible impacts on tissue gathering. Evaluating the GIT tract's chemical and biological activity is crucial during the product development process. To aid in the creation of new products, these investigations might initially be carried out in vitro, particularly about the stability of the materials and their resistance to typical digestive circumstances.

It is crucial to assess the bio-accessibility and bioavailability of NPs, understand their route through the GIT, from the mouth to the colon, evaluate chemical changes that occur during digestion and the effective quantities that reach the intestine and will be available for absorption, before conducting gut microbiota studies. The various phases of digestion, variations in pH, and the presence of enzymes will cause chemical and physical changes that could result in changes to the chemical and physical characteristics of NPs (agglomeration, dissolution, etc.). The best model to test NPs might be a standardized one that incorporates all phases of digestion, like the INFOGEST protocol.

Research has been done on the relationship between various NP kinds and the gut to better understand their effects and determine how best to apply them to promote human health and well-being. Testing NPs' impact on single bacteria or species that are representative of the gut microbiome is the first strategy. The microorganisms that are screened may be species associated with infectious illnesses or representative of helpful bacteria. A significant portion of these investigations replicate the conditions found in the colon by performing fermentation trials using human feces as substrates. The testing of various doses and conditions, including modifications to the morphology of the bacteria, is made possible by the use of fecal samples.

Animal models may be employed after cell line toxicity has been confirmed. In fact, in vivo research is a great way to learn more about the potential uses of NPs. It makes it possible to gather biochemical information, track the encapsulated compound's routes of absorption and secretion, and determine whether NPs are present in organs. Additionally, it makes it possible to gather animal feces for analysis during the trial and characterize changes in the diversity and metabolic chemicals produced by the gut microbiota. Furthermore, it is possible to evaluate prebiotic activity, growth-promoting properties, antibacterial activity, and inhibition of particular microbiota groups. The literature indicates that the gut microbiota can be impacted by NPs' physical format and dose, although there is no clear pattern in terms of size.

However, it is clear that dosage matters because excessive dosages cause significant changes in the microbiota and/or elicit clinical symptoms that may result in dysbiosis of the microbiota. Furthermore, NPs may exacerbate symptoms brought on by dysbiosis of the microbiota. The most researched NPs are inorganic ones (TiO2, Ag, and SiO2), which have been shown to have a modest to significant effect on the makeup and activity of the gut microbiota.

It is important to conduct additional research to enhance in vitro models and closely resemble in vivo settings to prevent in vivo animal studies that involve animal sacrifice. By the INFOGEST protocol, our research team has optimized a continuous GIT process that comprises an absorption stage following stomach and intestinal digestion. Following absorption, research is being done on how the molecules interact with blood cells and how to include other significant cell lines to mimic the tissues of other significant organs and forecast the full pharmacokinetic pathway of the metabolized compounds.

REFERENCES

Abdullah, B. J. (2022). Size effect of band gap in semiconductor nanocrystals and nanostructures from density functional theory within HSE06. *Materials Science in Semiconductor Processing*, *137*, 106214. https://doi.org/10.1016/j.mssp.2021.106214

Ahmad, N., Sharma, S., Singh, V. N., Shamsi, S. F., Fatma, A., and Mehta, B. R. (2011). Biosynthesis of Silver Nanoparticles from Desmodium triflorum: A Novel Approach Towards Weed Utilization. *Biotechnology Research International*, *2011*, 1–8. https://doi.org/10.4061/2011/454090

Ayode Otitoju, T., Ugochukwu Okoye, P., Chen, G., Li, Y., Onyeka Okoye, M., and Li, S. (2020). Advanced ceramic components: Materials, fabrication, and applications. *Journal of Industrial and Engineering Chemistry*, *85*, 34–65. https://doi.org/10.1016/j.jiec.2020.02.002

Baig, N., Kammakakam, I., and Falath, W. (2021). Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. *Materials Advances*, *2*(6), 1821–1871. https://doi.org/10.1039/D0MA00807A

Bhatia, S. (2016). Nanoparticles Types, Classification, Characterization, Fabrication Methods and Drug Delivery Applications. In S. Bhatia (Ed.), *Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae* (pp. 33–93). Springer International Publishing. https://doi.org/10.1007/978-3-319-41129-3_2

Chen, B.-W., He, Y.-C., Sung, S.-Y., Le, T. T. H., Hsieh, C.-L., Chen, J.-Y., Wei, Z.-H., and Yao, D.-J. (2020). Synthesis and characterization of magnetic nanoparticles coated with polystyrene sulfonic acid for biomedical applications. *Science and Technology of Advanced Materials*, *21*(1), 471–481. https://doi.org/10.1080/14686996.2020.1790032

Danaraj, J., Periakaruppan, R., Usha, R., Venil, C. K., and Shami, A. (2022). Chapter 15 - Mycogenic nanoparticles: Synthesis, characterizations and applications. In K. A. Abd-Elsalam, R. Periakaruppan, and S. Rajeshkumar (Eds.), *Agri-Waste and Microbes for Production of Sustainable Nanomaterials* (pp. 357–373). Elsevier. https://doi.org/10.1016/B978-0-12-823575-1.00005-6

Dong, Y., Du, X., Liang, P., and Man, X. (2020). One-pot solvothermal method to fabricate 1D-VS4 nanowires as anode materials for lithium-ion batteries. *Inorganic Chemistry Communications*, *115*, 107883. https://doi.org/10.1016/j.inoche.2020.107883

Dubchak, S., Ogar, A., Mietelski, J. W., and Turnau, K. (2010). Influence of silver and titanium nanoparticles on arbuscular mycorrhiza colonization and accumulation of radiocaesium in Helianthus annuus. *Spanish Journal of Agricultural Research*, *8*, 103–108.

Elfeky, A. S., Salem, S. S., Elzaref, A. S., Owda, M. E., Eladawy, H. A., Saeed, A. M., Awad, M. A., Abou-Zeid, R. E., and Fouda, A. (2020). Multifunctional cellulose nanocrystal /metal oxide hybrid, photo-degradation, antibacterial and larvicidal activities. *Carbohydrate Polymers*, *230*, 115711. https://doi.org/10.1016/j.carbpol.2019.115711

Elkhenany, H., Abd Elkodous, M., Ghoneim, N. I., Ahmed, T. A., Ahmed, S. M., Mohamed, I. K., and El-Badri, N. (2020). Comparison of different uncoated and starch-coated superparamagnetic iron oxide nanoparticles: Implications for stem cell tracking. *International Journal of Biological Macromolecules*, *143*, 763–774. https://doi.org/10.1016/j.ijbiomac.2019.10.031

Farré, M., and Barceló, D. (2012). Chapter 1—Introduction to the Analysis and Risk of Nanomaterials in Environmental and Food Samples. In M. Farré and D. Barceló (Eds.), *Comprehensive Analytical Chemistry* (Vol. 59, pp. 1–32). Elsevier. https://doi.org/10.1016/B978-0-444-56328-6.00001-3

Fouda, A., EL-Din Hassan, S., Salem, S. S., and Shaheen, T. I. (2018). *In-Vitro* cytotoxicity, antibacterial, and UV protection properties of the biosynthesized Zinc oxide nanoparticles for medical textile applications. *Microbial Pathogenesis*, *125*, 252–261. https://doi.org/10.1016/j.micpath.2018.09.030

Frantellizzi, V., Conte, M., Pontico, M., Pani, A., Pani, R., and De Vincentis, G. (2020). New Frontiers in Molecular Imaging with Superparamagnetic Iron Oxide Nanoparticles (SPIONs): Efficacy, Toxicity, and Future Applications. *Nuclear Medicine and Molecular Imaging*, *54*(2), 65–80. https://doi.org/10.1007/s13139-020-00635-w

Grady, W. M. (2005). Epigenetic events in the colorectum and in colon cancer. *Biochemical Society Transactions*, *33*(4), 684–688. https://doi.org/10.1042/BST0330684

Gupta, A., Singh, D., Singh, S. K., Singh, V. K., Singh, A. V., and Kumar, A. (2019). 10—Role of actinomycetes in bioactive and nanoparticle synthesis. In A. Kumar, A. K. Singh, and K. K. Choudhary (Eds.), *Role of Plant Growth Promoting Microorganisms in Sustainable Agriculture and Nanotechnology* (pp. 163–182). Woodhead Publishing. https://doi.org/10.1016/B978-0-12-817004-5.00010-5

Hasanin, M., Al Abboud, M. A., Alawlaqi, M. M., Abdelghany, T. M., and Hashem, A. H. (2022). Ecofriendly Synthesis of Biosynthesized Copper Nanoparticles with Starch-Based Nanocomposite: Antimicrobial, Antioxidant, and Anticancer Activities. *Biological Trace Element Research*, *200*(5), 2099–2112. https://doi.org/10.1007/s12011-021-02812-0

Hashem, A. H., Abdelaziz, A. M., Askar, A. A., Fouda, H. M., Khalil, A. M. A., Abd-Elsalam, K. A., and Khaleil, M. M. (2021). Bacillus megaterium-Mediated Synthesis of Selenium Nanoparticles and Their Antifungal Activity against Rhizoctonia solani in Faba Bean Plants. *Journal of Fungi*, *7*(3), Article 3. https://doi.org/10.3390/jof7030195

Hassan, S. E.-D., Fouda, A., Radwan, A. A., Salem, S. S., Barghoth, M. G., Awad, M. A., Abdo, A. M., and El-Gamal, M. S. (2019). Endophytic actinomycetes Streptomyces spp mediated biosynthesis of copper oxide nanoparticles as a promising tool for biotechnological applications. *JBIC Journal of Biological Inorganic Chemistry*, *24*(3), 377–393. https://doi.org/10.1007/s00775-019-01654-5

Hulkoti, N. I., and Taranath, T. C. (2014). Biosynthesis of nanoparticles using microbes—A review. *Colloids and Surfaces B: Biointerfaces*, *121*, 474–483. https://doi.org/10.1016/j.colsurfb.2014.05.027

Husen, A. (2020). Chapter 1—Introduction and techniques in nanomaterials formulation. In A. Husen and M. Jawaid (Eds.), *Nanomaterials for Agriculture and Forestry Applications* (pp. 1–14). Elsevier. https://doi.org/10.1016/B978-0-12-817852-2.00001-9

Ijaz, I., Gilani, E., Nazir, A., and Bukhari, A. (2020). Detail review on chemical, physical and green synthesis, classification, characterizations and applications of nanoparticles. *Green Chemistry Letters and Reviews*, *13*(3), 223–245. https://doi.org/10.1080/17518253.2020.1802517

Immanuel, S., Aparna, T. K., and Sivasubramanian, R. (2019). Chapter 5—Graphene–Metal Oxide Nanocomposite Modified Electrochemical Sensors. In A. Pandikumar and P. Rameshkumar (Eds.), *Graphene-Based Electrochemical Sensors for*

Biomolecules (pp. 113–138). Elsevier. https://doi.org/10.1016/B978-0-12-815394-9.00005-4

Iqbal, J., Abbasi, B. A., Ahmad, R., Shahbaz, A., Zahra, S. A., Kanwal, S., Munir, A., Rabbani, A., and Mahmood, T. (2020). Biogenic synthesis of green and cost effective iron nanoparticles and evaluation of their potential biomedical properties. *Journal of Molecular Structure*, *1199*, 126979. https://doi.org/10.1016/j.molstruc.2019.126979

Jagannathan, S. V., Manemann, E. M., Rowe, S. E., Callender, M. C., and Soto, W. (2021). Marine Actinomycetes, New Sources of Biotechnological Products. *Marine Drugs*, *19*(7), Article 7. https://doi.org/10.3390/md19070365

Kankala, R. K., Han, Y.-H., Na, J., Lee, C.-H., Sun, Z., Wang, S.-B., Kimura, T., Ok, Y. S., Yamauchi, Y., Chen, A.-Z., and Wu, K. C.-W. (2020). Nanoarchitectured Structure and Surface Biofunctionality of Mesoporous Silica Nanoparticles. *Advanced Materials*, *32*(23), 1907035. https://doi.org/10.1002/adma.201907035

Karim, N., Afroj, S., Lloyd, K., Oaten, L. C., Andreeva, D. V., Carr, C., Farmery, A. D., Kim, I.-D., and Novoselov, K. S. (2020). Sustainable Personal Protective Clothing for Healthcare Applications: A Review. *ACS Nano*, *14*(10), 12313–12340. https://doi.org/10.1021/acsnano.0c05537

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, *12*(7), 908–931. https://doi.org/10.1016/j.arabjc.2017.05.011

Khan, S., Naushad, M, Al-Gheethi, A., and Iqbal, J. (2021). Engineered nanoparticles for removal of pollutants from wastewater: Current status and future prospects of nanotechnology for remediation strategies. *Journal of Environmental Chemical Engineering*, *9*(5), 106160. https://doi.org/10.1016/j.jece.2021.106160

Konishi, Y., Ohno, K., Saitoh, N., Nomura, T., Nagamine, S., Hishida, H., Takahashi, Y., and Uruga, T. (2007). Bioreductive deposition of platinum nanoparticles on the bacterium *Shewanella algae*. *Journal of Biotechnology*, *128*(3), 648–653. https://doi.org/10.1016/j.jbiotec.2006.11.014

Kumar, P. S., Sundaramurthy, J., Sundarrajan, S., Babu, V. J., Singh, G., Allakhverdiev, S. I., and Ramakrishna, S. (2014). Hierarchical electrospun nanofibers for energy harvesting, production and environmental remediation. *Energy and Environmental Science*, *7*(10), 3192–3222. https://doi.org/10.1039/C4EE00612G

Lyu, H., Gao, B., He, F., Ding, C., Tang, J., and Crittenden, J. C. (2017). Ball-Milled Carbon Nanomaterials for Energy and Environmental Applications. *ACS Sustainable Chemistry and Engineering*, *5*(11), 9568–9585. https://doi.org/10.1021/acssuschemeng.7b02170

Mabrouk, M., Elkhooly, T. A., and Amer, S. K. (2021). Actinomycete strain type determines the monodispersity and antibacterial properties of biogenically synthesized silver nanoparticles. *Journal of Genetic Engineering and Biotechnology*, *19*(1), 57. https://doi.org/10.1186/s43141-021-00153-y

Madkour, L. H. (2019). Examples of Nanomaterials with Various Morphologies. In L. H. Madkour (Ed.), *Nanoelectronic Materials: Fundamentals and Applications* (pp. 141–164). Springer International Publishing. https://doi.org/10.1007/978-3-030-21621-4_6

Malandrino, G. (2009). Chemical Vapour Deposition. Precursors, Processes and Applications. Edited by Anthony C. Jones and Michael L. Hitchman. *Angewandte Chemie International Edition*, *48*(41), 7478–7479. https://doi.org/10.1002/anie.200903570

Mallikarjunaiah, S., Pattabhiramaiah, M., and Metikurki, B. (2020). Application of Nanotechnology in the Bioremediation of Heavy Metals and Wastewater Management. In D. Thangadurai, J. Sangeetha, and R. Prasad (Eds.), *Nanotechnology for Food, Agriculture, and Environment* (pp. 297–321). Springer International Publishing. https://doi.org/10.1007/978-3-030-31938-0_13

Marooufpour, N., Alizadeh, M., Hatami, M., and Asgari Lajayer, B. (2019). Biological Synthesis of Nanoparticles by Different Groups of Bacteria. In R. Prasad (Ed.), *Microbial Nanobionics: Volume 1, State-of-the-Art* (pp. 63–85). Springer International Publishing. https://doi.org/10.1007/978-3-030-16383-9_3

Martínez-Alcalá, I., and Bernal, M. P. (2020). Environmental Impact of Metals, Metalloids, and Their Toxicity. In *Metalloids in Plants* (pp. 451–488). John Wiley and Sons, Ltd. https://doi.org/10.1002/9781119487210.ch21

Mohamed, A. E.-M. A., and Mohamed, M. A. (2020). 2 - Carbon nanotubes: Synthesis, characterization, and applications. In K. A. Abd-Elsalam (Ed.), *Carbon Nanomaterials for Agri-Food and Environmental Applications* (pp. 21–32). Elsevier. https://doi.org/10.1016/B978-0-12-819786-8.00002-5

Mohl, M., Dobo, D., Kukovecz, A., Konya, Z., Kordas, K., Wei, J., Vajtai, R., and Ajayan, P. M. (2011). Formation of CuPd and CuPt Bimetallic Nanotubes by Galvanic Replacement Reaction. *The Journal of Physical Chemistry C*, *115*(19), 9403–9409. https://doi.org/10.1021/jp112128g

Mohmed, A., Hassan, S., Fouda, A., Elgamal, M., and Salem, S. (2017). Extracellular Biosynthesis of Silver Nanoparticles Using Aspergillus sp. And Evaluation of their Antibacterial and Cytotoxicity. *Journal of Applied Life Sciences International*, *11*(2), Article 2. https://doi.org/10.9734/JALSI/2017/33491

Nie, M., Sun, K., and Meng, D. D. (2009). Formation of metal nanoparticles by short-distance sputter deposition in a reactive ion etching chamber. *Journal of Applied Physics*, *106*(5), 054314. https://doi.org/10.1063/1.3211326

Parashar, M., Shukla, V. K., and Singh, R. (2020). Metal oxides nanoparticles via sol–gel method: A review on synthesis, characterization and applications. *Journal of Materials Science: Materials in Electronics*, *31*(5), 3729–3749. https://doi.org/10.1007/s10854-020-02994-8

Rane, A. V., Kanny, K., Abitha, V. K., and Thomas, S. (2018). Chapter 5—Methods for Synthesis of Nanoparticles and Fabrication of Nanocomposites. In S. Mohan Bhagyaraj, O. S. Oluwafemi, N. Kalarikkal, and S. Thomas (Eds.), *Synthesis of Inorganic*

Nanomaterials (pp. 121–139). Woodhead Publishing. https://doi.org/10.1016/B978-0-08-101975-7.00005-1

Saifullah, Md., Shishir, M. R. I., Ferdowsi, R., Tanver Rahman, M. R., and Van Vuong, Q. (2019). Micro and nano encapsulation, retention and controlled release of flavor and aroma compounds: A critical review. *Trends in Food Science and Technology*, *86*, 230–251. https://doi.org/10.1016/j.tifs.2019.02.030

Saravanan, A., Kumar, P. S., Karishma, S., Vo, D.-V. N., Jeevanantham, S., Yaashikaa, P. R., and George, C. S. (2021). A review on biosynthesis of metal nanoparticles and its environmental applications. *Chemosphere*, *264*, 128580. https://doi.org/10.1016/j.chemosphere.2020.128580

Shaheen, T. I., Salem, S. S., and Fouda, A. (2021). Current Advances in Fungal Nanobiotechnology: Mycofabrication and Applications. In A. Lateef, E. B. Gueguim-Kana, N. Dasgupta, and S. Ranjan (Eds.), *Microbial Nanobiotechnology: Principles and Applications* (pp. 113–143). Springer. https://doi.org/10.1007/978-981-33-4777-9_4

Shu, M., He, F., Li, Z., Zhu, X., Ma, Y., Zhou, Z., Yang, Z., Gao, F., and Zeng, M. (2020). Biosynthesis and Antibacterial Activity of Silver Nanoparticles Using Yeast Extract as Reducing and Capping Agents. *Nanoscale Research Letters*, *15*(1), 14. https://doi.org/10.1186/s11671-019-3244-z

Sibuyi, N. R. S., Meyer, M., Aboyewa, J. A., and Oguntibeju, O. O. (2021). *Green Synthesis of Metallic Nanoparticles using some Selected Medicinal Plants from Southern Africa and their Biological Applications*. https://doi.org/10.3390/plants10091929

Silbernagel, C., Aremu, A., and Ashcroft, I. (2020). Using machine learning to aid in the parameter optimisation process for metal-based additive manufacturing. *Rapid Prototyping Journal*, *26*(4), 625–637. https://doi.org/10.1108/RPJ-08-2019-0213

Sivaraj, A., Kumar, V., Sunder, R., Parthasarathy, K., and Kasivelu, G. (2020). Commercial Yeast Extracts Mediated Green Synthesis of Silver Chloride Nanoparticles and their Anti-mycobacterial Activity. *Journal of Cluster Science*, *31*(1), 287–291. https://doi.org/10.1007/s10876-019-01626-4

Son, H. H., Seo, G. H., Jeong, U., Shin, D. Y., and Kim, S. J. (2017). Capillary wicking effect of a Cr-sputtered superhydrophilic surface on enhancement of pool boiling critical heat flux. *International Journal of Heat and Mass Transfer*, *113*, 115–128. https://doi.org/10.1016/j.ijheatmasstransfer.2017.05.055

Song, R., Wang, Q., Mao, B., Wang, Z., Tang, D., Zhang, B., Zhang, J., Liu, C., He, D., Wu, Z., and Mu, S. (2018). Flexible graphite films with high conductivity for radio-frequency antennas. *Carbon*, *130*, 164–169. https://doi.org/10.1016/j.carbon.2018.01.019

Stylios, G. K., Giannoudis, P. V., and Wan, T. (2005). Applications of nanotechnologies in medical practice. *Injury*, *36*(4, Supplement), S6–S13. https://doi.org/10.1016/j.injury.2005.10.011

Terna, A. D., Elemike, E. E., Mbonu, J. I., Osafile, O. E., and Ezeani, R. O. (2021). The future of semiconductors nanoparticles: Synthesis, properties and applications. *Materials Science and Engineering: B*, *272*, 115363. https://doi.org/10.1016/j.mseb.2021.115363

Wagner, V., Dullaart, A., Bock, A.-K., and Zweck, A. (2006). The emerging nanomedicine landscape. *Nature Biotechnology*, *24*(10), 1211–1217. https://doi.org/10.1038/nbt1006-1211

Wallyn, J., Anton, N., and Vandamme, T. F. (2019). Synthesis, Principles, and Properties of Magnetite Nanoparticles for In Vivo Imaging Applications—A Review. *Pharmaceutics*, *11*(11), Article 11. https://doi.org/10.3390/pharmaceutics11110601

Wang, L., Liu, C., Chen, M., Ya, T., Huang, W., Gao, P., and Zhang, H. (2015). A novel *Lactobacillus plantarum* strain P-8 activates beneficial immune response of broiler chickens. *International Immunopharmacology*, *29*(2), 901–907. https://doi.org/10.1016/j.intimp.2015.07.024

Wilczewska, A. Z., Niemirowicz, K., Markiewicz, K. H., and Car, H. (2012). Nanoparticles as drug delivery systems. *Pharmacological Reports*, *64*(5), 1020–1037. https://doi.org/10.1016/S1734-1140(12)70901-5

Wu, Q., Wongwiriyapan, W., Park, J.-H., Park, S., Jung, S. J., Jeong, T., Lee, S., Lee, Y. H., and Song, Y. J. (2016). *In situ* chemical vapor deposition of graphene and hexagonal boron nitride heterostructures. *Current Applied Physics*, *16*(9), 1175–1191. https://doi.org/10.1016/j.cap.2016.04.024

Xu, K., and Chen, J. (2020). High-resolution scanning probe lithography technology: A review. *Applied Nanoscience*, *10*(4), 1013–1022. https://doi.org/10.1007/s13204-019-01229-5

Yi, S., Dai, F., Zhao, C., and Si, Y. (2017). A reverse micelle strategy for fabricating magnetic lipase-immobilized nanoparticles with robust enzymatic activity. *Scientific Reports*, *7*(1), 9806. https://doi.org/10.1038/s41598-017-10453-4

Zhang, J., Chaker, M., and Ma, D. (2017). Pulsed laser ablation based synthesis of colloidal metal nanoparticles for catalytic applications. *Journal of Colloid and Interface Science*, *489*, 138–149. https://doi.org/10.1016/j.jcis.2016.07.050

Zhuang, S., Lee, E. S., Lei, L., Nunna, B. B., Kuang, L., and Zhang, W. (2016). Synthesis of nitrogen-doped graphene catalyst by high-energy wet ball milling for electrochemical systems. *International Journal of Energy Research*, *40*(15), 2136–2149. https://doi.org/10.1002/er.3595

Chapter 35

Harnessing Nanomedicine for Targeted Sepsis Therapy

Zaman Javed[1], Muhammad Sabir Farooq[2], Muhammad Saqlain[3], Kashif Javed[4], Riaz Hussain Pasha[5], Mujeeb ur Rehman Sohoo[5], Muhammad Zishan Ahmad[1], Muhammad Farhan Rahim[6], Adnan Hassan Tahir[6] and Muhammad Arif Zafar[6*]

[1]Department of Veterinary Pathology, [5]Deparmtent of Veterinary Biomedical Sciences, [6]Department of Clinical Studies, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
[2]Poultry Research Institute, Rawalpindi, Livestock and Dairy Development Department, Government of Punjab, Pakistan
[3]Department of Veterinary Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]University Institute of Management Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
*Corresponding author: dr.mazafar@uaar.edu.pk

ABSTRACT

Sepsis is an extreme host response to microbial invasion that is characterized by excessive release of cytokines, reactive oxygen species, and coagulopathies, leading to multiple organ failure and mortality. Sepsis remained the most common cause of mortalities throughout the world for centuries. Conventional sepsis management includes antibiotic therapy, anti-inflammatory drugs, and fluid therapy. However, due to the extensive application of antibiotics, most microorganisms are resistant to commercially available antimicrobial drugs, demanding new methods to control sepsis. Nanomedicines and other nanoparticles hold a promising potential in sepsis theragnostic due to their drug carrying, site targeting, and sustained release of the drugs. Scientists have successfully applied these nanomedicines to overcome tissue damage due to the excessive release of cytokines and reactive oxygen species and eliminate the microbes from the body. Nanomedicines have also shown their action against antibiotic resistance by targeting microbial biofilms. Similarly, several nanoplatforms have been discovered to detect and quantify sepsis-associated biomarkers, such as pro-inflammatory cytokines, PCT, and CRP. Although nanotechnology offers several opportunities to reduce sepsis-associated mortalities, toxicity and other complications associated with nanomedicines and nanoparticles can be a major hurdle in their clinical applications. Thus, scientists should explore the natural sources for the preparation of nanomedicines and prepare guidelines for their safe applications.

KEYWORDS
Nanomedicine, Cytokines, Sepsis, Immunosuppression, Antimicrobials

Received: 15-Jun-2024
Revised: 18-Jul-2024
Accepted: 21-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Javed Z, Farooq MS, Saqlain M, Javed K, Pasha RH, Sohoo MUR, Ahmad MZ, Rahim MF, Tahir AH and Zafar MA, 2024. Harnessing nanomedicine for targeted sepsis therapy. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 302-309. https://doi.org/10.47278/book.CAM/2024.373

INTRODUCTION

Sepsis is defined as a life-threatening extreme host response to infectious agents, leading to multiple organ failure due to the release of inflammatory mediators into the circulation. Sepsis is characterized by the disruption in a finely tuned immunological balance between the inflammatory and anti-inflammatory mediators, cytokines, and pathogen-related molecules, resulting in the activation of coagulation and complement cascades (Jarczak et al., 2021). Despite the improvement in therapeutic algorithms and an increase in research to understand the pathophysiological mechanisms, sepsis is still considered the major global health issue, responsible for 2.8 million deaths annually (Maneta et al., 2023). According to a report published by Vincent et al. (2014), mortality rates with sepsis are higher than those of myocardial infarction and stroke. Bacteria are considered the most common cause of sepsis in an intensive care unit (ICU). According to a study conducted with 7,000 sepsis patients, gram-negative bacteria are a major cause of sepsis (62.2%), followed by Gram-positive bacteria (46.8%) and fungi 19.4%) (Esparza et al., 2023). The release of microbial products, such as endotoxins from gram-negative bacteria, activates toll-like receptors (TLR) on monocytes and other antigen-presenting cells, leading to the upregulation of pro and anti-inflammatory pathways. The storm of pro-inflammatory cytokines (IL-1, IL-12, IL-18, and TNF-α) and other inflammatory mediators leads to tissue damage, an aberration in the coagulation cascade, and irreversible damage to vital organs (Hollenberg and Singer, 2021).

Early diagnosis of sepsis and timely therapeutic interventions are necessary to reduce mortality and improve clinical outcomes. Conventionally, sepsis can be managed with broad-spectrum antibiotics, fluid therapy, and end-organ support through mechanical ventilation and stabilization of hemodynamics (Gauer, 2013). However, due to the irrational use of

antibiotics in both human and veterinary medicine, most pathogens are resistant to antibiotics, demanding new therapeutical approaches to manage the severity of sepsis. Furthermore, due to the complex pathophysiology of sepsis, the targeted delivery of antibiotics and other drugs is generally not achieved. Similarly, due to non-specific signs and symptoms and a lack of guidelines, sepsis diagnosis can be challenging for clinicians. The standard methods to diagnose sepsis include microbial culture, isothermal amplification methods, and molecular techniques, such as PCR. These conventional methods for sepsis diagnosis are time-consuming, require trained personnel, and are multi-step and resource intensive, with a restricted limit of detection (LOD) and specificity. Hence the complications associated with sepsis treatment and diagnosis demands advanced platforms and therapeutic strategies for sepsis management (Claxton et al., 2020; Pant et al., 2021).

The advancement in the field of nanotechnology and drug delivery system has revolutionized the diagnostic and treatment of life-threatening diseases. Nanotechnology and nanomedicines have now enabled clinicians to diagnose and treat sepsis more easily, providing an innovative solution to longstanding challenges. Nanoparticles, with their unique properties, enable more sensitive and specific detection of sepsis biomarkers, improving early diagnosis and timely intervention. Furthermore, nano-based drug delivery systems enhance the targeted delivery of therapeutics, optimizing treatment and efficacy while minimizing side effects. These advancements hold promising potential to transform sepsis management, offering hope for improved patient outcomes and reduced mortality rates (Claxton, Papafilippou, Hadjidemetriou, Kostarelos, and Dark, 2020).

Pathophysiology of Sepsis

Sepsis is an overwhelming hyperinflammatory and immunosuppressive stage characterized by a "cytokine storm" resulting in fever, refractory shock followed by multiple organ failure and death. The triggering event of sepsis starts with the recognition of pathogen-associated molecular patterns (PAMPs) or Danger-associated molecular patterns, such as LPS in the case of gram-negative bacteria and Polysaccharides in the case of gram-positive bacteria. The recognition of these microbial products by the body's innate immune system leads to the activation of complex intracellular signaling pathways, leading to the release of inflammatory mediators. The signaling molecules pathways and microbially derived molecules determined the intensity of inflammatory response. For example, recognition of LPS by Toll-like receptors (TLR-4) of macrophages activates nuclear factor-κB (NF-κB) pathways, resulting in the release of inflammation-active mediators (such as IL-1, IL-6, IL-18, TNF-α to clear microbial invasion. However, excessive activation of macrophages causes a "cytokine storm" that impairs the host immune system, leading to tissue damage. This hyperinflammatory stage also causes the activation of the complement system and the release of vasoactive molecules from endothelial cells and chemoattractant, thus switching from an anticoagulant to a procoagulant state. The activation of the complement system also causes the generation of Reactive Oxygen Species (ROS) and the release of granular enzymes, leading to more tissue damage (Hotchkiss et al., 2016; Luo et al., 2021).

Along with the hyper-inflammatory stage, sepsis also causes long-term immunosuppression in surviving patients, leading to persistent catabolism syndrome. This clinical syndrome is characterized by markedly increased C-reactive protein (CRP) concentrations, neutrophilia, and the release of immature myeloid cells. The release of immature myeloid cells into the circulation has defective antimicrobial activity and releases anti-inflammatory cytokines. The exact etiology of immature myeloid cells is still unknown. However, it is likely driven by DAMPs produced by injured tissues and organs (Gentile et al., 2012; Hawkins et al., 2018).

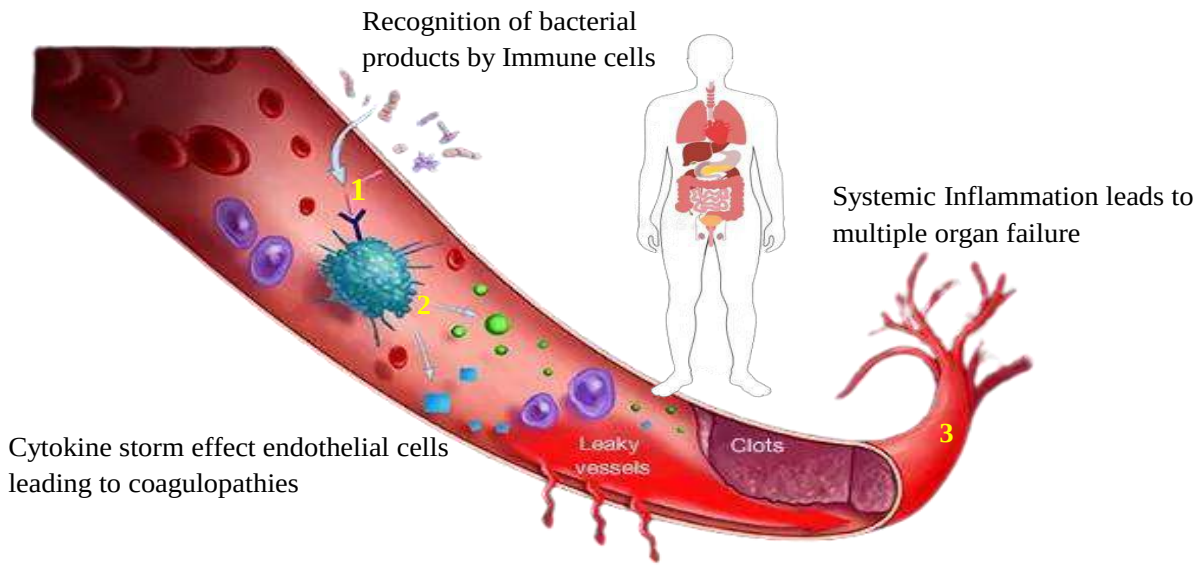


Fig. 1: Pathophysiology of sepsis from recognition of microbes to multiple organ failure

Pathway	Description	Reference
TREM	• Upregulate pro-inflammatory cytokines and chemokines, leading to amplification of inflammatory cascades. • Blocking TREM1 signaling pathways can prevent Polymicrobial and LPS induced sepsis.	(Cohen, 2001; Siskind et al., 2022)
S1PR	• S1PR2 member of this pathway prevent phagocytic activity of macrophages, triggers macrophages proptosis, and stimulates complications associated with gram negative sepsis.	Luo et al., 2021
P2X	• P2X7 riggers macrophages proptosis and activates caspase-1 when interacting with HNP1, worsening the sepsis. • Inhibition of this pathway can prevent septic renal damage and improve sepsis outcomes.	(Antonioli et al., 2019; Savio, 2022)
TRPM	• TRPM2 of this pathway causes clearance of invaded microbes and their products. • TRPM2 deletion leads to microbial load, organ damage, systemic inflammation, resulting in increased mortality.	(Liu et al., 2019)

Decoding Sepsis: Nanomedicine's Promising Frontier

The emergence and rapid progression of nanotechnology in recent eras have allowed clinicians and researchers to manage life-threatening diseases and overcome the serious adverse effects and resistance of drugs. Nanomaterials are now being used in the medical field for targeted drug delivery and diagnosis of several life-threatening conditions, including sepsis and other hyperinflammatory disorders. The smaller size of the nanoparticles enables them to cross the small capillaries and actively targeting the target site, proving a more effective option to treat sepsis compared to conventional method of sepsis management. For example, nanomedicine with the size of 0.5µm to 5µm can easily cross the pulmonary capillaries and prevent lung injury. Similarly, a nanocarrier drug-delivery system with a particle size of 70-90nm (size smaller than endothelial fenestration) can pass glomerulus membrane and endothelial fenestrations. Fabrication or encapsulation of active drugs modulates the pharmacokinetics of the drug, improving its bioavailability, efficacy, and stability. Nanomedicines have a characteristic dimension of 1 to 100 nm and are designed based on the desired biological properties and functions with specific physical (Vasconcelos and Santos, 2023). Chemical and surface properties. Generally, nanoparticles can be classified into two categories:

1. Organic Nanoparticles
2. Inorganic nanoparticles.

Organic Nanoparticles

Organic nanoparticles usually contain carbon skeletons and are classified as lipid bases or synthetic polymeric nanoparticles. Common types of organic nanomedicines include chitosan, protein-based, polysaccharides, liposomes, polymeric micelles, and poly-amidoamine. Organic nanomedicines are usually less toxic, with excellent biocompatibility, and do not elicit immune responses due to the presence of bio-elements such as carbon, oxygen, and nitrogen in their structure. Several studies have proved their effectiveness in sepsis (Abdelkader et al., 2017; Wu et al., 2021; Guo et al., 2023). Organic nanoparticles are also currently being used for vaccine development, immunotherapy, and diagnostics.

Inorganic Nanoparticles

Inorganic nanoparticles can be prepared by using inorganic metals such as zinc, copper, gold, and aluminum and semiconductors such as cadmium selenide, zinc oxide, and carbon nanotubes. Iron oxide and Calcium phosphate can also be used to synthesize inorganic nanoparticles. Due to their tunable properties, inorganic nanoparticles have been used for the diagnosis and treatment of several infectious diseases, inflammatory disorders, cancers, and wound healing. Inorganic metal-based nanoparticles also have high drug-loading ability and long circulation and cause the sustained release of the encapsulated drug. In sepsis, metallic nanomedicines show their action according to the microenvironment, such as pH, H_2O_2, and O_2, resulting in the removal of dangerous signals and lowering the severity of sepsis (Yang et al., 2019; Luo et al., 2021).

Nanomedicines as a Potential Sepsis Treatment

The conventional methods of sepsis early diagnosis, antimicrobial therapy, and sepsis response regulation. Antimicrobial therapy with antibiotics is the standard in clinical guidelines for sepsis. However, due to increased antibiotic resistance and a lack of effective antibiotics, treatment of persistent sepsis is a significant challenge for clinicians. According to a study, E-coli, the most common cause of sepsis, is resistance to β-lactam antibiotics and aminoglycosides. Similarly, *Staphylococcus aureus* vancomycin and methicillin. This drug resistance is a significant cause of sepsis-associated mortalities, especially in neonates (Chauhan et al., 2017).

Additionally, most antibiotics are ineffective against the systemic release of various cytokines, ROS, and other biomolecules triggered by sepsis. This storm of pro-inflammatory mediators can cause death due to multiple organ damage and long-term immunosuppression in surviving patients. Therefore, new adjuvant therapies, including anti-inflammatory drugs, antioxidant agents, and immunomodulators, are being explored by the researchers. However, these therapeutical options have limitations such as low solubility, poor bioavailability, short half-life, and lack of cell-specific

targeting ability. The emergence of nanomedicine in the past few decades has opened up new pathways to overcome drug resistance, improved the pharmacokinetics of potential drugs, and improved the cell-targeting ability of medicines. Nanomedicines can actively target the sepsis microenvironment, providing a novel avenue for precision treatment and early diagnosis. The below points highlight the major applications of nanomedicines in sepsis treatment.

Nanocarriers and Targeted Drug Delivery for Sepsis Treatment

Conventional medicines have poor pharmacokinetics due to either their larger size, which makes their solubility and membrane crossing ability poor, or smaller size, which results in rapid clearance, high toxicity, and side effects. Similarly, most antimicrobial, and anti-inflammatory drugs do not actively reach the target site. Properties, such as surface charge and size of nanoparticles, can be used to overcome this challenge. For example, the short half-life of the meropenem makes the drug ineffective against sepsis. To overcome this challenge, scientists have successfully encapsulated Meropenem into chiston nanoparticles, dramatically improving these antibiotics' pharmacokinetic properties (Abdelkad et al., 2017). Furthermore, these encapsulated nanomedicines can easily cross the cell membrane, leading to their accumulation in specific tissues or organ preferentially. Similarly, many antimicrobial peptides, a promising theragnostic option to manage sepsis, have poor solubility, bioavailability and pharmacokinetic properties. Studies have shown that these antimicrobial peptides can be successfully encapsulated into a methacrylate nanocarrier. This fabrication of AMPs have successfully rescued 100% of the sublethal experimentally induced sepsis (Qian et al., 2022; Meng et al., 2023). A study published by Falciani et al. (2020) have shown the successful fabrication of these AMPs into single-chain dextran nanoparticl3es to eliminate *P. aeruginosa* in acute lung sepsis.

Another common hallmark of sepsis is the excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These ROS and RNS can module a series of intracellular signaling pathways and alter the function of different enzymes and ion channels. Thus, reducing the mitochondrial ROS and RNS can reduce the abnormal inflammatory response. Conventional antioxidants have poor ROS and RNS scavenging activity and structural stability. Several researchers have proved that the application of various nanoparticles (nanosheets) and nanomedicines in sepsis patients can successfully remove mitochondrial ROS and RNS (Yim et al., 2020).

In sepsis, most of the damage is caused by excessive release of pro-inflammatory cytokines. Most antibiotics are ineffective against this excessive release of inflammatory mediators and demand some alternate sources to alter the pathways that cause the release of pro-inflammatory cytokines. Scientists have successfully utilized the green nano-synthesis approach to convert the natural green agents, especially plants and fungi, to reduce the release of cytokines during sepsis (Beg et al., 2020; Elbagory, 2019; Phukan et al., 2021). Wang et al. (2015) have successfully prepared curcumin-loaded solid lipid nanoparticles to reduce and evaluate their therapeutic potential for LPS-induced sepsis. The results of an enzyme-linked immunosorbent assay showed that the curcumin-loaded solid lipid nanoparticles can successfully reduce the secretion of IL-6 and TNF-α inflammatory factors in the serum and increase the release of anti-inflammatory cytokines.

Modulating the Host Immune Response

Immunomodulation is one of the most effective strategies to treat sepsis. Studies have shown that the administration of nicotinamide adenine dinucleotide (NAD+) in sepsis patients can prevent oxidative stress and multiple organ failure. Loading the NAD and NADH into the liposomes and zeolitic imidazolate frameworks improves the cell oxygen supply, reduces inflammation-induced cell pyroptosis and apoptosis, and decreases the extent of inflammation. The application of these nanomedicine in CLP and *P. Aeruginosa* induced sepsis has shown improved therapeutic outcomes, indicating their promising ability to trat and diagnose sepsis (Grahnert et al., 2011; Ye et al., 2022).

Studies have proved that different types of nanoparticles modulate the host immune response to improve antibiotic therapy. For instance, the use of polymeric nanoparticles has shown their action against the release of pro-inflammatory cytokine, reducing the chance of tissue damage and multiple organ failure. Nanoparticles neutralize the endotoxins released by bacteria and sequestering cytokines released by host immune response dur to these endotoxins. Another innovative approach to manage sepsis is the application of a nano trap, also known as Tele-dendrimer, along with antibiotic therapy. These telodendrimer effectively absorbs septic molecules due to the different charges of pro and anti-inflammatory cytokines (Shi et al., 2020). It is also believed that nanomedicines actively target the macrophages, altering their pro-inflammatory function and reducing the release of cytokines.

Targeting the Macrophages

Macrophages or monocytes, as an important member of the host's immune response, play an important role in the pathophysiology of the sepsis, including the killing of microbes, and release of cytokines and chemokines. During sepsis, over activation of the macrophages results in the release of cytokine storm, which worsen the pathophysiological status of clinical patients, leading to poor response of the conventional sepsis therapy. Nanomedicines are important tool to alter the pro-inflammatory activity of the macrophages. Macrophages binds with the plasma protein, acquiring the new biological property, known as protein corona (PC), which changes the physiochemical properties of nanomedicines (Boraschi et al., 2017). Binding of nanoparticles with plasma protein results in the uptake of NPs by monocytes (Corbo et al., 2017). Other

mechanism to target the macrophages and preventing the release of pro-inflammatory cytokines include altering the activation of pathogen-associated molecular pattern and directly effecting the release of pro-inflammatory signals (Song et al., 2022).

Nanomedicines with Anti-microbial Properties

Biofabrication of different naturally derived metal-based nanoparticles can be effectively used as antimicrobial agents. Furthermore, studies have shown that the positive charged nanoparticles interact with microbial cell, leading to direct killing. Positive charged nanoparticles bind with negatively charged microbial cell membrane, leading to membrane disruption and desensitization, which causes loss of membrane integrity, leakage of cellular content, and cell death (Lam t al., 2016). Another mechanism responsible for the antimicrobial activity of nanomedicines is its electrostatic attraction, which causes the uptake of nanomedicine by the bacteria. Once internalized, nanomedicines disturb the normal metabolic pathway and induce cell death (Xie at al., 2019). Studies have shown that several nanoparticles result in the generation of reactive oxygen species (ROS), which facilitates the killing of invaded bacteria. Positive charged nanoparticles cause the generation of hydrogen peroxide or hydroxyl radicals, leading to oxidative stress in the bacterial cell. Along with generation of ROS, nanomedicines also interact with biofilm, a component that play a key role in antibiotic resistance in bacteria (Jiang et al., 2022). Biofilm matrix contain negative charge that interact with positively charged nanoparticles, increasing the susceptibility of the bacteria to antimicrobial agents (Koo et al., 2017). Although nanomedicines hold a promising potential to manage sepsis, some challenges need to be addressed to increase the efficacy of the drugs. These include size, surface charge, and composition of nanoparticles. Incorporating the metal-based greenly synthesized nanomedicines for antimicrobial therapy is one of the best options to lower the toxicity associated with nanoparticles (Saratale et al., 2021; Zhu et al., 2019).

Nanoparticles for Early Detection of Bacterial Sepsis

Early diagnosis of the sepsis is essential to prevent the disease progression and effective treatment. Along with their therapeutic potential, nanomedicines are also being used in sepsis diagnosis. The conventional methods of sepsis diagnosis are expensive and demand intricate procedure, altering the diagnosis of sepsis. Nanoparticles have been applied in the biomedical field to detect the specie of bacteria and guide the proper antibiotic administration. These nanoplatforms has now enabled clinicians to overcome the challenges associated with conventional methods of sepsis theragnostic.

Below few points highlight the application of nanomedicines in sepsis diagnosis:

Detection of Bacteria

Scientists have successfully used gold nanoparticles as a novel diagnostic tool for sepsis diagnosis. Biofabricated antibodies or Gold nanoparticles (AuNPs) binds with bacterial products such as LPS or peptidoglycans, resulting in color change in face plasma resonance. This technique has been successfully used for the detection of *E. coli, P. aeruginosa,* and *S. aureus*. Similarly, magnetic nanoparticles have also been investigated for the detection of bacteria (Fu et al., 2018; Rocha-Santos, 2014).

Carbon nanotubes are another important tool to detect the bacteria responsible for induction of sepsis. Binding of these nanotubes with bacterial cell membrane results in the change in electric conductivity of the CNTs, which can be detected by field effect transistor (FET). Nanomaterial-based detection of the bacteria has several advantages over conventional methods, such as PCR and ELISA, due to small amount of sample and rapid detection (Munzer at al., 2013).

Detection of Sepsis Biomarkers

Sepsis biomarkers, including ROS, Cytokine, C-reactive protein, CRP, and OCT, are commonly used in clinical setting for the early diagnosis of the sepsis. However, limitations and sensitivity associated with traditional methods demand more sensitive tool for the sepsis diagnosis. The application of nanosensors has now made the sepsis diagnosis more accurate and accessible. For examples, scientists have successfully applied nanotubes for the detection of C-reactive protein (Luo et al., 2021). Furthermore, Gold nanoparticles have also been used for the detection of pro-inflammatory cytokines (Khan and Mujahid; 2020).

The table below summarize the different types of biosensors used for sepsis diagnosis. Data is extracted from the review published by Luo et al., (2021).

Biomarker	Nanoparticles	Mechanism
E. coli	Azide fabricated AuNPs	Biomimetic strategy based on bacterial metabolic pathway
Polymicrobes	PMNs-derived microvesicles	Agglutination of bacteria due to microvesicles
S. aureus	Silica NPs	Antibody detection
CRP	Magnetic NPs	Antibody detection
CRP	Iron oxide nanocrystal	Antibody detection
CRP	Gold nanorod	Antibody detection
PCT	Ferrocene encapsulated AuNPs	Electrochemistry

PCT	Streptavidin-coated AuNPs	Immune sensing
PCT	Fluorescent microspheres	Immune sensing
IL-6	ZnS nanocrystals	Immune; optical
TNF-α	Axoplasmic AuNPs	Immune detection

Challenges and Opportunities

Nanotechnology holds promising potential for the therapy of sepsis. Several studies have shown the efficacy of nanomedicines against sepsis due to their site-targeting and antimicrobial properties. For example, liposomes loaded with vancomycin have been investigated to improve the survival rate and reduce the bacterial load in sepsis induced by methicillin-resistant Staphylococcus aureus (Nwabuife et al.,2021). Similarly, polymeric nanoparticles have shown their action against pro-inflammatory cytokines in experimentally induced sepsis.

Despite these promising results in sepsis, nanoparticles also have some limitations that must be addressed before their application in clinical practice. Formulation of the nanomedicines and nanoparticles for the theragnostic of sepsis requires diverse materials, e.g., supramolecular nanomaterials organic and inorganic nanocomposite. Safety considerations and regulatory requirements are essential for the clinical application of nanomedicines. Since most of these nanomaterials are not approved by FDA as pharmaceutically acceptable vehicles, these can be toxic for both the environment and the individual. Thus, it is essential to consider the pharmacokinetics properties, such as absorption, distribution, and elimination from the body.

Studies have shown that nanoparticles can cause oxidative stress and cause damage to tissues when applied in large quantities. Thus, researchers should consider the dose of nanomedicines before their application in living organisms. Another major challenge in the application of nanomedicines in clinical practices is their optimizing the design and formulation of NPs to maximize drug delivery and efficacy while minimizing off-target effects. The efficacy of the nanomedicines against a specific disease depends upon their size, pH, and surface charge. Thus, these conditions should be considered to maximize the results of nanomedicines.

In the recent era, nanosynthesis has gained more interest due to less toxicity and environmentally friendly properties, providing an opportunity to treat sepsis and other inflammatory conditions more effectively. The unique biomarkers in plants, fungi, and other green agents have been extensively studied due to their anti-inflammatory, anti-microbial, and antioxidant properties. Thus, researchers should focus on the application of these green agents for drug nanosynthesis. Furthermore, safety assessments of nanomedicines should include comprehensive toxicity studies to evaluate potential adverse effects on human health Zhai et al., 2022).

Conclusion

In the past few decades, the extensive use of antibiotics and the increased toxicity of conventional sepsis therapy have compelled researchers to explore alternative and novel theragnostic approaches for sepsis management. Due to targeted drug delivery and antimicrobial, antioxidant, and anti-inflammatory properties, nanomedicines provide an opportunity for clinicians to overcome the applications associated with conventional sepsis therapy.

Several types of nanomedicines have been studied to enhance the target drug delivery and lower the release of cytokines, oxidative stress, and sepsis-associated mortalities. However, due to a lack of regulatory and safety guidelines, several nanomaterials are toxic to living organisms and the environment when exposed in large quantities. Thus, researchers should design guidelines to minimize the complications and enhance the opportunities offered by these nanomedicines. Furthermore, extensive study is needed to study the factors that can affect the efficacy of nanomedicines when administered in living organisms.

REFERENCES

Abdelkader, A., El-Mokhtar, M. A., Abdelkader, O., Hamad, M. A., Elsabahy, M., and El-Gazayerly, O. N. (2017). Ultrahigh antibacterial efficacy of meropenem-loaded chitosan nanoparticles in a septic animal model. *Carbohydrate Polymers, 174*, 1041-1050.

Antonioli, L., Blandizzi, C., Fornai, M., Pacher, P., Lee, H. T., and Haskó, G. (2019). P2X4 receptors, immunity, and sepsis. *Current Opinion in Pharmacology, 47*, 65-74.

Beg, M. R., Ghodinde, S., and Gupta, V. (2020). Plant mediated green synthesis of Zinc Oxide Nanoparticles for burn wound therapy.

Boraschi, D., Italiani, P., Palomba, R., Decuzzi, P., Duschl, A., Fadeel, B., and Moghimi, S. M. (2017). *Nanoparticles and innate immunity: new perspectives on host defence*. Paper presented at the Seminars in immunology.

Chauhan, N., Tiwari, S., and Jain, U. (2017). Potential biomarkers for effective screening of neonatal sepsis infections: an overview. *Microbial Pathogenesis, 107*, 234-242.

Claxton, A., Papafilippou, L., Hadjidemetriou, M., Kostarelos, K., and Dark, P. (2020). The challenge of recognising sepsis: Future nanotechnology solutions. *Journal of the Intensive Care Society, 21*(3), 241-246.

Cohen, J. (2001). TREM-1 in sepsis. *The Lancet, 358*(9284), 776-778.

Corbo, C., Molinaro, R., Tabatabaei, M., Farokhzad, O. C., and Mahmoudi, M. (2017). Personalized protein corona on nanoparticles and its clinical implications. *Biomaterials Science, 5*(3), 378-387.

Elbagory, A. M. M. N. (2019). Green synthesis and characterization of gold nanoparticles from South African plants and their biological evaluations.

Esparza, K., Oliveira, S., Castellon, M., Minshall, R., and Onyuksel, H. (2023). Thiostrepton-nanomedicine, a TLR9 inhibitor, attenuates sepsis-induced inflammation in mice. *Mediators of Inflammation, 2023*.

Falciani, C., Zevolini, F., Brunetti, J., Riolo, G., Gracia, R., Marradi, M., and Llop, J. (2020). Antimicrobial peptide-loaded nanoparticles as inhalation therapy for Pseudomonas aeruginosa infections. *International Journal of Nanomedicine*, 1117-1128.

Fu, F., Li, L., Luo, Q., Li, Q., Guo, T., Yu, M., and Song, E. (2018). Selective and sensitive detection of lysozyme based on plasmon resonance light-scattering of hydrolyzed peptidoglycan stabilized-gold nanoparticles. *Analyst, 143*(5), 1133-1140.

Gauer, R. L. (2013). Early recognition and management of sepsis in adults: the first six hours. *American Family Physician, 88*(1), 44-53.

Gentile, L. F., Cuenca, A. G., Efron, P. A., Ang, D., Bihorac, A., McKinley, B. A., and Moore, F. A. (2012). Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *Journal of Trauma and Acute Care Surgery, 72*(6), 1491-1501.

Grahnert, A., Grahnert, A., Klein, C., Schilling, E., Wehrhahn, J., and Hauschildt, S. (2011). NAD+: a modulator of immune functions. *Innate Immunity, 17*(2), 212-233.

Guo, J., Miao, Y., Nie, F., Gao, F., Li, H., Wang, Y., and Liu, L. (2023). Zn-Shik-PEG nanoparticles alleviate inflammation and multi-organ damage in sepsis. *Journal of Nanobiotechnology, 21*(1), 448.

Hawkins, R. B., Raymond, S. L., Stortz, J. A., Horiguchi, H., Brakenridge, S. C., Gardner, A., and Moore, F. A. (2018). Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. *Frontiers in Immunology, 9*, 1511.

Hollenberg, S. M., and Singer, M. (2021). Pathophysiology of sepsis-induced cardiomyopathy. *Nature Reviews Cardiology, 18*(6), 424-434.

Hotchkiss, R. S., Moldawer, L. L., Opal, S. M., Reinhart, K., Turnbull, I. R., and Vincent, J.-L. (2016). Sepsis and septic shock. *Nature Reviews Disease Primers, 2*(1), 1-21.

Jarczak, D., Kluge, S., and Nierhaus, A. (2021). Sepsis—pathophysiology and therapeutic concepts. *Frontiers in Medicine, 8*, 628302.

Jiang, Y., Zheng, W., Tran, K., Kamilar, E., Bariwal, J., Ma, H., and Liang, H. (2022). Hydrophilic nanoparticles that kill bacteria while sparing mammalian cells reveal the antibiotic role of nanostructures. *Nature Communications, 13*(1), 197.

Khan, M. A., and Mujahid, M. (2020). Recent advances in electrochemical and optical biosensors designed for detection of Interleukin 6. *Sensors, 20*(3), 646.

Koo, H., Allan, R. N., Howlin, R. P., Stoodley, P., and Hall-Stoodley, L. (2017). Targeting microbial biofilms: current and prospective therapeutic strategies. *Nature Reviews Microbiology, 15*(12), 740-755.

Lam, S. J., O'Brien-Simpson, N. M., Pantarat, N., Sulistio, A., Wong, E. H., Chen, Y.-Y., and Reynolds, E. C. (2016). Combating multidrug-resistant Gram-negative bacteria with structurally nanoengineered antimicrobial peptide polymers. *Nature Microbiology, 1*(11), 1-11.

Liu, F., Sheng, S., Shao, D., Xiao, Y., Zhong, Y., Zhou, J., and Yang, C. (2021). Targeting multiple mediators of sepsis using multifunctional tannic acid-Zn2+-gentamicin nanoparticles. *Matter, 4*(11), 3677-3695.

Liu, H., Wang, S.-Y., Li, X.-D., Yang, S., Liu, X.-Y., Yang, C.-W., and Liu, Y.-F. (2019). The expression of TRPM7 in serum of patients with sepsis, its influences on inflammatory factors and prognosis, and its diagnostic value. *European Review for Medical and Pharmacological Sciences, 23*(9).

Luo, G., Zhang, J., Sun, Y., Wang, Y., Wang, H., Cheng, B., and Fang, X. (2021). Nanoplatforms for sepsis management: rapid detection/warning, pathogen elimination and restoring immune homeostasis. *Nano-micro Letters, 13*, 1-64.

Maneta, E., Aivalioti, E., Tual-Chalot, S., Emini Veseli, B., Gatsiou, A., Stamatelopoulos, K., and Stellos, K. (2023). Endothelial dysfunction and immunothrombosis in sepsis. *Frontiers in Immunology, 14*, 1144229.

Meng, Z., Pan, L., Qian, S., Yang, X., Pan, L., Chi, R., and Shi, C. (2023). Antimicrobial peptide nanoparticles coated with macrophage cell membrane for targeted antimicrobial therapy of sepsis. *Materials and Design, 229*, 111883.

Münzer, A. M., Michael, Z. P., and Star, A. (2013). Carbon nanotubes for the label-free detection of biomarkers. *ACS Nano, 7*(9), 7448-7453.

Nwabuife, J. C., Pant, A. M., and Govender, T. (2021). Liposomal delivery systems and their applications against Staphylococcus aureus and methicillin-resistant Staphylococcus aureus. *Advanced Drug Delivery Reviews, 178*, 113861.

Pant, A., Mackraj, I., and Govender, T. (2021). Advances in sepsis diagnosis and management: a paradigm shift towards nanotechnology. *Journal of Biomedical Science, 28*, 1-30.

Phukan, K., Devi, R., and Chowdhury, D. (2021). Green synthesis of gold nano-bioconjugates from onion peel extract and evaluation of their antioxidant, anti-inflammatory, and cytotoxic studies. *ACS Omega, 6*(28), 17811-17823.

Qian, M., Ma, D., Zhao, X., Guo, W., and Zhang, Y. (2021). A novel fast-releasing formulation containing curcumin and anti-microbial peptide-encapsulated transdermal hydrogels into microneedles to reduce inflammation in the therapy of neonatal sepsis. *Materials Express, 11*(7), 1101-1108.

Rocha-Santos, T. A. (2014). Sensors and biosensors based on magnetic nanoparticles. *TrAC Trends in Analytical Chemistry, 62*, 28-36.

Saratale, R. G., Saratale, G. D., Ahn, S., and Shin, H.-S. (2021). Grape pomace extracted tannin for green synthesis of silver nanoparticles: Assessment of their antidiabetic, antioxidant potential and antimicrobial activity. *Polymers, 13*(24), 4355.

Savio, L. E. B. (2022). P2X receptors in the balance between inflammation and pathogen control in sepsis. *Purinergic Signalling, 18*(3), 241-243.

Shi, C., Wang, X., Wang, L., Meng, Q., Guo, D., Chen, L., and Luo, J. (2020). A nanotrap improves survival in severe sepsis by attenuating hyperinflammation. *Nature Communications, 11*(1), 3384.

Siskind, S., Brenner, M., and Wang, P. (2022). TREM-1 modulation strategies for sepsis. *Frontiers in Immunology, 13*, 907387.

Song, C., Xu, J., Gao, C., Zhang, W., Fang, X., and Shang, Y. (2022). Nanomaterials targeting macrophages in sepsis: A promising approach for sepsis management. *Frontiers in Immunology, 13*, 1026173.

Vasconcelos, I., and Santos, T. (2023). Nanotechnology applications in sepsis: essential knowledge for clinicians. *Pharmaceutics, 15*(6), 1682.

Vincent, J.-L., Marshall, J. C., Ñamendys-Silva, S. A., François, B., Martin-Loeches, I., Lipman, J., and Njimi, H. (2014). Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *The Lancet Respiratory Medicine, 2*(5), 380-386.

Wang, J., Wang, H., Zhu, R., Liu, Q., Fei, J., and Wang, S. (2015). Anti-inflammatory activity of curcumin-loaded solid lipid nanoparticles in IL-1β transgenic mice subjected to the lipopolysaccharide-induced sepsis. *Biomaterials, 53*, 475-483.

Wu, Y., Jiang, W., Huo, S., Li, S., Xu, Y., Ding, S., and Wang, Y. (2021). Nano-metal–organic-frameworks for treating H2O2-Secreting bacteria alleviate pulmonary injury and prevent systemic sepsis. *Biomaterials, 279*, 121237.

Xie, J., Zhou, M., Qian, Y., Cong, Z., Chen, S., Zhang, W., and Ji, Z. (2021). Addressing MRSA infection and antibacterial resistance with peptoid polymers. *Nature Communications, 12*(1), 5898.

Yang, B., Chen, Y., and Shi, J. (2019). Reactive oxygen species (ROS)-based nanomedicine. *Chemical Reviews, 119*(8), 4881-4985.

Ye, M., Zhao, Y., Wang, Y., Xie, R., Tong, Y., Sauer, J.-D., and Gong, S. (2022). NAD (H)-loaded nanoparticles for efficient sepsis therapy via modulating immune and vascular homeostasis. *Nature Nanotechnology, 17*(8), 880-890.

Yim, D., Lee, D.-E., So, Y., Choi, C., Son, W., Jang, K., and Kim, J.-H. (2020). Sustainable nanosheet antioxidants for sepsis therapy via scavenging intracellular reactive oxygen and nitrogen species. *ACS Nano, 14*(8), 10324-10336.

Zhai, Z., Ouyang, W., Yao, Y., Zhang, Y., Zhang, H., Xu, F., and Gao, C. (2022). Dexamethasone-loaded ROS-responsive poly (thioketal) nanoparticles suppress inflammation and oxidative stress of acute lung injury. *Bioactive Materials, 14*, 430-442.

Zhu, X., Pathakoti, K., and Hwang, H.-M. (2019). Green synthesis of titanium dioxide and zinc oxide nanoparticles and their usage for antimicrobial applications and environmental remediation. In *Green Synthesis, Characterization and Applications of Nanoparticles* (pp. 223-263): Elsevier.

Chapter 37

Nanoanthelmintics: A Way Forward Towards Anthelmintic Resistance

Hira Altaf[1], Sadia Nageen[1], Sidra Ayub[1], Faisal Hafeez[1], Naveed Ahmad[2], Muhammad Kasib Khan[1], Muhammad Imran[3], Haider Abbas[4], and Muhammad Imran[1*]

[1]Department of Parasitology, University of Agriculture-38040, Faisalabad, Pakistan
[2]Institute of Animal and Dairy Sciences, University of Agriculture-38040, Faisalabad, Pakistan
[3]Department of Pathology, University of Agriculture-38040, Faisalabad, Pakistan
[4]Department of Pathobiology (Parasitology Section), KBCMA College of Veterinary and Animal Sciences Narowal, Sub-Campus UVAS, Lahore, Pakistan, Pakistan
*Corresponding author: imran.asghar@uaf.edu.pk

ABSTRACT

Anthelmintic resistance poses a significant threat to global animal health and agricultural sustainability. This chapter investigates the emerging field of Nanoanthelmintics as a possible solution to anthelmintic resistance in ruminants. Beginning with an overview of the current state of anthelmintic resistance, its widespread impact on livestock industries, and the urgent need for novel interventions. Nanoanthelmintics is a novel approach that uses nanotechnology to design and deliver anthelmintic agents with increased efficacy and lower risk of resistance development. The chapter discusses the fundamental principles of nanotechnology and explains how it can be used to develop anthelmintic drugs with improved properties. Key topics include nanoparticle synthesis methodologies, anthelmintic compound encapsulation techniques, and drug delivery strategies to parasite sites. It provides various benefits, including improved drug bioavailability, sustained release kinetics, and reduced adverse effects. Furthermore, the chapter investigates how resistance mechanisms are found in traditional anthelmintics, thereby providing a pathway to restore sensitivity in resistant parasite populations. The review of case studies and experimental evidence highlights the efficacy of nanoanthelmintics against resistant parasites, indicating their potential to revolutionize parasite control strategies. Furthermore, nanoanthelmintics show promise for improving animal welfare and reducing environmental contamination caused by conventional anthelmintic use. The chapter concludes by outlining future directions and challenges in nanoanthelmintic development and implementation, emphasizing their critical role in ensuring long-term parasite control in the face of increasing anthelmintic resistance.

KEYWORDS
Anthelmintic resistance, Nanoparticles, Nanoanthelmintics, Helminths, Ruminants

Received: 29-Jun-2024
Revised: 24-Jul-2024
Accepted: 06-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Altaf H, Nageen S, Ayub S, Hafeez F, Ahmad N, Khan MK, Imran M, Abbas H and Imran M, 2024. Nanoanthelmintics: A way forward towards anthelmintic resistance. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 310-321. https://doi.org/10.47278/book.CAM/2024.374

INTRODUCTION

Helminth Infection and Animal Health

Parasitism is the most species-rich mode of animal life on earth with majority of species is still undiscovered (Chacon et al., 2023). The global diversity and distribution of parasites up to 149 tropical and subtropical climatic conditions is a topic of particular concern, in the light of the accelerating rate of disease emergence in livestock, humans, companion animals and wildlife (Teixeira et al., 2020). Helminth parasites are one of the most significant polyphyletic groups of parasitic worms showing immense diversity and tremendous ecological and epidemiological significance (Beesley et al., 2017). They are one of the most important concerns for animal health and welfare. Grazing livestock nearly 350 million cattle and 250 million sheep is at a permanent risk of trichostrongylide infection, particularly with nematode, trematode and cestodes (Esteban et al., 2002).

Economic Losses Caused by Helminth Infection

Helminth usually causes hemorrhagic anemia, edema, diarrhea, stunted growth and death of severely affected animals. Livestock is the backbone of the poorest and most marginalized communities living in regions of Asia and Africa. These health losses affect millions of animals annually, resulting in substantial economic losses in terms of meat, milk,

decrease wool production and cost of treatment (Fleming et al., 2015). Globally 941 million dollars economic losses are caused by this infection of which 38 million dollar is associated to handle anthelmintic resistance (Charlier et al., 2020).

In addition to their veterinary significance, several helminthes have public health significance (e.g Fasciola spp, Taenia spp, Paragonimus spp, Clonorchis spp, Echinococuss and Ascaris) may also be transmitted to and cause diseases in humans ,which make their prevention and control a priority from a public health perspective as well (Lustigman et al., 2012).

Use of Anthelmintic Drug against Helminth

Pharmacotherapy has become the most popular approach for controlling helminths over the last 40 years, though other strategies are also available. An anthelmintic dose is easily available, requires minimal management, provides immediate results and is relatively inexpensive. Benzimidazoles are safe and effective against a wide range of worms but ivermectin was a game changer because it effectively treated both helminths and ectoparasites, it is one of the most successful veterinary products ever. Levamisole and other organophosphate groups are also used against nematode as regular dewormers (Ali et al., 2018).

Anthelmintic Resistance and its Mechanism

Resistance is the loss of sensitivity of an anthelmintic in a parasite population that was previously susceptible to the same anthelmintic, this may be because the parasites change their drug target site, or another drug selection with the same mechanism (Ali et al., 2018). The extensive use of anthelmintic in small and large ruminants has led to a serious and dramatic level of anthelmintic resistance (Potarniche et al., 2021). Presently, the three kinds of anthelmintic that are most frequently used in small ruminants are cholinergic agonists' imidothiazoles (levamisole), macrocyclic lactones (ivermectin, mobemectin) and benzimidazole. Resistance against Benzimidazole is mostly due to single nucleotide polymorphism in beta-tubulin protein (Espinoza et al., 2018). In ivermectin resistance parasite change their specific site (ligand-gated chloride channels), the drug is designed to bind with them, while the mechanism of resistance against levamisole is related to changes in Nicotinic acetylcholine receptors (Fissiha et al., 2021) as shown in the Figure (a)

Factors behind Resistance Development

The most resilient portion of the population is made up of a tiny number of tolerant parasites. These parasites that survive are released into the environment, contaminating the pasture, transferring genes to the next generations and are responsible for resistant generations (Kaplan et al., 2004). Furthermore, as a result of selection pressure, frequency of treatment which accelerate the process of resistance development and genetic diversity/variation the ability of rapid reproduction which allow them to adapt quickly against drug exposure (Jabbar et al., 2006).

Hurdles in the Way of New Anthelmintic Formation

Millions of dollars must be invested and years of research are needed to develop a novel anthelmintic before a commercial formulation is made accessible. Nevertheless, anthelmintic resistance has developed in innovative products even after only a few years of usage, limiting their economic life as shown in the figure (b) (Sepúlveda and Crespo, 2020). Monepantel, for example, was introduced as a novel chemical against sheep worms in 2009. However a study from New Zealand only three years later detailed the first instances of resistance in sheep and goats against this drug (Bartley et al., 2015).Therefore, it is important to develop alternate methods and improve existing anthelmintic by using novel techniques in nanotechnology.

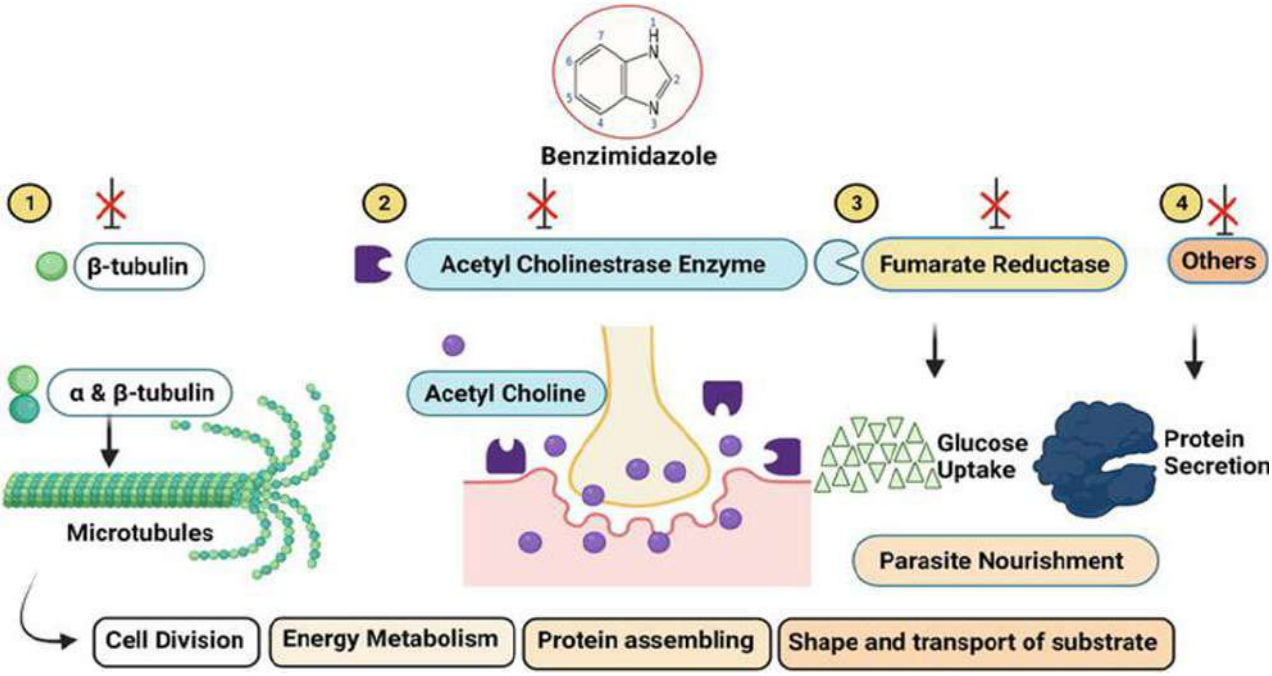


Fig. (a): Mechanism of Resistance against anthelmintic

Nanotechnology as a Solution to Combat Anthelmintic Resistance

Nanotechnology brought up a new approach, by modification of the already existing drugs. Organic nanoparticles (NPs) especially chitosan are mostly used with anthelmintic, they are a potential source to improve existing drugs (Real et al., 2018).

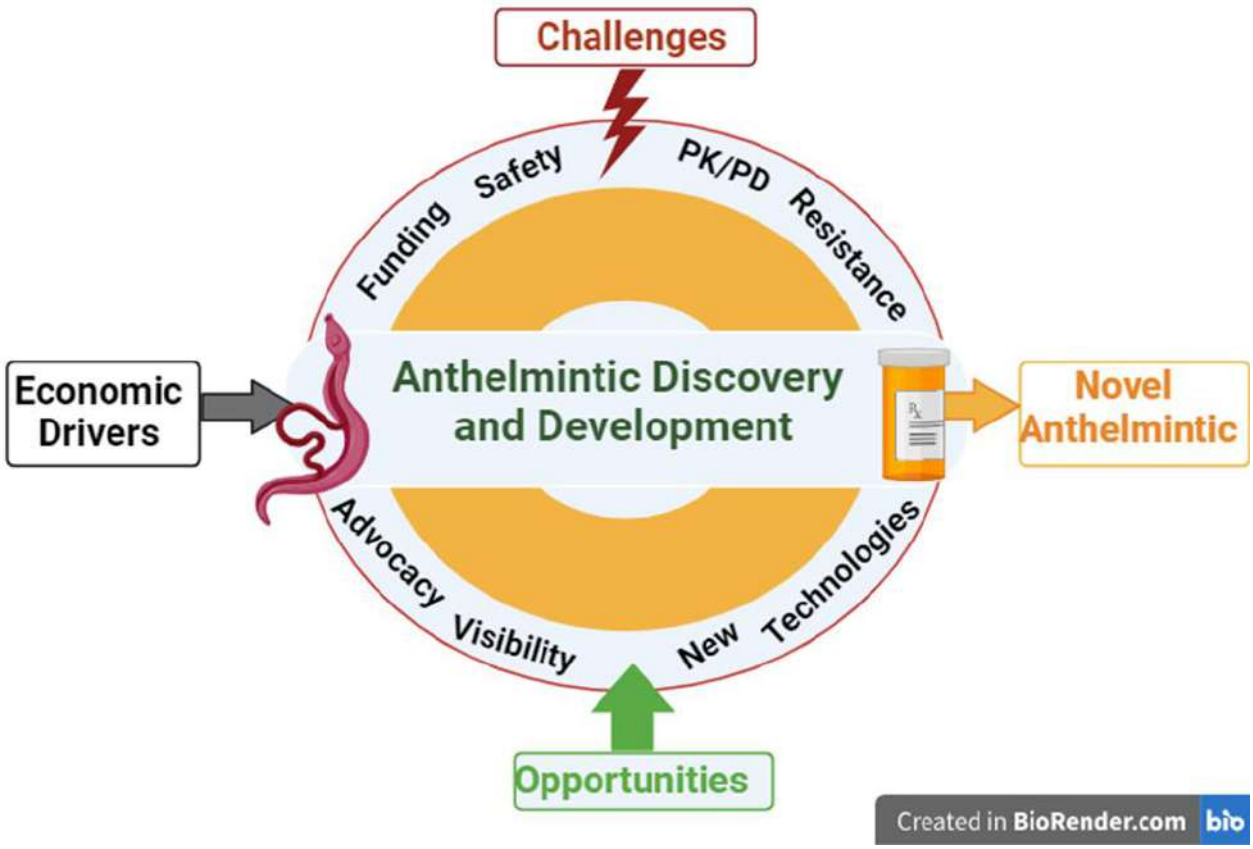


Fig. (b): Hurdles and challenges in the way of new anthelmintic development

Nanoparticle Definition

Nanoparticles are usually 1 to 100nm in size, also known as "zero-dimensional" nanomaterials with catalytic and absorptive properties, show unprecedented growth in different research areas such as nanomedicine, nanoelectronics and

energy production areas, especially in pharmaceuticals and medicine in terms of diagnosis, treatment and diseases prevention (Modena et al., 2019) They are the new game player in field of modern medicine from basic drug delivery system to genetic level changes such as gene manipulation for the treatment of genetic and inherited diseases such as thalassemia to tumor treatment (Liu et al., 2023).

Role of Nanoparticles in Drug Delivery

Nanotechnology helps us to create an object by manipulating the individual atoms of matter and creation of modified molecular structures. They possess an ability to serve as drug delivery system or implants by supplying organic and inorganic biologically compatible polymers, help researchers to understand molecular basis of disease and supply of active drug (Nasibova et al., 2023). They proved as novel therapeutics and drug delivery systems for various drugs (Najahi et al., 2020).

In the pharmaceutical industry, Nano-delivery structures or nanotechnology-based drug carriers have shown promising results by enhancing the effectiveness of anthelmintic drugs and reducing resistance by improving the drug kinetics by several mechanisms for example targeted delivery, increased drug solubility, synergistic and Immunomodulatory effect and increase in bioavailability of drug as shown in the figure (c).

Targeted Drug Delivery

Small size of nanoparticles allow direct contact with subcellular compartment to target specific cells that can effectively pass through physiological barriers, which provides an opportunity to interfere with intracellular processes and makes them good drug delivery systems (Fan et al., 2017). They can improve the therapeutic efficiency of drug deliveries by conjugating cell-specific ligands onto the nanoparticle surface which binds to specific receptors which only expressed in affected cells (Lu et al., 2012).

For Example

Levamisole causes spastic paralysis in worms by binding to the nicotinic acetylcholine receptors which are activated after binding with the drug. The alteration in the target site receptors are the mechanism of resistance to the imidothiazole group (Sarai et al., 2015). Nanoparticles aid in the tight adhesion of drugs with binding surfaces and multiple interactions with cell surfaces to confer a receptor-mediated uptake of nanoparticles by the cell (Wang et al., 2020).

Increased Drug Bioavailability

Oral administration has been the most common and reliable method of drug delivery for ages because of its compliance and convenience. Despite of its advantages, it faces some issues regarding bioavailability like premature degradation, pre-systemic metabolism and poor permeability in the gastrointestinal tract and liver (Han et al., 2017).The combination of these drugs with nanoparticles increases their bioavailability (Rehman et al., 2019).

Nanoparticle-assisted Drug Delivery

Nanomaterial due to their physicoshemistry and small size can cross the body barriers and cause significant changes in drug interaction with biological pathways and alter efficacy. They increase the adherence of the drug with the mucus surface and in this way; improve drug stability and solubility (Singhvi et al., 2018).

For example, a drug Nano carrier ethylene glycol of size 200 nm is more absorbed by the GI tract, reducing interaction with both luminal components and mucus in the gut (Zhao et al., 2019).

Synergistic and Immunomodulatory Effects

Immunomodulatory nanosytems can improve the therapeutic effects of drugs through various mechanisms like molecular targeted therapy, immune cell activation etc and molecular targeted drugs (Feng et al., 2019). In this way, it removes many obstacles in the way of treatment such as inadequate immune stimulation, unable to reach the targeted site and bioactivity loss of immune agents during blood circulation. They improve efficacy of drugs by protection of antigen and adjuvant, reprogramming of immune cells and efficient delivery to antigen presenting cells (Lafuento et al., 2022).

Nanomaterial's, such as PLGA, iron oxide nanoparticle and conjugated polymers, could enhance the cell uptake by APCs and stimulate an immune response (Hammadi et al., 2022). In the past few years, pharmaceutical development in veterinary has benefited greatly from nanotechnology.

Nanoparticles are synthesized from various methods like green synthesis, chemical precipitation sol gel method and nanoemulsions.

Approaches for Synthesis of Nanoparticles

Nanostructures can be synthesized by using a variety of methods from chemical precipitation to green synthesis of nanoparticles. There are two basic ways to create nanoparticles, building from atoms or shrinking from microparticle to nanoparticle size is ways to create nanostructures. Here are few methods used for nanoparticle synthesis, that can be used as a drug carrier for anthelmintic (Zahoor et al., 2021).

Chemical Precipitation

Chemical precipitation is an ideal method for achieving nanoparticles of uniform size and shape (Yang et al., 2006). Particle size is the main controlling factor for choosing this method, size of nanostructures affects many properties for example the particle size in the range of 30 to 50nm, which can easily pass through a capillary, can bind with DNA to make mutations and use as a drug carrier for targeted delivery (Hu et al., 2006).

A spherical form with particles smaller than 25 nm is produced by chemical co-precipitation (Ealia et al., 2017). Moreover, magnetite nanoparticles' surface modification can influence interfacial characteristics, inhibit particle aggregation and increase the particles' stability in the solvent (Oh et al., 2011). For biotechnology applications, the surface coating of nanoparticles is therefore especially crucial. However, the naturally occurring fatty acid with the carboxylic group found in animal fats can be utilized to coat the magnetite (Lassoued et al., 2017).

Green Synthesis of Nanoparticles

Green synthesis is the synthesis of nanoparticle from plant or microorganisms, most effective, low cost and safe method for nanoparticle synthesis. Plant-based NP synthesis is undoubtedly more suitable process; using plant extract. In green synthesis, a metal salt is created and the reaction takes only a few hours to several minutes at room temperature (Varma et al., 2012).The last ten years have seen a significant increase of interest in this technique, especially for silver (Ag) and gold (Au) NPs, which are safer than other synthetically prepared metallic NPs as shown in the figure (d). Green approaches for producing nanoparticles are not only economically wise but also easily scalable, manageable and achievable (Gour et al., 2019).

The Activity of Green Synthesized Silver Nanoparticle as Anthelmintic

Ag nanoparticles are known to exhibit anthelmintic activity when synthesized through green synthesis. The positive charge on the surface of silver particles attracts the negatively charged cell membranes of parasites through electrostatic interaction. In this way, phytochemicals attach with free proteins present in the gastrointestinal tract and cause cuticle lysis of the parasite (Dibrov et al., 2001).

The anthelmintic effect of silver nanoparticles is more pronounced when AgNPs are combined with *Momordica Charantia* extract, these two-show synergism and proved as excellent anthelmintic drugs (Rashid et al., 2016).

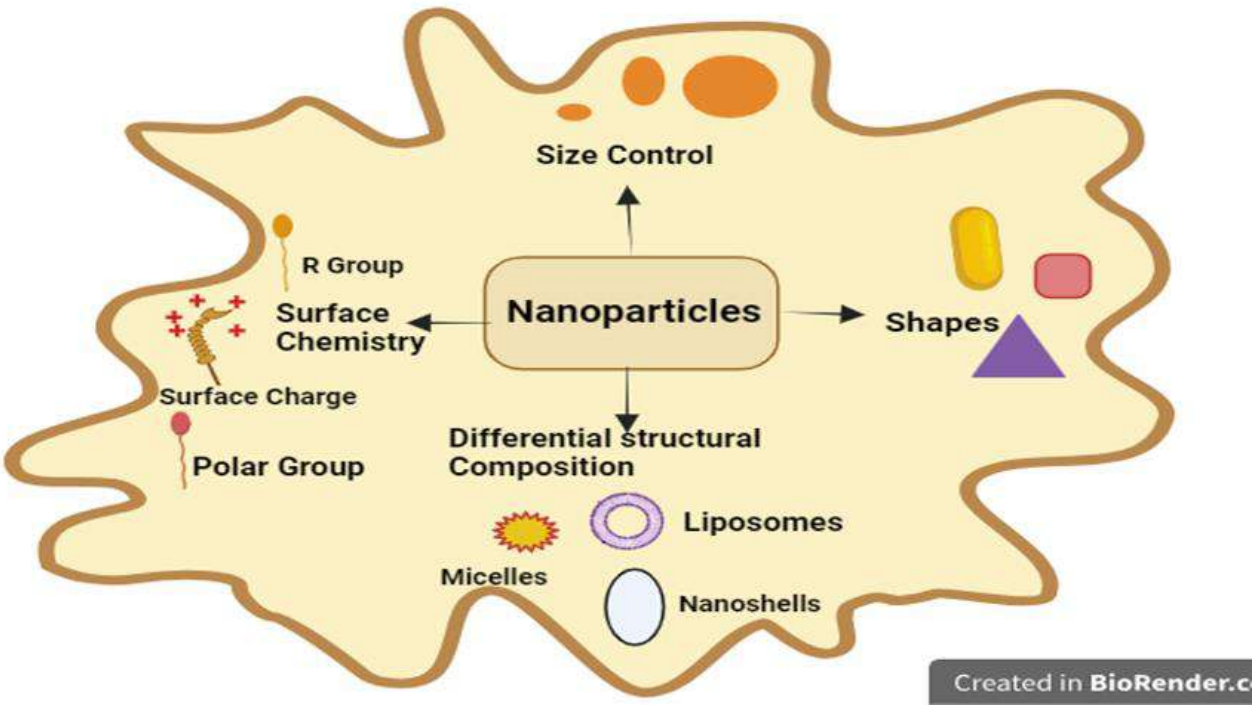
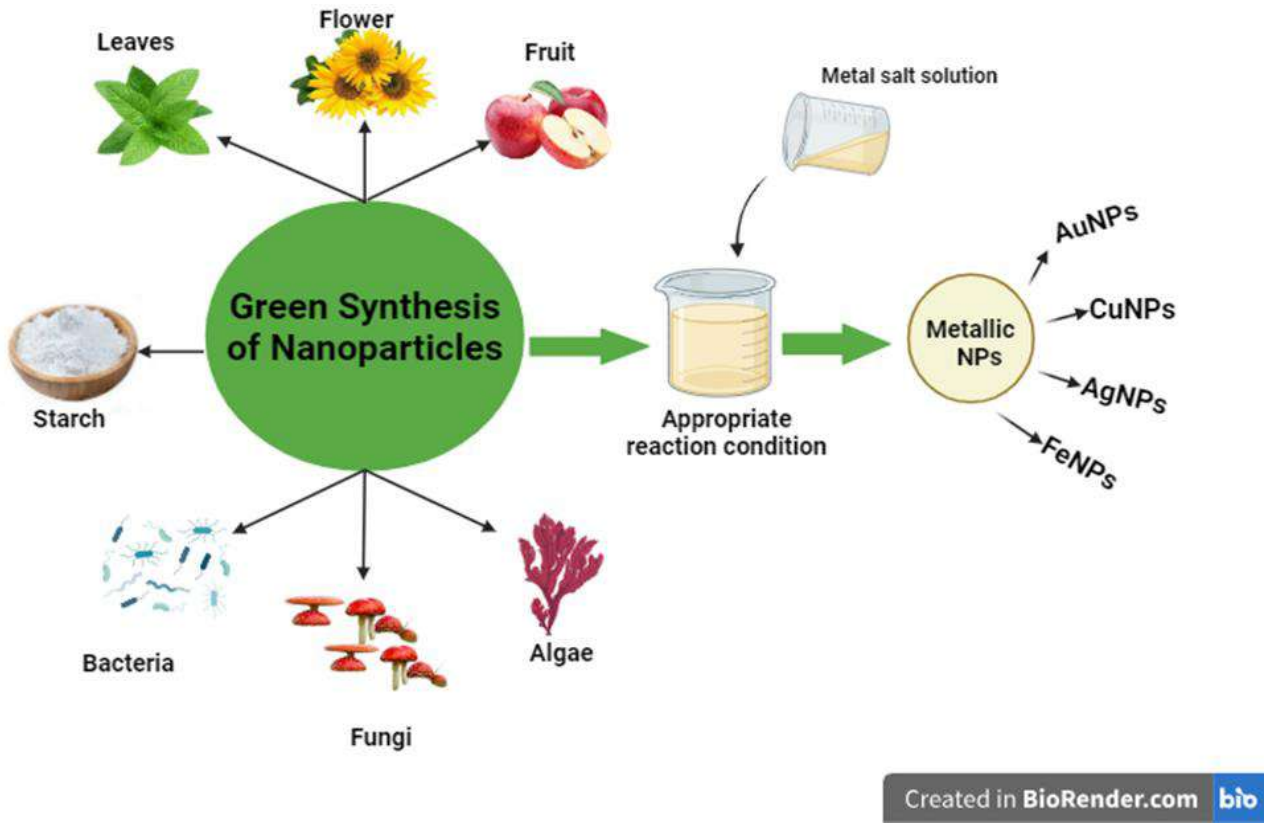


Fig. (c): Role of Nanoparticles in Drug delivery



FsgCD

Fig. (d): Green Synthesis of Nanoparticles

The Activity of Green Synthesized ZnO and MGo NPs as Anthelmintic

Zinc oxide and Magnesium oxide nanoparticles synthesized from dragon fruit by green method show significant anthelmintic activity against earthworm and gastrointestinal nematode. A higher concentration of zinc oxide shows paralysis of muscles by increasing hyperpolarization and reduced excitability of worm (Puttaraju et al., 2021; Kavitha et al., 2023).

Application of Nanotechnology to Improve Anthelmintic Resistance

Nanotechnology plays a significant role in improving pharmacological drugs and research. Various nanoparticles such as silver, magnesium and zinc show anthelmintic activities. By keeping in mind these properties and their significance against parasites we can combine these nanoparticles with different anthelmintic drugs to solve the problem of drug resistance in parasite. For this purpose Encapsulation methods are ideal.

Nano Encapsulation to Combine Drug with Anthelmintic

Nanoencapsulation technique is the development of particles having a core and material of interest like drug coated by a secondary material and make Nano sized encapsulated composite as shown in the figure (F).The core provide protection to coated material, controlled release ,ease in handling and ideal for pharmaceutical and medical industry (Azar et al., 2022). For drugs, nanoencapsulated particles shows better efficiencies as sustained release of drug, targeted delivery, bioavailibilty and stability of solution .Various methods are used for encapsulation of drugs such as sol gel method, nanoemulsions etc.

Nanoemuslions

Submicron-sized emulsions known as nanoemulsions are use as drug carriers to enhance the delivery of medicines to target site.By uing the right surfactants, two imiscible liquids (oil and water) are combined to produce a single phase in a thermodynamically stable isotropic system called a nanoemulsion (Jadhav et al., 2020).The normal range of nanoemulsion droplet size is 20–200 nm (Soni et al., 2021).

Ablendazole Nanoemuslions with Lipid Particle

Solid lipid nanoparticles loaded with albendazole by double emulsion technique, the drug was loaded in the lipid matrix (Sarmento et al., 2007).As a result, ablendazole loaded lipid nanoparticle are prepared which shows high mortality against Haemonchus by causing paralysis and nerve depolarization. Nanoparticles help in sustained release of drug by overcome the hydrophobic nature of ablendazole (Sharma et al., 2023).

Sol Gel Method

Compared to other current approaches, the sol-gel method is more popular and has more industrial applications (Esposito et al., 2023). This process can produce high-quality nanoparticles of the same size on an industrial scale because of its special qualities and traits (Chang et al., 2021). This process can create two or more kinds of nanoparticles at the same time, which means that alloy products can be created in a single step by combining two or more metal (or metal oxide) precursors in a specific ratio.

Highly homogenous composites with a very high purity (99.99% purity), particularly the need of pharmacological industry can be produced using this method (Khurana et al., 2021). Another advantage of this method compared to conventional methods is the lower temperature range between 70 and 320°C while other methods produce nanomaterial in the temperature range of 1400–3600°C (Li et al., 2003; Verma et al., 2015).

Nano Technological Improvement of Anthelmintics

Nanoparticles like liposomes, polysaccharides, dendrimers and metals are used to assist drugs. These groups of nanoparticles are used with almost all groups of anthelmintics as shown in the table 1.

Lipid Based Nanoparticles

Lipid nanoparticles or liposomes are designed for delivery of lipophilic drugs and composed by a lipid matrix made of glycerides, waxes and triglycerides. Liposomes formulations are used to reduce toxic effects of potent drugs provide high stability, control release, specific site targeting and protection from degradation (XU et al., 2022).

Liposomes Entrapped Ablendazole against Rats

In one of the earliest publications on liposomes, albendazole was entrapped with lipid nanoparticle to enhance its absorption in rats following oral co-administration of cimetidine. The tested preparation in this experiment enhanced the amounts of albendazole and its primary metabolites in the plasma and decreased the biomass of cysts by up to 94% (Gamboa et al., 2016).

In another study, Schistosoma mansoni-infected mice were given liposomes containing praziquantel .Compared to standard praziquantel therapy; the authors saw a decrease in adult worms, eggs, and hepatic cysts (Frezza et al., 2013).

Macrocylical Nanoformulation against Echinococcus Granuloses

Ivermectin shows efficacy against E.granulosus but when the researcher compared the pure ivemectin with the nanoformulation of ivermection with lipsomoes,the later demonstrated a greater efficacy in terms of scolicidal activity and DNA damage (Ahmadpour et al., 2019). While ivermectin is the recommended treatment for hydatid disease, the nanaoformulation of ivermectin mixture produced encouraging outcomes which shows that lipid particles make significant improvement to enhance pharmacokinetics of ivermectin.

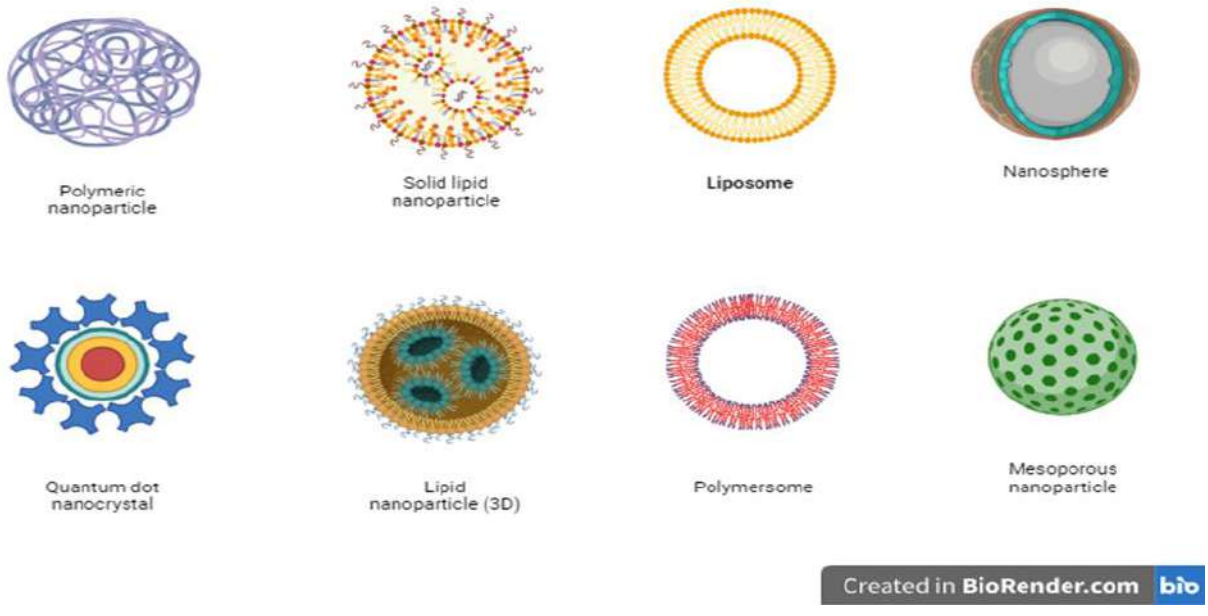


Fig. (e): Different type of nanoparticle used to assist drug.

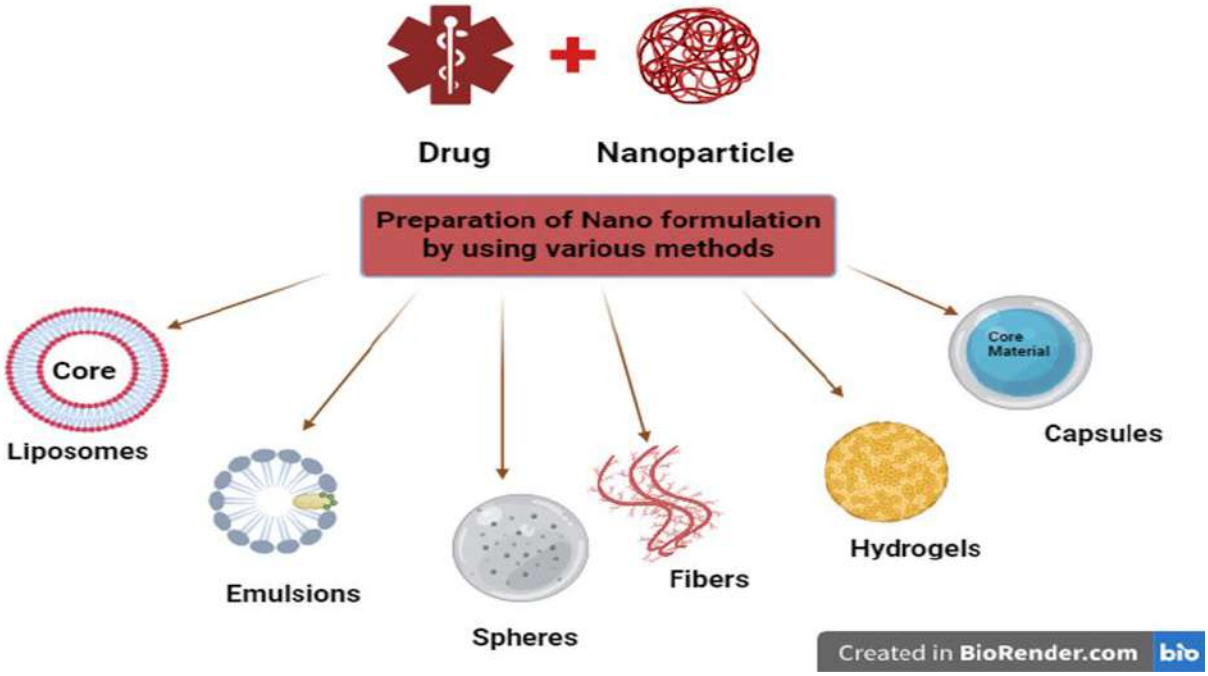


Fig. (F): Encapsulated drug with nanoparticles

Liposome Diethylcarbamazine against Filarial Nematodes

A liposome-diethylcarbamazine formulation co-administered with immunomodulator tufts, was used to treat a filarial infection caused by Brugia malayi and the treatment was successful for up to 60 days after the initial administration (Owais et al., 2003). Another study reported, SLN formulation intended for the treatment of echinococcosis was reported to increase the half-life and scarce solubility of praziquantel. The formulation avoided the negative consequences of long term medication (Xie et al., 2011).

Polysaccharide Based Nanoparticles

Polymeric structures are of two type natural polysaccharide and synthetic like polyethylene glycol. Natural biopolymers exhibit favorable characteristics such as low toxicity, biodegradability, abundance and compatibility (Prasher et al., 2021).Polysaccharides such as dextran, agarose and chitosan.

Table 1: An overview of recent anthelminthic treatment in combination with nanoparticle

Anthelmintic	Nanoparticle	Targeted Parasite	Targeted Effect	Reference
Benzimidazole Group	Natural polymers	*Echinococcus granulosis*	Significant increase in solubility of drug and deleterious effect against cysts.	Pensel (2014)
Albendazole				
Flubendazole	Synthetic polymers	*Trichinella spirallis*	Dissolution rate improved	Ceballos (2018)
Triclabendazole	Natural Polymer	*Echinococcus granulosus*	Reduction of weight and no of cysts	Farhadi (2018)
	Dendrimers	-	Increased half-life duration and mean residence time.	Mansuri (2016)
	Micellar	-	Increased solubility	Vinarov (2018)
	Lipid Nanoparticle	*Echinococcus granulosis*	94 percent reduction of cyst biomass.	Wen (1996)
	Polymer	*Fasciola Hepatica*	Increased solubility of triclabendazole	Real (2018)
Ivermectin	Lipid Nanoparticle	*E. granulosus protoescoleces*	Structural and DNA damage of scolex of *E.granulosus*	Farhadi (2018)
	Liposomes	-	Enhance plasmatic concentration	Gamboa (2016)
	Synthetic polymers	*Brugia malayi*	Improved efficacy and 50 percent dose reduction	Ali (2014)
Praziquantel	Lipid nanoparticles	*Schistosoma mansoni*	Adult worms, eggs and hepatic cysts reduction.	Frezza (2013)
	Lipid nanoparticles	*E. granulosus*	5 fold increased bioability and the mean residence time. 10 fold reduction of the standard dose	Xie (2011)

	Micellar	-	Increased solubility and peak concentration, time.	Vinarov (2011)
Diethylcarbamazine	Lipid nanoparticles	*Brugia malayi*	High filaricidal efficacy up to sixty days post-treatment.	Owais (2011)
Niclosamide	Dendrimers	-	Enhanced solubility and prolonged release.	Devarakonda (2005)

Chitosan the Safest Nanoparticle for Drugs

Chitosan is a hydrophilic linear polysaccharide consisting of [(1 → 4)-β-linked 2-amino-2-deoxy-d-glucose]. Chitosan is regarded as a flexible biopolymer that may be modified in a number of ways, making it appropriate for a number of worthwhile uses. Chitosan has demonstrated its superiority as a biopolymer shell material for encasing several active components (Narmani et al*.,* 2021).

The usage of chitosan-coated microcapsules shields active components from environmental elements such pH changes and temperature fluctuations. Chitosan can be used as the shell material to microencapsulate a variety of core components, including active medicinal compounds, food products, catalysts, oils and pigments (Sun et al., 2019).

Drugs with chitosan microcapsules as an active ingredient enable a drug's gradual release to the targeted spot in the body under particular circumstances. For instance, lipophilic medications were encapsulated in chitosan so that they may be released later on in the human digestive system (Lang et al*.,* 2020).

Chitosan Encapsulated Bromelain aginst Haemonchus Contortus

Bromelain that has been extracted from pineapple fruits are utilized as a supplemental therapy for treating dogs, birds, intestinal parasite-infected people and pigs in underdeveloped nations. Because bromelain is an enzymatic substance, its catalytic activity is limited to a pH range of 5.5 to 8.0 (Wang et al*.,* 2020). Chitosan nanoparticles loaded with bromelain have demonstrated anthelmintic effect on Haemonchus contortus eggs, larvae, and adult worms. The effectiveness of bromelain encapsulation as a novel anthelmintic medication for the control of Haemonchosis in ruminants (Hunduza et al., 2022).

Nanoformulation of Triclabendazole against Fasciola

Triclabendazole is a poorly-water soluble drug and commonly used to treat fasccioliosis. The triclabendazole and chitosan-based nanocapsules and nanoemulsions were thoroughly studied in terms of their stability in biological medium, in-vitro release and polydispersity index and zeta potential. The drug's average hydrodynamic size was found to be approximately 160 nm for empty nanoemulsions, while it rose significantly to approximately 190 nm for loaded ones. On the other hand, when triclabendazole was added to the nanocapsules, their average hydrodynamic size rose from about 160 nm to about 400 nm. As a result, the availability of drug was increased (Real et al*.,* 2018).

Polyethylene Glycol and Albendazole

An additional investigation sought to enhance albendazole low solubility, which restricts the drug's absorption via the digestive system. To do this, mice were used to test formulations containing poloxamer and polyethylene glycol in addition to albendazole, as contrast to pure albendazole. Albendazole's solubility and the peak concentration of its primary metabolite, albendazole sulphoxide, were both markedly enhanced in mice(Castro et al*.,* 2013).In another study, a methoxy polyethylene glycol polycaprolactone formulation loaded with flubendazole shown encouraging outcomes against the Echinococcus (Farhadi et al*.,* 2018)

Dendrimers and Micellar Nanostructures

Dendrimers and anthelmintic combinations are exemplified. The solubility of this medication was enhanced in vitro by a Poly amidoamine-albendazole linked structure, indicating that amidoamines may enhance drug absorption in vivo (Fernández et al*.,* 2011). Similarly, albendazole oral tables combined with fifth generation PPI dendrimer linked to chitosan (muco-dendrimer) were developed in a mouse model. This formulation resulted in an increase in albendazole's half-life and mean residence time when compared to the free medication (Mansuri et al*.,* 2016).

Dendrimer Assisted Niclosamide

Dendrimers were used to boost the hydro solubility of niclosamide, a salicylanilide anthelmintic intended for the treatment of trematodes and cestodes. The authors observed that the medication's solubility had increased and that a prolonged drug release was caused by niclosamide's strong binding to Poly amidamine which increase drug bioavailability and biocompatibility (Devarakonda et al., 2005).

Micellar Nanostructure as Anthelmintic Carrier

Micellar nanostructures are incredibly adaptable units, which range in size from 8 to 125 nm, may carry either water soluble or insoluble substances and are good for large medication loads. A few studies on anthelmintic and micellar

nanostructures are available (Bai et al., 2018). They shows promising results in lowering the dose of praziquantel which is highly dissoluble drug. (Cioli et al., 2003). In order to get around these negative consequences, the combination of praziquantel micellar nanoformulation based on glycyrrhizic acid was prepared in one of the study .The drug's solubility was significantly boosted (up to 3.5 times) by this combination, as were certain pharmacokinetic properties (Meteleva et al., 2019).

Metallic Nanoparticle

These are synthetic particles with a size range of 1 to 100 nm that can be used to pair medications, proteins, antibodies, and medicinal compounds. In addition to the medications' defense against potential immunological responses, the drug-metal nanoparticle combination provides an additional benefit (Aderibigbe et al., 2015). Furthermore, certain metallic nanoparticles themselves exhibit antioxidant and antibacterial properties and anthelmintic effects. In combination with other anthelmintic drugs nanoparticle shows new therapeutic advantages. For example, In vitro tests were conducted by Kar et al. using gold nanoparticles generated in Nigrospora oryzae cultures against the chicken tapeworm Raillietina sp. (Kar et al., 2014) .The authors observed a detrimental structural impact in worms exposed to particles as comparison to a control group.

In additional studies, the effects of silver nanoparticles and a phytochemical extract of Tribulus terrestris were combined and examined .In opposition to the water buffalo's amphistome Gigantocotyle explanatum (Khan et al., 2015). The Pasrasite exposed to the corresponding nanoparticles, shows physical damage, decreased motility, increases in reactive oxygen species and a decrease in superoxide dismutase and glutathione activities, suggesting oxidative damage to the flukes (Dorostkar et al., 2017).

Conclusion

In conclusion, Overreliance on traditional anthelmintic drugs has fueled the evolution of resistant parasite strains, making many treatment options ineffective. In this context nanoanthelmintics represent a significant advancement in the fight against anthelmintic resistance.The development of nanoanthelmintics represents a paradigm shift in the approach to parasite control, emphasizing the importance of innovation and interdisciplinary collaboration in dealing with complex biological problems Nano-scale drug delivery systems have the potential to revolutionize parasite control strategies by protecting human and animal health and reducing the spread of drug-resistant parasites. However, while nanoanthelmintics show great promise, several challenges remain. This includes the need for additional research into the long-term safety and environmental impacts.

As we move forward, we must remain vigilant in our efforts to combat anthelmintic resistance, adopting new technologies and approaches to ensure a long-term future for parasite control.

REFERENCES

Aderibigbe, B.A. (2017). Metal-based nanoparticles for the treatment of infectious diseases. *Molecules*, 22(8): 1370

Ahmadpour, E., Godrati-Azar, Z., Spotin, A., et al. (2019). Nanostructured lipid carriers of ivermectin as a novel drug delivery system in hydatidosis. *Parasit Vectors*, 12(1): 469.

Ali M, Afzal M, Verma M, et al. Therapeutic efficacy of poly (lactic-co-glycolic acid) nanoparticles encapsulated ivermectin (nano-ivermectin) against Brugian filariasis in experimental rodent model. Parasitol Res 2014; 113(2): 681-91. http://dx.doi.org/10.1007/s00436-013-3696-5 PMID: 24366812

Ali, M. S., Saeed, K., Rashid, I., Ijaz, M., Akbar, H., Rashid, M., and Ashraf, K. (2018). Anthelmintic drugs: their efficacy and cost-effectiveness in different parity cattle. *The Journal of Parasitology*, 104(1), 79-85.

Azar, F. A. N., Pezeshki, A., Ghanbarzadeh, B., Hamishehkar, H., and Mohammadi, M. (2020). Nanostructured lipid carriers: Promising delivery systems for encapsulation of food ingredients. *Journal of Agriculture and Food Research*, 2, 100084.

Bai DP, Lin XY, Huang YF, Zhang XF. Theranostics aspects of various nanoparticles in veterinary medicine. Int J Mol Sci 2018; 19(11): 3299. http://dx.doi.org/10.3390/ijms19113299 PMID: 30352960

Bartley DJ, Devin L, Nath M, Morrison AA. Selection and characterisation of monepantel resistance in Teladorsagia circumcincta isolates. Int J Parasitol Drugs Drug Resist 2015; 5(2): 69-76. http://dx.doi.org/10.1016/j.ijpddr.2015.05.001 PMID: 26042197

Beesley NJ, Williams DJ, Paterson S, Hodgkinson J. Fasciola hepatica demonstrates high levels of genetic diversity, a lack of population structure and high gene flow: Possible implications for drug resistance. Int J Parasitol 2017; 47(1): 11-20

Ceballos L, Krolewiecki A, Juárez M, et al. Assessment of serum pharmacokinetics and urinary excretion of albendazole and its metabolites in human volunteers. PLoS Negl Trop Dis 2018; 12(1): e0005945

Chacon, S. C. (2023). Vector Borne Diseases Related with Companion Animals in Panama: A Review. *European Journal of Veterinary Medicine*, 3(1), 1-10.

Chang, H., Kim, J., Rho, W. Y., Pham, X. H., Lee, J. H., Lee, S. H., ... and Jun, B. H. (2021). Silica nanoparticles. *Nanotechnology for Bioapplications*, 41-65.

Charlier, J., Rinaldi, L., Musella, V., Ploeger, H. W., Chartier, C., Vineer, H. R., and Claerebout, E. (2020). Initial assessment of the economic burden of major parasitic helminth infections to the ruminant livestock industry in Europe. *Preventive Veterinary Medicine*, 182, 105103.

Cioli D, Pica-Mattoccia L. Praziquantel. Parasitol Res 2003; 90(Suppl. 1): S3-9. http://dx.doi.org/10.1007/s00436-002-0751-z PMID: 12811543

Devarakonda B, Hill RA, Liebenberg W, Brits M, de Villiers MM. Comparison of the aqueous solubilization of practically insoluble niclosamide by polyamidoamine (PAMAM) dendrimers and cyclodextrins. Int J Pharm 2005; 304(1-2): 193-209. http://dx.doi.org/10.1016/j.ijpharm.2005.07.023 PMID: 16198076

Dibrov P, Dzoiba J, Gosink KK, Häse CC. Chemiosmotic mechanism of antimicrobial activity of Ag(+) in vibrio cholera. Antimicrob Agents Chemother. 2002;46(8):2668–70.

Dorostkar R, Ghalavand M, Nazarizadeh A, Tat M, Hasemzadeh M. Anthelmintic effects of zinc oxide and iron oxide nanoparticles against Toxocara vitulorum. Int Nano Lett 2017; 7: 157. http://dx.doi.org/10.1007/s40089-016-0198-3

Ealia, S. A. M., and Saravanakumar, M. P. (2017). A review on the classification, characterisation, synthesis of nanoparticles and their application. In IOP conference series: materials science and engineering (Vol. 263, No. 3, p. 032019). IOP Publishing.

El-Hammadi, M. M., and Arias, J. L. (2022). Recent advances in the surface functionalization of PLGA-based nanomedicines. *Nanomaterials*, 12(3), 354.

Espinoza M. Drug resistance in parasitic helminths of veterinary importance in Chile: status review and research needs. Austral J Vet Sci. 2018;50:65–76. doi:10.4067/S0719-81322018000200065

Esposito, S. (2023). Evolution of Sol–Gel Chemistry. In Sol-Gel Synthesis Strategies for Tailored Catalytic Materials (pp. 43-51). Cham: Springer International Publishing.

Esteban JG, González C, Bargues MD, et al. High fascioliasis infection in children linked to a man-made irrigation zone in Peru. Trop Med Int Health 2002; 7(4): 339-48

Fan X, Jiang S, Li Z et al. Conjugation of poly(ethylene glycol) to poly(lactide)-based polyelectrolytes: an effective method to modulate cytotoxicity in gene delivery. Mater. Sci. Eng. C Mater. Biol. Appl. 73, 275–284 (2017).

Farhadi M, Haniloo A, Rostamizadeh K, Faghihzadeh S. Efficiency of flubendazole-loaded mPEG-PCL nanoparticles: A promising formulation against the protoscoleces and cysts of Echinococcus granulosus. Acta Trop 2018; 187: 190-200. http://dx.doi.org/10.1016/j.actatropica.2018.08.010

Feng, X., Xu, W., Li, Z., Song, W., Ding, J., and Chen, X. (2019). Immunomodulatory nanosystems. *Advanced Science*, 6(17), 1900101.

Fernández L, Sigal E, Otero L, Silber J, Santo M. Solubility improvement of an anthelmintic benzimidazole carbamate by association with dendrimers. Braz J Chem Eng 2011; 28: 679-89. http://dx.doi.org/10.1590/S0104-66322011000400013

Fissiha, W., and Kinde, M. Z. (2021). Anthelmintic resistance and its mechanism: a review. *Infection and Drug Resistance*, 5403-5410.

Fleming, J. O., and Weinstock, J. V. (2015). Clinical trials of helminth therapy in autoimmune diseases: rationale and findings. *Parasite Immunology*, 37(6), 277-292.

Frezza TF, Gremião MP, Zanotti-Magalhães EM, Magalhães LA, de Souza AL, Allegretti SM. Liposomal-praziquantel: Efficacy against Schistosoma mansoni in a preclinical assay. Acta Trop 2013; 128(1): 70-5.

Gamboa GV, Palma SD, Lifschitz A, et al. Ivermectin-loaded lipid nanocapsules: toward the development of a new antiparasitic delivery system for veterinary applications. Parasitol Res 2016; 115(5): 1945-53.

Gour, A., and Jain, N. K. (2019). Advances in green synthesis of nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology*, 47(1), 844-851.

Han, T., Wang, M., Zhang, G., Han, D., Li, X., Liu, G., and Wang, Z. (2017). Gastrointestinal nematodes infections and anthelmintic resistance in grazing sheep in the Eastern Inner Mongolia in China. *Acta Parasitologica*, 62(4), 815-822.

Hu, F. X., Neoh, K. G., and Kang, E. T. (2006). Synthesis and in vitro anti-cancer evaluation of tamoxifen-loaded magnetite/PLLA composite nanoparticles. Biomaterials, 27(33), 5725-5733.

Hunduza, A., Kagira, J., Maina, N., Andala, D., Cheruiyot, K., and Kahiro, S. (2020). In vitro anthelmintic activity of chitosan encapsulated bromelain against eggs, larval and adult stages of Haemonchus contortus. *Journal of Applied Life Sciences International*, 23(3), 28-38.

Jabbar A, Iqbal Z, Kerboeuf D, Muhammad G, Khan N, Afaq M. Anthelmintic resistance: the state of play revisited. Life Sci. 2006;79 (26):2413–2431. doi:10.1016/j.lfs.2006.08.010

Jadhav, R. P., Koli, V. W., Kamble, A. B., and Bhutkar, M. A. (2020). A review on nanoemulsion. *Asian Journal of Research in Pharmaceutical Science*, 10(2), 103-108.

Kaplan RM. Drug resistance in nematodes of veterinary importance: a status report. Trends Parasitol. 2004;20(10):477–481. doi:10.1016/ j.pt.2004.08.001

Kar PK, Murmu S, Saha S, Tandon V, Acharya K. Anthelmintic efficacy of gold nanoparticles derived from a phytopathogenic fungus, Nigrospora oryzae. PLoS One 2014; 9(1): e84693.

Kavitha, M., Singaravelu, G., Nagalingam, M., and Rajeshkumar, S. (2023). Nanoparticles of magnesium oxide with an anthelmintic activity produced by a green principle. Journal of Survey in Fisheries Sciences, 10(1S), 18-32.

Khan YA, Singh BR, Ullah R, Shoeb M, Naqvi AH, Abidi SM. Anthelmintic effect of biocompatible zinc oxide nanoparticles (ZnO NPs) on Gigantocotyle explanatum, a neglected parasite of indian water buffalo. PLoS One 2015; 10(7): e0133086.

Khurana, P., Lingayat, S., and Thatai, S. (2023). Synthesis of silica spherical to Y-shape nanoparticles: A review with surface

modifications and its characterization. *Analytical Chemistry Letters*, 1-21.

Lafuente-Gómez, N., Wang, S., Fontana, F., Dhanjani, M., García-Soriano, D., Correia, A., and Somoza, Á. (2022). Synergistic immunomodulatory effect in macrophages mediated by magnetic nanoparticles modified with miRNAs. *Nanoscale*, 14(31), 11129-11138.

Lang, X., Wang, T., Sun, M., Chen, X., and Liu, Y. (2020). Advances and applications of chitosan-based nanomaterials as oral delivery carriers: A review. *International Journal of Biological Macromolecules*, 154, 433-445.

Lassoued, A., Dkhil, B., Gadri, A., and Ammar, S. (2017). Control of the shape and size of iron oxide (α-Fe2O3) nanoparticles synthesized through the chemical precipitation method. *Results in Physics*, 7, 3007-3015.

Li, B., Wang, X., Yan, M., and Li, L. (2003). Preparation and characterization of nano-TiO2 powder. *Materials Chemistry and Physics*, 78(1), 184-188.

Liu, R., Luo, C., Pang, Z., Zhang, J., Ruan, S., Wu, M., and Gao, H. (2023). Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment. *Chinese Chemical Letters*, 34(2), 107518.

Lu Y, Low PS. Folate-mediated delivery of macromolecular anticancer therapeutic agents. Adv. Drug Deliv. Rev. 64, 342–352 (2012).

Lustigman, S., Prichard, R. K., Gazzinelli, A., Grant, W. N., Boatin, B. A., McCarthy, J. S., and Basanez, M. G. (2012). A research agenda for helminth diseases of humans: the problem of helminthiases. *PLoS Neglected Tropical Diseases*, 6(4), e1582.

Mansuri S, Kesharwani P, Tekade RK, Jain NK. Lyophilized mucoadhesive-dendrimer enclosed matrix tablet for extended oral delivery of albendazole. Eur J Pharm Biopharm 2016; 102: 202-13. http://dx.doi.org/10.1016/j.ejpb.2015.10.015 PMID: 26563727

Meteleva E, Chistyachenko Y, Suntsova L, et al. Disodium salt of glycyrrhizic acid - A novel supramolecular delivery system for anthelmintic drug praziquantel. J Drug Deliv Sci Tec 2019; 50: 66-http://dx.doi.org/10.1016/j.jddst.2019.01.014

Modena, M. M., Rühle, B., Burg, T. P., and Wuttke, S. (2019). Nanoparticle characterization: what to measure?. *Advanced Materials*, 31(32), 1901556.

Najahi-Missaoui, W., Arnold, R. D., and Cummings, B. S. (2020). Safe nanoparticles: are we there yet?. *International Journal of Molecular Sciences*, 22(1), 385.

Narmani, Asghar, and Seid Mahdi Jafari. "Chitosan-based nanodelivery systems for cancer therapy: Recent advances." Carbohydrate Polymers 272 (2021): 118464.

Nasibova, A. (2023). Generation of nanoparticles in biological systems and their application prospects. *Advance Biology Earth Science*, 8(2), 140-6.

Oh, J. K., and Park, J. M. (2011). Iron oxide-based superparamagnetic polymeric nanomaterials: design, preparation, and biomedical application. *Progress in Polymer Science*, 36(1), 168-189.

Owais M, Misra-Bhattacharya S, Haq W, Gupta CM. Immunomodulator tuftsin augments antifilarial activity of diethylcarbamazine against experimental Brugian filariasis. J Drug Target 2003; 11(4): 247-

Pensel PE, Castro S, Allemandi D, Bruni SS, Palma SD, Elissondo MC. Enhanced chemoprophylactic and clinical efficacy of albendazole formulated as solid dispersions in experimental cystic echinococcosis. Vet Parasitol 2014; 203(1-2): 80-6. http://dx.doi.org/10.1016/j.vetpar.2014.01.027 PMID: 24572043

Potârniche AV, Mickiewicz M, Olah D, et al. First report of anthelmintic resistance in gastrointestinal nematodes in goats in Romania. Animals. 2021;11:2761. doi:10.3390/ani1110276

Prasher, P., Sharma, M., Mehta, M., Satija, S., Aljabali, A. A., Tambuwala, M. M., and Dua, K. (2021). Current-status and applications of polysaccharides in drug delivery systems. *Colloid and Interface Science Communications*, 42, 100418.

Puttaraju, T. D., Manjunatha, M., Maruti, G., Srinivasan, V., Buvabi, S. H., and Bharathi, T. R. (2021). Anthelmintic and antibacterial studies of zinc oxide NPs: Synthesized using dragon fruit juice as novel fuel. *Materials Today: Proceedings*, 47, 4652-4656.

Rashid, M. M. O., Ferdous, J., Banik, S., Islam, M. R., Uddin, A. M., and Robel, F. N. (2016). Anthelmintic activity of silver-extract nanoparticles synthesized from the combination of silver nanoparticles and M. charantia fruit extract. *BMC Complementary and Alternative Medicine*, 16, 1-6.

Real, D., Hoffmann, S., Leonardi, D., Salomon, C., and Goycoolea, F. M. (2018). Chitosan-based nanodelivery systems applied to the development of novel triclabendazole formulations. *PLoS One*, 13(12), e0207625.

Rehman, A., Ullah, R., Uddin, I., Zia, I., Rehman, L., and Abidi, S. M. A. (2019). In vitro anthelmintic effect of biologically synthesized silver nanoparticles on liver amphistome, Gigantocotyle explanatum. *Experimental Parasitology*, 198, 95-104.

Sarai S, Steven R, Kopp M, et al. In vitro levamisole selection pressure on larval stages of Haemonchus contortus over nine generations gives rise to drug resistance and target site gene expression changes specific to the early larval stages only. Vet Parasitol. 2015;211:45–53

Sarmento, B., Martins, S., Ferreira, D., and Souto, E. B. (2007). Oral insulin delivery by means of solid lipid nanoparticles. *International Journal of Nanomedicine*, 2(4), 743-749.

Sepúlveda-Crespo, D., Reguera, R. M., Rojo-Vázquez, F., Balaña-Fouce, R., and Martínez-Valladares, M. (2020). Drug discovery technologies: Caenorhabditis elegans as a model for anthelmintic therapeutics. *Medicinal Research Reviews*, 40(5), 1715-1753.

Sharma, S., Goel, V., Kaur, P., Gadhave, K., Garg, N., Singla, L. D., and Choudhury, D. (2023). Targeted drug delivery using

beeswax-derived albendazole-loaded solid lipid nanoparticles in Haemonchus contortus, an albendazole-tolerant nematode. *Experimental Parasitology*, 253, 108593

Singhvi, G., Banerjee, S., and Khosa, A. (2018). Lyotropic liquid crystal nanoparticles: a novel improved lipidic drug delivery system. In Organic materials as smart nanocarriers for drug delivery (pp. 471-517). William Andrew Publishing.

Soni, H., and Sharma, S. (2021). Current update on nanoemulsion: a review. *Sch. International Journal Anat Physiology,* 4(1), 6-13.

Sun, X., Jia, P., Zhe, T., Bu, T., Liu, Y., Wang, Q., and Wang, L. (2019). Construction and multifunctionalization of chitosan-based three-phase nano-delivery system. *Food Hydrocolloids*, 96, 402-411.

Teixeira de Moraes Gomes, P. A., Veríssimo de Oliveira Cardoso, M., Dos Santos, I. R., Amaro de Sousa, F., da Conceicao, J. M., Gouveia de Melo Silva, Varun and Lima Leite, A. C. (2020). Dual parasiticidal activities of phthalimides: synthesis and biological profile against Trypanosoma cruzi and Plasmodium falciparum. ChemMedChem, 15(22), 2164-2175.

Varma RS. Greener approach to nanomaterials and their sustainable applications. Curr Opin Chem Eng. 2012;1:123–128

Verma, R., Mantri, B., and Kumar Srivastava, A. (2015). shape control synthesis, characterizations, mechanisms and optical properties of larg scaled metal oxide nanostructures of ZnO and TiO2. *Advanced Materials Letters*, 6(4), 324-333.

Vinarov Z, Gancheva G, Katev V, Tcholakova SS. Albendazole solution formulation via vesicle-to-micelle transition of phospholipid-surfactant aggregates. Drug Dev Ind Pharm 2018; 44(7): 1130-8.

Wang, Y., Pi, C., Feng, X., Hou, Y., Zhao, L., and Wei, Y. (2020). The influence of nanoparticle properties on oral bioavailability of drugs. *International Journal of Nanomedicine*, 6295-6310.

Wen H, New RR, Muhmut M, et al. Pharmacology and efficacy of liposome-entrapped albendazole in experimental secondary alveolar echinococcosis and effect of co-administration with cimetidine. Parasitology 1996; 113: 111-21.

Xie S, Pan B, Shi B, et al. Solid lipid nanoparticle suspension enhanced the therapeutic efficacy of praziquantel against tapeworm. Int J Nanomedicine 2011; 6: 2367-74.

Xu, L., Wang, X., Liu, Y., Yang, G., Falconer, R. J., and Zhao, C. X. (2022). Lipid nanoparticles for drug delivery. *Advanced NanoBiomed Research*, 2(2), 2100109.

Yang, J., Park, S. B., Yoon, H. G., Huh, Y. M., and Haam, S. (2006). Preparation of poly ε-caprolactone nanoparticles containing magnetite for magnetic drug carrier. *International Journal of Pharmaceutics*, 324(2), 185-190.

Zahoor, M., Nazir, N., Iftikhar, M., Naz, S., Zekker, I., Burlakovs, J., and Ali Khan, F. (2021). A review on silver nanoparticles: Classification, various methods of synthesis, and their potential roles in biomedical applications and water treatment. *Water*, 13(16), 2216.

Zhao Y, Chen G, Meng Z, et al. A novel nanoparticle drug delivery system based on PEGylated hemoglobin for cancer therapy. Drug Deliv. 2019;26(1):717–723. doi:10.1080/10717544.2019.163984631293178doi:10.1016/j.jconrel.2016. 07.05127480450

Chapter 37

Potential Application of Nanoparticles in Human Medicine

Fatima Azam[1*], Shaiza Muqadus[2], Rimsha Jamil[1], Sadia Yousuf[3], Zia ud Din Sindhu[4], Muhammad Kasib Khan[4], Muhammad Imran[5] and Shah Nawaz[6]

[1]Department of Zoology Wildlife and Fisheries, University of Agriculture -38040, Faisalabad, Pakistan
[2]Department of Zoology, University of Education Lahore, Vehari Campus Pakistan
[3]Institue of Microbiology, University of Agriculture -38040, Faisalabad, Pakistan
[4]Department of Parasitology, University of Agriculture -38040, Faisalabad, Pakistan
[5]Department of Pathology, University of Agriculture -38040, Faisalabad, Pakistan
[6]Department of Anatomy, University of Agriculture -38040, Faisalabad, Pakistan
*Corresponding author: azam.ffatima@gmail.com

ABSTRACT

Nanoparticles, are ultrafine particles with unique properties and have a variety of applications throughout medicine, electronics and environmental remediation. The origins of nanoparticles date back to ancient times, but modern exploration started in the late 20th century. Field of health and medicine is facilitated by dendrimers, liposomes, carbon-based nanoparticles and other types, nanoparticles are developing capabilities for targeted delivery of pharmaceutical agents through the blood-brain barrier, specifically to cancer cells, alternatively to diseased arteries, or to disease signals they emit. Additionally, a multitude of nanoparticles promise to revolutionize medical imaging, by boosting contrast and sensitivity. Inspired by this, gold nanoparticles and quantum dots have transformed diagnostic capabilities by targeting only those tissues or cells of interest with minimal background effects. Therapeutically, nanoparticles have changed the landscape of innovative strategies in cancer therapy, infectious diseases, neurological disorders, and cardiovascular diseases by allowing for the delivery of therapeutic agents selectively to diseased cells with concomitant minimum systemic side effects, opening the avenues for curing these disorders. In biosensing, they have served as labels or signal enhancers and amplified the sensitivity of detection for a variety of biomolecules. Gold nanoparticle sensors, magnetic nanoparticle sensors, and as in case of this study iron oxide nanoparticles sensors contributed to highly sensitive and reliable biosensing platforms. The journey of nanoparticles to the clinic, however, remains challenging, with issues such as safety, regulatory, and biological barriers needing to be overcome before the biomedical applications of nanoparticles.

KEYWORDS
Nanoparticles, Targeted delivery, Medical imaging, Cancer therapy, Therapeutic agents, Biosensing

Received: 30-Jun-2024
Revised: 14-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Azam F, Muqadus S, Jamil R, Yousuf S, Sindhu ZUD, Khan MK, Imran M and Nawaz S, 2024. Potential application of nanoparticles in human medicine. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 322-330. https://doi.org/10.47278/book.CAM/2024.378

INTRODUCTION

Nanoparticles are very tiny particles that generally range between 1 to 100 nanometers (nm), with one nanometer equaling one billionth of a meter. These particles can be made of a variety of materials, including metals, metal oxides, polymers, and biological molecules (Anselmo and Mitragotri, 2016). They find uses in a variety of sectors, including medicine, electronics, and remediation of the environment. Engineered nanoparticles provide specialized functions and promise advances in targeted medication administration, imaging agents, and catalysis (Astruc, 2020; Xia et al., 2021).

Their modern exploration began in the 20th century with advances in microscopy and synthesis, and national research centers for nanotechnology were established by mid-century (Leon et al., 2020; Raza et al., 2018). Nanoparticles' small size gives them a high surface area-to-volume ratio, enhancing their optical, electrical, and magnetic properties (Verma and Stellacci, 2010; Xia et al., 2021). In biomedicine, nanoparticles enable precise drug delivery and functionalization for diagnostics and therapy (Shin et al., 2015). In environmental science, they aid in pollution prevention and toxin detection. Overall, nanoparticles drive innovation across various fields and address critical societal issues (Khan et al., 2019).

Nanoparticle in Medicine

Nanoparticles have transformed the field of medicine by providing targeted drug delivery, imaging, and therapy at a molecular level. In medicine they can encapsulate drugs, ensuring specific delivery to targeted cells or tissues while

minimizing overall side effects (Hofmann-Amtenbrink et al., 2015). Nanoparticles also play a vital role in imaging technologies such as MRI and CT scans, improving contrast and enabling early disease detection (Martins et al., 2021).

Their application also extends to therapeutics, where they can directly target cancer cells or pathogens, enhancing treatment effectiveness and minimizing damage to healthy tissues (Anselmo and Mitragotri, 2016). In biomedicine, nanoparticles are used as medication delivery agents because of their capacity to cross biological barriers and target specific cells or tissues. Furthermore, their customised surface chemistry enables precise functionalization, enhancing interactions with biomolecules for diagnostic or therapeutic applications (Shin et al., 2015).

Importance of Nanoparticles in Modern Medicine

In recent years, nanoparticles have been used in a variety of therapeutic applications. Nanoparticles have been designed to overcome the restrictions associated with free therapies and to effectively cross biological barriers (Anselmo and Mitragotri, 2016). Nanoparticles play a vital role in modern medicine because of their unique features and multiple applications. They provide tremendous potential in medication administration, diagnostics, imaging, and therapies. (Hofmann-Amtenbrink et al., 2015). Their tiny size enables precise targeting of certain cells or tissues, increasing therapeutic efficiency while lowering adverse effects (Anselmo and Mitragotri, 2016). Furthermore, nanoparticles can encapsulate pharmaceuticals, preventing degradation and assuring regulated release at the target spot.

In diagnostics, they provide very sensitive detection methods, allowing for early disease identification and surveillance. In addition, nanoparticles act as contrast agents in medical imaging techniques such as MRI, CT scans, and fluorescence imaging, providing detailed functional and anatomical information (Kostevšek, 2020).

II. Targeted Drug Delivery Systems

Overview of Conventional Drug Delivery Methods

Conventional methods of drug delivery include a broad range of approaches designed for distributing medications to target sites within the body. One of the most common approaches, oral administration, involves swallowing pills or liquid formulations, allowing systemic distribution through the digestive tract (Kumaran et al., 2010). Injectables, including intravenous, intramuscular, and subcutaneous routes, enable rapid drug absorption (Alqahtani et al., 2021).

Drugs can be applied directly to the skin (topical application) or inhaled (inhalation route) for local or systemic effects, while inhalation routes deliver medications directly to the respiratory tract for rapid absorption into the bloodstream (Jain, 2020). Additionally, drugs can be administered rectally or vaginally for systemic or localized drug delivery. Common drug delivery methods involve using formulations like tablets, capsules, solutions, suspensions, creams, and gels to maintain proper dosage and administration (Rathi et al., 2022). These methods are easy to use, boost patient compliance, and offer predictable pharmacokinetics.

Limitations of Conventional Drug Delivery Methods

In spite of being effective, traditional drug administration ways have potential pitfalls to hinder their therapeutic efficiency. The first case is oral administration that is faced with issues like enzymatic degradation in the gastrointestinal tract as well as poor absorption causing reduced bioavailability of drugs (2019; Astruc, 2020). Furthermore, injections for drug delivery may also cause pain to patients; they should be administered by somebody who has skills and there may be risks of infection or harm to tissue. Last but not least, non-specific targeting during systemic distribution of drugs through these means can result in harmful effects on normal tissues (Homayun et al., 2019).

Drug release kinetics can be poorly controlled by traditional drug delivery techniques, which produce less than optimum therapeutic results and necessitate frequent dosing. These methods also face problems delivering drugs directly to some areas in the body such as inaccessible parts of the brain and tumors because of barriers like the blood-brain barrier or heterogeneity of tumor microenvironments (Jumelle et al., 2020)

Role of Nanoparticles in Drug Delivery for Disease Treatment

Nanoparticles offer an efficient means of delivering therapeutic drugs due to their high surface area-to-volume ratio. Their compact size allows them to penetrate biological barriers, like cell membranes, facilitating drug uptake by targeted cells and tissues (Astruc, 2020). Nanoparticles can be tailored to encapsulate diverse types of drugs, shielding them from degradation and premature release within the body. This controlled release mechanism ensures prolonged drug action, reducing the frequency of administration and minimizing potential adverse effects as per showed in firgure1.

Surface modifications of nanoparticles with various ligands or targeting moieties can increase their affinity toward diseased tissues or particular cells. This, in turn, enhances the effectiveness of the treatment while reducing side effects (Dang and Guan, 2020). Additionally, nanoparticles can be designed to respond to specific stimuli, such as pH, temperature, or enzymatic activity, triggering the release of drugs precisely at the site of action. This controlled release enhances the treatment precision and improves overall outcomes. This approach minimizes off-target effects, reduces systemic toxicity, and improves patient compliance (Yu et al., 2020).

Examples of Nanoparticles used in Targeted Drug Delivery

Nanoparticles are gaining popularity as promising drug delivery vehicles due to their unique features, such as tiny size and high surface area-to-volume ratio. Here are some examples of nanoparticles widely utilised in targeted drug delivery:

Dendrimers

Dendrimers are highly branched macromolecules having a unique structure. They can be synthesised with precise control over their dimension, size shape and surface properties. Dendrimers have been investigated for targeted drug delivery due to their ability to encapsulate pharmaceuticals and combine with targeting moieties (Najafi et al., 2021).

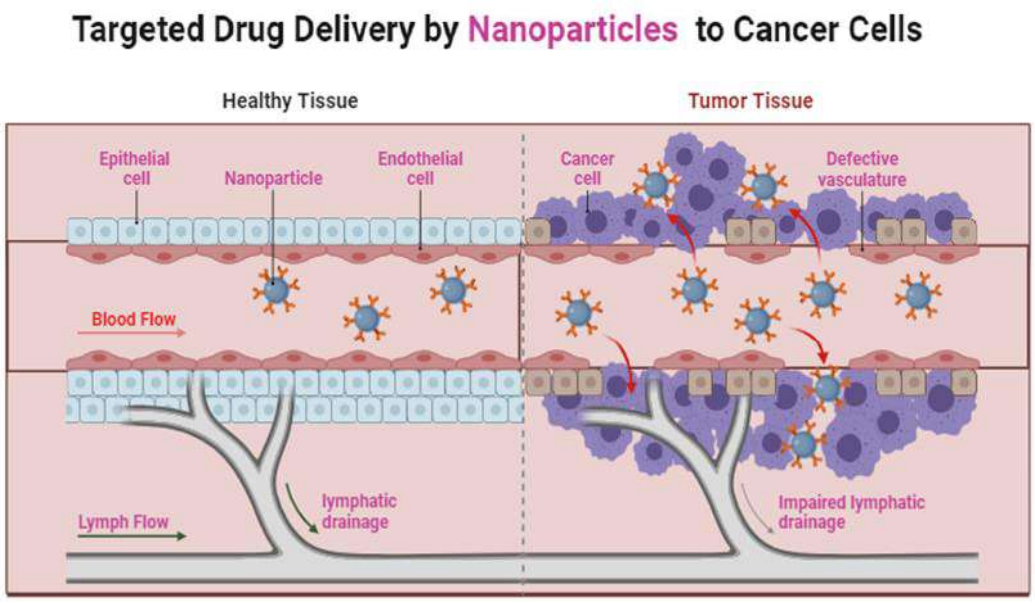


Fig. 1: Mechanisms of Delivery of Medicine to Targeted Cancerous Cells

Liposomes

Liposomes consist of a structure similar to cells, composed of two layers of lipids that form small spheres filled with a watery fluid. These vesicles can hold both water-soluble and fat-soluble drugs, in their core and between the lipid layers, respectively. Liposomes have been widely researched as a way to deliver drugs in a targeted manner, especially in the treatment of cancer (Liu et al., 2021).

Inorganic Nanoparticles

Inorganic nanoparticles possess distinctive optical, magnetic, and electrical characteristics. These nanoparticles, like gold, iron oxide, and quantum dots, have potential applications in targeted drug delivery and imaging. By attaching targeting molecules and drugs to their surfaces, these nanoparticles can be precisely directed towards certain diseases (Shi et al., 2020).

Polymeric Nanoparticles

Polymeric nanoparticles made of bio-friendly polymers, like poly(lactic-co-glycolic acid) (PLGA) and chitosan, have gained significance in drug delivery. These nanoparticles offer controlled drug release and can be customized with specific ligands to target diseased tissues or cells, improving drug delivery efficiency and reducing side effects (Castro et al., 2022).

Carbon-based Nanoparticles

Carbon-based nanoparticles, Carbon nanotubes and graphene oxide nanoparticles have shown promising potential in targeted drug delivery due to their vast surface area and distinct physicochemical properties. These nanomaterials can be tailored with targeting ligands to guide them to specific sites in the body, while also being loaded with therapeutic agents for localized drug delivery (Sajjadi et al., 2021).

Table 1 provides a brief overview of common types of nanoparticles utilized in various medicines. The data presented in Table 1 is derived from research studies on the applications of nanoparticles in medicine (Shi et al., 2020; Najafi et al., 2021).

Table 1: Brief overview of common types of Nanoparticles utilized in various Medicines

Type of Nanoparticle	Description
Dendrimers	Highly branched, tree-like structures used for drug delivery and imaging.
Liposomes	Spherical vesicles composed of lipid bilayers, used for drug delivery and imaging.
Inorganic Nanoparticles	Nanoparticles composed of metals or metal oxides, utilized in drug delivery, imaging, and therapy.
Polymeric Nanoparticles	Nanoparticles made from polymers, employed for drug delivery and imaging purposes.
Carbon-based Nanoparticles	Nanoparticles based on carbon structures like nanotubes or graphene, used for drug delivery, imaging, and biosensing applications.

III. Imaging and Diagnosis

Introduction to Medical Imaging Techniques

Medical imaging tools help diagnose and monitor a variety of medical disorders by giving precise pictures of the human body's interior structures and processes. These medical imaging methods provide vital insights into the structure and function of the human body, allowing healthcare practitioners to provide precise diagnoses and personalised treatment regimens to patients (Lee et al., 2017). Here's an overview of several common medical imaging techniques:

X-ray

X-ray imaging is a commonly used medical technique that employs a small amount of radiation to generate images of internal body structures. It is widely used for diagnosing conditions related to bones, such as fractures, and for identifying abnormalities in the lungs and chest. Additionally, X-rays can detect tumors and monitor changes in internal organs over time. (Larue et al., 2018)

Computed Tomography (CT)

CT (computed tomography) scans employ a combination of X-rays and computer processing to create intricate cross-sectional images of the body. These scans yield high-resolution visuals of bones, organs, and soft tissues, proving valuable in diagnosing various medical conditions. Notably, CT scans are used to identify and assess cancers, injuries from trauma, and vascular (blood vessel) ailments (Ginat and Gupta, 2014)

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a cutting-edge technology that uses powerful magnets and radio waves to provide detailed, three-dimensional images of the body's inner workings (Yang et al., 2020). Unlike X-rays, which primarily visualize bones, MRI excels at producing high-resolution images of soft tissues, intricate organs, muscles, the brain, and the intricate neural network of the spinal cord. (Glover, 2011; Grover et al., 2015).

Ultrasound

Ultrasound imaging utilizes high-frequency sound waves to generate real-time visualizations of internal organs, blood flow, and fetal development. Its non-invasive nature, portability, and lack of ionizing radiation render it safe for use in various medical applications, including during pregnancy (Miller et al., 2012).

Role of Nanoparticles in Medical Imaging

Nanoparticles revolutionize medical imaging by serving as contrast agents. Their unique properties enable them to selectively target specific tissues or cells, resulting in improved sensitivity and accuracy of imaging techniques (Pellico et al., 2021). Advanced nanoparticles play a crucial role in enhancing the performance of various imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) (Fang and Zhang, 2009).

Engineered nanoparticles can be used as imaging tools to locate specific areas of the body with abnormalities like tumors or inflamed tissues. Conventional imaging techniques are improved with the use of nanoparticles (Xie et al., 2011). These particles allow for multiple imaging techniques to be combined, providing more comprehensive information about a biological process or structure. For example, nanoparticles can emit fluorescence for optical imaging and possess magnetic properties for MRI, enabling a more thorough diagnosis (Huang and Davis, 2011)..

Examples of Nanoparticles used for Imaging and Diagnosis

Nanoparticles have revolutionised medical imaging and diagnostics by providing unique features that improve diagnostic accuracy and sensitivity. Figure 2 provides a brief overview of application of different nanoparticles for targeted therapies. Here are some noteworthy examples of nanoparticles used in imaging and diagnosis:

Gold Nanoparticles (GNPs)

These are commonly used in imaging due to their remarkable optical characteristics. They can improve contrast in a variety of imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and photoacoustic imaging, because to their excellent optical characteristics and biocompatibility. Their surfaces can also be functionalized with ligands that target certain tissues or cells (Li et al., 2020; Pellico et al., 2021; Singh and Amiji, 2022).

Iron Oxide Nanoparticles

Iron oxides, particularly superparamagnetic iron oxide nanoparticles (SPIONs), have been utilized in MRI extensively. Their high contrast signal makes iron oxide nanoparticles well-suited for imaging of tissues, tumors, and organs, particularly in the liver and spleen. In addition, they have been explored for targeted drug delivery (Elahi and Rizwan, 2021).

Quantum Dots

These are nanoparticles made of semiconductor materials, which emit particular wavelengths of light dependant on

the size, and are therefore valuable for fluorescence imaging (Elahi and Rizwan, 2021). Quantum dots provide a stable and bright signal that is crucial in applications such as live-cell imaging, and the multiplexed sensing of biomolecules. They are essential for fluorescence imaging by labeling and tracking biomolecules, cells, and tissues with excellent specificity (Wang et al., 2020).

Silica Nanoparticles

Silica nanoparticles serve as diverse substrates for imaging and diagnosis.They are imaging agents that can be loaded with fluorescents, contrast agents, or drugs, for targeted delivery of drugs to tumors or other diseases. They can make use of contrast agents or drugs and can be directed towards particular tissues to serve as agents for imaging or medication (Gubala et al., 2020; Yang et al., 2020).

Carbon Nanotubes

Carbon nanostructures have unique optical and electrical features that make them ideal for imaging applications. Functionalized carbon nanotubes may target specific cells and tissues, making them useful for both imaging and medication administration. They can be modified with targeting ligands and imaging agents to enable imaging and detection of specific biomolecules and cells (Nekoueian et al., 2019; Sajjadi et al., 2021).

Liposomes/Lipid Nanoparticles

Lipid nanoparticles like liposomes and lipid-based micelles carrying imaging agents or drugs are used for imaging and drug delivery. Their ability to encapsulate hydrophobic substances and flexibility to incorporate targeting ligands makes them effective in specific imaging and therapeutic applications. They are valuable in nuclear medicine and fluorescence imaging due to their easy surface modification for targeted delivery (Liu et al., 2021).

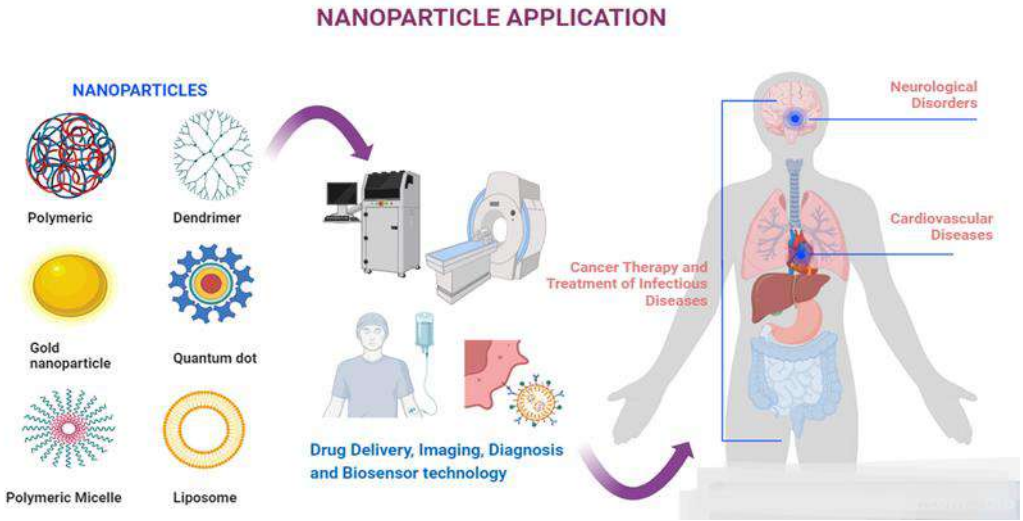


Fig. 2: Application of Different Nanoparticles for Targeted Therapies and Advanced Diagnostics in Human Health

IV. Therapeutic Applications

Nanoparticles in cancer therapy

Nanoparticles, due to their unique properties, offer innovative diagnostic, imaging, and treatment strategies in cancer therapy (Xia et al., 2021). These structures can target cancer cells specifically while minimizing harm to healthy tissues. They can transport therapeutic agents like chemotherapy drugs, antibodies, and nucleic acids directly to tumor sites via the enhanced permeability and retention (EPR) effect (Dang and Guan, 2020). Their small size allows deep tissue penetration and navigation through faulty blood vessels. Tumors often have leaky blood vessels and poor lymphatic drainage, enabling selective nanoparticle accumulation (Sajjadi et al., 2021).

Nanoparticles can be tailored with specific molecules that selectively bind to targeted receptors on cancer cells. They can also be engineered to respond to changes in the tumor microenvironment, precisely releasing therapeutic drugs within the tumor (Fries et al., 2021). Additionally, nanoparticles can be equipped with imaging agents, enabling detailed visualization of tumor properties using techniques like MRI, CT, or fluorescence imaging, aiding in diagnosis and treatment monitoring (Yang et al., 2020).

Nanoparticles regulate and sustain the controlled release of therapeutic agents, such as chemotherapeutic drugs and imaging agents. By packaging these agents, nanoparticles shield them from degradation, extend circulation time, and release them gradually at the tumor site (Xie et al., 2011). This maintains optimal therapeutic concentrations, improving treatment outcomes. Additionally, nanoparticles enable triggered drug release within the tumor, enhancing treatment effectiveness and reducing systemic toxicity (Homayun et al., 2019).

Nanoparticles in Treatment of other Diseases

Infectious Diseases

Nanoparticles, with their exceptional properties, are promising agents against infectious diseases, effectively targeting bacteria, viruses, and fungi (Zazo et al., 2016). Their high surface-to-volume ratio allows efficient encapsulation and targeted delivery of antimicrobial agents (Kumaran et al., 2010). By protecting these agents from degradation, nanoparticles ensure precise delivery to infection sites, minimizing unintended effects and reducing antimicrobial resistance (Astruc, 2020).

Nanoparticles modified with antibodies can precisely target and attach to disease-causing microorganisms, concentrating treatments at infection sites and minimizing impact on healthy tissues (Fries et al., 2021). Silver nanoparticles disrupt microbial cell membranes, offering potent antimicrobial properties (Aderibigbe, 2017). Additionally, nanoparticles coated with antimicrobial peptides or essential oils effectively kill pathogens and can be tailored to enhance the host immune response (Orosco, 2024). Overall, nanoparticles offer innovative therapies for infectious diseases, improving efficacy and reducing adverse effects (Zazo et al., 2016).

Neurological Disorders

Nanoparticles are promising in treating neurological disorders due to their ability to traverse the blood-brain barrier, delivering drugs, genes, or imaging agents directly to targeted brain areas (Asefy et al., 2021).They increase drug solubility, stability, and bioavailability while reducing systemic side effects. Their small size allows efficient penetration of brain tissue and targeting of specific cell types, such as neurons or glial cells (Ceña and Játiva, 2018). Nanoparticles facilitate gene therapy by delivering therapeutic genes to afflicted brain cells, potentially treating genetic neurological disorders (Flores et al., 2019).

Cardiovascular Diseases

Nanoparticles hold significant potential for treating cardiovascular diseases (CVDs) due to their unique properties. They enable precise drug delivery to atherosclerotic plaques or damaged blood vessels, enhancing treatment efficacy (Jiang et al., 2017; Nasra et al., 2022). Nanoparticles are also used in gene therapy to transfer beneficial genes to damaged tissues, correcting cellular dysfunctions caused by CVDs (Flores et al., 2019). They can deliver anti-inflammatory drugs, antioxidants, or genetic material specifically to targeted sites, reducing systemic side effects and maximizing therapeutic benefits (Pala et al., 2020; Castro et al., 2022).

V. Nanoparticles in Biomedical Sensing and Monitoring

Nanoparticles have revolutionized biosensor technology by enhancing signal strength and improving detection capabilities (McNamara and Tofail, 2017). They are used as markers or enhancers to increase sensor sensitivity and accuracy by attaching specifically to target molecules like proteins, DNA, or antigens (Maduraiveeran et al., 2018). Nanoparticles can be integrated into transduction methods, such as electrochemical and magnetic platforms, to convert biological interactions into detectable signals. For example, gold nanoparticles in surface plasmon resonance (SPR) biosensors enable real-time tracking of biomolecular interactions with high sensitivity (Elahi et al., 2018).

Examples of Nanoparticle-based Sensors for Medical Applications

Nanoparticle-based sensors are getting a lot of focus in the field because of their sensitivity, specificity and ability to monitor in real time. Some of the examples are listed below:

Gold Nanoparticle Sensors

Gold particles modified with chemicals can identify biological substances, like DNA, proteins and small molecules. When these particles come into contact with target molecules, their characteristics, such as surface plasmon resonance change, allowing for detection. These sensors are used in applications like identifying microorganisms, cancer markers and genetic changes (Elahi et al., 2018; Shi et al., 2020).

Magnetic Nanoparticle Sensors

Magnetic particles coated with chemicals or antibodies can attach to molecules making it possible to detect them using magnetic resonance imaging (MRI) or magnetic relaxation methods. These sensors are essential, for spotting cancer cells tracking drug delivery processes and diagnosing illnesses (Grover et al., 2015; Yang et al., 2020).

Carbon Nanotube Sensors

Functionalized carbon nanotubes possess high surface area-to-volume ratios and excellent electrical conductivity, making them suitable for detecting various analytes such as glucose, neurotransmitters, and gases. Changes in electrical conductivity upon binding to target molecules enable sensitive detection with applications in diabetes management and neurochemical monitoring (Nekoueian et al., 2019).

Quantum Dot Sensors

Quantum dots are semiconductor nanoparticles with tunable optical properties. They can be functionalized to

selectively bind to target molecules, leading to changes in fluorescence emission spectra. Quantum dot-based sensors offer high sensitivity and multiplexing capabilities for detecting biomolecules, pathogens, and cancer markers.

Silica Nanoparticle Sensors

Silica nanoparticles functionalized with fluorescent dyes or targeting molecules can detect specific analytes by changes in fluorescence intensity or resonance energy transfer. These sensors are versatile and find applications in point-of-care diagnostics, drug delivery monitoring, and environmental sensing (Yang et al*.,* 2020).

VI. Challenges and Future Directions

Safety Concerns of Nanoparticles in Medicine

Nanoparticles afety issues related to their use in medicine are raised by their potential toxicity, biodistribution, and long-term effects. Small size makes them able to penetrate readily into cell and the misuse or accumulation in vital organs can be noticed (Asefy et al*.,* 2021). Furthermore, nanoparticles may cause inflammations or immune responses which result in undesirable complication of patients. Also, opinions are still disputable in relation to the environmental component of the problem as well as to bioaccumulation within the ecosystems (Su et al*.,* 2018). Another biggest safety concerns associated with nanoparticles is that they can cause inflammation and oxidative stress among the body's cells. Nanoparticles can interact with a variety of biological systems, including cells, proteins, and DNA, which can lead to the generation of reactive oxygen species (ROS) and other inflammatory mediators. It causes cell damage, tissue inflammation, and, in severe cases, organ failure (Horie and Tabei, 2021).

Regulatory Challenges and Approval Processes

Regulating nanoparticles in medicine involves rigorous approval processes due to their unique properties. Regulatory bodies like the FDA and EMA require thorough safety, efficacy, and manufacturing assessments (Namiot et al*.,* 2023). This includes evaluating toxicity profiles, pharmacokinetics, and environmental impact. Standardized characterization and risk assessment protocols are crucial. Collaboration among researchers, regulatory agencies, and industry members is essential to ensure safe and effective nanoparticle-based therapies while addressing biological reactions and long-term impacts (Araújo et al*.,* 2015).

Future Prospects and Emerging Trends in Nanoparticle Research

Nanoparticles, with their small size and unique properties, hold significant promise in scientific research, especially in medicine. Their applications include drug delivery systems, diagnostic imaging, and therapeutic treatments (Patra et al., 2018). Multifunctional nanoparticles are particularly exciting as they can combine imaging, drug delivery, and therapeutic activities, targeting specific cells or tissues for personalized therapies with fewer side effects (Rathi et al., 2022).

Advances in nanoparticle synthesis and surface modification enhance control over their physicochemical properties, ensuring better biocompatibility and stability. Innovations include RNA interference (RNAi) and DNA editing for precise disease management (Moazzam et al., 2024). Nanoparticles can deliver DNA to target sites, potentially curing genetic disorders, cancer, and infectious diseases. Furthermore, integrating nanoscience with immunotherapy shows potential for enhancing immune system function to combat cancer, leading to more effective and personalized treatments (Kong et al., 2023).

VII. Conclusion

In summary, nanoparticles have the potential to revolutionize healthcare by introducing innovative treatments and diagnostics. Their precise drug delivery capabilities enhance effectiveness and minimize side effects by targeting specific cells or tissues. Additionally, nanoparticles improve imaging techniques, facilitating earlier disease detection and enabling personalized medicine tailored to individual patient needs.

The impact of nanoparticles on healthcare is profound, offering advancements in disease diagnosis, treatment, and prevention. Their role in transforming medical industry practices includes more effective medication delivery, reduced adverse effects, and improved therapeutic outcomes. Ongoing innovation and interdisciplinary collaboration will be crucial to optimizing nanoparticle compositions, enhancing biocompatibility, and ensuring long-term safety and efficacy in clinical applications. Continued research in these areas promises to address significant health concerns and improve patient outcomes.

REFERENCES

Aderibigbe, B. A. (2017). Metal-based nanoparticles for the treatment of infectious diseases. Molecules, 22(8): 1370.

Alqahtani, M. S., Kazi, M., Alsenaidy, M. A., and Ahmad, M. Z. (2021). Advances in oral drug delivery. *Frontiers in Pharmacology,* 12, 618411.

Anselmo, A. C., and Mitragotri, S. (2016). Nanoparticles in the clinic. *Bioengineering and Translational Medicine*, 1(1): 10-29.

Araújo, F., Shrestha, N., Granja, P. L., Hirvonen, J., Santos, H. A., and Sarmento, B. (2015). Safety and toxicity concerns of orally delivered nanoparticles as drug carriers. *Expert Opinion on Drug Metabolism and Toxicology*, 11(3): 381-393.

Asefy, Z., Hoseinnejhad, S., and Ceferov, Z. (2021). Nanoparticles approaches in neurodegenerative diseases diagnosis and treatment. *Neurological Sciences*, 42: 2653-2660.

Astruc, D. (2020). Introduction: nanoparticles in catalysis. *Chemical Reviews*, 120(2): 461-463.

Castro, K. C. D., Costa, J. M., and Campos, M. G. N. (2022). Drug-loaded polymeric nanoparticles: a review. International *Journal of Polymeric Materials and Polymeric Biomaterials*, 71(1): 1-13.

Ceña, V., and Játiva, P. (2018). Nanoparticle crossing of blood–brain barrier: a road to new therapeutic approaches to central nervous system diseases. *Nanomedicine*, 13(13): 1513-1516.

Dang, Y., and Guan, J. (2020). Nanoparticle-based drug delivery systems for cancer therapy. *Smart Materials in Medicine*, 1: 10-19.

Elahi, N., and Rizwan, M. (2021). Progress and prospects of magnetic iron oxide nanoparticles in biomedical applications: A review. *Artificial Organs*, 45(11): 1272-1299.

Fang, C., and Zhang, M. (2009). Multifunctional magnetic nanoparticles for medical imaging applications. *Journal of Materials Chemistry*, 19(35): 6258-6266.

Flores, A. M., Ye, J., Jarr, K. U., Hosseini-Nassab, N., Smith, B. R., and Leeper, N. J. (2019). Nanoparticle therapy for vascular diseases. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 39(4): 635-646.

Fries, C. N., Curvino, E. J., Chen, J. L., Permar, S. R., Fouda, G. G., and Collier, J. H. (2021). Advances in nanomaterial vaccine strategies to address infectious diseases impacting global health. *Nature Nanotechnology*, 16(4): 1-14.

Ginat, D. T., and Gupta, R. (2014). Advances in computed tomography imaging technology. *Annual Review of Biomedical Engineering*, 16: 431-453.

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics*, 22(2): 133-139.

Grover, V. P., Tognarelli, J. M., Crossey, M. M., Cox, I. J., Taylor-Robinson, S. D., and McPhail, M. J. (2015). Magnetic resonance imaging: principles and techniques: lessons for clinicians. *Journal of Clinical and Experimental Hepatology*, 5(3): 246-255.

Gubala, V., Giovannini, G., Kunc, F., Monopoli, M. P., and Moore, C. J. (2020). Dye-doped silica nanoparticles: synthesis, surface chemistry and bioapplications. *Cancer Nanotechnology*, 11(1): 1-43.

Hofmann-Amtenbrink, M., Grainger, D. W., and Hofmann, H. (2015). Nanoparticles in medicine: Current challenges facing inorganic nanoparticle toxicity assessments and standardizations. *Nanomedicine: Nanotechnology, Biology and Medicine*, 11(7): 1689-1694.

Homayun, B., Lin, X., and Choi, H. J. (2019). Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics*, 11(3): 129.

Horie, M., and Tabei, Y. (2021). Role of oxidative stress in nanoparticles toxicity. Free radical research, 55(4): 331-342.

Huang, W. Y., and Davis, J. J. (2011). Multimodality and nanoparticles in medical imaging. *Dalton Transactions*, 40(23): 6087-6103.

Jain, K. K. (2020). An overview of drug delivery systems. *Drug Delivery Systems*, 2059: 1-54.

Jiang, W., Rutherford, D., Vuong, T., and Liu, H. (2017). Nanomaterials for treating cardiovascular diseases: *A Review*. *Bioactive Materials*, 2(4): 185-198.

Jumelle, C., Gholizadeh, S., Annabi, N., and Dana, R. (2020). Advances and limitations of drug delivery systems formulated as eye drops. *Journal of Controlled Release*, 321, 1-22.

Khan, I., Saeed, K., and Khan, I. (2019). Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, 12(7), 908-931.

Kong, X., Gao, P., Wang, J., Fang, Y., and Hwang, K. C. (2023). Advances of medical nanorobots for future cancer treatments. *Journal of Hematology and Oncology*, 16(1): 74-79.

Kostevšek, N. (2020). A review on the optimal design of magnetic nanoparticle-based T 2 MRI contrast agents. *Magnetochemistry*, 6(1): 11.

Kumaran, K. S. G. A., Karthika, K., and Padmapreetha, J. (2010). Comparative review on conventional and advanced ocular drug delivery formulations. *International Journal Pharmacy Pharm Science*, 2(4): 1-5.

Larue, L., Mihoub, A. B., Youssef, Z., Colombeau, L., Acherar, S., André, J. C., and Frochot, C. (2018). Using X-rays in photodynamic therapy: An overview. *Photochemical and Photobiological Sciences*, 17(11): 1612-1650.

Lee, J. G., Jun, S., Cho, Y. W., Lee, H., Kim, G. B., Seo, J. B., and Kim, N. (2017). Deep learning in medical imaging: general overview. *Korean Journal of Radiology*, 18(4): 570-584.

Leon, L., Chung, E. J., and Rinaldi, C. (2020). A brief history of nanotechnology and introduction to nanoparticles for biomedical applications. In Nanoparticles for biomedical applications. pp. 1-4.

Li, H., Pan, S., Xia, P., Chang, Y., Fu, C., Kong, W., and Qi, Z. (2020). Advances in the application of gold nanoparticles in bone tissue engineering. Journal of biological engineering, 14: 1-15.

Liu, Y., Bravo, K. M. C., and Liu, J. (2021). Targeted liposomal drug delivery: a nanoscience and biophysical perspective. *Nanoscale Horizons*, 6(2): 78-94.

Liu, Y., Chen, Q., Cullen, D. A., Xie, Z., and Lian, T. (2020). Efficient hot electron transfer from small Au nanoparticles. *Nano Letters*, 20(6), 4322-4329.

Maduraiveeran, G., Sasidharan, M., and Ganesan, V. (2018). Electrochemical sensor and biosensor platforms based on advanced nanomaterials for biological and biomedical applications. *Biosensors and Bioelectronics*, 103: 113-129.

Martins, P. M., Lima, A. C., Ribeiro, S., Lanceros-Mendez, S., and Martins, P. (2021). Magnetic nanoparticles for biomedical applications: from the soul of the earth to the deep history of ourselves. *ACS Applied Bio Materials*, 4(8): 5839-5870.

McNamara, K., and Tofail, S. A. (2017). Nanoparticles in biomedical applications. *Advances in Physics: X*, 2(1): 54-88.

Miller, D. L., Smith, N. B., Bailey, M. R., Czarnota, G. J., Hynynen, K., Makin, I. R. S., and Bioeffects Committee of the American Institute of Ultrasound in Medicine. (2012). Overview of therapeutic ultrasound applications and safety considerations. *Journal of Ultrasound in Medicine*, 31(4): 623-634.

Moazzam, M., Zhang, M., Hussain, A., Yu, X., Huang, J., and Huang, Y. (2024). The landscape of nanoparticle-based siRNA delivery and therapeutic development. *Molecular Therapy,* 32(2): 284-312.

Montaño, M. D., von der Kammer, F., Cuss, C. W., and Ranville, J. F. (2019). Opportunities for examining the natural nanogeochemical environment using recent advances in nanoparticle analysis. *Journal of Analytical Atomic Spectrometry*, 34(9), 1768-1772.

Najafi, F., Salami-Kalajahi, M., and Roghani-Mamaqani, H. (2021). A review on synthesis and applications of dendrimers. *Journal of the Iranian Chemical Society*, 18: 503-517.

Namiot, E. D., Sokolov, A. V., Chubarev, V. N., Tarasov, V. V., and Schiöth, H. B. (2023). Nanoparticles in Clinical Trials: Analysis of Clinical Trials, FDA Approvals and Use for COVID-19 Vaccines. *International Journal of Molecular Sciences*, 24(1): 787.

Nasra, S., Bhatia, D., and Kumar, A. (2022). Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. *Nanoscale Advances,* 4(17): 3479-3494.

Nekoueian, K., Amiri, M., Sillanpää, M., Marken, F., Boukherroub, R., and Szunerits, S. (2019). Carbon-based quantum particles: an electroanalytical and biomedical perspective. *Chemical Society Reviews*, 48(15): 4281-4316.

Orosco, F. (2024). Recent advances in peptide-based nanovaccines for re-emerging and emerging infectious diseases. *Journal Advance Biotechnology Experiment Ther*, 7(1): 106-117.

Pala, R., Anju, V. T., Dyavaiah, M., Busi, S., and Nauli, S. M. (2020). Nanoparticle-mediated drug delivery for the treatment of cardiovascular diseases. *International Journal of Nanomedicine*, 15: 3741-3769.

Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., and Shin, H. S. (2018). Nano based drug delivery systems: recent developments and future prospects. *Journal of Nanobiotechnology*, 16(1): 1-33.

Pellico, J., Gawne, P. J., and de Rosales, R. T. (2021). Radiolabelling of nanomaterials for medical imaging and therapy. *Chemical Society Reviews*, 50(5): 3355-3423.

Pellico, J., Gawne, P. J., and de Rosales, R. T. (2021). Radiolabelling of nanomaterials for medical imaging and therapy. *Chemical Society Reviews*, 50(5): 3355-3423.

Rathi, R., Sanshita, Kumar, A., Vishvakarma, V., Huanbutta, K., Singh, I., and Sangnim, T. (2022). Advancements in Rectal Drug Delivery Systems: Clinical Trials, and Patents Perspective. *Pharmaceutics*, 14(10): 2210.

Raza, A., Hayat, U., Rasheed, T., Bilal, M., and Iqbal, H. M. (2018). Redox-responsive nano-carriers as tumor-targeted drug delivery systems. *European Journal of Medicinal Chemistry*, 157, 705-715.

Sajjadi, M., Nasrollahzadeh, M., Jaleh, B., Soufi, G. J., and Iravani, S. (2021). Carbon-based nanomaterials for targeted cancer nanotherapy: Recent trends and future prospects. Journal of Drug Targeting, 29(7): 716-741.

Shi, Z., Zhou, Y., Fan, T., Lin, Y., Zhang, H., and Mei, L. (2020). Inorganic nano-carriers based smart drug delivery systems for tumor therapy. *Smart Materials in Medicine*, 1: 32-47.

Shin, S. W., Song, I. H., and Um, S. H. (2015). Role of physicochemical properties in nanoparticle toxicity. *Nanomaterials*, 5(3), 1351-1365.

Singh, A., and Amiji, M. M. (2022). Application of nanotechnology in medical diagnosis and imaging. *Current Opinion in Biotechnology*, 74: 241-246.

Su, H., Wang, Y., Gu, Y., Bowman, L., Zhao, J., and Ding, M. (2018). Potential applications and human biosafety of nanomaterials used in nanomedicine. *Journal of Applied Toxicology*, 38(1): 3-24.

Verma, A., and Stellacci, F. (2010). Effect of surface properties on nanoparticle–cell interactions. *Small*, 6(1): 12-21.

Wang, L., Xu, D., Gao, J., Chen, X., Duo, Y., and Zhang, H. (2020). Semiconducting quantum dots: Modification and applications in biomedical science. *Science China Mater*, 63(9): 1631-1650.

Xia, Y., Campbell, C. T., Roldan Cuenya, B., and Mavrikakis, M. (2021). Introduction: Advanced materials and methods for catalysis and electrocatalysis by transition metals. *Chemical Reviews*, 121(2): 563-566.

Xie, J., Liu, G., Eden, H. S., Ai, H., and Chen, X. (2011). Surface-engineered magnetic nanoparticle platforms for cancer imaging and therapy. *Accounts of Chemical Research*, 44(10): 883-892.

Yang, Y., Zhang, M., Song, H., and Yu, C. (2020). Silica-based nanoparticles for biomedical applications: from nanocarriers to biomodulators. *Accounts of Chemical Research*, 53(8): 1545-1556.

Yu, W., Liu, R., Zhou, Y., and Gao, H. (2020). Size-tunable strategies for a tumor targeted drug delivery system. *ACS Central Science*, 6(2): 100-116.

Zazo, H., Colino, C. I., and Lanao, J. M. (2016). Current applications of nanoparticles in infectious diseases. *Journal of Controlled Release*, 224: 86-1020

Chapter 38

Role of Platelet Membrane Coated Nanoparticles to Treat Rheumatoid Arthritis

Tasawar Iqbal[1*], Mahvish Fatima[2] and Sidra Altaf[3]

[1]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
[2]Department of Epidemiology and Public Health, University of Agriculture Faisalabad, Pakistan
[3]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: tasawariqbal177@gmail.com

ABSTRACT

Rheumatoid arthritis is a severe autoimmune condition marked by persistent joint inflammation that significantly impacts those affected by it. Traditional methods of treatment frequently have restrictions, requiring the investigation of new and creative healing approaches. Platelet-coated nanoparticles have become a hopeful method for treating rheumatoid arthritis, taking advantage of the special characteristics of platelets to improve focused drug delivery. This review offers a thorough examination of how platelet membrane-coated nanoparticles can help overcome the obstacles of treating rheumatoid arthritis. The platelet membranes' inherent biocompatibility and targeting capabilities, along with their composition and structure, make them a perfect choice for coating nanoparticles. This method mimics nature by using the innate ability of platelets to target inflamed joints, resulting in accurate and targeted drug delivery. The way in which nanoparticles work involves targeted interactions with synovial cells, modulation of the immune system, and continued release of medication in the inflamed area. In order to overcome these challenges, it is crucial to develop surface modification methods and incorporate them with additional therapeutic methods. In the future, improvements in designing nanoparticles, such as creating smart and versatile platforms, combined with personalized medicine approaches, offer the potential for customizing treatments for each patient. This new method represents a significant change in the way medicine is practiced, focusing on precision and customization. It provides optimism for improved and personalized therapies for those dealing with rheumatoid arthritis.

KEYWORDS
Rheumatoid arthritis; Platelet membrane-coated nanoparticles; Targeted drug delivery; Autoimmune disorder; Precision medicine; Inflammation modulation; Biomimetic Nanomedicine

Received: 20-Jun-2024
Revised: 04-Jul-2024
Accepted: 17-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Iqbal T, Fatima M and Altaf S, 2024. Role of platelet membrane coated nanoparticles to treat rheumatoid arthritis. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 331-338. https://doi.org/10.47278/book.CAM/2024.460

INTRODUCTION

Overview of Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a long-term disease where the lining of our joints gets swollen and causes pain. It is caused by our immune system attacking our body. This condition causes pain, and swelling, and can damage the joints over time (Finckh et al., 2022). Rheumatoid arthritis can harm many joints, changing their shape and making it hard to live a normal life. We don't know exactly what causes RA, but it's related to the immune system attacking the body's tissues (Zou, 2020). Controlling RA usually means using different types of medicine like pain relievers, drugs that can change the course of the disease, and stronger medicine in severe cases. Although these treatments can help with symptoms and slow down the disease, they may not work completely, have bad side effects, and need to be taken for a long time (Akram et al., 2021). Also, some patients may not get better with current treatments, so we need new and better ways to treat them. Tiny particles used in medicine look hopeful for helping with the problems of regular RA treatments. Nanoparticles are very tiny and have special qualities (Gisbert-Garzarán et al., 2020). They can be used to send medicine to a specific place in the body, make medicines work better, and lower the side effects on the body. Platelets wrapped around tiny particles are a new and hopeful way to help in this situation.

Platelet Membrane Coated Nanoparticles for RA Treatment

Rationale for Platelet Membrane Coating

Platelets are very important for the body's defenses and responses to injury. The surface of their cells has special parts

that help them communicate with injured areas and places with inflammation (Portier & Campbell, 2021). Covering tiny particles with platelet membranes helps them act like natural cells, making them better at finding and treating inflamed joints (Hu et al., 2015). Platelet-covered nanoparticles can use the body's natural way of finding specific places. The proteins on the outside of platelets help the nanoparticles go to the swollen joints of people with rheumatoid arthritis. This method helps drugs work better and causes less harm to healthy tissues (Jiménez-Jiménez et al., 2020a).

Mechanisms of Action

Nanoparticles covered with platelet membranes might be able to help control the abnormal immune response seen in RA. These tiny particles can help calm down swelling in the joints by working with the body's immune cells. The platelet coating on nanoparticles helps them reduce inflammation and deliver medicine (Deng et al., 2022). This can help reduce swelling and pain in the joints for people with RA.

Current Research and Future Prospects

Many tests in animals have shown that coating nanoparticles with platelet membranes could help treat rheumatoid arthritis. These studies have found that treatment works better, has fewer side effects, and can get to swollen joints more easily (Kunde and Wairkar, 2021). Platelet-coated nanoparticles show potential, but we need to figure out how to make them in large quantities, make sure they are safe for a long time, and follow the rules before we can use them in medicine (Adhalrao et al., 2024). Current research is working to make these tiny particles better and check how they affect animals over a long time (Sekhon et al., 2022). The creation of tiny particles covered in platelet membranes for treating rheumatoid arthritis is a new and interesting area of study in medicine using very small particles (Gisbert-Garzarán et al., 2020). More study is needed to make sure that this new treatment works well, is safe, and is made in the best way. If they work, platelet-coated nanoparticles could change the way doctors treat rheumatoid arthritis. They would be a precise, effective, and well-tolerated treatment for patients with this serious autoimmune disease.

Platelet Membrane-Coated Nanoparticles

A. Platelet Membrane Structure and composition

Platelets are tiny, round blood cells that are important for stopping bleeding and fighting off infections. Covering very tiny particles with the outer layer of cells to make them look like cells. The structure of a platelet membrane is made up of two layers of fats with proteins and receptors in them. These things are like bricks that make up the membrane. They come together in two layers to make the membrane strong. The surface of platelet membranes has glycoproteins that help them stick to other cells and tissues and send signals to them. Platelet walls have receptors that help them stick to other things and respond to signals (Robier, 2020). Different proteins on the outside of platelets help them do their job in fighting off germs, reducing swelling, and healing cuts and injuries. Covering tiny particles with platelet membranes uses the natural abilities of these components to stick to and target inflamed tissues, like the synovium in rheumatoid arthritis.

Table 1: Role of platelet membrane coated nanoparticles Core Materials

Sr.No	Platelet Membrane-Coated Nanoparticles	Nanoparticle Core Material	Target Site	Benefits	References
1	Platelet Membrane	Lipids, Polymers	Inflamed Joints, Synovial Tissue, Inflammatory Sites	Biocompatibility, Enhanced Targeting, Prolonged Circulation Time, Reduced Immune Response	(Y. Song et al., 2019)
2	Platelet Membrane	Inorganic Nanoparticles	Inflamed Joints, Synovial Tissue, Inflammatory Sites	Biocompatibility Enhanced Targeting, Reduced Immune Response, Prolonged Circulation Time	(W. Song et al., 2022)
3	Platelet Membrane	Hybrid Materials	Inflamed Joints, Synovial Tissue, Inflammatory Sites	Prolonged Circulation Time, Reduced Immune Response, Enhanced Targeting, Biocompatibility	(Chen et al., 2020)

Nanoparticle Core Material

Nanoparticles have a middle part that holds the medicine. Choosing the right materials is very important for making sure the medicine is delivered properly. Some commonly used materials for the small particles in the center include (Joseph et al., 2023). Lipid-based tiny particles like liposomes or lipid nanoparticles are commonly used as the main material. These fats can trap drugs that don't dissolve in water inside their fatty layers (García-Pinel et al., 2019). Polymer materials that are safe for the body, like PLGA or chitosan, are often used for the center of the material. These substances can wrap up both water-fearing and water-loving medications (Liu et al., 2021). Silica or gold particles can be used as the center. Inorganic tiny particles have special abilities and can be designed to release medicine in a planned way (Moreira et al., 2018) Mixing different materials together can make tiny particles that are really strong because each material brings its own strengths.

Advantages of Platelet Membrane Coating

Platelet-coated nanoparticles are very safe and work well in the body because they are made from platelet membranes. Platelets are a part of blood that works with the body without causing any problems. Covering tiny particles with platelet

membranes reduces the chance of our bodies reacting to them, so they can be used for medical treatments. Platelet membrane-coated nanoparticles can hit their target better. Platelets are good at finding their way to areas of the body that are inflamed. The proteins and receptors on the outside of platelets help the nanoparticles find and go to specific inflamed tissues, like the synovium in people with rheumatoid arthritis(Iqbal, Altaf, Salma, et al., 2024). This special delivery helps drugs work better in certain places and reduces their side effects in other areas. The covering on the outside of platelets helps them stay in the bloodstream longer. Platelets can avoid being cleared by the immune system, and they pass this ability on to the nanoparticles they coat. The stealth effect makes it harder for the body to remove the nanoparticles quickly, so they can stay in the body for longer. The nanoparticles stay in the body longer, which makes it more likely they will reach and build up at the inflamed areas we want to target. Covering tiny particles with platelet membranes can help reduce the body's reaction to the particles. The platelet membrane acts like a shield that makes it harder for the immune system to notice the nanoparticles (C.-M. J. Hu et al., 2015). This is really helpful for long-term conditions like rheumatoid arthritis, where people often need to take medicine regularly. Reducing the body's reactions to the treatment makes it safer and more effective, which helps patients get better results (He et al., n.d.).

Mechanisms of Action

Targeting Inflamed Joints and Platelet Membrane Interaction with Inflammatory Sites

Platelet-covered nanoparticles go to inflamed joints in conditions like rheumatoid arthritis by interacting with the inflamed areas in a specific way. Platelets have special parts on their surface that help them stick to inflamed cells in blood vessels near sore joints. These parts are called adhesion molecules and receptors. This recognition is increased because adhesion molecules are turned up when there is inflammation. Platelets can react to signals released when the body is inflamed(Altaf & Iqbal, 2023). The platelet membrane-coated nanoparticles can use the signals released in the synovium of rheumatoid joints. When the swollen joints are nearby, tiny particles covered with platelets stick to them and go through the body's barrier. This process, called extravasation, lets the tiny particles get into the synovial tissue and reach the inflamed area. When platelets interact with nanoparticles, they gather in rheumatoid joints using special methods. The EPR effect means nanoparticles collect in areas with leaky blood vessels, like inflamed tissues. In rheumatoid arthritis, the blood vessels and synovial membrane in the joints are not working well. This allows platelet-coated nanoparticles to build up in the affected joints. The outside of platelet-covered nanoparticles can attach specifically to cells in swollen joints. Platelet receptors connect with molecules on the surface of cells that cause inflammation or are found in joint tissues. This particular attachment helps nanoparticles get inside the right cells and release the medicine they contain. After entering the swollen joints, the tiny particles slowly let out the enclosed medicine. The slow release of the medicine makes it last a long time, which helps with the long-term treatment of rheumatoid arthritis(Iqbal & Altaf, 2024). This special way of giving medicine to the body helps to lower the amount of medicine in the whole body and reduces the side effects of treatment (He et al., n.d.).

Modulation of Immune Response and Inhibition of Inflammatory Cytokines

Platelet-covered particles can help control the immune response in rheumatoid arthritis by stopping the production and activity of harmful substances. Tiny particles covered in platelet membranes can capture inflammatory molecules like TNF-α, IL-1β, and IL-6. The platelet membrane's ability to attract these cytokines allows the nanoparticles to attach to and stop them from causing harm during inflammation. Platelet parts on tiny particles can stop inflammation signals. This problem might make important signals in the body slow down, which can reduce inflammation in the joints. Platelet membrane-coated nanoparticles have anti-inflammatory drugs inside them. These medicines stop the production or action of inflammation-causing substances in the affected area, which reduces the immune system's reaction. Tiny particles covered with platelet membranes also help control immune cells that cause rheumatoid arthritis. Macrophages are a key part of the body's inflammatory response in RA. Tiny particles covered with platelet membranes can change the way certain immune cells behave, making them less inflamed and more helpful (Muhammad et al., 2020). This change helps make a setting that is not good for ongoing swelling. T cells, especially T helper cells, play a part in the autoimmune reaction in rheumatoid arthritis. Tiny particles covered with platelet membranes can affect T cells, changing how they work and develop. This rule can stop the too-strong immune response that causes harm to the joints. Abnormal activation of certain cells in the joints makes rheumatoid arthritis more damaging and aggressive. Platelet-covered tiny particles might stop synovial fibroblasts from causing harm to joint tissues (Lin et al., 2023).

Experimental Studies

In vitro Studies and Interaction with Synovial Cells

Scientists have done experiments in a lab on platelet membrane-coated nanoparticles interacting with synovial cells. This helps us understand how these nanoparticles could be used to treat rheumatoid arthritis. They used special nanoparticles that glow to the cells and take them in. These studies want to learn how well nanoparticles get inside cells, especially how receptors and mechanisms on platelets and synovial cells work together. Scientists studied what happens to nanoparticles covered with platelet membranes inside synovial cells. By watching the tiny particles for a while, they can see if the covered particles stay in certain parts of the cell, like endosomes or lysosomes, and check if the medicine keeps coming out for a long time. In lab research, scientists are also testing if platelet membrane-coated nanoparticles are harmful to synovial cells (Zhou et al., 2023). We test the nanoparticles to make sure they won't harm cells. We check if the cells are alive if they're dying, and for other signs of their health.

Evaluation of Anti-Inflammatory Effects

In the lab, we are studying platelet-covered nanoparticles can reduce inflammation. Scientists are checking that certain chemicals in joints change when they are treated with tiny particles covered in platelet membranes. These chemicals are important in causing inflammation. This shows nanoparticles can change the levels of inflammation in rheumatoid arthritis. Laboratory tests are looking at tiny particles covered with platelet membranes that affect certain enzymes and substances that cause inflammation in the body. This includes looking at the effects on enzymes like COX-2 and MMPs. These studies are trying to figure out how nanoparticles help reduce inflammation(Umair et al., 2022). Scientists study platelet membrane-coated nanoparticles affect the body's inflammation pathways within cells. This involves studying proteins are changed, how a factor called NF-κB becomes active, and other signals that control the way genes that because inflammation is turned on.

In vivo Studies and Animal Models of Rheumatoid Arthritis

Studying animals with arthritis is important for testing if platelet-coated nanoparticles can help treat the disease and if they are safe to use. Animal models that are often used include. CIA is a common way to imitate many parts of human rheumatoid arthritis in research. In this model, animals like mice or rats are given collagen to make their immune system attack their own body and cause joint swelling. Doctors will check how bad the arthritis is and examine the damage to the joints as time goes on (Floris et al., 2020). AIA models use adjuvants like complete Freund's adjuvant to make animals show symptoms similar to arthritis (Jones et al., 2018). This model is often used to study how arthritis develops and how new treatments might work. This model includes taking serum from mice with arthritis and giving it to other mice, which causes joint inflammation. Researchers can use it to learn about how arthritis affects the whole body and to see if treatments work.

Therapeutic Efficacy of Platelet Membrane-Coated Nanoparticles

In live animal tests, researchers are studying if platelet membrane-coated nanoparticles can be effective in treating rheumatoid arthritis (Deng et al., 2022). Scientists are coating tiny particles with platelet membranes can help make arthritis symptoms and joint damage less severe. This assessment looks at the joints by looking at them, using special pictures, and examining their tissues under a microscope. We are checking the levels of certain substances in the blood and joint fluid to see if platelet-coated nanoparticles can help reduce inflammation in the joints. Scientists are studying how platelet membrane-coated nanoparticles affect the immune cells in the joints (Zhu et al., 2021). This involves immune cell change and reaction in rheumatoid arthritis. This means looking at how certain types of immune cells are affected in the disease. In vivo studies also look at how platelet-covered nanoparticles move through the body as long they stay in the bloodstream (Zhu et al., 2021), where they go into the body, and are removed from the body. It is important to carefully study the possible negative effects and long-term safety of using platelet membrane-coated nanoparticles to make sure they are a good treatment option (Han et al., 2022). This includes checking organs are working, evaluating whether the body is being harmed, and looking for any signs of immune system reactions.

Challenges and Solutions

Potential Obstacles in Clinical Translation and Immunogenicity Concerns

Nanomaterials, like platelet membrane-coated nanoparticles, could cause they might affect the immune system. The immune system might see these tiny particles as invaders and launch an attack, which could make them less effective or safe for medical treatment. We need to do careful tests before using platelet membrane-coated nanoparticles they affect the immune system. This means checking to see if the body's immune system reacts to the nanoparticles by making antibodies or activating specific pathways(Iqbal, Altaf, Fatima, et al., 2024). We can look at changing the surface or adding a coating to reduce the body's immune response. Careful watching during medical trials will help find and deal with any unexpected immune reactions in people (Ernst et al., 2021). Moving from making a small amount of something in a laboratory to making a lot of it for use in hospitals and clinics can be difficult. It is important to keep the platelet membrane-coated nanoparticles consistent and reliable when making them in large amounts for medical use. It is very important to have strong manufacturing methods and good checks to control quality. Using advanced technology to make things in a better and faster way can help make more of them. "Working with industry partners are familiar with making lots of tiny particles can give us helpful information. " Furthermore, following the rules for making things well and the government's guidelines is very important to make sure nanoparticles for medical use are consistent and high-quality (Isaac et al., 2022).

Strategies to Overcome Challenges and Surface Modification Techniques

Addressing Immunogenicity

Using stealth coatings like polyethylene glycol (PEG) on the surface of platelet membrane-coated nanoparticles can make them less likely to cause an immune response. PEGylation makes nanoparticles hard for the immune system to notice and helps them stay in the body for longer (Fam et al., 2020). Modifying the surface of platelet membrane-coated nanoparticles to make them more like natural membranes can help them avoid detection by the immune system. This means making the coating better so it works well with the body and doesn't cause a bad reaction (Wang et al., 2020). Using cross-linking techniques to make the platelet membrane coating stronger can make nanoparticles more stable. Cross-linking agents help make the membrane components stronger, so the coated nanoparticles can last longer when they are moving around in the body or being stored (C. Hu et al., 2020). Adding specific molecules to the outside of platelet-covered

nanoparticles can help them stick better to inflamed tissues. This change makes sure that medicine goes to the right place in the body better (Pires et al., 2021).

Integration with other Therapeutic Approaches and Combination Therapies

Combining different treatments and putting them inside platelet capsules helps in delivering multiple therapies at once (Wilkins et al., 2024). This method can work together to target many different parts of rheumatoid arthritis, making the treatment work better. Platelet membrane-coated nanoparticles can be created to help improve current treatments for rheumatoid arthritis. Mixing these tiny particles with regular DMARDs or biologics may lead to a better and more powerful treatment plan (Radu & Bungau, 2021). Adding imaging dyes to platelet-covered nanoparticles lets us see where they go in the body and how well they hit their target. This combination helps doctors make special treatment plans by giving them information about the disease and how well the treatment is working. Creating tiny particles covered in platelet membranes that release medicine in a certain way when they sense certain signals like pH or inflammation (Jiménez-Jiménez et al., 2020b). This makes it easier to deliver medicine to the right place and reduces any unwanted effects.

Future Directions

Emerging Technologies, Innovations and Advancements in Nanoparticle Design

Future studies might look at making tiny particles that can release drugs in response to something. These tiny particles can be made to release medicine when certain things happen in the body, like a change in pH or temperature, or when there are signs of inflammation in the joints. This would make delivering drugs more accurate and controlled (Mitchell et al., 2021). Developments in making tiny particles could mean creating versatile platforms that can carry several treatments at once. Combining different medicines or treatments into one tiny particle could help treat different parts of rheumatoid arthritis, and make the treatment work better. In the future, tiny particles could be made with other biological parts like enzymes or proteins to make medicines work better (Pandit et al., 2022). Nano-biohybrids could use the combined effects of man-made tiny particles and natural molecules to better target specific areas and help the immune system (Guo et al., 2020).

Integration with Personalized Medicine Approaches and Patient-specific Formulations

Personalized medicine means making tiny particles that are coated with material from a patient's blood cells (Vaz & Kumar, 2021). These particles can be customized based on each patient's specific traits. Many things, like sick someone is, their genes, they react to treatment, can affect how nanoparticles are made to help each patient the most. Discoveries in finding markers in the body could help create tiny particles covered with platelet membranes. These particles would be made to seek out and treat the specific signs of rheumatoid arthritis in each patient (Alghamdi et al., 2022). This precise targeting can make the treatment work better and reduce the side effects. In the future, new ideas may include adding tests to platelet-covered nanoparticles(Altaf et al., 2023). This could help doctors keep track of how a disease is developing and how the treatment is working. It would allow them to change the treatment plan if the patient's condition changes. New tiny particles that can give both treatment and diagnostic images might become more common (Yu et al., 2021). These combined systems can give important information about the disease and also give the right treatment. This helps to make treatments personalized and more effective.

Clinical Implications

Potential for Patient-specific Treatment and Tailored Nanoparticle Therapeutics

Using platelet membrane-coated nanoparticles in hospitals could help make personalized medicine for patients (Zhu et al., 2021). This method might mean changing the makeup, size, and amount of medication in tiny particles to fit each patient's needs and reactions. Tailoring small particle therapies to the individual needs of a patient with rheumatoid arthritis, taking into account the severity and progression of the disease, may enhance the effectiveness of the treatment (An et al., 2024). Customized medicines can change to match the disease, making sure that patients get the best and most personalized treatments. Customized medicine using platelet-coated nanoparticles could have benefits beyond just the nanoparticles (Yaman et al., 2020). Working together with other customized treatments, like special medications or biologics, could provide complete treatment plans that take into account all the different aspects of a person's rheumatoid arthritis.

Predictive Biomarkers for Treatment Response

Using platelet membrane-coated nanoparticles in patients may require finding biomarkers that can show if the patient will respond well to this treatment (Jiménez-Jiménez et al., 2020b). Molecular or genetic signs linked to how bad a disease is and how well the body responds to nanoparticles could help doctors decide on the best treatment. Predictive biomarkers can help the treatment work and change the treatment plan if necessary (Mahler et al., 2020). Regularly checking these markers while receiving treatment might help identify who is responding well and who is not. This would allow us to make changes to the treatment plan earlier to try to improve results. Using platelet membrane-coated nanoparticles in personalized treatment for rheumatoid arthritis could become a common practice. These computer programs would look at each patient's information, like their biomarker status, to help doctors choose the best treatment(Iqbal et al., 2023). Using predictive biomarkers can help improve long-term results by allowing for a more personalized and proactive treatment approach (Tufail et al., 2024). This might help people with rheumatoid arthritis to control their disease better, have fewer side effects, and have a better quality of life.

Conclusion

Research into the use of platelet membrane-coated nanoparticles as a potential therapeutic approach for rheumatoid arthritis has resulted in encouraging findings. Rheumatoid arthritis is a persistent autoimmune condition typified by inflammation of the joints, with existing treatment modalities encountering difficulties related to insufficient effectiveness and the occurrence of adverse reactions. The utilization of nanoparticle-based therapeutics, in particular platelet membrane-coated nanoparticles, offers an innovative strategy with potential benefits for precise drug delivery. Platelet membrane coating is a technique that harnesses the inherent properties of platelets to augment the performance of nanoparticles. The nanoparticles exhibit a high degree of biocompatibility, improved localization to inflamed joints, extended circulation within the body, and decreased immune reactivity. The modulation of the immune response occurs through the inhibition of inflammatory cytokines and the regulation of immune cells that contribute to the pathology of rheumatoid arthritis. The identification of challenges, such as immunogenicity concerns and scale-up production challenges has been reported in the literature. Various strategies incorporating surface modification techniques and integration with other therapeutic approaches have been suggested as a means to address these challenges. Recent developments in technology encompass innovations in the design of nanoparticles, demonstrating the emergence of smart nanoparticles and multifunctional platforms. The potential for future treatments of rheumatoid arthritis may involve the incorporation of platelet membrane-coated nanoparticles into current therapeutic modalities, which could provide complementary and synergistic effects. The identification of predictive biomarkers linked to the responsiveness of platelet membrane-coated nanoparticles holds promise for improved patient monitoring and personalized treatment adjustments in the future.

REFERENCES

Adhalrao, S. B., Jadhav, K. R., Patil, P. L., & Kadam, V. J. (2024). Engineering Platelet Membrane Imitating Nanoparticles for Targeted Therapeutic Delivery. Current Pharmaceutical Biotechnology.

Akram, M., Daniyal, M., Sultana, S., Owais, A., Akhtar, N., Zahid, R., Said, F., Bouyahya, A., Ponomarev, E., & Shariat, M. A. (2021). Traditional and modern management strategies for rheumatoid arthritis. Clinica Chimica Acta, 512, 142–155.

Alghamdi, M. A., Fallica, A. N., Virzì, N., Kesharwani, P., Pittalà, V., & Greish, K. (2022). The promise of nanotechnology in personalized medicine. Journal of Personalized Medicine, 12(5), 673.

Altaf, S., & Iqbal, T. (2023). Bee Venom Used for the Treatment of Rheumatoid Arthritis. Biomedical Journal of Scientific & Technical Research, 53(2), 44503–44507.

Altaf, S., Iqbal, T., Majeed, W., Farooq, M. A., Naseer, D., Saleem, M., Babar, S. U. R., & Ikram, M. (2023). Plasma membrane camouflaged nanoparticles: an emerging antibacterial approach. One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, 2, 193–200.

An, X., Yang, J., Cui, X., Zhao, J., Jiang, C., Tang, M., Dong, Y., Lin, L., Li, H., & Wang, F. (2024). Advances in local drug delivery technologies for improved rheumatoid arthritis therapy. Advanced Drug Delivery Reviews, 115325.

Chen, H.-Y., Deng, J., Wang, Y., Wu, C.-Q., Li, X., & Dai, H.-W. (2020). Hybrid cell membrane-coated nanoparticles: a multifunctional biomimetic platform for cancer diagnosis and therapy. Acta Biomaterialia, 112, 1–13.

Deng, C., Zhao, X., Chen, Y., Ai, K., Zhang, Y., Gong, T., Zeng, C., & Lei, G. (2022). Engineered platelet microparticle-membrane camouflaged nanoparticles for targeting the golgi apparatus of synovial fibroblasts to attenuate rheumatoid arthritis. ACS Nano, 16(11), 18430–18447.

Ernst, L. M., Casals, E., Italiani, P., Boraschi, D., & Puntes, V. (2021). The interactions between nanoparticles and the innate immune system from a nanotechnologist perspective. Nanomaterials, 11(11), 2991.

Fam, S. Y., Chee, C. F., Yong, C. Y., Ho, K. L., Mariatulqabtiah, A. R., & Tan, W. S. (2020). Stealth coating of nanoparticles in drug-delivery systems. Nanomaterials, 10(4), 787.

Finckh, A., Gilbert, B., Hodkinson, B., Bae, S.-C., Thomas, R., Deane, K. D., Alpizar-Rodriguez, D., & Lauper, K. (2022). Global epidemiology of rheumatoid arthritis. Nature Reviews Rheumatology, 18(10), 591–602.

Floris, I., García-González, V., Palomares, B., Appel, K., & Lejeune, B. (2020). The micro-immunotherapy medicine 2LARTH® reduces inflammation and symptoms of rheumatoid arthritis in vivo. International Journal of Rheumatology, 2020.

García-Pinel, B., Porras-Alcalá, C., Ortega-Rodríguez, A., Sarabia, F., Prados, J., Melguizo, C., & López-Romero, J. M. (2019). Lipid-based nanoparticles: application and recent advances in cancer treatment. Nanomaterials, 9(4), 638.

Gisbert-Garzarán, M., Manzano, M., & Vallet-Regí, M. (2020). Mesoporous silica nanoparticles for the treatment of complex bone diseases: Bone cancer, bone infection and osteoporosis. Pharmaceutics, 12(1), 83.

Guo, Z., Richardson, J. J., Kong, B., & Liang, K. (2020). Nanobiohybrids: Materials approaches for bioaugmentation. Science Advances, 6(12), eaaz0330.

Han, H., Bartolo, R., Li, J., Shahbazi, M.-A., & Santos, H. A. (2022). Biomimetic platelet membrane-coated nanoparticles for targeted therapy. European Journal of Pharmaceutics and Biopharmaceutics, 172, 1–15.

He, Y., Li, R., Liang, J., Zhu, Y., Zhang, S., Zheng, Z., Qin, J., Pang, Z., & Wang, J. (n.d.). Drug targeting through platelet membrane-coated nanoparticles for the treatment of rheumatoid arthritis. https://doi.org/10.1007/s12274-018-2126-5

Hu, C.-M. J., Fang, R. H., Wang, K.-C., Luk, B. T., Thamphiwatana, S., Dehaini, D., Nguyen, P., Angsantikul, P., Wen, C. H., & Kroll, A. V. (2015). Nanoparticle biointerfacing by platelet membrane cloaking. Nature, 526(7571), 118–121.

Hu, C., Luo, R., & Wang, Y. (2020). Heart valves cross-linked with erythrocyte membrane drug-loaded nanoparticles as a

biomimetic strategy for anti-coagulation, anti-inflammation, anti-calcification, and endothelialization. ACS Applied Materials & Interfaces, 12(37), 41113–41126.

Iqbal, T., Ahmad, A., Naveed, M. T., Ali, A., & Ahmad, M. (2023). Potential Role of Zoonoses in Bioterrorism. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 1, 499–512.

Iqbal, T., & Altaf, S. (2024). Nigella Sativa use for the Treatment of Cancer. https://doi.org/10.26717/BJSTR.2024.55.008660

Iqbal, T., Altaf, S., Fatima, M., Rasheed, R., Laraib, K., Azam, M., Karamat, M., Salma, U., & Usman, S. (2024). A narrative review on effective use of medicinal plants for the treatment of parasitic foodborne diseases. Agrobiological Records 16: 79-92.

Iqbal, T., Altaf, S., Salma, U., Fatima, M., Khan, M. N., Farooq, S., Abrar, M., Tasleem, M., & Afzal, A. (2024). Cell membrane coated polymeric nanocarriers: a novel drug delivery approach for the targeted therapy of rheumatoid arthritis. Agrobiological Records 15: 91-102.

Isaac, N. A., Pikaar, I., & Biskos, G. (2022). Metal oxide semiconducting nanomaterials for air quality gas sensors: operating principles, performance, and synthesis techniques. Microchimica Acta, 189(5), 196.

Jiménez-Jiménez, C., Manzano, M., & Vallet-Regí, M. (2020a). Creating tiny particles covered in platelet membranes that release medicine in a certain way when they sense certain signals like pH or inflammation. Biology, 9(11), 406.

Jiménez-Jiménez, C., Manzano, M., & Vallet-Regí, M. (2020b). Nanoparticles coated with cell membranes for biomedical applications. Biology, 9(11), 406.

Jones, G. W., Hill, D. G., Sime, K., & Williams, A. S. (2018). In vivo models for inflammatory arthritis. Inflammation and Cancer: Methods and Protocols, 101–118.

Joseph, T. M., Kar Mahapatra, D., Esmaeili, A., Piszczyk, Ł., Hasanin, M. S., Kattali, M., Haponiuk, J., & Thomas, S. (2023). Nanoparticles: Taking a unique position in medicine. Nanomaterials, 13(3), 574.

Kunde, S. S., & Wairkar, S. (2021). Platelet membrane camouflaged nanoparticles: biomimetic architecture for targeted therapy. International Journal of Pharmaceutics, 598, 120395.

Lin, Y., Guan, X., Su, J., Chen, S., Fu, X., Xu, X., Deng, X., Chang, J., Qin, A., & Shen, A. (2023). Cell Membrane-Camouflaged Nanoparticles Mediated Nucleic Acids Delivery. International Journal of Nanomedicine, 8001–8021.

Liu, E., Zhao, S., Li, X., Meng, X., & Liu, B. (2021). Preparation, characterization of PLGA/chitosan nanoparticles as a delivery system for controlled release of DHA. International Journal of Biological Macromolecules, 185, 782–791.

Mahler, M., Martinez-Prat, L., Sparks, J. A., & Deane, K. D. (2020). Precision medicine in the care of rheumatoid arthritis: Focus on prediction and prevention of future clinically-apparent disease. Autoimmunity Reviews, 19(5), 102506.

Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery, 20(2), 101–124.

Moreira, A. F., Rodrigues, C. F., Reis, C. A., Costa, E. C., & Correia, I. J. (2018). Gold-core silica shell nanoparticles application in imaging and therapy: A review. Microporous and Mesoporous Materials, 270, 168–179.

Muhammad, Q., Jang, Y., Kang, S. H., Moon, J., Kim, W. J., & Park, H. (2020). Modulation of immune responses with nanoparticles and reduction of their immunotoxicity. Biomaterials Science, 8(6), 1490–1501.

Pandit, C., Roy, A., Ghotekar, S., Khusro, A., Islam, M. N., Emran, T. Bin, Lam, S. E., Khandaker, M. U., & Bradley, D. A. (2022). Biological agents for synthesis of nanoparticles and their applications. Journal of King Saud University-Science, 34(3), 101869.

Pires, I. S., Hammond, P. T., & Irvine, D. J. (2021). Engineering strategies for immunomodulatory cytokine therapies: challenges and clinical progress. Advanced Therapeutics, 4(8), 2100035.

Portier, I., & Campbell, R. A. (2021). Role of platelets in detection and regulation of infection. Arteriosclerosis, Thrombosis, and Vascular Biology, 41(1), 70–78.

Radu, A.-F., & Bungau, S. G. (2021). Management of rheumatoid arthritis: an overview. Cells, 10(11), 2857.

Robier, C. (2020). Platelet morphology. Journal of Laboratory Medicine, 44(5), 231–239.

Sekhon, U. D. S., Swingle, K., Girish, A., Luc, N., de la Fuente, M., Alvikas, J., Haldeman, S., Hassoune, A., Shah, K., & Kim, Y. (2022). Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding. Science Translational Medicine, 14(629), eabb8975.

Song, W., Jia, P., Zhang, T., Dou, K., Liu, L., Ren, Y., Liu, F., Xue, J., Hasanin, M. S., & Qi, H. (2022). Cell membrane-camouflaged inorganic nanoparticles for cancer therapy. Journal of Nanobiotechnology, 20(1), 289.

Song, Y., Huang, Z., Liu, X., Pang, Z., Chen, J., Yang, H., Zhang, N., Cao, Z., Liu, M., & Cao, J. (2019). Platelet membrane-coated nanoparticle-mediated targeting delivery of Rapamycin blocks atherosclerotic plaque development and stabilizes plaque in apolipoprotein E-deficient (ApoE−/−) mice. Nanomedicine: Nanotechnology, Biology and Medicine, 15(1), 13–24.

Tufail, M., Hu, J.-J., Liang, J., He, C.-Y., Wan, W.-D., Huang, Y.-Q., Jiang, C.-H., Wu, H., & Li, N. (2024). Predictive, preventive, and personalized medicine in breast cancer: targeting the PI3K pathway. Journal of Translational Medicine, 22(1), 15.

Umair, M., Altaf, S., Muzaffar, H., Iftikhar, A., Ali, A., Batool, N., Iqbal, T., & Saif-ur-Rehman, B. S. R. (2022). Green nanotechnology mediated silver and iron oxide nanoparticles: Potential antimicrobials. Agrobiol Rec, 10, 35–41.

Vaz, V. M., & Kumar, L. (2021). 3D printing as a promising tool in personalized medicine. Aaps Pharmscitech, 22, 1–20.

Wang, S., Duan, Y., Zhang, Q., Komarla, A., Gong, H., Gao, W., & Zhang, L. (2020). Drug Targeting via Platelet Membrane–Coated Nanoparticles. Small Structures, 1(1), 2000018. https://doi.org/10.1002/SSTR.202000018

Wilkins, C. A., Hamman, H., Hamman, J. H., & Steenekamp, J. H. (2024). Fixed-Dose Combination Formulations in Solid Oral Drug Therapy: Advantages, Limitations, and Design Features. Pharmaceutics, 16(2), 178.

Yaman, S., Chintapula, U., Rodriguez, E., Ramachandramoorthy, H., & Nguyen, K. T. (2020). Cell-mediated and cell membrane-coated nanoparticles for drug delivery and cancer therapy. Cancer Drug Resistance, 3(4), 879.

Yu, Z., Gao, L., Chen, K., Zhang, W., Zhang, Q., Li, Q., & Hu, K. (2021). Nanoparticles: a new approach to upgrade cancer diagnosis and treatment. Nanoscale Research Letters, 16(1), 88.

Zhou, K., Yang, C., Shi, K., Liu, Y., Hu, D., He, X., Yang, Y., Chu, B., Peng, J., & Zhou, Z. (2023). Activated macrophage membrane-coated nanoparticles relieve osteoarthritis-induced synovitis and joint damage. Biomaterials, 295, 122036.

Zhu, C., Ma, J., Ji, Z., Shen, J., & Wang, Q. (2021). Recent advances of cell membrane coated nanoparticles in treating cardiovascular disorders. Molecules, 26(11), 3428.

Zou, S.-R. (2020). Management of Rheumatoid Arthritis.

Chapter 39

Therapeutic Effect of Nanoparticles as Anti-inflammatory, Antibacterial and Anti-parasitic

Muhammad Asif[1,*], Ayesha Safdar Ch.[1*], Ubaidullah[2], Zia-Ullah[3,] Naveed Hussain[1], Muhammad Hassan Saleem[4], Muhammad Azhar[4], Zeeshan Ahmad Bhutta[5,] Sana Sagheer[6,] Muhammad Fakhar-e-Alam Kulyar[7], Shah Nawaz[7], Rida Fatima Hussain[8], Muhammad Awais[3], Muhammad Tauseef Ahmad[9] , Inam ul Hassan[1] , Aisha Arhad[10,] Syeda Faiza Muzammal[11]

[1]Department of Veterinary Surgery, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
[2]Department of Parasitology, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
[3]Department of Small Animal Clinical Sciences, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
[4]Department of Veterinary Medicine, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
[5]Laboratory of Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju 28644, Republic of Korea
[6]Department of Physiology, Islamia University of Bahawalpur, 63100, Pakistan
[7]College of Veterinary Medicine, Huazhong Agricultural University, Wuhan 430070, China
[8]Faculty of Veterinary Medicine, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
[9]Veterinary officer (Animal Health) Livestock and diary development department government of Punjab, Pakistan
[10]Clinical Department for Small Animals and Horses, Clinical Center for Equine Health and Research, University of Veterinary Medicine Vienna, Vienna, Austria
[11]Institute of Biochemistry, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan
*Corresponding author: drasifmalik55@gmail.com ; ayesha.hassan@uvas.edu.pk

ABSTRACT

Nanotechnology is currently being widely used in a number of scientific fields. In particular, nanoparticles (NPs) are used in both *in-vitro* and *in-vivo* studies on parasites and bacteria which can be used as anti-parasitic and anti-bacterial drugs. Particles created in various forms and sizes, ranging roughly from 1 to 100 nanometers, are called nanoparticles (NPs). Antimicrobial resistance (AMR), which posed a threat to the prevention and treatment of an increasing number of infections caused by bacteria, parasites, viruses, and fungi that no longer respond to the standard treatments that have been used to treat them, is one of the important risk factors of the twenty-first century. To effectively treat infectious disorders, it is strategically advantageous to use nano size metals, metal oxides, (NPs), and nanocomposites. NPs which have antibacterial action against a number of bacteria species including *E. faecium*, *St. aureus*, *K. pneumoniae*, *A. baumannii, P. aeruginosa,* and *Enterobacter* species comprise of NPs containing Silver, Gold, Yttrium, Cadmium, Aluminum, Selenium, Zinc, Copper, Titanium, Magnesium, Nickel, Cerium, or Iron. Utilizing nanoparticles made of metals and their oxides is highly significant. Nanoparticles are also effective against the parasitic infection. There are commonly used nanoparticles against parasites such as Zinc, Silver, Cu and Mg nanoparticles. Various substances, such as oxidized metals, silver, chitosan, and gold nanoparticles, can inhibit the growth of various parasites, such as *Giardia*, *Leishmania, Plasmodium*, and *Toxoplasma*, as well as helminthes, such as *Echinococcus multilocularis, Trichinella spiralis*, and *Fasciola hepatica*. NPs can be used either alone or in conjunction with existing medications to treat parasites. NPs are recommended as more potent medications with less adverse effects for the prevention and management of parasites. Over the past ten years, significant progress has been made in the field of Nano medicine for the control of parasites.

KEYWORDS
Nanoparticles, Anti-inflammatory, Antibacterial and Anti-parasitic

Received: 05-Jun-2024
Revised: 14-Jul-2024
Accepted: 18-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Asif M, Ch AS, Ubaidullah, Rashid M, Bhutta ZA, Saleem MH, Azhar M, Kulyar MF-E-A, Nawaz S, Hussain RF, Sagheer S, Zia-Ullah and Awais M, 2024. Therapeutic effect of Nanoparticles as anti-inflammatory, antibacterial and anti-parasitic. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 339-349. https://doi.org/10.47278/book.CAM/2024.466

INTRODUCTION

Nanoparticles as Anti-inflammatory and Antibacterial

Antibiotics have proven essential in achieving substantial medical and surgical improvements in addition to saving patients' lives (Gould and Bal, 2013). They have been successful in preventing or treating infections that may occur in patients who have been undergoing chemotherapy, the ones with persistent illnesses like diabetes, kidney diseases, or

arthritis, or the patients who have undergone complex surgeries (Rossolini et al., 2014). Antibiotics have also increased longevity by modifying the course of bacterial infections (Piddock, 2012). The use of antibiotics has been beneficial everywhere in the world. In developing countries with still poor sanitation, the use of antibiotics lowers. The number of cases and fatalities resulting from food-borne and other diseases associated with poverty (Rossolini et al., 2014).

Antimicrobial resistance (AMR), which posed a threat to the prevention and treatment of an increasing number of infections caused by bacteria, parasites, viruses, and fungi that no longer respond to the standard treatments that have been used to treat them, is one of the important risk factors of the twenty-first century (Prestinaci et al., 2015).

The World Health Organization has long recognized the need for a robust and very well coordinated international effort to avoid AMR (WHO). The WHO Global Strategy for Containment of Antimicrobial Resistance presented a framework of measures in 2001 to prevent the establishment and spread of antimicrobial-resistant microorganisms. (Organization, 2001). In its 2012 report, The Evolving Threat of Antimicrobial Resistance - Options for Action, the World Health Organization (WHO) made a number of recommendations for interventions, including strengthening health systems and encouraging the development of new drugs and vaccines (Organization, 2012). The World Health Organization its report on antimicrobial resistance in 2014, from both domestic and international sources (Organization, 2014). Antibiotics have revolutionized the treatment and saved countless lives, but there has been a sharp increase of bacteria that are resistant to them all around the world (Golkar et al., 2014). Infections produced by bacteria are now again a serious threat decades after the first patients got antibiotic therapy (Spellberg and Gilbert, 2014). The problem of antibiotic resistance has been linked to the unwanted use and exploitation of antibiotics, along with challenges within the biopharmaceutical industry. These challenges include reduced financial incentives and burdensome regulatory requirements, which have hindered drug discovery and development in this field (Viswanathan, 2014).

Decades before humans began to manufacture antibiotics in large quantities to prevent and cure infections, many bacterial species had already developed the capacity to resist them (Bhullar et al., 2012). Modifications in a bacterium's genome can result in antibiotic resistance. In humans or animals treated with antibiotics, mutations easily happen and become fixed. There are fewer instances of such a significant selection pressure on pathogens elsewhere (Larsson and Flach, 2022). Furthermore, the process is unaffected by other species' genetic reserves. Therefore, external factors are frequently less likely to significantly contribute to the mutation-based establishment of resistance for the vast majority of illnesses. When considering the emergence of new resistance factors, it's important to acknowledge that water, soil, and other environments characterized by highly diverse ecological niches offer an unparalleled source of genetic diversity. This diversity surpasses that found within the microbiota of humans and domesticated animals (Schulz et al., 2017).

In England in 1961, the term "methicillin-resistant Staph. aureus" was initially adopted shortly after methicillin was used in medicine (Jevons, 1961). Methicillin is no longer available for human consumption. Safer penicillins have taken its place (Dzintars and Grayson, 2018). The terminology ‘Methicillin-resistant S. aureus’ is still in use. MRSA healthcare-associated MRSA (HA-MRSA) in many regions worldwide after its original recognition (Chambers and DeLeo, 2009). When MRSA was discovered in patients who had never had any prior medical contact (also known as community-associated MRSA, or CA-MRSA), a significant shift in MRSA prevalence was evident (Faoagali et al., 1992). It has additionally been attributed to contact with livestock since the twenty-first century (livestock-associated MRSA) (Lee et al., 2018).

The use of antibiotics in modern medicine to treat bacterial infections has revolutionized the field. Nevertheless, throughout time, the indiscriminate, improper, and frequently abusive use of antibiotics has accelerated the establishment of pathogenic bacteria AMR. These bacterial strains are resistant to common therapeutic approaches. Realizing that the emergence of AMR has outrun the introduction of new antibiotics is disappointing (Chakraborty et al., 2022). The main source of nanoscale confinement of materials combined with multivalent interactions and high surface-to-volume ratio is the therapeutic impact of nanomaterials. To effectively treat infectious disorders, it is strategically advantageous to use nano size metals, metal oxides, (NPs), and nanocomposites. (Chakraborty et al., 2022).

Pathogenic microorganisms' cell membranes can be penetrated by nanoparticles (NPs), which then create special antimicrobial mechanisms by interfering with crucial biochemical processes. NPs have shown synergy when used with the strongest antibiotics, and they may help to control the universal challenge of growing resistance to antibiotics (Lee et al., 2019).

Antimicrobial Resistance and Wound Healing

Antimicrobial-resistant microorganisms from an infected wound could affect the patient's overall well-being and raise medical expenses (Filius and Gyssens, 2002). The process of cutaneous wound recovery is extremely intricate and regulated. If the wound healing process does not go quickly and efficiently, an extended cutaneous wound may form (Han and Ceilley, 2017). One of the main obstacles to wound healing is bioburden (Rhoads et al., 2012). Pathogens' colonization of the wound site significantly increases the persistence of the wound (Rahim et al., 2017). Besides being susceptible to basic skin infections, prior research has demonstrated that surgical site infections (SSIs), wounds brought on by diabetes, hypertension, venous disorders, and surgery are more prone to harbor harmful bacteria (Călina et al., 2017). Among these, SSIs account for 15% of the total nosocomial infections and are very challenging to treat as a result of their drug resistance (Dulon et al., 2011). S. aureus, E. faecalis, P. aeruginosa, and P. mirabilis have been identified as the most common bacteria in persistent wounds based on a number of sources (Kirketerp-Møller et al., 2008). Microbial infection is the most common challenge to wound healing. A wound is considered infected if the bacteria exceeds a threshold of 10^5 per gram of wound

tissue (Stojadinovic et al., 2008). The majority of pathogenic microorganisms that commonly colonize chronic wounds are more prone to produce biofilms, which directly contribute to a slower recovery (Wu et al., 2019). S. aureus, P. aeruginosa, and E. coli are bacteria that frequently populate wounds. Typically, these bacterial species have a negative impact on the rate at which wounds heal (Serra et al., 2015). The emergence of antibiotic resistance has urged the careful application of systemic antimicrobials, particularly in the treatment of local diseases such cutaneous wounds. Topical antimicrobials are crucial for managing chronic wounds because they help stop bacterial biofilm formation and wound infection. Topical antibiotics such polymyxin B and silver sulfadiazine are suggested for systemic antibiotic therapy for infected wounds; after the wound is healed, antibiotic usage should be stopped. (Tang et al., 2022). The management of wounds is vital because wound recovery is a difficult problem. Nanotechnology enables a wide range of contemporary regenerative medicine approaches. Many biocompatible self-assembling nanoparticles (NPs) have recently been created (Thapa et al., 2020). NPs enhance delayed wound healing and injury care. In addition to having low in vivo toxicity, metal nanoparticles (NPs) have shown promising features (Mirzahosseinipour et al., 2020). Three potential explanations for their antimicrobial activity have been established: (1) the alteration of microbial membrane perviousness due to NP accumulation will release proteins, LPs, and biomolecules; (2) the release of reactive oxygen species via nanoparticles, inducing oxidative damage to cells; and (3) NPs undergo metabolism by the microbes, resulting in a decline of intracellular NP concentration (Rowe et al., 2020).

Table 1: List of nanoparticles with different biomedical activities.

Sr. no	Nanoparticles	Effect	References
1	ZnO-Nps	Antibacterial	(Asif et al., 2023)
		Anti-inflammatory	(Zahoor et al., 2023)
		Antioxidant	(Vera et al., 2023)
2	Cu-Nps	Antibacterial	(Ma et al., 2022)
		Anti-inflammatory	(Ma et al., 2022)
		Antioxidant	(Ssekatawa et al., 2022)
3	MgO-Nps	Antibacterial	(Rodríguez-Hernández et al., 2023)
		Anti-inflammatory	(Behera et al., 2021)
		Antioxidant	(Shahid et al., 2022)
4	Ag-Nps	Antibacterial	(Palau et al., 2023)
		Anti-inflammatory	(Xu et al., 2023)
		Antioxidant	(Zhang et al., 2022)

Nanoparticles as Antimicrobial Agents

NPs have antimicrobial capabilities that can go through typical resistance mechanisms, such enzyme inactivation, reduced cell permeability, alteration of target sites/enzymes, and enhanced efflux by overexpression of efflux pumps (Baptista et al., 2018). Additionally, Antibiotics and NPs have been used in combination to combat MDROs and have synergistic effects against bacteria that result in the production of biofilms (Pelgrift and Friedman, 2013). Complex antibacterial mechanisms are provided by the combinations of NPs and antibiotic compounds to combat antibiotic resistance (Gupta et al., 2017).

Therefore, NPs are thought of as next-generation antibiotics. NPs, primarily metallic, have demonstrated effectiveness against bacteria in investigations conducted both in vitro and in vivo (Zazo et al., 2016).

NPs which have antibacterial action against a number of bacteria species including E. faecium, St. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter species (Beyth et al., 2015) comprise of NPs containing Silver, Gold, Yttrium, Cadmium, Aluminum, Selenium, Zinc, Copper, Titanium, Magnesium, Nickel, Cerium, or Iron (Hemeg, 2017). Cell membrane structure can be adversely affected by nanoparticles, resulting in changes to permeability and surface loading. Reactive oxygen species (ROS) generation is most likely the most prevalent way that nanoparticles affect bacteria (Karwowska, 2017). The following figure provides a summary of the molecular pathways underlying the antibacterial action of nanomaterials (Fig: 1).

Zinc oxide Nanoparticles

Utilizing nanoparticles made of metals and their oxides is highly significant. Both zinc (Zn) and zinc oxide (ZnO), two thoroughly studied metals, have an effect on living things. Zinc is an active element because it has strong reduction properties. Zinc oxide is easily produced when it is oxidized. The human body needs zinc since it is one of the important trace elements (Maret, 2011). Zinc is present in all human body tissues, although myocytes contain the most of it (85% of the body's total zinc concentration) (Król et al., 2017). It has been proven that zinc is required for the correct operation of a considerable number of biomolecules and coenzyme. As a result, zinc finger structures offer a special framework that enables protein domains to interact with DNA or other proteins (Klug and Rhodes, 1987). Zinc is necessary for the normal operation of metalloproteins. Even while it is generally accepted that free zinc ions are not hazardous, there is growing evidence to suggest that these ions may be harmful to cells. Usually, animal cell cultures are used to assess a test chemical's in vitro toxicity. Nerve cells are thought to be the cells most susceptible to outside influences (Timashev et al., 2016). Neuronal degradation is an evident side effect that is seen in individuals that have been exposed to zinc ions

(Sindhu et al., 2022). Zinc cations are attached to bioactive ligands (such as proteins) and zinc NPs are produced in order to reduce the cytotoxic impact of zinc ions. Nanostructured ZnO can have a wide range of morphological characteristics. There are numerous uses for ZnO in both engineering and medicine (Beek et al., 2004). ZnO is a biosafe substance with a variety of uses, such as photo-oxidizing and photocatalysis effects on biological and chemical species (Khater et al., 2020). Numerous studies have demonstrated that zinc oxide nanoparticles (ZnONPs) work against both gram positive and negative bacteria with their antimicrobial properties. ZnONPs are also thought to be excellent candidates for transporting pharmaceutically active compounds (Abebe et al., 2020). Cell migration, angiogenesis and re-epithelization can all be induced by ZnO NPs. These qualities are all very important for wound healing (Khan et al., 2021). ZnO nanoparticles exerts antibacterial effect by producing reactive oxygen species (ROS) like H2O2 or by producing Zinc ion (Zn^{2+}) or by the direct contact of nanoparticles with the bacterial cell membrane (Fig:1) (Ijaz et al., 2020).

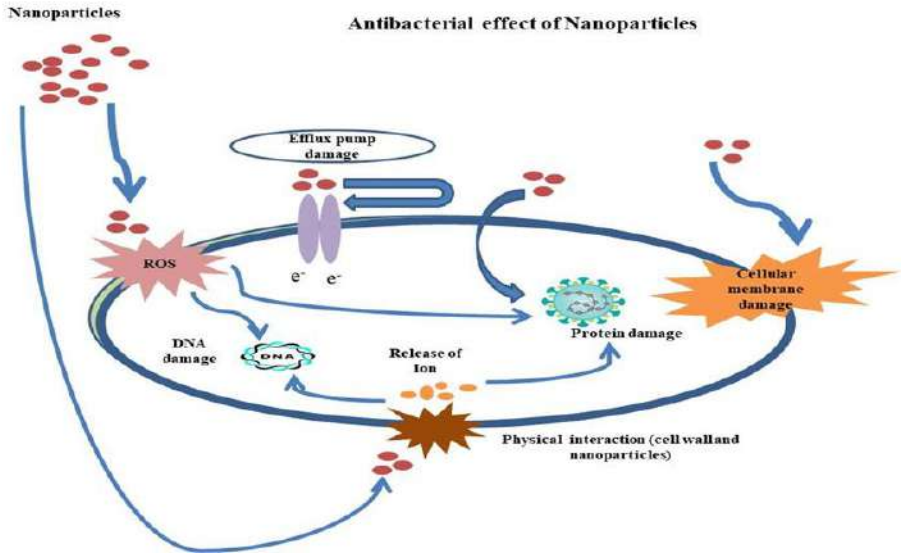


Fig. 1: Mechanism of action of antibacterial effect of nanoparticles

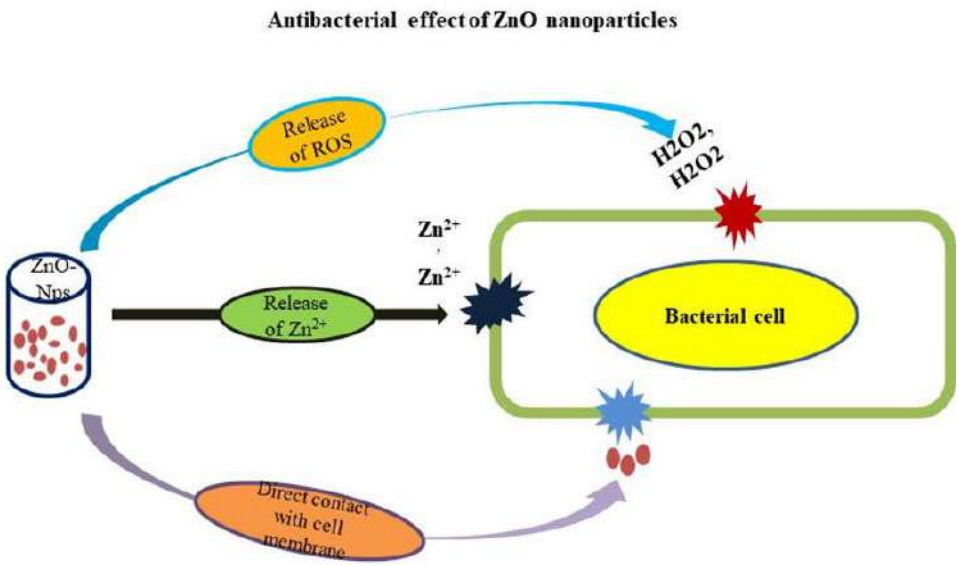


Fig. 2: Antibacterial effect of ZnO nanoparticles (ZnO-Nps)

Sliver Nanoparticles

Silver is employed in medical applications more frequently than other metals including gold, copper, iron, titanium, and zinc because of its inherent antibacterial properties. There is proof that plant-derived silver nanoparticles, which are typically present in secondary metabolites, have an innate capacity to inhibit antibiotic-resistant bacteria and foodborne pathogens (Jain and Mehata, 2017). (Morones et al., 2005) recommended that the changes made by the silver nanoparticles to the bacteria's membrane shape may have contributed to the amount of AgNPs found on and inside the bacteria. Phosphorus and Sulphur are components of the machinery found in bacterial cells. Acidic silver encourages the collapse of the pathogen's respiratory and replication framework, resulting in cell death, by forming sulphydryl groups (S-H), which are found in bacterial proteins and DNA in the cellular matrix. Proteomic analysis of silver-regulated membrane proteins in P. aeruginosa exposed to silver nitrate and silver NPs revealed that the silver binding proteins for silver NPs and Silver ions had a similar pattern, but in cells exposed to silver NPs, it was discovered that the bio-uptake of silver ions and the formation of reactive oxygen species were both increased (Chinnasamy et al., 2021). Previous research have

demonstrated that silver has pro-healing qualities that not only serve as an antibacterial agent but also hasten healing process and recovery (Seo et al., 2017). Studies show that silver nanoparticles can speed up the wound healing process by lowering inflammation and reducing the presence of scars (Liu et al., 2010). The mechanical function of the skin that has been treated with silver nanoparticles is found to be similar to that of regular skin (Kwan et al., 2011).

CU Nanoparticles

Traditional inorganic antibacterial substances include copper-containing compounds like CuSO4 and Cu(OH)2 (Hughes and Poole, 1989). Because there are more carboxylic groups than necessary in the lipoproteins at the bacterial surface, when these groups dissociate, the bacterial surface becomes negatively charged, giving bacteria a general negative charge at biological pH levels (Stoimenov et al., 2002). Due to their opposite charges, electrostatic forces are thought to be the cause of the adherence and bioactivity between bacteria and the copper ions created by nanoparticles. Peptidoglycans, which are negatively charged molecules, bind the Cu2+ ions that copper nanoparticles discharge into the liquid growth medium. Gram-negative bacteria, such as E. coli, may let more Cu2+ ions to permeate the plasma membrane as opposed to Gram-positive bacteria, although these latter are often believed to be comparatively sensitive to antibiotics (Koch, 1990). The antibacterial action of copper nanoparticles has been linked to Cu2+ ions that are released from copper nanoparticles and taken up by bacteria at high concentrations. Copper ions, which affect the cell membrane by altering protein structure or altering enzyme function, are exposed to the bacterial cell surface (Dan et al., 2005). Due to its angiogenesis, regeneration, and antibacterial capabilities, wound dressings containing copper oxide accelerate wound healing. (Salvo and Sandoval, 2022). Copper (Cu), one of the bioactive NPs, has a complicated role in a variety of cells, affects a number of cytokines' and growth factors' modes of action, and is fundamentally engaged in every stage of the healing process. (Kornblatt et al., 2016).

Mg Nanoparticles

Increasing research has been done on a novel class of antimicrobial agents called metal oxide nanoparticles, such as MgO, for its potential use in food, the environment, and medicine. (Dizaj et al., 2014). The impact of metal oxide nanoparticles on bacteria involves a complex and incompletely understood process. Reactive oxygen species (ROS), which lead to bacterial lipid peroxidation, are said to be responsible for the antibacterial activities of MgO nanoparticles (Scallan et al., 2011). MgO nanoparticles, however, also exhibited non-ROS driven bacterial toxicity, indicating that oxidative stress may not be the main cause of cell death. (Leung et al., 2014). Due to its promising mechanical and biological qualities, magnesium and magnesium alloys have received more and more attention as bioresorbable metals for orthopedic applications in recent years. (Cipriano et al., 2017). Mg is biodegradable and biocompatible (Trumbo et al., 2002). Mg-based implants do not demand further procedures for implant removal, in contrast to typical nondegradable metals. (Song et al., 2019). For load-bearing implants, magnesium and magnesium alloys are preferable over ceramics due to their higher elastic modulus, strength, and fracture toughness (Geetha et al., 2009). Escherichia coli and Staphylococcus aureus were only two of the bacteria that magnesium oxide (MgO) nanoparticles shown antibacterial capabilities against in vitro *(Nguyen et al., 2018)*.

Nanoparticles as Anti-parasitic Drugs

Nanotechnology is currently being widely used in a number of scientific fields. In particular, nanoparticles (NPs) are used in both *in-vitro* and *in-vivo* studies on parasites and used as anti-parasitic drugs (H. U. R. Bajwa et al., 2022). Particles created in various forms and sizes, ranging roughly from 1 to 100 nanometers, are called nanoparticles (NPs). The use of materials and systems at the atomic scale in nanotechnology is expected to create new avenues for the control and destruction of germs. Nanotechnology is an emerging field. Millions of individuals are afflicted with parasitic infections globally, particularly in developing nations, and there are numerous treatment options that are restricted. Drug resistance has recently been shown by several parasites, which has raised the need for safer, more effective treatments or for developing new medications to prevent parasitic infections. Chemotherapy is currently the basis of control because there is no vaccination available to prevent many parasite diseases. Since current anti-parasitic medications have some negative effects and their usefulness is still being investigated, NPs have drawn the most attention as anti-parasitic drugs in the last few decades. Nevertheless, the application of derivatives of nanoparticles as an anti-parasitic medication has received minimal attention. Antiparasitic effects of nanoparticles are given id fallowing table (Table: 2).

Table 2: Antiparasitic effect of different nanoparticles

Sr. no	Nanoparticles	Effect	References
1	ZnO-Nps	Anti-Parasitic against Protozoon (*Giardiasis*)	(Anah et al., 2022)
		Leishmaniosis	(Norouzi, 2017)
		Toxoplasmosis	
2	Au-Nps	*Leishmaniosis*	
		Echinococcus multilocularis	(Raj et al., 2022)
		Trichinella spiralis	
3	Antimony sulfide	*Leishmaniosis*	

		Giardiasis	(Mohtasebi et al., 2019)
4	Ag-Nps	*Cryptosporidiosis*	
		Toxoplasmosis	(Zhang et al., 2023)
		Flukes	

Different Types of Nanoparticles against Different Parasitic Diseases

As Research has shown that various substances, such as oxidized metals, silver, chitosan, and gold nanoparticles, can inhibit the growth of various parasites, such as Giardia, Leishmania, Plasmodium, and Toxoplasma, as well as helminthes, such as Echinococcus multilocularis, Trichinella spiralis, and Fasciola hepatica. NPs can be used either alone or in conjunction with existing medications to treat parasites. As a result, NPs are recommended as more potent medications with less adverse effects for the prevention and management of parasites (Norouzi, 2017). Generally nanoparticles works in different ways, that include damaging the parasite membrane, DNA (Deoxyribonucleic acid) disruption, protein synthesis inhibition and free-radical formation (Fig: 3) (H. U. Bajwa et al., 2022).

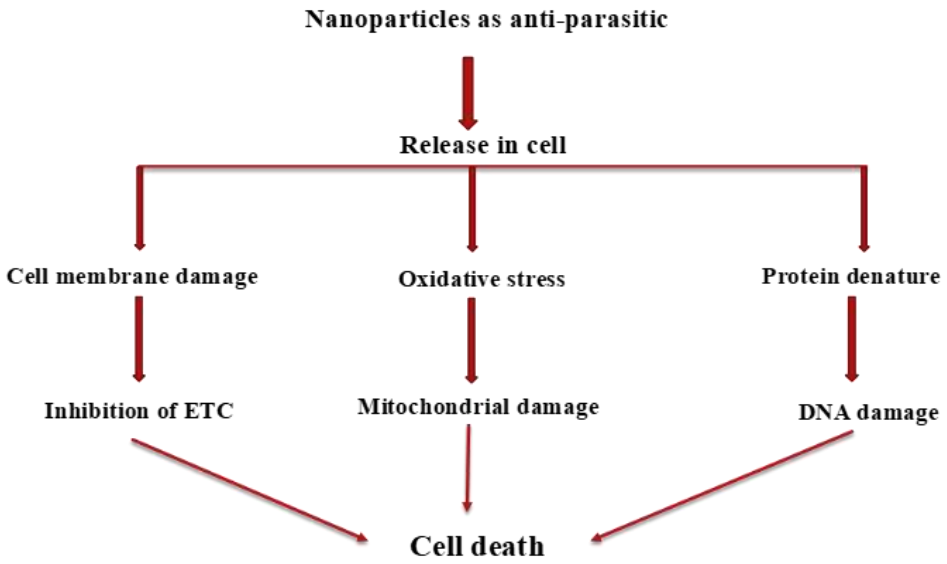


Fig. 3: Antiparasitic effect of nanoparticles

Helminths, ectoparasites, and protozoa are the three primary types of parasites found across the world. These days, anti-helminthic, anti-ectoparasitic, and chemotherapeutic antiprotozoal drugs are utilized to treat these parasites; however, the side effects of these drugs have caused drug resistance over time. In this regard, it is demonstrated that the use of nanoparticles has significantly improved the diagnosis, treatment, and management of parasite diseases. Over the past ten years, significant progress has been made in the field of Nano medicine for the control of parasites. When using gold and silver nanoparticles to treat various parasitic infections, promising results have been seen. Numerous traditional and molecular technologies are used to produce these incredibly powerful nanoparticles. They tear down the parasite membrane, interfere with the synthesis of proteins, damage DNA (deoxyribonucleic acid), and produce free radicals, among other things. These compounds are also effective against parasites that live inside cells. Other nanoparticles, such as those composed of iron, nickel, zinc, and platinum, have also shown promise in the management and treatment of parasitic illnesses. It is anticipated that research in this field will progress the creation of modern drugs (H. U. R. Bajwa et al., 2022).

The primary motivation for these studies is their potential for use in the treatment of various parasitic diseases. Utilizing microorganisms as distinct biofactories, a novel biotechnology approach has made it easier to produce targeted nanoparticles. Biofactories and Biosynthetic methods have been used to create applications such as magnetite iron oxide NPs, silver (Ag), gold (Au), selenium (Se), cadmium-sulfide and sulfoxide, due to their specific properties, rapid synthesis, and regulated toxicity, biogenic synthesized nanoparticles are considered environmentally friendly (Kandeel et al., 2022).

Nano-medicine against Parasitic Disease

The Nano-medicine effectively treats parasites and removed these barriers to the advancement of animal husbandry and health; but, due to their short half-lives and insolubility, which lowers their bioavailability, these medications need to be given often. The advantages of anti-parasitic drugs are increased when these obstacles are removed by using nano-medicines (Sun et al., 2019). Nano-medicine uses nanoparticles to control, monitor, detect, halt, and treat infectious parasitic diseases (Gutiérrez et al., 2016). Under UV light, ZnO NPs show photocatalytic activity. Their anti-parasitic efficacy can be increased by taking use of this characteristic. ZnO NPs produce reactive oxygen species (ROS) when illuminated, which cytotoxically affects parasites and increases their potential for therapeutic use.

Depending on the medication's characteristics and the stage of the illness, it may be administered intravenously, topically, orally, or by other methods. When these drugs enter the body, their delusion and disruption occur. Depending

on the medication's characteristics and the stage of the illness, it may be given intravenously, topically, orally, intra-gastrically, or by other methods. Research has shown that nano-medicine effectively treats parasites. All three types of nanoparticles—organic, inorganic, and polymer-based—show potential for both *in-vivo* and *in-vitro* applications. Numerous different types of nanoparticles are available to treat parasite illnesses.

Antimony sulfide nanoparticles effect both *in-vitro* and *in-vivo* against Leishmaniosis

Biological antimony sulfide NPs have been successfully synthesized in *S. marcescens* and have demonstrated antibacterial efficacy against Escherichia coli and Staphylococcus aureus. Furthermore, studies have demonstrated that antimony sulfide nanoparticles have cytotoxic and parasiticidal effects on protozoan parasites such as *L. infantum*. Even though the chemical synthesis of antimony sulfide NPs has been reported in literature. In recent years, there has been a lot of interest in the use of inorganic nanoparticles in various industrial and therapeutic items. Inorganic nanoparticles (NPs) have become increasingly prevalent in a wide range of commercial and medicinal products. Examples include microelectronic devices, lubricants, catalysts, and antimicrobials. To the best of the author's knowledge, no studies on *L. major* have been published that examine the effects of biogenic antimony sulfide nanoparticles both *in-vitro* and *in-vivo* (Mohtasebi et al., 2019). An increasing amount of study is being conducted on nanoparticles for anti-parasitic drugs can be made from a variety of nanoparticle types and applications. The following is a list of potential applications for nanoparticles as anti-parasitic drugs uses for anti-parasitic nanoparticles in pharmaceutical formulations. The drugs on this list minimize the application of nanoparticles as agents that fight parasites. It is possible to create nanoparticles that specifically target parasites with the least amount of harm to healthy cells. Therapy efficacy is increased and side effects are reduced by this targeted delivery. Medicines in nanoparticle form may be more bioavailable, allowing them to enter the infected area more effectively. This is particularly beneficial for parasite infections that are difficult to treat due to inadequate medication distribution.

Sustained Release

Medicines can be liberated from nanoparticles in a way that maintains therapeutic concentrations steadily over time. When treating chronic parasite infections, this is beneficial counselling.

Protection of Substance Molecules from Breakdown

Drug molecules can be protected from the body's breakdown by nanoparticles, which extends their half-life and ensures their efficacy until they reach their intended target.

Combination Counselling

Combination therapy can target multiple stages of the parasite's life cycle or target drug-resistant parasites since a variety of drugs or therapeutic ingredients can be incorporated into nanoparticles. Attacks by parasites can be fatal for both people and animals. Since parasite infections don't often have obvious signs, they can be more fatal than bacterial infections because they're harder to identify and cure. On the other hand, parasite infections could not show any obvious signs, which makes them difficult to diagnose and treat. This is due to the fact that bacterial illnesses usually exhibit unique symptoms. Trypanosomiasis, malaria, and leishmaniosis are among the infectious parasite diseases that have significant fatality rates in developing countries (Wang et al., 2017). Human malaria is caused by four different species of Plasmodium, with Plasmodium falciparum having the highest global fatality rate (Barnes and White, 2005). Twelve million people were afflicted with leishmaniosis, of which 1-2 million had cutaneous cases and 0.5 million visceral cases. Their infections have become global health concerns due to resistant parasite strains. The anti-parasitic drugs have to be administered constantly due to their short half-life and insolubility, which lowers their bioavailability. However, they are essential for the advancement of animal husbandry and the safety of animal health.

Zinc Oxide Nanoparticle as Anti-parasitic Drug

It has been demonstrated that ZnO NPs naturally contain anti-parasitic qualities. When they interact with parasites, they may damage their membranes, obstruct their metabolic activities, and finally cause them to perish. They are potential candidates to fight different parasite illnesses because of their direct activity (do Carmo Neto et al., 2022). Nanomaterials can be used to treat a wide range of illnesses that affect both human and animal health. Primarily, these materials are employed to tackle the problem of pathogenic organisms becoming resistant to conventional drugs. One thoroughly investigated example of a potential component for biomedical applications is zinc oxide (ZnO) nanoparticles (NPs). Its anti-parasitic effect is intimately associated with its capacity to generate or induce ROS that affect the pathogen's homeostasis. Prior exposure to helminths and protozoa, which are detrimental to both human health and animal productivity, resulted in this type of nanoparticle. Zinc oxide nanoparticles are effective to treat the protozoal diseases (Anah et al., 2022).

Gold Nanoparticle as Anti-parasitic Drugs

It has been demonstrated that AuNPs have anti-parasitic activity against a variety of parasites, such as helminths and protozoa. They have the potential to cause oxidative stress, damage cellular structures, and interfere with parasite metabolism, all of which can result in parasite mortality. Antibodies or ligands that specifically target receptors or antigens on the surface of parasites can be used to functionalize AuNPs. By improving AuNP accumulation at the infection site, this

focused delivery maximizes its effectiveness while reducing off-target impacts on host cells.

It has been demonstrated recently that CHY quickly neutralizes Leishmania by targeting the parasite's MAP kinase 3 enzyme. However, the use of CHY is restricted due to problems with quick excretion, limited absorption, and low bioavailability. In this work, a new CHY-gold nanoformulation with enhanced efficacy against the parasites was created and tested. Gold nanoparticles were reduced and conjugated using CHY's reducing power. In mammalian macrophages, conjugated CHY and gold nanoparticles—which are already well-known for their anti-leishmanial qualities—showed a reduced parasite load (Raj et al., 2022).

Silver Nanoparticle as Anti-parasitic Drugs

The potential of nanoparticles of silver (AgNPs) as anti-parasitic medicines attracts attention owing to their particular features and methods of action. AgNPs have been effective against a variety of parasites, such as helminths, ectoparasites, and protozoa. They have the ability to interfere with several phases of the parasite life cycle, such as metabolism, growth, and replication. AgNPs have the ability to interact with parasite cell membranes, causing permeabilization and structural damage. This damage weakens the integrity of the membrane, which allows cell contents to seep out and ultimately results in cell death.

AgNPs, or silver nanoparticles, are extremely small silver particles that range in size from one to one hundred nanometers. They have distinct chemical and physical characteristics, in contrast to bulk silver. AgNPs have been demonstrated in numerous studies to have positive biological effects on a range of disorders, including antioxidant, antibacterial, anti-inflammatory, and antiparasitic ones. AgNPs are a promising contender for antibacterial drugs because to their tremendous ability to eradicate germs that are resistant to several drugs. This is one of their most well-known uses in the field of antibacterial applications. In comparison to conventional antiparasitic medications, AgNPs produced from plant extracts have demonstrated exceptional antiparasitic activities, including a reduced half-life and improved capacity to impede parasite multiplication. The types, traits, and mode of action of AgNPs in anti-parasitism, with a particular emphasis on their impact on *leishmaniasis, flukes*, *cryptosporidiosis*, *toxoplasmosis*, *Haemonchus*, *Blastocystis hominis*, and *Strongylides*. The purpose is to offer a resource for the use of AgNPs in the management and prevention of parasitic infections (Zhang et al., 2023).

REFERENCES

Abebe, B., Zereffa, E. A., Tadesse, A., and Murthy, H. A. (2020). A review on enhancing the antibacterial activity of ZnO: Mechanisms and microscopic investigation. *Nanoscale Research Letters*, *15*, 1-19.

Anah, S. A., Anah, S. A., and Al-Khalidy, K. A. H. J. K. J. V. R. (2022). Anti-parasitic activity of zinc oxide nanoparticles against Eimeria tenella in broilers experimentally infected. *62*(4), e30.

Asif, M., Chaudhry, A. S., Ashar, A., Rashid, H. B., Saleem, M. H., Aslam, H. B., and Aziz, A. (2023). Zinc oxide nanoparticles accelerate the healing of methicillin-resistant Staphylococcus aureus (MRSA)-infected wounds in rabbits. *Asian Pacific Journal of Tropical Biomedicine*, *13*(11), 488-496. https://doi.org/10.4103/2221-1691.389574

Bajwa, H. U., Khan, M. K., Abbas, Z., Riaz, R., Rehman, T. U., Abbas, R. Z., Aleem, M. T., Abbas, A., Almutairi, M. M., Alshammari, F. A., Alraey, Y., and Alouffi, A. (2022). Nanoparticles: Synthesis and Their Role as Potential Drug Candidates for the Treatment of Parasitic Diseases. *Life*, *12*(5).

Bajwa, H. U. R., Khan, M. K., Abbas, Z., Riaz, R., Rehman, T. u., Abbas, R. Z., Aleem, M. T., Abbas, A., Almutairi, M. M., and Alshammari, F. A. J. L. (2022). Nanoparticles: Synthesis and their role as potential drug candidates for the treatment of parasitic diseases. *12*(5), 750.

Baptista, P. V., McCusker, M. P., Carvalho, A., Ferreira, D. A., Mohan, N. M., Martins, M., and Fernandes, A. R. (2018). Nano-strategies to fight multidrug resistant bacteria—"A Battle of the Titans". *Frontiers in Microbiology*, *9*, 1441.

Barnes, K. I., and White, N. J. J. A. t. (2005). Population biology and antimalarial resistance: The transmission of antimalarial drug resistance in Plasmodium falciparum. *94*(3), 230-240.

Beek, W. J., Wienk, M. M., and Janssen, R. A. (2004). Efficient hybrid solar cells from zinc oxide nanoparticles and a conjugated polymer. *Advanced Materials*, *16*(12), 1009-1013.

Behera, K., Nasim, I., and Rajesh Kumar, S. (2021). Antioxidant and anti inflammatory activity of magnesium oxide nanoparticles-an in vitro study. *International Journal Dent Oral Science*, *8*(5), 2913-2917.

Beyth, N., Houri-Haddad, Y., Domb, A., Khan, W., and Hazan, R. (2015). Alternative antimicrobial approach: nano-antimicrobial materials. *Evidence-based Complementary and Alternative Medicine*, *2015*.

Bhullar, K., Waglechner, N., Pawlowski, A., Koteva, K., Banks, E. D., Johnston, M. D., Barton, H. A., and Wright, G. D. (2012). Antibiotic resistance is prevalent in an isolated cave microbiome. *PLoS One*, *7*(4), e34953.

Călina, D., Docea, A. O., Rosu, L., Zlatian, O., Rosu, A. F., Anghelina, F., Rogoveanu, O., Arsene, A. L., Nicolae, A. C., and Drăgoi, C. M. (2017). Antimicrobial resistance development following surgical site infections. *Molecular Medicine Reports*, *15*(2), 681-688.

Chakraborty, N., Jha, D., Roy, I., Kumar, P., Gaurav, S. S., Marimuthu, K., Ng, O.-T., Lakshminarayanan, R., Verma, N. K., and Gautam, H. K. (2022). Nanobiotics against antimicrobial resistance: harnessing the power of nanoscale materials and technologies. *Journal of Nanobiotechnology*, *20*(1), 375. https://doi.org/10.1186/s12951-022-01573-9

Chambers, H. F., and DeLeo, F. R. (2009). Waves of resistance: Staphylococcus aureus in the antibiotic era. *Nature Reviews Microbiology*, *7*(9), 629-641.

Chinnasamy, G., Chandrasekharan, S., Koh, T. W., and Bhatnagar, S. (2021). Synthesis, characterization, antibacterial and wound healing efficacy of silver nanoparticles from Azadirachta indica. *Frontiers in Microbiology*, *12*, 611560.

Cipriano, A. F., Lin, J., Lin, A., Sallee, A., Le, B., Cortez Alcaraz, M. C., Guan, R.-G., Botimer, G., Inceoğlu, S., and Liu, H. (2017). Degradation of bioresorbable Mg–4Zn–1Sr intramedullary pins and associated biological responses in vitro and in vivo. *ACS Applied Materials and Interfaces*, *9*(51), 44332-44355.

Dan, Z., Ni, H., Xu, B., Xiong, J., and Xiong, P. (2005). Microstructure and antibacterial properties of AISI 420 stainless steel implanted by copper ions. *Thin Solid Films*, *492*(1-2), 93-100.

Dizaj, S. M., Lotfipour, F., Barzegar-Jalali, M., Zarrintan, M. H., and Adibkia, K. (2014). Antimicrobial activity of the metals and metal oxide nanoparticles. *Materials Science and Engineering: C*, *44*, 278-284.

do Carmo Neto, J. R., Guerra, R. O., Machado, J. R., Silva, A. C., and da Silva, M. V. J. C. M. C. (2022). Antiprotozoal and anthelmintic activity of zinc oxide Nanoparticles. *29*(12), 2127-2141.

Dulon, M., Haamann, F., Peters, C., Schablon, A., and Nienhaus, A. (2011). MRSA prevalence in European healthcare settings: a review. *BMC Infectious Diseases*, *11*, 1-13.

[Record #444 is using a reference type undefined in this output style.]

Faoagali, J., Thong, M., and Grant, D. (1992). Ten years' experience with methicillin-resistant Staphylococcus aureus in a large Australian hospital. *Journal of Hospital Infection*, *20*(2), 113-119.

Filius, P. M. G., and Gyssens, I. C. (2002). Impact of Increasing Antimicrobial Resistance on Wound Management. *American Journal of Clinical Dermatology*, *3*(1), 1-7. https://doi.org/10.2165/00128071-200203010-00001

Geetha, M., Singh, A. K., Asokamani, R., and Gogia, A. K. (2009). Ti based biomaterials, the ultimate choice for orthopaedic implants–A review. *Progress in Materials Science*, *54*(3), 397-425.

Golkar, Z., Bagasra, O., and Pace, D. G. (2014). Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. *The Journal of Infection in Developing Countries*, *8*(02), 129-136.

Gould, I. M., and Bal, A. M. (2013). New antibiotic agents in the pipeline and how they can help overcome microbial resistance. *Virulence*, *4*(2), 185-191.

Gupta, A., Saleh, N. M., Das, R., Landis, R. F., Bigdeli, A., Motamedchaboki, K., Campos, A. R., Pomeroy, K., Mahmoudi, M., and Rotello, V. M. (2017). Synergistic antimicrobial therapy using nanoparticles and antibiotics for the treatment of multidrug-resistant bacterial infection. *Nano Futures*, *1*(1), 015004.

Gutiérrez, V., Seabra, A. B., Reguera, R. M., Khandare, J., and Calderón, M. J. C. S. R. (2016). New approaches from nanomedicine for treating leishmaniasis. *45*(1), 152-168.

Han, G., and Ceilley, R. (2017). Chronic wound healing: a review of current management and treatments. *Advances in Therapy*, *34*, 599-610.

Hemeg, H. A. (2017). Nanomaterials for alternative antibacterial therapy. *International Journal of Nanomedicine*, 8211-8225.

Hughes, M. N., and Poole, R. K. (1989). Metals and Micro-organisms.

Ijaz, M., Zafar, M., Islam, A., Afsheen, S., and Iqbal, T. (2020). A review on antibacterial properties of biologically synthesized zinc oxide nanostructures. *Journal of Inorganic and Organometallic Polymers and Materials*, *30*, 2815-2826.

Jain, S., and Mehata, M. S. (2017). Medicinal plant leaf extract and pure flavonoid mediated green synthesis of silver nanoparticles and their enhanced antibacterial property. *Scientific Reports*, *7*(1), 15867.

Jevons, M. P. (1961). "Celbenin"-resistant staphylococci. *British medical journal*, *1*(5219), 124.

Kandeel, M., Akhtar, T., Zaheer, T., Ahmad, S., Ashraf, U., and Omar, M. J. P. V. J. (2022). Anti-parasitic Applications of Nanoparticles: A Review. *42*(2).

Karwowska, E. (2017). Antibacterial potential of nanocomposite-based materials – a short review. *Nanotechnology Reviews*, *6*(2), 243-254. https://doi.org/doi:10.1515/ntrev-2016-0046

Khan, A. u. R., Huang, K., Jinzhong, Z., Zhu, T., Morsi, Y., Aldalbahi, A., El-Newehy, M., Yan, X., and Mo, X. (2021). Exploration of the antibacterial and wound healing potential of a PLGA/silk fibroin based electrospun membrane loaded with zinc oxide nanoparticles [10.1039/D0TB02822C]. *Journal of Materials Chemistry B*, *9*(5), 1452-1465. https://doi.org/10.1039/D0TB02822C

Khater, M., Khater, S. S., Gholap, H., Patil, R., and Kulkarni, G. (2020). Comparative studies on measurement of membrane potential of bacterial cells treated with ZnO nanoparticles by spectrofluorometry, fluorescence microscopy and flowcytometry. *Journal of Microbiological Methods*, *173*, 105920.

Kirketerp-Møller, K., Jensen, P. Ø., Fazli, M., Madsen, K. G., Pedersen, J., Moser, C., Tolker-Nielsen, T., Høiby, N., Givskov, M., and Bjarnsholt, T. (2008). Distribution, organization, and ecology of bacteria in chronic wounds. *Journal of Clinical Microbiology*, *46*(8), 2717-2722.

Klug, A., and Rhodes, D. (1987). Zinc fingers: a novel protein fold for nucleic acid recognition. Cold Spring Harbor symposia on quantitative biology,

Koch, A. L. (1990). Growth and form of the bacterial cell wall. *American Scientist*, *78*(4), 327-341.

Kornblatt, A. P., Nicoletti, V. G., and Travaglia, A. (2016). The neglected role of copper ions in wound healing. *Journal of Inorganic Biochemistry*, *161*, 1-8.

Król, A., Pomastowski, P., Rafińska, K., Railean-Plugaru, V., and Buszewski, B. (2017). Zinc oxide nanoparticles: Synthesis,

antiseptic activity and toxicity mechanism. *Advances in Colloid and Interface Science*, *249*, 37-52.

Kwan, K. H., Liu, X., To, M. K., Yeung, K. W., Ho, C.-m., and Wong, K. K. (2011). Modulation of collagen alignment by silver nanoparticles results in better mechanical properties in wound healing. *Nanomedicine: Nanotechnology, Biology and Medicine*, *7*(4), 497-504.

Larsson, D. G. J., and Flach, C.-F. (2022). Antibiotic resistance in the environment. *Nature Reviews Microbiology*, *20*(5), 257-269. https://doi.org/10.1038/s41579-021-00649-x

Lee, A. S., de Lencastre, H., Garau, J., Kluytmans, J., Malhotra-Kumar, S., Peschel, A., and Harbarth, S. (2018). Methicillin-resistant Staphylococcus aureus. *Nature Reviews Disease Primers*, *4*(1), 18033. https://doi.org/10.1038/nrdp.2018.33

Lee, N.-Y., Ko, W.-C., and Hsueh, P.-R. (2019). Nanoparticles in the treatment of infections caused by multidrug-resistant organisms. *Frontiers in Pharmacology*, *10*, 1153.

Leung, Y. H., Ng, A. M., Xu, X., Shen, Z., Gethings, L. A., Wong, M. T., Chan, C. M., Guo, M. Y., Ng, Y. H., and Djurišić, A. B. (2014). Mechanisms of antibacterial activity of MgO: non-ROS mediated toxicity of MgO nanoparticles towards Escherichia coli. *Small*, *10*(6), 1171-1183.

Liu, X., Lee, P. y., Ho, C. m., Lui, V. C., Chen, Y., Che, C. m., Tam, P. K., and Wong, K. K. (2010). Silver nanoparticles mediate differential responses in keratinocytes and fibroblasts during skin wound healing. *ChemMedChem*, *5*(3), 468-475.

Ma, X., Zhou, S., Xu, X., and Du, Q. (2022). Copper-containing nanoparticles: Mechanism of antimicrobial effect and application in dentistry-a narrative review. *Front Surg*, *9*, 905892. https://doi.org/10.3389/fsurg.2022.905892

Maret, W. (2011). Metals on the move: zinc ions in cellular regulation and in the coordination dynamics of zinc proteins. *Biometals*, *24*, 411-418.

Mirzahosseinipour, M., Khorsandi, K., Hosseinzadeh, R., Ghazaeian, M., and Shahidi, F. K. (2020). Antimicrobial photodynamic and wound healing activity of curcumin encapsulated in silica nanoparticles. *Photodiagnosis and Photodynamic Therapy*, *29*, 101639.

Mohtasebi, S., Mohebali, M., Elikaee, S., Akhoundi, B., Foroushani, A. R., Teimouri, A., and Yarizadeh, H. J. P. r. (2019). In vitro and in vivo anti-parasitic activity of biogenic antimony sulfide nanoparticles on Leishmania major (MRHO/IR/75/ER). *118*, 2669-2678.

Morones, J. R., Elechiguerra, J. L., Camacho, A., Holt, K., Kouri, J. B., Ramírez, J. T., and Yacaman, M. J. (2005). The bactericidal effect of silver nanoparticles. *Nanotechnology*, *16*(10), 2346.

Nguyen, N.-Y. T., Grelling, N., Wetteland, C. L., Rosario, R., and Liu, H. (2018). Antimicrobial activities and mechanisms of magnesium oxide nanoparticles (nMgO) against pathogenic bacteria, yeasts, and biofilms. *Scientific Reports*, *8*(1), 16260.

Norouzi, R. J. J. B. T. s. W. (2017). A review on most nanoparticles applied against parasitic infections. *6*(10), 196-203.

Organization, W. H. (2001). *WHO global strategy for containment of antimicrobial resistance*.

Organization, W. H. (2012). *The evolving threat of antimicrobial resistance: options for action*. World Health Organization.

Organization, W. H. (2014). *Antimicrobial resistance: global report on surveillance*. World Health Organization.

Palau, M., Muñoz, E., Gusta, M. F., Larrosa, N., Gomis, X., Gilabert, J., Almirante, B., Puntes, V., Texidó, R., and Gavaldà, J. (2023). In Vitro Antibacterial Activity of Silver Nanoparticles Conjugated with Amikacin and Combined with Hyperthermia against Drug-Resistant and Biofilm-Producing Strains. *Microbiology Spectrum*, *11*(3), e00280-00223. https://doi.org/doi:10.1128/spectrum.00280-23

Pelgrift, R. Y., and Friedman, A. J. (2013). Nanotechnology as a therapeutic tool to combat microbial resistance. *Advanced Drug Delivery Reviews*, *65*(13-14), 1803-1815.

Piddock, L. J. (2012). The crisis of no new antibiotics—what is the way forward? *The Lancet infectious diseases*, *12*(3), 249-253.

Prestinaci, F., Pezzotti, P., and Pantosti, A. (2015). Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health*, *109*(7), 309-318. https://doi.org/10.1179/2047773215y.0000000030

Rahim, K., Saleha, S., Zhu, X., Huo, L., Basit, A., and Franco, O. L. (2017). Bacterial contribution in chronicity of wounds. *Microbial Ecology*, *73*, 710-721.

Raj, S., Sasidharan, S., Tripathi, T., and Saudagar, P. J. I. J. o. B. M. (2022). Biofunctionalized Chrysin-conjugated gold nanoparticles neutralize Leishmania parasites with high efficacy. *205*, 211-219.

Rhoads, D. D., Wolcott, R. D., Sun, Y., and Dowd, S. E. (2012). Comparison of culture and molecular identification of bacteria in chronic wounds. *International Journal of Molecular Sciences*, *13*(3), 2535-2550.

Rodríguez-Hernández, A. P., Vega-Jiménez, A. L., Vázquez-Olmos, A. R., Ortega-Maldonado, M., and Ximenez-Fyvie, L. A. (2023). Antibacterial Properties In Vitro of Magnesium Oxide Nanoparticles for Dental Applications. *Nanomaterials (Basel)*, *13*(3). https://doi.org/10.3390/nano13030502

Rossolini, G. M., Arena, F., Pecile, P., and Pollini, S. (2014). Update on the antibiotic resistance crisis. *Current Opinion in Pharmacology*, *18*, 56-60.

Rowe, S. E., Wagner, N. J., Li, L., Beam, J. E., Wilkinson, A. D., Radlinski, L. C., Zhang, Q., Miao, E. A., and Conlon, B. P. (2020). Reactive oxygen species induce antibiotic tolerance during systemic Staphylococcus aureus infection. *Nature Microbiology*, *5*(2), 282-290.

Salvo, J., and Sandoval, C. (2022). Role of copper nanoparticles in wound healing for chronic wounds: literature review. *Burns Trauma*, *10*, tkab047. https://doi.org/10.1093/burnst/tkab047

Scallan, E., Hoekstra, R. M., Angulo, F. J., Tauxe, R. V., Widdowson, M.-A., Roy, S. L., Jones, J. L., and Griffin, P. M. (2011). Foodborne illness acquired in the United States—major pathogens. *Emerging Infectious Diseases*, *17*(1), 7.

Schulz, F., Eloe-Fadrosh, E. A., Bowers, R. M., Jarett, J., Nielsen, T., Ivanova, N. N., Kyrpides, N. C., and Woyke, T. (2017). Towards a balanced view of the bacterial tree of life. *Microbiome*, *5*, 1-6.

Seo, S. B., Dananjaya, S., Nikapitiya, C., Park, B. K., Gooneratne, R., Kim, T.-Y., Lee, J., Kim, C.-H., and De Zoysa, M. (2017). Silver nanoparticles enhance wound healing in zebrafish (Danio rerio). *Fish and Shellfish Immunology*, *68*, 536-545.

Serra, R., Grande, R., Butrico, L., Rossi, A., Settimio, U. F., Caroleo, B., Amato, B., Gallelli, L., and De Franciscis, S. (2015). Chronic wound infections: the role of Pseudomonas aeruginosa and Staphylococcus aureus. *Expert Review of anti-Infective Therapy*, *13*(5), 605-613.

Shahid, S., Ejaz, A., Javed, M., Mansoor, S., Iqbal, S., Elkaeed, E. B., Alzhrani, R. M., Alsaab, H. O., Awwad, N. S., Ibrahium, H. A., Fatima, U., Zaman, S., and Nazim Sarwar, M. (2022). The Anti-Inflammatory and Free Radical Scavenging Activities of Bio-Inspired Nano Magnesium Oxide [Original Research]. *Frontiers in Materials*, *9*. https://doi.org/10.3389/fmats.2022.875163

Sindhu, R. K., Yadav, S. K., Kaur, A., Kumar, M., and Kumar, P. (2022). X-Ray Fluorescence: Current Trends and Future Scope. *X-Ray Fluorescence in Biological Sciences: Principles, Instrumentation, and Applications*, 623-646.

Song, M.-S., Zeng, R.-C., Ding, Y.-F., Li, R. W., Easton, M., Cole, I., Birbilis, N., and Chen, X.-B. (2019). Recent advances in biodegradation controls over Mg alloys for bone fracture management: A review. *Journal of Materials Science and Technology*, *35*(4), 535-544.

Spellberg, B., and Gilbert, D. N. (2014). The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. *Clinical Infectious Diseases*, *59*(suppl_2), S71-S75.

Ssekatawa, K., Byarugaba, D. K., Angwe, M. K., Wampande, E. M., Ejobi, F., Nxumalo, E., Maaza, M., Sackey, J., and Kirabira, J. B. (2022). Phyto-Mediated Copper Oxide Nanoparticles for Antibacterial, Antioxidant and Photocatalytic Performances [Original Research]. *Frontiers in Bioengineering and Biotechnology*, *10*. https://doi.org/10.3389/fbioe.2022.820218

Stoimenov, P. K., Klinger, R. L., Marchin, G. L., and Klabunde, K. J. (2002). Metal oxide nanoparticles as bactericidal agents. *Langmuir*, *18*(17), 6679-6686.

Stojadinovic, A., Carlson, J. W., Schultz, G. S., Davis, T. A., and Elster, E. A. (2008). Topical advances in wound care. *Gynecologic Oncology*, *111*(2), S70-S80.

Sun, Y., Chen, D., Pan, Y., Qu, W., Hao, H., Wang, X., Liu, Z., and Xie, S. J. D. D. (2019). Nanoparticles for antiparasitic drug delivery. *26*(1), 1206-1221.

Tang, J., Guan, H., Dong, W., Liu, Y., Dong, J., Huang, L., Zhou, J., and Lu, S. (2022). Application of compound polymyxin B ointment in the treatment of chronic refractory wounds. *The International Journal of Lower Extremity Wounds*, *21*(3), 320-324.

Thapa, R. K., Kiick, K. L., and Sullivan, M. O. (2020). Encapsulation of collagen mimetic peptide-tethered vancomycin liposomes in collagen-based scaffolds for infection control in wounds. *Acta Biomaterialia*, *103*, 115-128.

Timashev, P., Bardakova, K., Minaev, N., Demina, T., Mishchenko, T., Mitroshina, E., Akovantseva, A., Koroleva, A., Asyutin, D., and Pimenova, L. (2016). Compatibility of cells of the nervous system with structured biodegradable chitosan-based hydrogel matrices. *Applied Biochemistry and Microbiology*, *52*, 508-514.

Trumbo, P., Schlicker, S., Yates, A. A., and Poos, M. (2002). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids.(Commentary). *Journal of the American Dietetic Association*, *102*(11), 1621-1631.

Vera, J., Herrera, W., Hermosilla, E., Díaz, M., Parada, J., Seabra, A. B., Tortella, G., Pesenti, H., Ciudad, G., and Rubilar, O. (2023). Antioxidant Activity as an Indicator of the Efficiency of Plant Extract-Mediated Synthesis of Zinc Oxide Nanoparticles. *Antioxidants*, *12*(4), 784. https://www.mdpi.com/2076-3921/12/4/784

Viswanathan, V. (2014). Off-label abuse of antibiotics by bacteria. *Gut Microbes*, *5*(1), 3-4.

Wang, Y., Yu, L., Kong, X., and Sun, L. J. I. j. o. n. (2017). Application of nanodiagnostics in point-of-care tests for infectious diseases. 4789-4803.

Wu, Y.-K., Cheng, N.-C., and Cheng, C.-M. (2019). Biofilms in chronic wounds: pathogenesis and diagnosis. *Trends in Biotechnology*, *37*(5), 505-517.

Xu, Z., Zha, X., Ji, R., Zhao, H., and Zhou, S. (2023). Green Biosynthesis of Silver Nanoparticles Using Aqueous Extracts of Ageratum Conyzoides and Their Anti-Inflammatory Effects. *ACS Applied Materials and Interfaces*, *15*(11), 13983-13992. https://doi.org/10.1021/acsami.2c22114

Zahoor, S., Sheraz, S., Shams, D. F., Rehman, G., Nayab, S., Shah, M. I. A., Ateeq, M., Shah, S. K., Ahmad, T., Shams, S., and Khan, W. (2023). Biosynthesis and Anti-inflammatory Activity of Zinc Oxide Nanoparticles Using Leaf Extract of Senecio chrysanthemoides. *Biomed Research International*, 3280708. https://doi.org/10.1155/2023/3280708

Zazo, H., Colino, C. I., and Lanao, J. M. (2016). Current applications of nanoparticles in infectious diseases. *Journal of Controlled Release*, *224*, 86-102.

Zhang, P., Gong, J., Jiang, Y., Long, Y., Lei, W., Gao, X., and Guo, D. J. P. (2023). Application of silver nanoparticles in parasite treatment. *15*(7), 1783.

Zhang, Y., Cui, L., Lu, Y., He, J., Hussain, H., Xie, L., Sun, X., Meng, Z., Cao, G., and Qin, D. (2022). Characterization of silver nanoparticles synthesized by leaves of Lonicera japonica Thunb. *International Journal of Nanomedicine*, 1647-1657.

Chapter 40

Utilizing Nano Vaccines for Enhanced Immunization against Lumpy Skin Disease

Shafiq ur Rehman[1], Farrah Deeba[2], Ehtasham ul Haq[3], Muhammad Adil[2], Hafiza Rikza Tanveer[4], Sheraz Ahmad[5], Ali Haider[6], Muhammad Ramzan[4], Nayyar Abbas[1], Haseeb Jamal[3*], and Muhammad Tayyab[1]

[1]Faculty of Veterinary & Animal Sciences, Gomal University, Dera Ismail Khan, Pakistan
[2]Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan
[3]PMAS Arid Agriculture University, Rawalpindi, Pakistan
[4]University of Veterinary & Animal Sciences, Lahore, Pakistan
[5]College of Veterinary Medicine Shanxi Agriculture University Taigu, Jinzhong China
[6]The University of Agriculture, Dera Ismail Khan, Pakistan
*Corresponding author: haseebjamal369@gmail.com

ABSTRACT

Significant economic losses have been caused by the infectious viral infection known as lumpy skin disease (LSD), which is afflicting livestock in Pakistan. Even while there are now vaccinations, they are not ideal because of certain constraints. This paper explores the exciting field of improved LSD immunization using vaccines based on nanoparticles. We examine how these sophisticated vaccines, equipped with their higher stability, tailored distribution, and immune response, may overcome the drawbacks of more conventional methods. In particular, we explore different kinds of nanoparticles, such as liposomes and polymer nanoparticles, explaining their benefits and mechanisms of action in promoting strong immune reactions against LSD. Although possible issues like toxicity from nanoparticles are acknowledged, we stress that thorough safety assessments are essential to responsible development. We describe current research efforts aimed at improving the design of nanovaccines and demonstrate how they could transform LSD control. Lastly, we stress that, in order to guarantee complete protection, more research into multi-epitope nanovaccines and combination approaches with additional control mechanisms is required. This research opens the door to protecting animals from LSD, enhancing Pakistan's economy, and releasing the Nano defense.

KEYWORDS
Lumpy skin disease, Nano vaccines, Nanoparticles, Immunization, Pakistan, Livestock health

Received: 11-Jun-2024
Revised: 21-Jul-2024
Accepted: 07-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Rehman SU, Deeba F, Haq EU, Adil M, Tanveer HR, Ahmad S, Haider A, RamzanM, Abbas N, Jamal H and Tayyab M, 2024. Utilizing nano vaccines for enhanced immunization against lumpy skin disease. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 350-355. https://doi.org/10.47278/book.CAM/2024.236

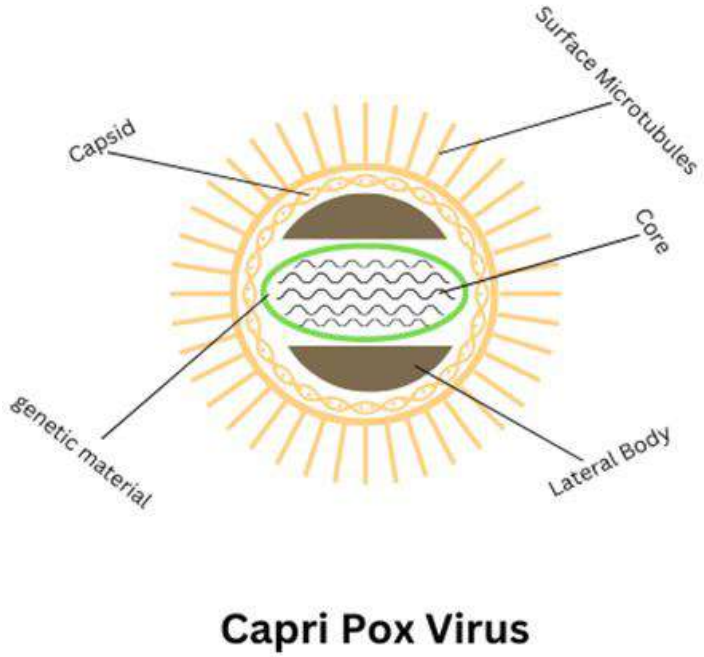
INTRODUCTION

The etiological agent of lumpy skin disease, the Lumpy skin disease virus (LSDV), is an infectious illness that is a member of the Poxviridae family, subfamily *Chordopoxvirniae* and genus *Capripoxvirus*. Some names for this illness include "Neethling virus disease," "exanthema nodularis bovis," "Pseudo-urticaria," and "knopvelsiekte," although "LSD" is the most often used (E.S.MTuppurainen et al., 2015). Lumpy skin disease is an illness spread by a transboundary vector. This illness is not zoonotic. It is believed that this disease's host range is quite restricted because it has mostly been documented in big ruminants, such as cattle and water buffalo. Among the most frequent carriers of this illness are ticks, mosquitoes, and biting flies (*Culicoides*) (S. Rouby et al., 2016). It has been demonstrated that caprine and ovine species can resist infection even while tied near diseased cattle and buffalo. But in certain experimental situations, skin lesions were created in a wide range of domestic and wild animals, including giraffes, impalas, sheep, and goats, in laboratory settings (H.G. Heine et al., 1999). LSD is linked to low death rates and high sickness rates. This illness's obvious symptoms are a high temperature, lymphadenitis, extreme thinness, bilateral epiphora, decreased milk supply, sterility, skin erythema, and nodules. The most significant financial consequences that farmers in LSD-endemic areas deal with include poor reproductive competence, loss of hide quality, decreased milk income, and persistent animal emaciation (Zheng, M. et al., 2007).

Given that LSD is considered a transboundary illness, the World Health Organization (WHO) has decided that it should be reported to international forums because of the disease's severe and ongoing consequences on cattle occupation worldwide. The illness was previously believed to be common exclusively in African nations, but reports of cases have recently come from other parts of the world. LSD is widely used in practically every country on the African, Asian, and

European continents, according to the OIE (O. Mangana-Vougiouka et al., 1999). Given that LSD is considered a transboundary illness, the World Health Organization (WHO) has decided that it should be reported to international forums due to the disease's severe and ongoing consequences on cattle occupation worldwide. The illness was previously believed to be common exclusively in African nations, but reports of cases have recently come from other parts of the world. LSD is widely used in practically every country on the African, Asian, and European continents, according to the OIE (O. Mangana-Vougiouka et al., 1999). Considering that Pakistan has a lengthy land border with both China and India, this is probably one of the main causes of disease transfer into

Fig. 1: Structure of a Capri Pox Virus



Pakistan. Livestock travels across international borders within Pakistan. Given that LSD has lately been observed in Iran, China, and India, another explanation would be the seasonal migration of vectors into Pakistan from surrounding nations. As a result, careful planning and epidemiological analysis have become essential for managing diseases effectively when it comes to these exotic diseases. Fig.1 shows the structure of a *capri-pox* virus.

Nanotechnology

Nanotechnology is an emerging field of research and advanced technology that exploits the physicochemical properties of nanoparticles to precisely manage their size, surface area, and shape, facilitating the development of novel and enhanced functional characteristics. (Prasad, 2008). To create nanoparticles, a variety of components, including proteins, lipids, and inorganic elements, can be utilized. Nonetheless, the most intriguing and promising nanoparticles seem to be polymeric ones, as alginate NPs (Girija, 2019). The United States Food and Drug Administration (US FDA) has already granted clearance for the use of alginate NPs, an environmentally benign and biocompatible co-polymer of guluronic acid and mannuronic acid, for human use. It is typically given orally (Ahmad et al., 2006). Their ultra-small nanoparticles (NPs) increase bioavailability, minimize cytotoxic effects, and maximize tissue compatibility. Applying polymeric nanoparticles. According to Joshy et al. (2018), certain research has started to demonstrate that alginate NPs can be utilized as an efficient carrier for antiviral medicines against the majority of viruses, including the human immunodeficiency virus (HIV). The in-vitro cellular internalization experiments revealed a much higher internalization efficiency, and the nanoparticles were shown to be biocompatible (Albarqi, 2019). According to Silva-Carvalho et al. (2015), propolis is a natural substance that is frequently added to food and drink to enhance health, prevent sickness, and have immunomodulatory effects. According to several studies (Abd El-Hady et al., 2002; 2007; Hegazi et al., 2004; Hegazi and Abd El-Hady, 2008), it has a major potential as an antiviral agent.

Nano Technology in the Field of Medicine

The use of nanotechnology to improve human health and wellbeing is known as nanomedicine. The field of medicine has changed as a result of the application of nanotechnology in several therapeutic areas. Nanoparticles with sizes ranging from 1 to 100 nm are created and utilized for biomedical research instruments, treatments, and diagnostics. With the aid of these instruments, therapy may now be administered at the molecular level, treating the illness and advancing the understanding of its pathophysiology. Because of the non-specificity of their mechanism of action, conventional medications are severely restricted in their ability to cause undesirable effects (A. Surrendering, S. Sandhiya, 2008). Among the nanoparticles utilized for analysis are paramagnetic nanoparticles, quantum dots, nanoshells, and nanosomic particles.

Nano Technology and Vaccine Development

Nanocarriers with a range of compositions, sizes, and surface characteristics are included in the nanotechnologies created for use in the vaccination industry (L.J. Peek, C.R. Middaugh, 2008). To encourage a protective immune response, a variety of vaccine nano carriers have been created and studied for their potential to transfer adjuvants and antigens to immune cells. Unfortunately, insufficient adjuvant activity may lead to restricted immunogenicity even though antigens may be taken up by immune cells. Certain strategies have involved designing nanocarriers to co-deliver an adjuvant and an antigen (A. Dunkle, 2013). Antigens or adjuvants can be targeted to antigen-presenting cells and/or released continuously with the help of nanocarriers. The effectiveness of nanocarriers in vaccine fields is supported by the working mechanisms of vaccine formulations based on nanotechnology. Dendritic cells and macrophages are examples of phagocytic cells that readily take up particles smaller than 10μm. This characteristic has been utilized to boost antigen absorption into cells, which has increased antigen recognition and presentation efficiency (M.O. Oyewumi, A. Kumar, 2010). In order to make protein-based antigen vaccines suitable for oral or mucosal distribution, solid nanocarriers can protect them from depletion and allow access to the gut-associated lymphoid tissue and mucosa-associated lymphoid tissues. Nano carriers with altered surfaces could help distribute antigens in a targeted manner. Along with the mannose, scavenger, and toll-like receptors (TLR) (V. Apostolopoulos, T. Thalhammer, 2013), immune cells express a number of surface receptors. Targeting these overexpressed receptors using nano carriers coated in immune cell-targeting compounds including peptides, antibodies, and carbohydrates may improve the effectiveness of antigen and adjuvant delivery and raise the production of particular and selective immune responses in preventive vaccinations (M. Masuyama and S. Misumi, 2009).

Composition of Nano Vaccines

Although the contents of nano vaccines might vary greatly, they usually consist of certain vaccine components and nanocarriers. Typical elements could be:

Nanocarriers: Polymeric or lipid-based nanoparticles, liposomes, micelles, and other nanoscale objects are utilized for antigenic or genetic information.

2. Antigens: The elements of the pathogen (or related proteins) that elicit an immune response are known as antigens. Antigens are frequently linked to or encapsulated within the nano carrier in nanovaccines.

3. Adjuvants: These could include substances that strengthen the immune response. Adjuvants can be given individually or integrated into the nanocarrier to increase the vaccine's efficacy.

4. Stabilizers: Stabilizers are frequently added to vaccines in order to preserve their structural integrity and efficacy.These could consist of proteins, carbohydrates, or other stabilizing agents.

5. Surface modifications: Coatings or other surface alterations on the nano-carrier can be used to increase stability, target certain cells, or boost the vaccine's overall effectiveness.

Nano Particles used in Nano Vaccines

To improve cow vaccinations, chitosan nanoparticles (CNP), silica nanoparticles, and polylactic acid-glycolic acid (PLGA) nanoparticles are employed as adjuvants or vaccine carriers. The bovine respiratory syncytial virus (BRSV) vaccine, for example, produced condensed clinical signs and viral loads matched to controls after BRSV challenge because recombinant cyclic nanoparticles, used as an adjuvant, induced the production of specific antibodies and specific cellular immunity in vaccinated calves (Riffault S, Meyer G and Deplanche M, 2010). Cattle developed a strong T-cell immunological response to the p67 antigen when the sporozoite surface antigen, p67C, was loaded into silica capsules (Lacasta A, Mody KT and De Goeyse I 2021). Furthermore, calf nasal mucus containing BPI3V-specific IgA antibodies was much higher when the bovine parainfluenza virus (BPI3V) vaccine was encapsulated in PLGA nanoparticles than it was in commercial vaccinations (Mansoor F, Earley B, Cassidy JP 2015). Chitosan-coated PLGA FMD DNA nanoparticle vaccine (Chi-PLGA-DNA) produced almost three times the amount of sIgA compared to conventional vaccines and increased mucosal, systemic, and cell immunity in cattle. It reduces the severity of the disease, slows the removal of the virus, and postpones the beginning of clinical symptoms, even though it does not offer total clinical protection (Pan L, Zhang Z, Lv J 2014).As innovative vaccine carriers, nanoparticles are safe, well-organized, and effective at delivering antigens to immune cells and boosting cellular and humoral immune responses. Furthermore, nanoparticles can stimulate mucosal immunity, offering fresh perspectives on the creation of vaccines. Because of these advantages, adjuvants and carriers of nanoparticles are highly sought after in the field of vaccine development.

Limitation of Conventional Vaccines for LSD

Recounts of LSD vaccination disappointment have been made in a number of Ethiopia's constituent nations. 11% of RM65 (Ramayer strain)-vaccinated cattle (4.2% in dairy and 33.7% in feedlot cattle) contracted the infection during the 2006 outbreak in Israel (Brenner et al., 2009). According to Abu Tarbush, (2014), cow populations inoculated with RM65 (Jovivac®) and an unnamed LSD vaccine in Jordan had a general LSD morbidity of 4.7%. According to Kumar, (2011), Oman saw an ongoing LSD outbreak for over three months following the immunization of cattle herds with the Kenyan sheep and goat pox vaccine. Since 1993, reports of LSD vaccination failure have been made in Ethiopia (Carn, 1993). According to Ayelet et. al, (2013), following vaccination with the KS1 O-180 virus strain vaccine, the expected morbidity in

the cattle population of central Ethiopia would be 23.8%. Nonetheless, a tenfold increase in the dose of the RM65 vaccine (1.85% morbidity) and the Neethling vaccine (1.11% morbidity) were found to provide superior protection (Ben-Gera et al., 2015). In general, vaccines may either protect a portion of the population (leaky vaccines) or only protect some people (all-or-nothing) (Smith et al., 1984). Furthermore, poor vaccination coverage or host-related or vaccination-quality-related issues resulting from vaccine handling, reconstitution, or administration may cause additional immunization failure (Quinn et al., 1999).

Immunized animals receive only partial protection from the KS1 O-180 vaccination. The degree of protection and how it affects the severity of the illness, however, have not been well studied in the field. In Ethiopia, the KS1 O-180 vaccine remains the only effective way to combat LSD. Therefore, the purpose of this study was to determine the impact of the KS1 O-180 viral strain vaccination on the transmission and severity of natural LSD infections below field circumstances. Traditional vaccinations have limitations despite being widely employed in clinical application and bovine vaccine enhancement because of their easy basis and high safety profile. For instance, inactivated vaccines need to be stored under controlled conditions, require multiple injections, and have a limited vaccination time. Moreover, live attenuated vaccines contain antigens that may persist within the host for an extended duration, potentially causing vaccinated animals to become long-term carriers of the virus. Additionally, conventional vaccinations could not offer adequate immune protection because of the virus's ongoing mutation and development. In conclusion, practicing supervision of pastures requires a thorough understanding of bovine vaccinations and adjuvants.

Mode of Action of Nanovaccines for LSD

Antibodies produced by plasma B cells in response to an antigen (foreign material) cause the generation of a specific antibody response, also known as antigenicity. Antibodies produced against both the combined antigen and the nanoparticle itself may be part of the immune response to nanovaccines. Even when generated, immunization with nanoscale gold colloidal systems, cationic dendrimers, and nanoparticles made entirely of carbon (fullerene) did not reveal any immune response specific to the nanoparticles.

Adjuvants function to improve and increase the immune system's reaction to antigens. Nanoparticles as adjuvants have been documented in numerous investigations. Nanoparticles elicited immunological responses that were either comparable to or greater than those caused by aluminum-containing adjuvants, such as alum, which are the most commonly employed in human medicine (E.J. Park et al., 2010; W. Zeng et al., 2012). Additionally, compared to an adjuvant based on alum, cobalt oxide nanoparticles promoted reduced generation of allergic antibodies and in-vivo inflammation at various injection locations (W. Zeng et al., 2012).

The immune system's cells secreting cytokines in reaction to foreign substances is known as an inflammatory response. In most cases, this sets off and attracts effector immune cells, which results in the foreign material being sanctioned. Numerous nanoparticles stimulate the immune system by producing inflammatory cytokines (A. Caputo et al., 2009). It has been shown that a variety of nanoparticles, including polymers, dendrimers, gold colloids, and others, might cause inflammatory cytokines (A. Caputo et al., 2009). A particular endocytosis route is used by cells to take up nanoparticles when they bind to their surface (J.J. Moon et al., 2011). Particle size, surface charge, surface modification, and hydrophobicity are some of the factors that can affect a nanoparticle's ability to absorb other materials (J.J. Moon et al., 2011). The way in which nanoparticles interact with cell membranes and go over physiological barriers is largely dependent on their size and distribution.

Research Work on Clinical application of Nano Technology

Treatment Protocol: During the summer of 2018, when the lumpy skin disease virus (LSDV) was spreading in Upper Egypt, a total of 35 clinically sick animals were collected from Beni-Suef Governorate, Egypt. They were split up into the two groups (Aand B) shown in Table 1. Group (A): Orally administered ALg-Propolis NPs at a dose of 300µl/animal for three consecutive days to twenty afflicted animals. Group (B): 15 diseased animals were given intramuscular injections of tetracycline (10%) at a dose of 1CC/10 kg per animal body weight over the course of three days. In certain circumstances, tetracycline ointment was used topically. (Babiuk et al., 2008): Clinical Examination of Animals: Clinical observations were made of infected cattle raised in the Bani-Suef Governorate, Egypt, between May and July 2018. These cattle suffered from depression, ocular-nasal discharges, appetence, salivation, and biphasic fever (40–41.5°C). Particularly the pre-scapular and precrural lymph nodes, there was a noticeable enlargement of the superficial lymph nodes. Getting Animal Samples Ready: From locally raised, diseased cattle raised in the Beni-Suef Governorate of Egypt, skin biopsies were taken, encompassing the epidermis, dermis, and subcutis of the nodular skin lesions. The same samples as in our earlier study by Allam et al. (2020) were utilized for separation and molecular investigations.

Toxicity and immune Response of Nano Vaccines

In addition to their amazing potential and range of uses, nanoparticles (NPs) have certain physicochemical qualities that make them unusually and unexpectedly harmful. By better understanding these traits and how they interact with cells, safer NPs can be developed. Numerous factors, including composition, size, charge, shape, hydrophobicity, and disclosure route, influence the harmful effects and immunological responses that the NPs elicit.

Therefore, it is crucial to look into the toxicity, immunological reaction, and long-term excretion of NPs before usage. Different cytotoxic features that make some NPs more toxic than others have been identified by several investigations

(Almeida JPM and Chen AL, 2011). This review [Hirsch C, Roesslein M, Krug HF 2011] addressed the current dependability of in vitro toxicity assays and suggested a number of controls to enhance experimental quality, which will eventually result in the safe and long-term usage of NPs. Numerous researchers looked into and concentrated on different facets of NPs (Fubini B and Fenoglio I, 2011). A number of other researchers have concentrated on enhancing NPs' biocompatibility and reducing their toxicity. It is advised that more research be done in order to fully comprehend the physicochemical properties and nanotoxicological standards of innovative nanomaterials, as well as their potential impact on human health.

Table 1: Research Work on Clinical application of Nano Technology (Allam et al., 2020).

Treatment	Number of Animals			Total
	Eye lesions	Skin lesion	wound lesions	
Group(A) ALg-Propolis NPs	1	16	3	20
Group(B) Tetracycline: (10%)	0	12	3	15

Conclusion

Finally, the development of vaccine tactiscs against lumpy skin disease appears to be enabled by the use of nano vaccines. Improved immunogenicity, tailored delivery, and increased efficacy are all provided by the nanotechnology-driven strategy. In addition to improving the health of our animals, adopting these creative approaches highlights the possibility of game-changing discoveries in the area of veterinary care as we traverse the complexities of livestock health.

Finally, the development of vaccine tactics against lumpy skin disease appears to be enabled by the use of nano vaccines. Improved immunogenicity, tailored delivery, and increased efficacy are all provided by the nanotechnology-driven strategy. In addition to improving the health of our animals, adopting these creative approaches highlights the possibility of game-changing discoveries in the area of veterinary care as we traverse the complexities of livestock health. As we adopt these innovative approaches, it becomes clear that nano-vaccines represent a significant advancement in veterinary medicine as well as a critical step in preserving the health of livestock. This novel strategy has the potential to completely rewrite vaccination guidelines and provide a glimmer of hope in the ongoing fight against lumpy skin disease.

REFERENCES

Abd El-Hady, F. K., and Hegazi, A. G. (2002). Egyptian propolis: Chemical composition, antiviral, and antimicrobial activities of East Nile Delta propolis. *Zeitschrift für Naturforschung C*, 57(3-4), 386–394. https://doi.org/10.1515/znc-2002-3-431

Abd El-Hady, F. K., Hegazi, A. G., and Wollenweber, E. (2007). Effect of Egyptian propolis on the susceptibility of LDL to oxidative modification and its antiviral activity with special emphasis on chemical composition. *Zeitschrift für Naturforschung C*, 62(9-10), 645–655. https://doi.org/10.1515/znc-2007-9-1004.

Abdallah, F. M., El Damaty, H. M., and Kotb, G. F. (2018). Sporadic cases of lumpy skin disease among cattle in Sharkia province, Egypt: Genetic characterization of lumpy skin disease virus isolates and pathological findings. *Veterinary World*, 11(8), 1150–1158. https://doi.org/10.14202/vetworld.2018.1150-1158.

Afsar, A., Bundza, A., Myers, D. J., Dulac, G. C., and Thomas, F. C. (1986). Sheep pox: Experimental studies with a West African isolate. *Canadian Veterinary Journal*, 27, 301–306.

Ahmad, Z., Pandey, R., Sharma, S., and Khuller, G. K. (2006). Alginate nanoparticles as antituberculosis drug carriers: Formulation development, pharmacokinetics, and therapeutic potential. *Indian Journal of Chest Diseases and Allied Sciences*, 48(3), 171–176.

Allam, A. M., Elbayoumy, M. K., Abdel-Rahman, E. H., and Hegazi, A. G., and Farag, T. K. (2020). Molecular characterization of the 2018 outbreak of lumpy skin disease in cattle in Upper Egypt. Veterinary World, 13(7), 1262–1268. https://doi.org/10.14202/vetworld.2020.1262-1268.

Al-Waili, N. (2018). Mixing two different propolis samples potentiates their antimicrobial activity and wound healing property: A novel approach in wound healing and infection. Veterinary World, 11(8), 1188–1195.

https://doi.org/10.14202/vetworld.2018.1188-1195.

Amin, A., El-Nahas, E., and El-Mashed, A. E. (2015). Pathological and virological studies on an outbreak of lumpy skin disease among cattle in Kalubia Governorate, Egypt. Journal of Advanced Veterinary Research, 5(4), 165–175.

Amoros, M., Simoes, C. M. O., Girre, L., Sauvage, F., and Cormier, M. (1992). Synergistic effect of flavones and flavonols against herpes simplex virus type 1 in cell culture. Comparison with the antiviral activity of propolis. Journal of Natural Products, 55(12), 1732–1740. https://doi.org/10.1021/np50090a003.

D.C. Ireland, D. C., and Binepal, Y. S. (1998). Improved detection of capripoxvirus in biopsy samples by PCR. Journal of Virological Methods, 74(1), 1–7. https://doi.org/10.1016/S0166-0934(98)00118-4.

Dementо, S. L., Siefert, A. L., Bandyopadhyay, A., Sharp, F. A., and Fahmy, T. M. (2011). Pathogen-associated molecular patterns on biomaterials: A paradigm for engineering new vaccines. Trends in Biotechnology, 29(6), 294–306. https://doi.org/10.1016/j.tibtech.2011.02.004.

Dementо, S. L., Cui, W., Criscione, J. M., Stern, E., Tulipan, J., Kaech, S. M., and Fahmy, T. M. (2012). Role of sustained antigen release from nanoparticle vaccines in shaping the T cell memory phenotype. Biomaterials, 33(19), 4957–4964. https://doi.org/10.1016/j.biomaterials.2012.03.041.

Forssen, E. A., Coulter, D. M., and Proffitt, R. T. (1992). Selective in vivo localization of daunorubicin small unilamellar vesicles in solid tumors. Cancer Research, 52(12), 3255–3260.

Gregoriadis, G., and Ryman, B. E. (1972). Fate of protein-containing liposomes injected into rats: An approach to the treatment of storage diseases. European Journal of Biochemistry, 24(3), 485–491. https://doi.org/10.1111/j.1432-1033.1972.tb01316.x

Gupta, T., Patil, P. K., Joshi, M. V., Prajapati, A., and Shinde, P. S. (2020). A review: Lumpy skin disease and its emergence in India. Veterinary Research Communications, 44(3), 111–118. https://doi.org/10.1007/s11259-020-09780-1.

Illum, L., and Davis, S. S. (1984). The organ uptake of intravenously administered colloidal particles can be altered using a nonionic surfactant (Poloxamer 338). FEBS Letters, 167(1), 79–82. https://doi.org/10.1016/0014-5793(84)80358-4.

Magori-Cohen, R., Louzoun, Y., Herziger, Y., Oron, E., Arazi, A., Tuppurainen, E., and Klement, E. (2012). Mathematical modeling and evaluation of the different routes of transmission of lumpy skin disease virus. Veterinary Research, 43(1), 1–10. https://doi.org/10.1186/1297-9716-43-1.

Mamo, T., and Poland, G. A. (2012). Nanovaccinology: The next generation of vaccines meets 21st-century materials science and engineering. Vaccine, 30(47), 6609–6611. https://doi.org/10.1016/j.vaccine.2012.08.060.

McCormack, B., and Gregoriadis, G. (1994). Drugs-in-cyclodextrins-in-liposomes: A novel concept in drug delivery. International Journal of Pharmaceutics, 112(3), 249–258. https://doi.org/10.1016/0378-5173(94)90258-5.

Medina, C., Santos-Martinez, M. J., Radomski, A., Corrigan, O. I., and Radomski, M. W. (2007). Nanoparticles: Pharmacological and toxicological significance. British Journal of Pharmacology, 150(5), 552–558. https://doi.org/10.1038/sj.bjp.0707137.

Moon, J. J., Suh, H., Polhemus, M. E., Ockenhouse, C. F., Yadava, A., and Irvine, D. J. (2012). Antigen-displaying lipid-enveloped PLGA nanoparticles as delivery agents for a Plasmodium vivax malaria vaccine. PLoS One, 7(2), e31472. https://doi.org/10.1371/journal.pone.0031472.

Mottram, P. L., Leong, D., Crimeen-Irwin, B., Gloster, S., Xiang, S. D., Meanger, J., and Plebanski, M. (2007). Type 1 and 2 immunity following vaccination is influenced by nanoparticle size: Formulation of a model vaccine for respiratory syncytial virus. Molecular Pharmaceutics, 4(1), 73–84. https://doi.org/10.1021/mp060096p

Rabkin, A., Samuha, S., Abutbul, R. E., Ezersky, V., Meshi, L., and Golan, Y. (2015). New nanocrystalline materials: A previously unknown simple cubic phase in the SnS binary system. Nano Letters, 15(3), 2174–2179. https://doi.org/10.1021/acs.nanolett.5b00209.

Reed, S. G., Orr, M. T., and Fox, C. B. (2013). Key roles of adjuvants in modern vaccines. Nature Medicine, 19(12), 1597–1608. https://doi.org/10.1038/nm.3409.

Senior, J., Delgado, C., Fisher, D., Tilcock, C., and Gregoriadis, G. (1991). Influence of surface hydrophilicity of liposomes on their interaction with plasma protein and clearance from the circulation: Studies with poly(ethylene glycol)-coated vesicles. Biochimica et Biophysica Acta, 1062(1), 77–82. https://doi.org/10.1016/0005-2736(91)90216-H.

Stern, S. T., and McNeil, S. E. (2008). Nanotechnology safety concerns revisited. Toxicological Sciences, 101(1), 4–21. https://doi.org/10.1093/toxsci/kfm169.

Sulczewski, F. B., Liszbinski, R. B., Romão, P. R. T., and Rodrigues Jr., L. C. (2018). Nanoparticle vaccines against viral infections. Archives of Virology, 163(9), 2313–2325. https://doi.org/10.1007/s00705-018-3856-0.

Tulman, E. R., Afonso, C. L., Lu, Z., Zsak, L., Sur, J. H., Sandy, J. R., and Rock, D. L. (2001). Genome of lumpy skin disease virus. Journal of Virology, 75(15), 7122–7130. https://doi.org/10.1128/JVI.75.15.7122-7130.2001.

Tuppurainen, E. S. M., and Oura, C. A. (2012). Lumpy skin disease: An emerging threat to Europe, the Middle East, and Asia. Transboundary and Emerging Diseases, 59(1), 40–48. https://doi.org/10.1111/j.1865-1682.2011.01242.

Tuppurainen, E. S. M., Venter, E. H., Shisler, J. L., Gari, G., and Mekonnen, G. A. (2017). Capripoxvirus diseases: Current status and opportunities for control. Transboundary and Emerging Diseases, 64(3), 729–745. https://doi.org/10.1111/tbed.12444.

Yadav, H. K., Dibi, M., Mohammad, A., and Srouji, A. E. (2018). Nano-vaccines formulation and applications: A review. Journal of Drug Delivery Science and Technology, 44, 380–387. https://doi.org/10.1016/j.jddst.2018.01.015.

Chapter 41

Effectiveness of Nanoparticles to Control Ticks and Tick-borne Diseases

Sajida Bibi[1], Sidra Abbas[1], Muhammad Arfan Zaman[2], Roquyya Gul[3], Aima Iram Batool[4], Dwight Bowman[5], Timothy Wu[5], Muhammad Zulqarnain[1], Iqra Khalil[1], Muhammad Zahid Sarfaraz[1] and Tashifa Naheed[1]

[1]Department of Zoology, University of Jhang, Jhang, Pakistan
[2]Department of Pathobiology, College of Veterinary and Animal Sciences, Jhang, sub-campus UVAS Lahore, Pakistan
[3]Institute of Life Sciences, Gulab Devi Educational Complex Lahore, Lahore, Pakistan
[4]Department of Zoology, University of Sargodha, Sargodha, Pakistan
[5]College of Veterinary Medicine, Cornell University, (14853) New York, USA
*Corresponding author: arfan.zaman@uvas.edu.pk

ABSTRACT

Nanotechnology is evolving technology with enormous potential for global revolutionization of animal sector. Ticks are parasitic insects that feed on the blood of vertebrate animals. They are external, and obligate parasites which can cause severe allergic reactions and carry a variety of viruses, bacteria, helminth and protozoans that can affect humans, pets, and livestock. Ticks are ectoparasites that cause skin irritation and injury as well as transmit infections such as tick-borne encephalitis, powassan, borreliosis, lyme, tularemia, ehrlichiosis, anaplasmosis, babesiosis, and theileriosis. The overuse of chemical acaricides (pesticides that kill ticks and mites) is often responsible for the development of fast growing drug resistance in ticks and wide presence of toxic residues in food and ultimately in the environment. Alternatively, plant based acaricides could be used in livestock farming and resistant tick strains, but there are some constraints regarding their commercialization because of quick degradation, less stabilization, and lack of standardization. The availability of vaccines to treat tick-borne diseases is still limited, and the currently available ones showed major limitations in their effectiveness. The metal (copper, zinc, silver, nickel, and gold) nanoparticles synthesized by chemical and biological methods showed broad spectrum of action against ticks parasites and vectors of veterinary importance. Chemically synthesized nanoparticles can be highly toxic to non-target animals due to the presence of hazardous chemicals and their possible side-effects. On the other hand, nanoparticles using plant extracts are easy to prepare, eco-friendly, cost-effective and promising in the control of tick. Nanoparticles effect the immune response of pests, induce oxidative stress, disrupt metabolic processes, and modify proteins or lipids that stop the reproduction and growth of ticks. However nanotechnology-based product against ticks is not available in the market till date.

KEYWORDS
Nanoparticles, Ticks, Ticks born disease, Control strategies, Photochemical

Received: 30-Jun-2024
Revised: 14-Jul-2024
Accepted: 21-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Bibi S, Abbas S, Zaman MA, Gul R, Batool AI, Bowman D, Wu T, Zulqarnain M, Khalil I, Sarfaraz MZ and Naheed T, 2024. Effectiveness of nanoparticles to control ticks and tick-borne diseases. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 356-363. https://doi.org/10.47278/book.CAM/2024.467

INTRODUCTION

Nanotechnology is the innovative approach with huge potential for to revolutimize the animal husbandry on the global scale. It offers the same benefits to veterinarians as physicians, including diagnosis and therapy. The nano-applications have the ability to use in animal nutrition, health, reproduction, and yield. It has the ability to solve associated several problems. They are external, and obligate parasites. Ticks have four life stages, egg, larva, nymph and adult. Ticks feed on the blood of vertebrate animals at each stage to survive. Ticks inject saliva into host animals during blood feeding, which contains bioactive substances which includes inflammatory, anti-hemostatic, anti- vasodilator, and immunosuppressive reagents. Mosquitoes considered first while ticks considered as the second most significant vectors of animal diseases globally. Ticks have largest effect on the cattle industry (Estrada-Pena et al., 2008; Peter et al., 2009). Hot and humid environments assist while cold environment hinder the survival of ticks. They are classified into two families,"Ixodidae" and "Argasidae". Because of their capability to spread diseases to humans and animals, ticks had long been studied for their medicinal and to discover viable treatment options. Several examinations on the threats of TBDs have basically focused on a few variables such as precipitation, temperature, and humidity of environment and hygienic condition .It has been reported that certain conditions of precipitation affecting humidity and temperature might impact

tick load in animals. Moderate rain and high humidity give conducive micro climatic conditions for mass proliferation of ticks and higher rate of infestation (Khan et al., 2016).

Effect of Ticks on Livestock

Ticks can cause severe allergic reactions and along with various viruses, bacteria, helminth and protozoa that can affect animals badly. Ticks are cause skin irritation, injury and transmit infections such as tick-borne encephalitis, powassan, borreliosis, lyme, tularemia, ehrlichiosis, anaplasmosis, babesiosis, and theileriosis. Being second to mosquitoes, ticks disseminate broader variety of pathogens as compared to any other than blood feeding, insects on a global scale, hence impacting pets, wildlife, livestock, and humans. From the centuries tick bite protection largely relies on the utilization of synthetic insecticides and bio-pesticide. Tick-Borne Diseases (TBDs) impact 80 percent of the world's cattle population, posing a serious threat to worldwide livestock production. However developing countries are suffering from this issue at higher rates because of a long list of associated risk factors of TBDs. Ticks cause enormous economic losses and have several detrimental impacts on the infected animals because anemia, reduced weight gain, and impair the quality of skin (Dantas-Torres et al., 2017). Blood sucking behaviour of ticks may cause transmission of protozoan and helminth parasites.

Control Strategies

To control the ticks, various measures have been adopted as described in fig. 1. Firstly, Chemicals were employed to control the ticks. Chemical, can be divided into groups and have played a significant role in ticks control activities. But repeated and improper exposure of chemicals to infected animals have result into developed of resistance in the tick. Further residues of the chemicals in the milk and meat can pose threats to the human health. These both have serious concerns need to be resolved alternately. Secondly,Plants have been shown to have anti-tick properties in laboratory but plant base acaricides are not available for commercial use (Theron and Magano, 2022). Thirdly, a vaccine against ticks was developed using a recombinant antigen (Willadsen, 2006). Vaccines against numerous tick species may be developed by utilizing antigens that cause immunological cross-reactions with distinct tick species. Vaccines containing a mixutre of essential and different protective antigens may significantly improve effectiveness ofvaccination or immunization (De la Fuente and Kocan, 2006). Lastly, nanobiotechnology is an emerging and unique way of controlling and combating ticks. Iron, nickel, zinc, copper, and silver are key metals nanoparticles have been proposed as anti-tick agents (Norouzi et al., 2019; Underwood and Van Eps, 2012).

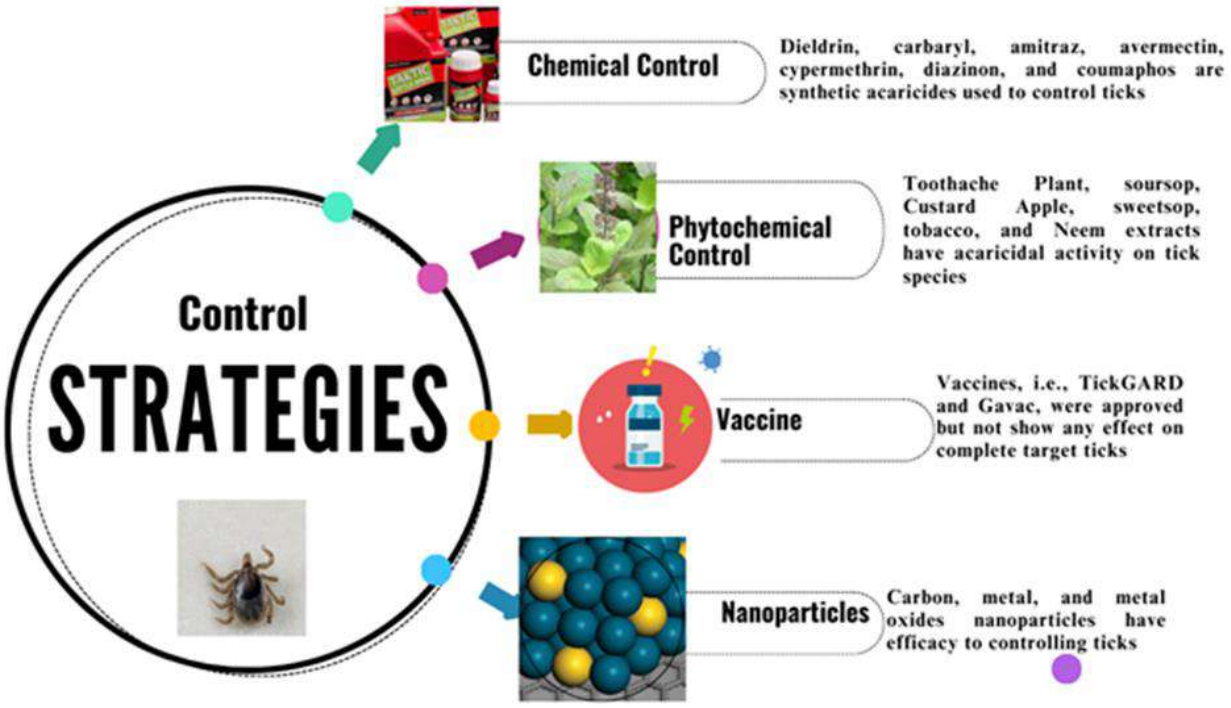


Fig. 1: Control Strategies

Chemical Control

Ticks are causing deterioration of the animal's health and reducing their productivity. Controlling ticks is highly required for the wellbeing of animals and earning the livelihood by cattle rearing communities. The chemical acaricides have been used extensively for their promising results in controlling cattle ticks. But the use of synthetic acaricides have certain side effects including poor and meat quality, and development of resistant in ticks (Reck et al., 2014).
Due to these reason several organochlorine chemicals are banned in various developed countries.

Frequently, lindane and dieldrin, carbaryl, amitraz, avermectin, cypermethrin, diazinon, and coumaphos are synthetic acaricides used to control the ticks. These effect on the nervous system of ticks and cause cell death (Chen et al., 2007; Li et al., 2003).

Dieldrin, carbaryl, amitraz, avermectin, cypermethrin,diazinon, and coumaphos are synthetic acaricides used to control the ticks.

Phytochemical Control

Many plants, mostly from the Lamiaceae family, showed acaricidal and repellent effects. Plant base acaricides could be used in organic farming and against resistant tick strains, but there are several constraints toward their commercialization related to their degradation, stabilization, and standardization.Over 200 plant species have tick-repellent and acaricidal properties. Essential oils, extracts, and allelochemicals of plants used to control the ticks. Methods like steam distillation, hydrodistillation, microwave-assisted extraction, maceration, sonication and methanolic extraction are used. Toothache Plant(*Acmella oleracea*), soursop (*Annona muricata*), Custard Apple (*Annona squamosa*), sweetsop (*Annona muricata*), Tobacco (*Nicotiana tabacum*), and Neem(*Azadirachta indica*) extracts have been tested for their acaricidal activity on various tick species and life stages. Medicinal plants demonstrated strong acaricidal effects against several tick species, but their exact mode of action is not fully understood (Quadros et al., 2020).

Vaccine

Vaccination characterizes as a nontoxic alternative method for controlling ticks. This method is environmental friendly and does not leave remains in milk and meat. Vaccine based on Bm86 have demonstrated varying levels of effectiveness in different regions worldwide. Vaccine against ticks have different antigen and pP0 antigen showed high effectiveness. Vaccines i-e TickGARD and Gavac were approved but not showed effect on complete target ticks (Freeman et al., 2010). More research is required to improve an effective vaccine against various tick strains and tick borne diseases (Pereira et al., 2022).

Nanoparticles

A nanopesticide is a product that uses nanoscale technology to enhance performance or effectiveness of pesticides.Nanotechnology is the application of materials with at least one size dimension in the range of 1-100 nm. Nanopesticides have a number of benefits in terms of pesticide use such as pesticide active ingredients to improve their effectiveness (Benelli and Duggan., 2018; Naqqash et al., 2016).NPs have been proposed as novel insecticides that have toxic effects on insect parasites and are important to world's economy(Amerasan et al., 2016; Benelli et al., 2017). Periplasmic manufacturing of metallic nanoparticles using plants and microbe-borne compounds is a cost-effective, one-step process that eliminates the need for hazardous substances (Lok et al., 2007; Kumar et al., 2015). When produced sustainably, carbon, metal, and metal oxides nanoparticles have demonstrated remarkable efficacy against economically important insect pests (Athanassiou et al., 2018). During the formation of oxides of metal and metal nanoparticles in green synthesis methods, chemicals from microbe processes or plant material could potentially work both as stabilizing and reducing agents (Benelli et al., 2017).There was a global trend to evaluate new agents that are effective, safe, inexpensive, easily available, and ecofriendly. Nanotechnology provides new and important tools expected to significant impact in sciences. The polymer-coated metal NPs have recently appeared active in advanced researches. Metal nanoparticles' stability is a major issue, but nanotechnology can enhance their formulation stability, bioavailability, solubility, slow release, and protect in against premature degradation.

Nanopesticides could have the advantage of having little effect on nontargeted organisms and being environment friendly. They can be made using a variety of processes, including chemical, biological, and green synthesis. Advantages of nanoparticle-based pesticide formulations are improved formulation consistency and improved water solubility of active ingredients. Nanoparticles have the ability to release active substances in a sustainable manner and to enhanced stability of substances to avoid early deterioration. All this occurs because of the reduced particle size. As the particle size is reduced surface area become increased hence mobility and insecticidal ability of the used substance increased that leading to greater and long lasting effect.

Nanoparticles against *Hyalomma spp*. ticks

The *Hyalomma spp* of ticks is hematophagous ectoparasite and responsible for transmission of protozoan, bacterial and viral infection in vertebrate animals and humans.*Hyalomma* genus is one of most prevalent ticks in Asia possessing high ecological plasticity.

The use of nanoparticles is considered as a novel approach for the control of ticks. However the development of a green, non-toxic, and environment friendly method for producing metal nanoparticles involves organisms from higher plants. So that metal reduce metal levels (Jayaseelan and Rahuman, 2012). SiO_2-NPs provide new acaricidal compounds for the effective control of *Hyalomma spp*. (Norouzi et al., 2022). Zinc Oxide nanoparticles (ZnO NPs) prepared from neem (*Azadirachta indica*) and lemon grass (*Cymbopogon citratus*) as effective, safer, and eco-friendly candidatures against *Hyalomma* ticks (Zaheer et al., 2021).

Nanoparticles against *Rhipicephalus Spp* Ticks

Rhipicephalus spp ticks are economically important ticks of bovines, acting as vectors for babesiosis, theileriosis, and anaplasmosis. *Rhipicephalus microplus* is the main cattle tick in the developing countries. The parasitic adaptation in *Rhipicephalus* tick vector has made successful parasites of public health importance. *Rhipicephalus* ticks are known for high genetic diversity, enabling them to thrive in different geographical regions of the world. The study investigated the acaricidal activity of titanium dioxide nanoparticles(TiO_2-NPs) synthesized from plant extract against *Rhipicephalus microplus* demonstrating their high stability (Marimuthu et al., 2013).The study found that the ZnO-NPs coated with cypermethrin led to better tick toxicity relative to the ZnS-NPs coating with cypermethrin, at the laboratory scale. There is statistically significant difference among the NPs treatments given at the egg, larval, and adult stages of the ticks (Zaheer et al.,2023). Neem (*Azadirachta indica*) in the form of green silver nanoparticles have better acaricidal activity against *Rhipicephalus* (Boophilus) *microplus* (Avinash at al., 2017).

Table 1: Metal and Metal Oxide Nanoparticles used to Control the Cattle tick *Rhipicephalus* (Boophilus) *microplus*.

Sr#	Nanoparticles	Mode of synthesis	Material used	References
1	Copper	Chemical synthesis	Copper acetate	Ramyadevi et al., (2011)
2	Nickel	Chemical synthesis	Nickel hydrazine	Rajakumar et al., 2013
3	Silver	Green synthesis	Aqueous leaf extract of *Mimosa pudica*	Marimuthu et al., 2011
		Green synthesis	stem aqueous extract of *Cissus quadrangulari*	Kumar et al., 2012
		Green synthesis	Aqueous leaf extract of *Manilkara zapota*	Rajakumar and Rahuman, 2012
4	Titanium dioxide	Green synthesis	Aqueous leaf extract of *Mangifera indica*	Rajakumar et al., 2015
		Green synthesis	Aqueous flower extract of *Calotropis gigantea*	Marimuthu et al., 2013
5	Zinc oxide (ZnO)	Green synthesis	Aqueous leaf extract of *Lobelia leschenaultiana*	Banumathi et al., 2016
		Chemical synthesis	Zinc nitrate and sodium hydroxide	Kirthi et al., 2011

Table 2: Comparative Study of traditional Chemical Synthesis and Green Synthesis of Nanopesticides

Chemical Synthesis	Green Synthesis
Chemically synthesized nanoparticles is costly and eco-unfriendly.	Green synthesis of nanoparticles is cost-effective and eco-friendly.
• Causes long-term environmental harm.	Easily decomposes and minimizing environmental harm.
The size of these nanoparticles varies between 25 and 450 nanometers.	The size of these nanoparticles varies between few nanometers up to approximately 100 nanometers.
Chemical Nanoparticles small size can lead to inhalation risks.	The primary drawback of green nanoparticle synthesis is its low yield.
	(Deepak et al., 2019)

Major Tick-Borne Diseases (TBDs) and Treatment with Naoparticles

Ticks (Acari: Ixodidae) and Tick-Borne Diseases affect the productivity of bovines in tropical and subtropical regions of the world, leading to significant socioeconomic impacts on the livelihood of farming communities.Globally, four main TBDs, namely theileriosis, anaplasmosis, babesiosis and heartwater/cowdriosis affect the bovines, and cause substantial economic losses to cattle industry(Jabbar et al.,2015). As nano-medications have developed in the last four decades, nano-delivery systems have been applied in treating various diseases. Lipid-based nanoparticles (LNPs) drug delivery system shows the most promising potential to cure diseases.Lipid-based nanoparticles have following advantages;

- High level of biocompatibility
- Less biodegradability
- Loading capability
- Immunogenicity (Lu et al., 2023).

Babesiosis

Ticks of the genera *Hyalomma*, *Rhipicephalus*, and *Amblyomma* serve as natural reservoirs for babesia (Homer et al., 2000). Tick fever (Redwater disease) is caused by *B. bigemina* and *B.bovis*, transmitted by the cattle tick *Rhipicephalus microplus* in many parts of the world. *Babesia* species possess complex life cycles that contain various stages in both the mammalian and the tick host (Elsworth and Duraisingh, 2021). More than 500 million cattle are estimated to be at danger of babesiosis globally (Ozubek et al., 2020). Main symptoms are high fever (over 40°C), hemolytic anemia, forced breathing, loss of appetite and weakness (AbouLaila et al., 2021).Human babesiosis is due to *Babesia microti* (Bloch et al., 2019).With the combination of nanotechnology and mass spectrometry, researchers have developed a method to treat acute *Babesia microti* infection. Using nanoparticle tracking analysis, show that there is a range of Extracellular vesicles (EVs) sizes from 30 to 1,000 nm, emanating from the Babesia-infected RBC. Multiple functional implications of EVs in Babesia-host interactions and support the potential that EVs have as agents in disease pathogenesis (Beri et al., 2022).

Theilerioses

Bovine theilerioses are caused by intracellular parasites of the genus *Theileria* are considered as one of the most economically important diseases of bovines globally. *Theileria annulata* and *Theileria parva* are known to be the most pathogenic species in bovines. Nanoparticles i.e Solid lipid nanoparticles (SLN) represent an attractive nanocarrier system for the hydrophobic drug Buparvaquone (BPQ). High accumulation of BPQ-SLN in the reticuloendotheileial system (RES) organs i.e liver, spleen and lungs, suggests the possibility of improved therapy in theileriosis (Soni et al., 2014).

Anaplasmosis

Anaplasmosis is a vector-borne, infectious and non-contagious disease. . Anaplasmosis has a wide range of host, including pets, livestock, humans, and it is distributed worldwide (Karlsen et al., 2020). The disease is caused by various pathogens of the genus *Anaplasma*. The infectious organism invades and destroys red blood cells, causing anaemia, weakness, and sometimes death of organism. The several species cause different types of anaplasmosis depending on which cells that are infected in the mammalian host.Oxytetracycline-loaded Poly-methyl Methacrylate (PMMA) nanoparticles were found to be an effective oral delivery vehicle and also an alternative pharmaceutical formulation in anaplasmosis treatment (SadguruPrasad et al., 2017).

Mode of Action of Nanoparticles based Pesticides on Ticks

Ticks are affected by nanoparticles based pesticides in various ways. Generally, nanoparticles stimulate the pest's immune system, cause oxidative stress, disrupt metabolisms, and change proteins or lipids that inhibit reproduction and growth of ticks as described in fig. 2.

Following nanoparticles based pesticides that are employed against ticks:

Graphene

By creating reactive oxygen species (ROS) graphene induces oxidative stress and cell death. Graphene also may cause enzyme inhibition and degradation.

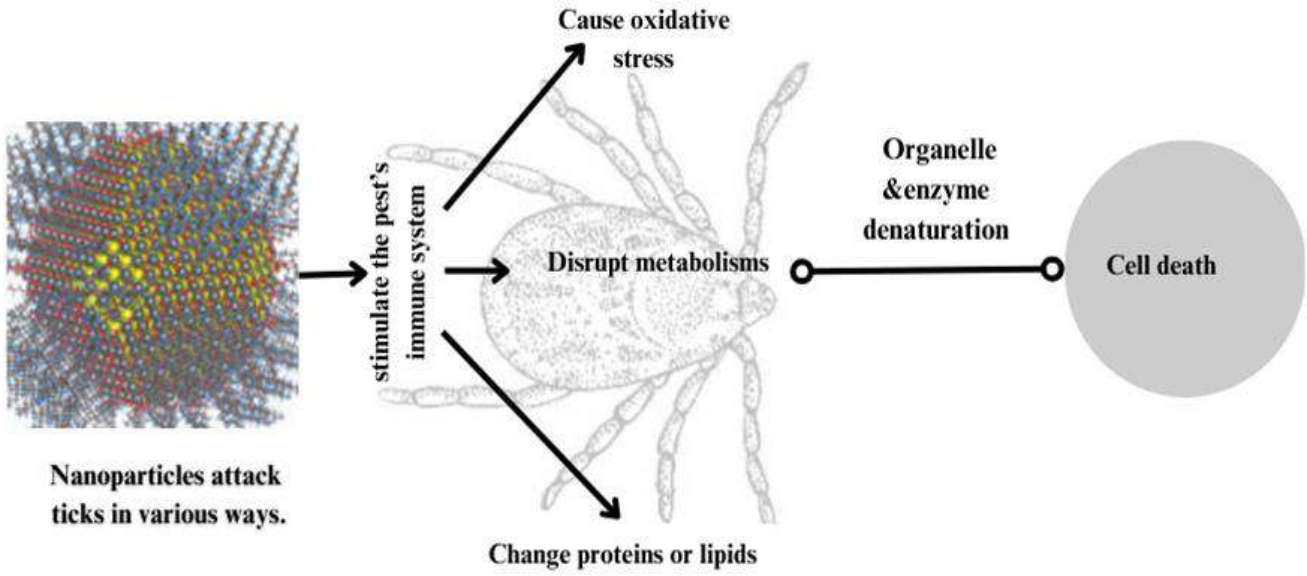


Fig. 2: Mode of Action of Nanoparticles based Pesticides on Ticks

Polystyrene

Polystyrene inhibits the cytochrome P450 isoenzyme through both noncompetitive and competitive mechanisms. Inhibition of enzyme triggers a range of additional processes, the most notable of which is oxidative stress, leading to cellular death.

Silver

Ag-NPs inhibited the activity of acetylcholinesterase. Silver nanoparticles function by binding with proteins and nucleic acids, reducing the permeability of the cell membrane. This is subsequently expanded to enzyme breakdown, which ultimately leads to cellular death. Silver nanoparticles synthesized from aqueous leaf extract of *Manilkara zapota* (Rajakumar andRahuman, 2012) and *Cissus quadrangularis* (Santhosh Kumar et al., 2012) showed the highest mortality rate of ticks.

Gold

Strong bonds are form between the gold nanoparticles and trypsin enzyme leading towards deactivation of malabsorption, poor reproduction and development of tick. Au-NPs can impact growth of ticks by inhibiting enzyme trypsin.

Silicon and Aluminum

Al and Si-NPs bind to tick's cuticle layers, causing the physical uptake of waxes and lipids leading to cell water loss and ultimately cellular death.

Titanium dioxide

Due to smaller size of nanoparticles, easily cross nuclear membrane, effect on the nucleic acids and protein synthesis. Titanium dioxide nanoparticles synthesized from plant impact exoskeleton of ectoparasites and hindering their mobility (Baun et al., 2008). TiO2-NPs synthesized from Crown Flower (*Calotropis gigantea*) showed 100 % mortality of ticks (Rajakumar et al., 2015).

Future Perspectives and Research Challenges

The potential negative effects of nanoparticles on the environment are yet unknown, and determining the dispersion and behavior of nanoparticles both during and after application towards the environment is crucial for understanding their potential influence on the ecosystems. The nanoparticles could be a promising tool against ticks and tick-borne diseases owing to the small and fine particle size causing the oxidative stress and cellular injury in non-mammalian cells only (Benelli, 2018). However as compared to widely used chemical acaricides, the process of nano-based acaricides may be more challenging (Arafa et al., 2019).The acceptability of conventional farmers, costs required to rationalize the dose and routes of administration, and labour expertise for nanomaterial synthesis and study of nano-acaricides. These are among few challenges associated with the usage of NPs to control ticks and tick-borne diseases. However, these factors may not restrict the application of nanomaterial's arised from the pre-existing chemical acaricides. Even though nanotechnology has numerous potential benefits against ticks, there is no nanotechnology-based product available in the market till date.

REFERENCES

AbouLaila, M., AbdEl-Aziz, A. R., Menshawy, S., Yokoyama, N., Igarashi, I., Al-Wabel, M., and Omar, M. (2021). Evaluation of the inhibitory effects of coumermycin A1 on the growth of Theileria and Babesia parasites in vitro and in vivo. *Pakistan Veternary Journal, 41*(4), 469-474.

Amerasan, D., Nataraj, T., Murugan, K., Panneerselvam, C., Madhiyazhagan, P., Nicoletti, M., and Benelli, G. (2016). Myco-synthesis of silver nanoparticles using Metarhizium anisopliae against the rural malaria vector *Anopheles culicifacies* Giles (Diptera: Culicidae). *Journal of Pest Science*, *89*(2), 249-256.

Arafa, W. M., Mohammed, A. N., and El-Ela, F. I. A. (2019). Acaricidal efficacy of deltamethrin-zinc oxide nanocomposite on Rhipicephalus (Boophilus) annulatus tick. *Veterinary Parasitology*, *268*, 36-45. https://doi.org/10.1016/j.vetpar.2019.03.002

Athanassiou, C. G., Kavallieratos, N. G., Benelli, G., Losic, D., Usha Rani, P., and Desneux, N. (2018). Nanoparticles for pest control: current status and future perspectives. *Journal of Pest Science*, *91*, 1-15.https://doi.org/10.1007/s10340-017-0898-0

Avinash, B., Venu, R., Raj, M. A., Rao, K. S., Srilatha, C., and Prasad, T. N. V. K. V. (2017). In vitro evaluation of acaricidal activity of novel green silver nanoparticles against deltamethrin resistance Rhipicephalus (Boophilus) microplus. *Veterinary Parasitology*, *237*, 130-136. https://doi.org/10.1016/j.vetpar.2017.02.017

Benelli, G. (2018). Mode of action of nanoparticles against insects. *Environmental Science and Pollution Research*, *25*(13), 12329-12341.

Benelli, G., and Duggan, M. F. (2018). Management of arthropod vector data–Social and ecological dynamics facing the One Health perspective. *Acta Tropica*, *182*, 80-91. https://doi.org/10.1016/j.actatropica.2018.02.015

Benelli, G., Pavela, R., Maggi, F., Petrelli, R., and Nicoletti, M. (2017). Commentary: making green pesticides greener? The potential of plant products for nanosynthesis and pest control. *Journal of Cluster Science*, *28*, 3-10. https://doi.org/10.1007/s10876-016-1131-7

Beri, D., Rodriguez, M., Singh, M., Liu, Y., Rasquinha, G., An, X., and Lobo, C. A. (2022). Identification and characterization of extracellular vesicles from red cells infected with Babesia divergens and Babesia microti. *Frontiers in Cellular and Infection Microbiology*, *12*, 962-944. https://doi.org/10.3389/fcimb.2022.962944

Bloch, E. M., Kumar, S., and Krause, P. J. (2019). Persistence of Babesia microti infection in humans. Pathogens, 8(3), 102.

Chen, A. C., He, H., and Davey, R. B. (2007). Mutations in a putative octopamine receptor gene in amitraz-resistant cattle ticks. *Veterinary Parasitology*, 148(3-4), 379-383.

Dantas-Torres, F., Alves, L. C., and Uilenberg, G. (2017). Babesiosis. *Arthropod borne diseases*, 347-354. https://doi.org/10.1007/978-3-319-13884-8-21

Deepak, P., Amutha, V., Kamaraj, C., Balasubramani, G., Aiswarya, D., and Perumal, P. (2019). Chemical and green synthesis

of nanoparticles and their efficacy on cancer cells. In *Green synthesis, characterization and applications of nanoparticles* (pp. 369-387). Elsevier.

De la Fuente, J., and Kocan, K. (2006). Strategies for development of vaccines for control of ixodid tick species. *Parasite Immunology*, *28*(7), 275-283.

Elsworth, B., and Duraisingh, M. T. (2021). A framework for signaling throughout the life cycle of Babesia species. *Molecular Microbiology, 115*(5), 882-890.

Estrada-Pena, A., Venzal, J. M., Kocan, K. M., and Sonenshine, D. E. (2008). Overview: ticks as vectors of pathogens that cause disease in humans and animals. *Frontiers in Bioscience*, *13*(18),6938-46.

Freeman, J. M., Davey, R. B., Kappmeyer, L. S., Kammlah, D. M., and Olafson, P. U. (2010). Bm86 midgut protein sequence variation in South Texas cattle fever ticks. *Parasites and Vectors, 3*, 1-8. https://doi.org/10.1186/1756-3305-3-101

Homer, M.J.J., Aguilar-Delfin, I., Telford, S.R.R., Krause, P.J.J., Persing, D.H.H., and Telford Iii, S.R. (2000). Babesiosis. *Clinical Microbiology Reviews, 13*(3), 451-469.

Jabbar, A., Abbas, T., Sandhu, Z. U. D., Saddiqi, H. A., Qamar, M. F., and Gasser, R. B. (2015). Tick-borne diseases of bovines in Pakistan: major scope for future research and improved control. *Parasites and Vectors*, *8*, 1-13. https://doi.org/10.1186/s13071-015-0894-2

Jayaseelan, C., and Rahuman, A. A. (2012). Acaricidal efficacy of synthesized silver nanoparticles using aqueous leaf extract of Ocimum canum against Hyalomma anatolicum anatolicum and Hyalomma marginatum isaaci (Acari: Ixodidae). *Parasitology Research*, *111*, 1369-1378. https://doi.org/10.1007/s00436-011-2559-1

Karlsen, A., Vojtek, B., Mojzisova, J., Prokes, M., and Drazovska, M. (2020). Anaplasmosis in animals. *Folia Veterinaria*, *64*(4), 17-26

Khan, A., Rehman, A. U., Hisham, M., Khan, A. Z., Rehman, H. U., Khan, M. I., and Fahim, M. (2016). Burden of babesiosis among domestic cattle of southern Khyber Pakhtunkhwa, Pakistan. *Journal of Entomology and Zoology Studies, 4*(5): 305-307

Kumar, S., Lather, V., and Pandita, D. (2015). Green synthesis of therapeutic nanoparticles: an expanding horizon. *Nanomedicine*, *10*(15), 2451-2471.

Kirthi, A. V., Rahuman, A. A., Rajakumar, G., Marimuthu, S., Santhoshkumar, T., Jayaseelan, C., and Velayutham, K. (2011). Acaricidal, pediculocidal and larvicidal activity of synthesized ZnO nanoparticles using wet chemical route against blood feeding parasites. *Parasitology Research*, *109*, 461-472. https://doi.org/10.1007/s00436-011-2277-8

Li, A. Y., Davey, R. B., Miller, R. J., and George, J. E. (2003). Resistance to coumaphos and diazinon in Boophilus microplus (Acari: Ixodidae) and evidence for the involvement of an oxidative detoxification mechanism. *Journal of Medical Entomology, 40*(4), 482-490.

Lok, C. N., Ho, C. M., Chen, R., He, Q. Y., Yu, W. Y., Sun, H., and Che, C. M. (2007). Silver nanoparticles: partial oxidation and antibacterial activities. *JBIC Journal of Biological Inorganic Chemistry*, *12*, 527-534. https://doi.org/10.1007/s00775-007-0208-z

Lu, Y., Pan, X., Nie, Q., Zhou, Z., Dai, X., and Liu, O. (2023). Administration methods of lipid-based nanoparticle delivery systems for cancer treatment. *Biomaterials Science*, *11*(11), 3800-3812.

Marimuthu, S., Rahuman, A. A., Rajakumar, G., Santhoshkumar, T., Kirthi, A. V., Jayaseelan, C., and Kamaraj, C. (2011). Evaluation of green synthesized silver nanoparticles against parasites. *Parasitology Research*, 108, 1541-1549.

Naqqash, M. N., Gokce, A., Bakhsh, A., and Salim, M. (2016). Insecticide resistance and its molecular basis in urban insect pests. *Parasitology Research*, *115*, 1363-1373. https://doi.org/10.1007/s00436-015-4898-9

Norouzi, R., Ataei, A., Hejazy, M., and Shahbazi, P. (2019). Acaricidal activity of zinc oxide nanoparticles against Hyalomma spp. *in vitro*. *Nanomedicine Research Journal*, *4*(4), 234-238.

Norouzi, R., Irani, S., Katiraee, F., and Hejazy, M. (2022). In vitro acaricidal activity of nano-SiO2 against Hyalomma spp. ticks and its toxicity. *Nanomedicine Research Journal*, *7*(1), 93-98.

Ozubek, S., Bastos, R. G., Alzan, H. F., Inci, A., Aktas, M., and Suarez, C. E. (2020). Bovine babesiosis in Turkey: Impact, current gaps, and opportunities for intervention. *Pathogens*, *9*(12), 1041.

Pereira, D. F. S., Ribeiro, H. S., Gonçalves, A. A. M., da Silva, A. V., Lair, D. F., de Oliveira, D. S., and Giunchetti, R. C. (2022). *Rhipicephalus microplus*: An overview of vaccine antigens against the cattle tick. *Ticks and Tick-borne Diseases*, *13*(1), 101828.

Peter, R. J., Van den Bossche, P., Penzhorn, B. L., and Sharp, B. (2009). Tick, fly, and mosquito control--lessons from the past, solutions for the future. *Journal of the South African Veterinary Association-Tydskrif Van Die Suid-Afrikaanse Veterinere Vereniging*, 80, 121-121.

Quadros, D. G., Johnson, T. L., Whitney, T. R., Oliver, J. D., and Oliva Chavez, A. S. (2020). Plant-derived natural compounds for tick pest control in livestock and wildlife: Pragmatism or Utopia. *Insects*, *11*(8), 490.

Rajakumar, G., and Rahuman, A. A. (2012). Acaricidal activity of aqueous extract and synthesized silver nanoparticles from *Manilkara zapota* against *Rhipicephalus* (Boophilus) *microplus. Research in Veterinary Science*, *93*(1), 303-309.

Rajakumar, G., Rahuman, A. A., Roopan, S. M., Chung, I. M., Anbarasan, K., and Karthikeyan, V. (2015). Efficacy of larvicidal activity of green synthesized titanium dioxide nanoparticles using *Mangifera indica* extract against blood-feeding parasites. *Parasitology Research*, *114,* 571-581. https://doi.org/10.1007/s00436-014-4219-8

Rajakumar, G., Rahuman, A. A., Velayutham, K., Ramyadevi, J., Jeyasubramanian, K., Marikani, A., and Siva, C. (2013). Novel

and simple approach using synthesized nickel nanoparticles to control blood-sucking parasites. *Veterinary Parasitology*, *191(*3-4), 332-339.

Ramyadevi, J., Jeyasubramanian, K., Marikani, A., Rajakumar, G., Rahuman, A. A., Santhoshkumar, T., and Marimuthu, S. (2011). Copper nanoparticles synthesized by polyol process used to control hematophagous parasites. *Parasitology Research*, *109*, 1403-1415. https://doi.org/10.1007/s00436-011-2387-3

Reck, J., Klafke, G. M., Webster, A., Dall'Agnol, B., Scheffer, R., Souza, U. A., and de Souza Martins, J. R. (2014). First report of fluazuron resistance in *Rhipicephalus microplus*: A field tick population resistant to six classes of acaricides. *Veterinary Parasitology*, *201*(1-2), 128-136.

SadguruPrasad, L. T., Madhusudhan, B., Kodihalli B, P., and Ghosh, P. C. (2017). Development and *in vitro* evaluation of oxytetracycline-loaded PMMA nanoparticles for oral delivery against anaplasmosis. *IET Nanobiotechnology*, *11*(1), 119-126.

Santhoshkumar, T., Rahuman, A. A., and Bagavan, A. (2012). Marimuth u S, Jayaseelan C, Kirthi AV, et al. Evaluation of stem aqueous extract and synthesized silver nanoparticles using *Cissus quadrangularis* against *Hippobosca maculat* a and Rhipicephalus (Boophilus) Microplus. *Experimental Parasitology*, *132*(2), 156-65.

Santhoshkumar, T., Rahuman, A. A., and Bagavan, A. (2012). Marimuth u S, Jayaseelan C, Kirthi AV, et al. Evaluation of stem aqueous extract and synthesized silver nanoparticle s using Cissus quadrangularis against Hippobosca maculat a and Rhipicephalus (Boophilus) microplus. *Experimental Parasitology*, *132*(2), 156-65.

Soni, M. P., Shelkar, N., Gaikwad, R. V., Vanage, G. R., Samad, A., and Devarajan, P. V. (2014). Buparvaquone loaded solid lipid nanoparticles for targeted delivery in theleriosis. *Journal of Pharmacy and Bioallied Sciences*, *6*(1), 22.

Theron, E. M. C., and Magano, S. R. (2022). A reflection on tick control and the potential role of botanical products in integrated management practices. *South African Journal of Plant and Soil*, *39*(3), 213-225.

Underwood, C., and Van Eps, A. W. (2012). Nanomedicine and veterinary science: The reality and the practicality. *The Veterinary Journal*, *193*(1), 12-23.

Yessinou, R. E., Akpo, Y., Adoligbe, C., Adinci, J., Assogba, M. N., Koutinhouin, B., and Farougou, S. (2016). Resistance of tick *Rhipicephalus microplus* to acaricides and control strategies. *Journal of Entomology and Zoology Studies*, *4*(6), 408-414.

Zaheer, T., Abbas, R. Z., Perveen, N., Sparagano, O. A., Khan, S. R., Rehman, T. U., and Arshad, M. I. (2023). Application of cypermethrin-coated ZnS and ZnO nanoparticles against rhipicephalus ticks. *Pathogens*, *12*(6), 807.

Zaheer, T., Imran, M., Pal, K., Sajid, M. S., Abbas, R. Z., Aqib, A. I., and ur Rahman, S. (2021). Synthesis, characterization and acaricidal activity of green-mediated ZnO nanoparticles against Hyalomma ticks. *Journal of Molecular Structure*, *1227*, 129652. https://doi.org/10.1016/j.molstruc.2020.129652

Chapter 42

Mathematical Pharmacokinetics and Drug Delivery

Muhammad Saleem[1*], Rabia Munir[2], Tooba Aslam[3], Sidra Altaf[4] and Amna Aziz[5]

[1]Institute of Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan
[2]Department of Mathematics and Statistics, University of Agriculture, Faisalabad, Pakistan
[3]Department of Mathematics and Statistics, University of Agriculture, Faisalabad, Pakistan
[4]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
[5]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: siyalfaizsaleem381@gmail.com

ABSTRACT

Mathematical pharmacokinetics plays a crucial role in understanding the absorption, distribution, metabolism, and excretion (ADME) of medications within biological systems, which is essential for optimizing drug delivery and therapeutic effectiveness. This abstract discusses key concepts and advancements in mathematical modeling applied to pharmacokinetics and drug delivery systems. The field of pharmacokinetics utilizes various mathematical models, ranging from simple compartmental models to complex physiologically-based models, to describe the concentration of drugs over time in different tissues and fluids. These models enable predictions of drug behavior under different dosing regimens and patient conditions, aiding in drug development and clinical practice. Strategies such as controlled release systems, targeted drug delivery, and nanotechnology have expanded the options for drug delivery techniques. Mathematical models support these advancements by elucidating how drugs are released from formulations, optimizing drug distribution to specific sites, and predicting therapeutic effects. These models include zero-order, first-order kinetics, and advanced models that consider factors such as tissue perfusion and cellular uptake kinetics. Future directions may involve integrating pharmacokinetics with systems biology and genomics to personalize treatment approaches. Computational techniques like machine learning and quantitative systems pharmacology are expected to improve model predictive power and accuracy, supporting individualized therapeutic strategies and speeding up drug development timelines. Regulatory frameworks ensure the reliability and safety of pharmacokinetic models in the drug approval process, aligning international standards for clinical use. As pharmacokinetics continues to evolve, its interdisciplinary nature and computational advancements are poised to revolutionize drug delivery and personalized medicine, enhancing patient care through precise and effective therapeutic interventions.

KEYWORDS
Pharmacokinetics; Drug delivery; Mathematical modeling; Controlled release; Targeted drug delivery; Systems biology; Computational pharmacology

Received: 13-Jun-2024
Revised: 04-Jul-2024
Accepted: 11-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Saleem M, Munir R, Aslam T, Altaf S and Aziz A, 2024. Mathematical pharmacokinetics and drug delivery. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 364-373. https://doi.org/10.47278/book.CAM/2024.468

INTRODUCTION

Overview of Pharmacokinetics (PK) and Pharmacodynamics (PD)

Pharmacokinetics (PK) refers to the study of how a drug moves through the body over time. It encompasses four main processes; Absorption is the process by which a drug enters the bloodstream. Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body. Metabolism is the body's process of transforming the drug, usually through enzymatic activity, into metabolites. Excretion: is the removal of substances from the body, primarily through the kidneys (urine) or the liver (bile) (Coelho et al., 2021). Understanding these processes is crucial for determining the appropriate dosage, frequency, and duration of treatment with a specific drug. On the other hand, Pharmacodynamics (PD) deals with the biochemical and physiological effects of drugs on the body and the mechanisms of their actions. It includes the study of drug-receptor interactions, or how drugs interact with cell receptors to produce their effects. Dose-reaction relationship is the relationship between the drug dose and the significance of its impact (Campbell et al., 2024).

The discipline of pharmacokinetics has developed considerably over time. Early twentieth Century is the concept of drug absorption, distribution, metabolism, and excretion (ADME) commenced to take form, prompted via the paintings of scientists like (Torald Sollmann and John J. Abel. 1950s). The period "pharmacokinetics" become coined, and mathematical fashions commenced to be advanced to explain the ADME tactics. The advent of compartmental fashions, which simplified the illustration of drug distribution within the body. Advances in technology and analytical methods

allowed for more precise measurement of drug concentrations in organic fluids. The improvement of non-compartmental evaluation methods and the software of computer software program for PK evaluation. Integration of pharmacokinetics with pharmacodynamics (PK-PD modeling) became extra commonplace, assisting within the optimization of healing regimens. Continued improvements in computational electricity and biotechnology have caused more sophisticated models, along with physiologically-based pharmacokinetic (PBPK) fashions and populace pharmacokinetics, which account for variability amongst people. Pharmacokinetics and pharmacodynamics are fundamental components of drug development and regulatory strategies, ensuring the protection and efficacy of medications (Zhang and Zhao, 2021).

The Role of Mathematical Modeling in Pharmacokinetics and Importance of Mathematical Modeling

Mathematical modeling plays a crucial role in pharmacokinetics by offering a quantitative framework to describe and predict the temporal changes in drug concentrations within the body. Precision and Accuracy are the models that aid in accurately forecasting drug concentrations at various time intervals, improving the accuracy of dosing regimens. Understanding Drug behavior mathematical models elucidate intricate processes involved in drug absorption, distribution, metabolism, and excretion, enabling a deeper comprehension of drug behavior in the body. Optimization of drug therapy by predicting drug concentrations and outcomes, models assist in optimizing therapeutic regimens for man or woman sufferers, maximizing efficacy while minimizing adverse effects. Risk assessment models can simulate exclusive scenarios, supporting in assessing potential dangers and protection concerns associated with drug remedy (Cottura et al., 2020). Cost and time efficiency in drug improvement, modeling reduces the want for great and expensive clinical trials using offering preliminary insights into drug conduct and capacity effects. Applications in drug development and therapeutic drug monitoring, drug development, Preclinical study models are utilized to forecast human pharmacokinetics, primarily relying on animal data to assist in dose selection for initial medical trials. During clinical trials, modeling plays a key role in devising optimal dosing strategies, understanding variability among participants, and interpreting trial data. Regulatory agencies mandate pharmacokinetic information for new drug submissions, and modeling provides a robust means of demonstrating drug behavior and safety. Models also aid in the development of specific drug formulations (e.g., tablets, injections) by predicting their pharmacokinetic profiles (Perry et al., 2020). Therapeutic Drug Monitoring and Individualized Therapy are important components of medication management for drugs with narrow therapeutic windows, such as antiepileptics and immunosuppressants. Individualized dosing models take into account patient-specific factors like age, weight, and organ function to tailor dosages accordingly. These models help clinicians to adjust dosages based on changes in patient conditions, such as renal impairment or drug. By simulating different dosing regimens, these models can predict outcomes and assist clinicians in selecting the most effective and safe treatment plan. Reducing adverse effects is a key focus for models who anticipate potential toxicities based on drug awareness profiles while considering adjustments to prevent unfavorable outcomes. Mathematical modeling plays a crucial role in pharmacokinetics, providing valuable insights and resources for drug development and personalized medicine. Its applications range from preclinical research to clinical practice, ensuring that medications are safe, effective, and customized to individual patient needs (Darwich et al., 2021) .

Fundamental Concepts in Pharmacokinetics

Absorption and Mechanisms of Drug Absorption

Drug absorption is the process through which a medication enters the bloodstream from its site of administration. Several mechanisms facilitate this process; Passive Diffusion is the most common mechanism, where medications move from an area of higher concentration to an area of lower concentration across cell membranes. Facilitated Diffusion is Similar to passive diffusion, but involves carrier proteins that assist in transporting the medication across the membrane without requiring energy. Active Transport Requires carrier proteins and energy (in the form of ATP) to move medications against their concentration gradient. Endocytosis and Exocytosis are Processes by which cells engulf drug particles (endocytosis) or expel them (exocytosis), commonly used for larger molecules or particles. These mechanisms all play a role in how drugs are absorbed into the body. Paracellular Transport involves the movement of drugs through the gaps between cells, facilitated by tight junctions and intercellular spaces (Foroozandeh et al., 2021). Several factors can impact the rate and extent of drug absorption. Physicochemical properties of the drug include the drug's molecular size, lipophilicity, ionization state, and solubility. Formulation Factors is the drug's dosage form (such as tablets, pills, or liquids) and the presence of excipients that can influence dissolution and absorption such as pH levels, gastric emptying time, intestinal motility, and the presence of food or other substances can also impact drug absorption. Larger Surface Areas (e.g., small intestine) can Promote Greater Absorption. Transporter Proteins, such as P-glycoprotein, can Efflux Drugs from Cells, impacting their Absorption (Alagga et al., 2024). Mathematical Models of Absorption Kinetics aid in Describing and Predicting Drug Absorption Rates. Common models include Describing a constant Drug Absorption Rate, regardless of Concentration. Often observed with Controlled-Release Formulations. The equation DAdt=k0fracdAdt = k_0dtdA=k0 represents zero-order rate constant and AAA represents the amount of drug absorbed. First-order kinetics describes absorption rate proportional to drug concentration, with most pills following this pattern. The equation DAdt=ka·CfracdAdt = k_a cdot CdtdA=ka·C represents the first-order absorption rate constant (ka) and drug concentration (C). Michaelis-Menten Kinetics is used for drugs that show saturable absorption, such as nutrients and certain antibiotics, where absorption becomes saturated at higher concentrations. The equation DAdt=Vmax·CKm CfracdAdt = fracV_max cdot CK_m CdtdA=Km CVmax·C represents the maximum absorption

rate (Vmax) and the Michaelis constant (Km). Compartmental Models involve drugs moving through compartments (e.g., gastrointestinal tract, bloodstream) with varying rates of absorption, distribution, and elimination (Damodharan, 2020).

Drug distribution is the process by which a drug is transferred from one location to another within the body. Once a drug enters the bloodstream, it is transported to various tissues and organs. Factors such as blood flow and tissue characteristics influence the distribution of drugs. For example, tissues with high blood flow, like the liver, kidneys, and brain, receive drugs more quickly than tissues with lower blood flow, such as muscle and fat. The volume of distribution (Vd) is a theoretical parameter that measures the extent of drug distribution in the body relative to the plasma concentration. It is calculated as Vd=AC0, where A is the total amount of drug in the body and C0 is the plasma concentration at time 0 after rapid intravenous administration. Compartmental models serve as mathematical representations to simplify the complex process of drug distribution and elimination within the body. These models assume that the body can be represented by one or more compartments in which the drug concentration is evenly distributed. This model posits that the entire body functions as a single, uniform compartment. The drug quickly reaches equilibrium throughout the body shortly after administration. This model is particularly useful for drugs that are distributed rapidly and consistently. The concentration-time profile for a one-compartment model following intravenous administration is expressed as C(t) = C0 * e^(-kt), where C(t) represents the drug concentration at time t, C0 is the initial concentration, and k is the elimination rate constant (Liu and Kang, 2024).

Metabolism and Drug Metabolism Pathways

Drug metabolism refers to the process in which pharmaceutical substances are chemically modified within living organisms, often through specialized enzymatic processes. The main objective of drug metabolism is to convert drug molecules that are fat-soluble into metabolites that are more water-soluble, making them easier to eliminate from the body. This process commonly occurs in the context of Hepatic Clearance and Liver Models. Hepatic clearance (CLhep) is defined as the rate at which the liver removes a drug from the blood per unit of time. It is influenced by three key factors: Blood Flow to the Liver (Q), Intrinsic Clearance (CL_int), and Fraction Unbound (f_u). The calculation of hepatic clearance can be determined using the well-stirred model (venous equilibrium model), which shows that hepatic clearance depends on both the liver's ability to metabolize the drug and the rate at which the drug enters the liver (Ward et al., 2022).

Renal and Non-renal Excretion Processes

Renal excretion is the primary route of elimination for many medications and their metabolites. It involves three main processes. Unbound medications are filtered from the bloodstream into the urine through the glomeruli in the kidneys. The rate of filtration depends on factors such as the drug's size, charge, and binding to plasma proteins. Active transport systems in the proximal tubules move drugs from the blood into the urine. This process is selective and can be saturated, involving transporters like organic anion transporters (OATs) and organic cation transporters (OCTs). Some drugs may be reabsorbed from the renal tubules back into the bloodstream, particularly if they are lipophilic. This reabsorption process is influenced by the drug's pH and the urine's pH. Clearance Concepts and Models: Clearance (CL) is a measure of the efficiency of the body in eliminating a drug, calculated as the amount of plasma cleared of the drug per unit time. It can be represented as CL=rate of elimination/plasma drug concentration. Total body clearance (CLtotal) is the sum of all individual clearance mechanisms, including renal clearance and non-renal clearance (e.g., hepatic clearance) (Bueters et al., 2020).

Mathematical Modeling Techniques in Pharmacokinetics

Deterministic Models and Ordinary Differential Equations in PK

Differential equations play a crucial role in pharmacokinetics by modeling the dynamics of drug concentration over time. These equations illustrate how drug levels in the body change as a result of processes such as absorption, distribution, metabolism, and elimination. In pharmacokinetic models, differential equations help to simulate the movement of drugs within different compartments and their elimination from the body. In zero-order kinetics, the rate of drug concentration remains constant regardless of the drug concentration level, which is common for drugs with saturation in the elimination process. The equation for zero-order kinetics is represented as dC/dt = -k0, where C is the drug concentration and k0 is the zero-order rate constant (Liu and Yang, 2021).

Stochastic Models and Introduction to Stochastic Processes in PK

Stochastic models integrate random variability into pharmacokinetic (PK) modeling to accommodate the inherent unpredictability in biological systems and drug response. Unlike deterministic models, which provide fixed outputs for specific inputs, stochastic models acknowledge that drug behavior can fluctuate due to various factors such as genetic differences, environmental factors, and measurement errors. Stochastic processes in PK involve the utilization of probability distributions and random variables to depict drug concentration and response over time (Liu and Shan, 2022).

Applications and Limitations

Personalized therapy stochastic models can help to predict the variability of drug responses in individual patients, leading to more tailored dosing regimens. These models assist in analyzing data from various populations, identifying sources of variability, and aiding in the design of more efficient clinical trials. Risk Assessment by taking into account the

variability, stochastic models can assess the likelihood of adverse drug reactions and treatment failures. Regulatory Decisions Quantify uncertainty in drug behavior and response to provide a solid basis for regulatory decision-making (Guidi et al., 2022).

Limitations

Sophisticated Stochastic models are mathematically and computationally intricate, necessitating specialized software and expertise. They require extensive datasets for accurate estimation of probability distributions and model parameters. Interpretation of results may be challenging and may not be easily understood by non-experts, such as clinicians and patients. The computational cost of running stochastic simulations can be significant, as it is time-consuming and resource-intensive, particularly for complex models (Silva et al., 2021).

Physiologically based Pharmacokinetic Models

Physiologically based pharmacokinetic (PBPK) models are advanced modeling techniques that simulate the absorption, distribution, metabolism, and excretion (ADME) of drugs based on physiological and anatomical characteristics. Unlike traditional compartmental models, PBPK models incorporate detailed information about organ sizes, blood flow rates, tissue composition, and enzyme activities to provide a mechanistic understanding of drug kinetics. The Structure and Components of PBPK Models involve dividing the body into multiple compartments, each representing a specific organ or tissue. These compartments are interconnected by blood flow, mimicking the movement of drugs between organs. Representing locations in the gastrointestinal tract or other sites where the drug enters the bloodstream. Consists of the blood and highly perfused organs like the heart and liver. Representing tissues with lower perfusion such as muscle and fat. Such as the liver and kidneys, where metabolism and excretion take place. Organ weights, blood flow rates, tissue composition (e.g., fat, water content), and partition coefficients. Physicochemical properties (e.g., solubility, lipophilicity), binding affinities, and enzyme kinetics. Differential equations that describe drug transport and transformation within and between compartments (Chou and Lin, 2023). Table 1 shows different aspects of mathematical pharmacokinetics and drug delivery and highlighting their significance.

Table 1: Different aspects of mathematical pharmacokinetics and drug delivery, highlighting their significance

Sr. No	Definition	Description	Importance	Methods/Models	Applications	Challenges	Future Directions	References
1	Pharmacokinetics	Study of drug absorption, distribution, metabolism, and excretion (ADME) in the body.	Essential for understanding drug behavior and optimizing dosing regimens.	Compartmental models, physiologically-based PK (PBPK) models, non-linear PK models	Drug development, dosage optimization, therapeutic drug monitoring	Variability in individual responses, complexity of biological systems	Integration with omics data, personalized medicine approaches	(McGinnity and Grime, 2023)
2	Drug Delivery	Techniques and systems for delivering drugs to target sites in the body.	Enhances drug efficacy, reduces side effects.	Controlled release systems, targeted drug delivery systems, nanotechnology	Cancer treatment, chronic disease management, local anesthesia	Achieving precise targeting, maintaining drug stability and bioavailability	Advancements in nanotechnology, novel delivery systems	(Jain, 2020)
3	Mathematical Modeling	Use of mathematical equations to describe drug absorption, distribution, metabolism, and excretion processes.	Provides quantitative insights into drug kinetics and dynamics.	Zero-order, first-order kinetics, compartmental modeling, PBPK modeling	Predicting drug behavior, optimizing dosing regimens, simulating clinical scenarios	Validation and reliability of models, computational complexity	Machine learning, AI applications, enhanced model predictability	(Peters, 2021)
4	Controlled Release Systems	Methods to release drugs at a predetermined rate over time.	Improves patient compliance, reduces dosing frequency.	Diffusion-controlled systems, osmotic pumps, polymer-based matrices, magnetic systems	Extended-release formulations, oral contraceptives, pain management	Achieving consistent release profiles, balancing burst release and sustained release	Advanced modeling of complex release kinetics, personalized dosing schedules	(Vrettos et al., 2021)

5	Targeted Drug Delivery	Delivery systems designed to deliver drugs specifically to target tissues or cells.	Enhances therapeutic efficacy, minimizes systemic toxicity.	Active targeting (ligand-based), passive targeting (EPR effect), nanocarriers	Cancer therapies, inflammatory diseases, gene therapy	Overcoming biological barriers, optimizing ligand-receptor interactions	Development of novel targeting ligands, integration with personalized medicine	(Doshi, 2022)
6	Systems Biology	Study of biological systems and their interactions using computational and mathematical approaches.	Provides holistic understanding of drug interactions within biological networks.	Network pharmacology, integration of omics data (genomics, proteomics, metabolomics)	Predicting drug responses, identifying biomarkers for drug efficacy and toxicity	Complexity of biological systems, data integration challenges	Personalized medicine approaches, precision therapeutics based on biological profiles	(Tolani et al., 2021)
7	Computational Pharmacology	Application of computational techniques to study drug actions and interactions within biological systems.	Accelerates drug discovery and development processes.	Machine learning, quantitative systems pharmacology (QSP), agent-based modeling	Predicting drug-drug interactions, optimizing drug combinations, virtual screening	Integration of multi-scale data, validation of predictive models	High-performance computing, virtual clinical trials, real-time pharmacokinetic modeling	(Aghamiri et al., 2022)

Parameter Estimation in Pharmacokinetics

Methods for Parameter Estimation

Accurate estimation of pharmacokinetic (PK) parameters is essential for understanding drug behavior and optimizing dosing regimens. Various techniques, such as Nonlinear Regression Analysis and Maximum Likelihood Estimation, are commonly employed for this purpose. Nonlinear regression analysis involves fitting a nonlinear model to PK data by adjusting model parameters to minimize the difference between observed and expected values. This method is widely utilized for its versatility and ability to accommodate various PK models (Jovanović et al., 2020). Maximum Likelihood Estimation (MLE) is a statistical approach that estimates parameters by maximizing the likelihood function, which indicates the likelihood of observing the given data with specific parameter values. The objective is to determine parameter values that maximize the likelihood of the observed data. The process involves defining the likelihood function based on the PK model and collected data. Utilize optimization algorithms to determine optimal parameter values that enhance the likelihood characteristic. Assess the model fit and parameter accuracy. Advantages of this approach include providing a robust statistical framework and the ability to handle various types of data distributions and censoring. Disadvantages include the need for complex mathematical and computational techniques, as well as sensitivity to model specification and initial parameter values (Goutelle et al., 2022). Bayesian techniques involve incorporating prior knowledge and observed data to estimate PK parameters. This method combines prior distributions (reflecting existing beliefs about parameters) with probability functions (derived from observed data) to generate posterior distributions of parameters (Brocks and Hamdy, 2020).

Software Tools for PK Modeling

Various software tools are commonly utilized for pharmacokinetic modeling and parameter estimation. These tools provide efficient functionality for data analysis, model fitting, and simulation. One such tool is NONMEM (Nonlinear Mixed-Effects Modeling), which is widely utilized for population pharmacokinetic/pharmacodynamic modeling. NONMEM is capable of handling mixed-effects models, allowing for the analysis of data from multiple subjects with inter-individual variability. Key features of NONMEM include support for a variety of pharmacokinetic/pharmacodynamic models, advanced statistical methods for parameter estimation, extensive diagnostic tools, and graphical capabilities. This software is commonly used in drug development, clinical trials, and regulatory submissions (Ayral et al., 2021).

Drug Delivery Systems and Strategies

Controlled Release Systems and Types of Controlled Release Systems

Controlled release systems are engineered to deliver capsules at a pre-set rate over an extended period, offering advantages such as decreased dosing frequency, enhanced patient adherence, and minimized side effects. Typical types include Diffusion-Controlled Systems, where drugs are released through diffusion across a membrane or matrix, such as reservoir systems and matrix capsules. Osmotic Systems harness osmotic pressure to release tablets through a semi-permeable membrane, ensuring a consistent release rate regardless of external factors. Polymer-based systems feature biodegradable polymers that break down gradually, releasing the drug as the polymer degrades. Magnetic Systems utilize magnetic fields to regulate drug release from magnetically responsive platforms, allowing for controlled release. Mathematical Models of Controlled Drug Release are integral in understanding and predicting drug release kinetics from controlled release systems. Common models include Zero-Order Release (constant release rate over time), First-Order Release (release rate proportional to the remaining drug concentration), Higuchi Model (release rate proportional to the square root of time, describing diffusion-controlled release from matrices), and Peppas-Sahlin Model (describing drug release from hydrophilic matrices considering swelling and erosion of polymers). These models aid in optimizing formulation parameters such as polymer composition, drug loading, and device geometry to achieve desired release profiles (Adepu and Ramakrishna, 2021).

Targeted Drug Delivery and Concepts of Targeting and Localized Delivery

Targeted drug delivery aims to deliver medications specifically to particular tissues, cells, or organelles to enhance therapeutic effectiveness and reduce systemic side effects. This approach involves utilizing Active Targeting, which involves utilizing ligands (such as antibodies or peptides) that bind to specific receptors on target cells to improve drug uptake and efficacy. Passive Targeting, on the other hand, relies on physiological differences (such as leaky vasculature in tumors) to accumulate drugs at target sites. Localized Delivery is another key principle, which involves delivering medications directly to the site of action to minimize exposure to healthy tissues (Hashida, 2020).

Mathematical Models and Optimization Techniques

Mathematical models are utilized in the field of focused drug delivery to predict drug distribution and accumulation at specific target sites. Optimization strategies involve the use of Computational Fluid Dynamics (CFD) to simulate blood flow and drug transport in the vasculature, as well as predict drug distribution in tissues. Pharmacokinetic-Pharmacodynamic (PK-PD) models are used to quantify the effects of drugs at target sites by correlating drug concentration with therapeutic outcomes. Optimization algorithms are employed to maximize drug delivery efficiency while minimizing off-target effects, taking into account factors such as drug stability and toxicity. These models serve as a guide in the design of focused delivery systems, optimizing drug carriers, targeting ligands, and administration routes (Elmas et al., 2020).

Nanotechnology in Drug Delivery and Overview of Nanocarriers

Nano-sized carriers, known as nanocarriers, have been specifically designed to encapsulate and deliver drugs to targeted tissues to enhance drug stability, bioavailability, and performance. Different types of nanocarriers include liposomes, which are phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs, polymeric nanoparticles made from biodegradable polymers like PLGA and chitosan to control drug release, micelles that solubilize poorly water-soluble drugs, and dendrimers with unique properties for precise drug delivery (Sahu et al., 2021).

Mathematical Modeling of Drug Release from Nanoparticles

Mathematical models are used to analyze drug release from nanoparticles, taking into account factors such as nanoparticle size, composition, and drug-polymer interactions. This model explains drug release from nanoparticles based on concentration gradients. This model is applied to nanoparticles where drug release is dependent on diffusion through the polymer matrix. This model characterizes complex release profiles, including initial burst release followed by sustained release. These models help in optimizing nanoparticle parameters (such as polymer composition and size) to achieve the desired release kinetics and improve therapeutic efficacy. Drug delivery systems utilize mathematical modeling to develop controlled release systems, target specific tissues, and utilize nanotechnology for efficient drug delivery. These processes aim to enhance therapeutic outcomes, minimize side effects, and advance personalized medicine and treatment effectiveness (Jahromi et al., 2020).

Optimization of Drug Dosage

Therapeutic Drug Monitoring and Importance and Methods of Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) involves the monitoring of drug concentrations in biological samples (e.g., blood, plasma) to optimize dosage regimens, ensuring the effectiveness of treatment while minimizing potential side effects. Patients may metabolize medications differently due to genetic factors, age, medical conditions, and interactions with other drugs. Maintaining drug levels within a narrow therapeutic range enhances treatment outcomes. Monitoring drug levels helps prevent adverse effects associated with under or over-dosing. Using specific antibodies to measure drug concentrations. High-performance liquid chromatography (HPLC) and gas chromatography (GC) are used to separate and

quantify drugs and their byproducts. Rapid tests for immediate feedback, such as bedside monitoring of antibiotics in intensive care units (Ates et al., 2020).

Dose Optimization Algorithms and Algorithms for Dose Adjustment

Dose optimization algorithms employ mathematical models and data-driven processes to adjust drug dosages, ensuring therapeutic effectiveness and reducing negative outcomes. Some common algorithms include Adaptive Control Methods, which adjust doses based on patient response and feedback to achieve and maintain target drug concentrations. Population Pharmacokinetic Models estimate individual pharmacokinetic parameters using population data to inform personalized dosing regimens. Bayesian Dose-Adaptation Software integrates prior knowledge, such as pharmacokinetic models, with new patient information, like therapeutic drug monitoring results, to update dose recommendations (Gu et al., 2020).

Applications in Different Therapeutic Areas

In the workplace, oncology adaptive management algorithms are utilized to optimize chemotherapy dosing to achieve maximum tumor response while minimizing toxicity to healthy tissues. In the field of psychiatry, the dosing of psychotropic medications such as antidepressants and antipsychotics is individualized based on patient-specific pharmacokinetic profiles and therapeutic drug monitoring results. In critical care settings, continuous infusion and adaptive control algorithms are used to adjust sedative and analgesic doses, ensuring optimal sedation levels without causing prolonged effects. These algorithms improve precision medicine by customizing drug dosages according to individual patient characteristics, leading to enhanced treatment outcomes across various medical specialties (Wu et al., 2022).

Case Studies and Applications

Case Study 1: Modeling and Simulation of a New Drug and Step-by-step Approach from Model Development to Simulation

The process of modeling and simulating a new drug involves several important steps to predict its pharmacokinetic (PK) and pharmacodynamic (PD) properties, guide dosing regimens, and optimize therapeutic outcomes. Develop a model based on the physiological and pharmacological mechanisms of drug movement, taking into consideration factors such as absorption, distribution, metabolism, and excretion (ADME). Create a mathematical model (e.g., compartmental, PBPK) using preclinical data and knowledge of drug behavior. Collect experimental data from preclinical studies, including drug concentrations in plasma or target tissues over time. Utilize techniques such as nonlinear regression or Bayesian inference to estimate model parameters (e.g., clearance, volume of distribution). Model validation and goodness-of-fit analysis comparing model predictions with observed data to assess the accuracy and reliability of the model. Examining the impact of model parameters on drug behavior and identifying key variables. Creating simulations for unique dosing regimens (e.g., dosage, frequency) to achieve desired drug concentrations and therapeutic outcomes. Predicting drug responses in diverse patient populations and across various medical conditions.Assessing potential risks (e.g., toxicity) and benefits (e.g., efficacy) of the drug based on simulation results.Utilizing modeling and simulation outcomes to support regulatory submissions and design clinical trials (Sugano, 2021).

Case Study 2: Optimization of Drug Dosage in a Clinical Trial and Application of pk/pd Modeling in Clinical Trials

Pharmacokinetic/pharmacodynamic (PK/PD) modeling in clinical trials improves understanding of drug behavior, refines dosing strategies, and enhances patient outcomes. In Study Design and Protocol Development, it is important to include PK/PD endpoints and modeling objectives in the clinical trial protocol. When selecting the population, factors such as patient demographics, disease characteristics, and inclusion/exclusion criteria that affect drug response variability should be considered. Data Collection and Analysis involve PK Sampling, where blood or tissue samples are collected at scheduled intervals to monitor drug concentrations, and PD Assessments, which measure biomarkers or clinical endpoints relevant to drug efficacy and safety. Utilize PK/PD models for statistical analysis to estimate individual and population-level parameters. Personalized Dosing: Adjust dosages based on predictions from PK/PD modeling and Therapeutic Drug Monitoring (TDM) results to maintain therapeutic levels. Modify dosing schedules during the trial based on interim analysis and model simulations. Evaluate drug effectiveness by comparing PK/PD model predictions with clinical outcomes. Safety Monitoring: Assess adverse events and potential toxicity with predicted drug exposures. Analyze PK/PD modeling results to support efficacy and safety claims in regulatory submissions. Labeling and Dosage Recommendations: Offer dosing guidance for healthcare professionals based on PK/PD modeling results. These case studies demonstrate the important role of modeling and simulation in drug development and clinical practice, optimizing drug dosing, improving therapeutic outcomes, and guiding regulatory decisions (Rodríguez-Gascón et al., 2021).

Future Directions and Challenges

Advances in Computational Methods and Emerging Computational Techniques in pk Modeling

Pharmacokinetic (PK) modeling is continually evolving alongside advancements in computational techniques, enhancing accuracy, efficiency, and applicability across various fields. Emerging techniques such as Machine Learning and Artificial Intelligence are being utilized to analyze large datasets and predict drug behaviors, leading to improved parameter estimation and personalized dosing. Quantitative Systems Pharmacology (QSP) involves integrating PK models with

pharmacodynamics and disease pathways to simulate drug effects at molecular and cellular levels. Agent-based modeling allows for the simulation of individual entities, such as cells and drug molecules, within complex biological structures, providing insights into spatial and temporal drug distribution. High-Performance Computing (HPC) involves the use of supercomputers and parallel processing to accelerate simulations and handle large-scale PK/PD modeling tasks. These computational advancements enable more robust modeling of drug interactions, population variability, and therapeutic responses, ultimately supporting precision medicine and therapeutic innovation (Wang et al., 2021).

Integration with Systems Biology and Linking Pharmacokinetics with Systems Biology and Genomics

The integration of pharmacokinetics with structural biology and genomics enhances our understanding of drug mechanisms, variability, and personalized treatment approaches in the workplace. Key aspects include Omics Data Integration, which involves incorporating genomic, proteomic, and metabolomic data to elucidate drug metabolism pathways and personalize treatment plans. Network Pharmacology is another important aspect, which involves analyzing drug-target interactions within biological networks to predict drug efficacy and potential adverse effects based on molecular interactions. Personalized Medicine involves tailoring drug treatment plans based on individual genetic profiles to predict drug responses and optimize dosing regimens. These integrative approaches help bridge the gap between pharmacokinetics and biological complexity, ultimately leading to more specific and effective therapeutic interventions in the workplace (Collin et al., 2022).

Regulatory Considerations and Regulatory Guidelines and their Impact on pk Modeling

Regulatory organizations play a crucial role in influencing pharmacokinetic modeling practices and their approval in the development of drugs and medical products. Key considerations include establishing standards for model reliability, robustness, and predictive performance to support regulatory submissions through Model Qualification and Validation. It is also important to validate biomarkers used in PK/PD modeling to accurately correlate drug exposure with clinical outcomes and safety through Biomarker Validation. Provide clear guidelines for adjusting dosing based on pharmacokinetic modeling outcomes to ensure safe and effective use in clinical practice. Global alignment of regulatory standards for pharmacokinetic modeling promotes consistency and innovation while safeguarding patient safety and public health. Continued advancements in computational methods, integration with systems biology, and adherence to regulatory guidelines will drive progress in pharmacokinetic modeling, leading to improved personalized medicine and therapeutic outcomes across diverse patient populations (Jean et al., 2021).

Conclusion

Pharmacokinetic modeling plays a crucial role in modern drug development and clinical practice, providing valuable tools to optimize treatment strategies and enhance patient outcomes. In recent years, significant advancements in computational techniques have transformed PK modeling, enabling more precise predictions of drug behavior and individualized dosing regimens. Emerging approaches such as machine learning, quantitative systems pharmacology, and integration with omics data show promise in enhancing our understanding of drug interactions and variability among different populations. Additionally, the integration of pharmacokinetics with systems biology and genomics holds the potential for personalized medicine, where treatments are tailored based on individual genetic profiles and disease pathways. Regulatory considerations continue to shape the landscape, ensuring that PK modeling meets strict standards of reliability and safety in drug approval processes. Looking ahead, ongoing innovation in PK modeling is likely to lead to more efficient clinical trials, expedited drug approvals, and improved therapeutic outcomes for patients worldwide. By leveraging these advancements, the industry is positioned to address current healthcare challenges and pave the way for future breakthroughs in pharmaceutical research and patient care.

REFERENCES

Adepu, S., and Ramakrishna, S. (2021). Controlled drug delivery systems: current status and future directions. *Molecules*, *26*(19), 5905.

Aghamiri, S. S., Amin, R., and Helikar, T. (2022). Recent applications of quantitative systems pharmacology and machine learning models across diseases. *Journal of Pharmacokinetics and Pharmacodynamics*, 1–19.

Alagga, A. A., Pellegrini, M. V, and Gupta, V. (2024). Drug absorption. In *StatPearls [Internet]*. StatPearls Publishing.

Ates, H. C., Roberts, J. A., Lipman, J., Cass, A. E. G., Urban, G. A., and Dincer, C. (2020). On-site therapeutic drug monitoring. *Trends in Biotechnology*, *38*(11), 1262–1277.

Ayral, G., Si Abdallah, J., Magnard, C., and Chauvin, J. (2021). A novel method based on unbiased correlations tests for covariate selection in nonlinear mixed effects models: The COSSAC approach. *CPT: Pharmacometrics and Systems Pharmacology*, *10*(4), 318–329.

Brocks, D. R., and Hamdy, D. A. (2020). Bayesian estimation of pharmacokinetic parameters: an important component to include in the teaching of clinical pharmacokinetics and therapeutic drug monitoring. *Research in Pharmaceutical Sciences*, *15*(6), 503–514.

Bueters, R., Bael, A., Gasthuys, E., Chen, C., Schreuder, M. F., and Frazier, K. S. (2020). Ontogeny and cross-species comparison

of pathways involved in drug absorption, distribution, metabolism, and excretion in neonates (review): kidney. *Drug Metabolism and Disposition*, *48*(5), 353–367.

Campbell, J. E., Thomas-Brown, P. G., and Cohall, D. H. (2024). Pharmacodynamics—a pharmacognosy perspective. In *Pharmacognosy* (pp. 579–596). Elsevier.

Chou, W.-C., and Lin, Z. (2023). Machine learning and artificial intelligence in physiologically based pharmacokinetic modeling. *Toxicological Sciences*, *191*(1), 1–14.

Coelho, M. M., Fernandes, C., Remião, F., and Tiritan, M. E. (2021). Enantioselectivity in drug pharmacokinetics and toxicity: Pharmacological relevance and analytical methods. *Molecules*, *26*(11), 3113.

Collin, C. B., Gebhardt, T., Golebiewski, M., Karaderi, T., Hillemanns, M., Khan, F. M., Salehzadeh-Yazdi, A., Kirschner, M., Krobitsch, S., and consortium, E.-S. (2022). Computational models for clinical applications in personalized medicine—guidelines and recommendations for data integration and model validation. *Journal of Personalized Medicine*, *12*(2), 166.

Cottura, N., Howarth, A., Rajoli, R. K. R., and Siccardi, M. (2020). The current landscape of novel formulations and the role of mathematical modeling in their development. *The Journal of Clinical Pharmacology*, *60*, S77–S97.

Damodharan, N. (2020). Mathematical modelling of dissolution kinetics in dosage forms. *Research Journal of Pharmacy and Technology*, *13*(3), 1339–1345.

Darwich, A. S., Polasek, T. M., Aronson, J. K., Ogungbenro, K., Wright, D. F. B., Achour, B., Reny, J.-L., Daali, Y., Eiermann, B., and Cook, J. (2021). Model-informed precision dosing: background, requirements, validation, implementation, and forward trajectory of individualizing drug therapy. *Annual Review of Pharmacology and Toxicology*, *61*(1), 225–245.

Doshi, K. A. (2022). Basics of Targeted Drug Delivery. *Targeted Drug Delivery*, 1–19.

Elmas, A., Akyüz, G., Bergal, A., Andaç, M., and Andaç, Ö. (2020). Mathematical modelling of drug release. *Research on Engineering Structures and Materials*, *6*(4).

Foroozandeh, P., Jusoh, S. A. M., and Shamsuddin, S. (2021). Passive drug delivery, mechanisms of uptake, and intracellular trafficking. In *Organelle and Molecular Targeting* (pp. 129–152). CRC Press.

Goutelle, S., Woillard, J., Neely, M., Yamada, W., and Bourguignon, L. (2022). Nonparametric methods in population pharmacokinetics. *The Journal of Clinical Pharmacology*, *62*(2), 142–157.

Gu, J., Guo, Y., Jiao, Z., Ding, J., and Li, G.-F. (2020). How to handle delayed or missed doses: a population pharmacokinetic perspective. *European Journal of Drug Metabolism and Pharmacokinetics*, *45*(2), 163–172.

Guidi, M., Csajka, C., and Buclin, T. (2022). Parametric approaches in population pharmacokinetics. *The Journal of Clinical Pharmacology*, *62*(2), 125–141.

Hashida, M. (2020). Role of pharmacokinetic consideration for the development of drug delivery systems: A historical overview. *Advanced Drug Delivery Reviews*, *157*, 71–82.

Jahromi, L. P., Ghazali, M., Ashrafi, H., and Azadi, A. (2020). A comparison of models for the analysis of the kinetics of drug release from PLGA-based nanoparticles. *Heliyon*, *6*(2).

Jain, K. K. (2020). An overview of drug delivery systems. *Drug Delivery Systems*, 1–54.

Jean, D., Naik, K., Milligan, L., Hall, S., Huang, S. M., Isoherranen, N., Kuemmel, C., Seo, P., Tegenge, M. A., and Wang, Y. (2021). Development of best practices in physiologically based pharmacokinetic modeling to support clinical pharmacology regulatory decision-making—A workshop summary. *CPT: Pharmacometrics and Systems Pharmacology*, *10*(11), 1271.

Jovanović, M., Vučićević, K., and Miljković, B. (2020). Understanding variability in the pharmacokinetics of atypical antipsychotics–focus on clozapine, olanzapine and aripiprazole population models. *Drug Metabolism Reviews*, *52*(1), 1–18.

Liu, Q., and Shan, Q. (2022). An optimization-based stochastic model of the two-compartment pharmacokinetics. *Mathematical Methods in the Applied Sciences*, *45*(10), 6062–6079.

Liu, Z., and Kang, R. (2024). Pharmacokinetics with intravenous infusion of two-compartment model based on Liu process. *Communications in Statistics-Theory and Methods*, *53*(14), 4975–4990.

Liu, Z., and Yang, Y. (2021). Pharmacokinetic model based on multifactor uncertain differential equation. *Applied Mathematics and Computation*, *392*, 125722.

McGinnity, D. F., and Grime, K. (2023). *ADME optimization in drug discovery*.

Perry, C., Davis, G., Conner, T. M., and Zhang, T. (2020). Utilization of physiologically based pharmacokinetic modeling in clinical pharmacology and therapeutics: an overview. *Current Pharmacology Reports*, *6*, 71–84.

Peters, S. A. (2021). *Physiologically based pharmacokinetic (PBPK) modeling and simulations: principles, methods, and applications in the pharmaceutical industry*. John Wiley and Sons.

Rodríguez-Gascón, A., Solinís, M. Á., and Isla, A. (2021). The role of PK/PD analysis in the development and evaluation of antimicrobials. *Pharmaceutics*, *13*(6), 833.

Sahu, T., Ratre, Y. K., Chauhan, S., Bhaskar, L., Nair, M. P., and Verma, H. K. (2021). Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *Journal of Drug Delivery Science and Technology*, *63*, 102487.

Silva, F. A., Fé, I., and Gonçalves, G. (2021). Stochastic models for performance and cost analysis of a hybrid cloud and fog architecture. *The Journal of Supercomputing*, *77*, 1537–1561.

Sugano, K. (2021). Lost in modelling and simulation? *ADMET and DMPK*, *9*(2), 75–109.

Tolani, P., Gupta, S., Yadav, K., Aggarwal, S., and Yadav, A. K. (2021). Big data, integrative omics and network biology. *Advances*

in Protein Chemistry and Structural Biology, *127*, 127–160.

Vrettos, N.-N., Roberts, C. J., and Zhu, Z. (2021). Gastroretentive technologies in tandem with controlled-release strategies: A potent answer to oral drug bioavailability and patient compliance implications. *Pharmaceutics*, *13*(10), 1591.

Wang, W., Ye, Z., Gao, H., and Ouyang, D. (2021). Computational pharmaceutics-A new paradigm of drug delivery. *Journal of Controlled Release*, *338*, 119–136.

Ward, L., Wilcock, J., and Butler, P. (2022). Drug metabolism assessment: Hepatocytes. In *The ADME Encyclopedia: A Comprehensive Guide on Biopharmacy and Pharmacokinetics* (pp. 368–379). Springer.

Wu, X., Hou, Y., and Zhang, K. (2022). Switched system optimal control approach for drug administration in cancer chemotherapy. *Biomedical Signal Processing and Control*, *75*, 103575.

Zhang, X., and Zhao, P. (2021). From a Mathematical Model to a Technology, the 100 Years' Evolution of PBPK. In *The Art and Science of Physiologically-Based Pharmacokinetics Modeling* (pp. 1–16). CRC Press

Chapter 43

Novel Nano-biosensors for the Detection of Organophosphate Residues in Food Commodities

Sidra Altaf[1*], Kinza Javed Iqbal[2], Muqaddas Saqib[3] and Ume Salma[4]

[1]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
[2]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[3]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
[4]Department of Zoology, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: sidra.altaf@uaf.edu.pk

ABSTRACT

Organophosphates pose significant health issues when present in food, challenging advanced discovery styles for timely intervention. Conventional approaches are time-consuming. In response, this study explores the eventuality of nano-biosensors as slice-edge volition for enhanced food safety. The nano-biosensors influence nanomaterial-grounded platforms characterized by unique parcels, including increased perceptivity, rapid-fire discovery capabilities, and the eventuality of miniaturization. The nano-biosensor enables on-point monitoring. Crucial technological advancements include face-enhanced Raman spectroscopy (SERS), and graphene-ground nano-biosensors. These technologies contribute to bettered discovery capabilities, addressing challenges related to selectivity. Likewise, enzyme-modified nanomaterials are explored for organophosphate discovery. The exploration emphasizes the significance of rigorous performance evaluation and confirmation, including perceptivity, and real-world testing. The study outlines challenges, including the disquisition of emerging technologies, addressing selectivity issues, and integrating nano-biosensors into routine food testing practices. The use of these nano biosensors for food safety and public health is profound, offering enhanced monitoring capabilities, and timely interventions.

KEYWORDS
Nano-biosensors; Organophosphate residues; Food safety; Detection technology; Sensitivity and specificity; Emerging technologies; Regulatory considerations

Received: 05-Jun-2024
Revised: 14-Jul-2024
Accepted: 18-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Altaf S, Iqbal KJ, Saqib M and Salma U, 2024. Novel Nano-biosensors for the detection of organophosphate residues in food commodities. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 374-382. https://doi.org/10.47278/book.CAM/2024.469

INTRODUCTION

Organophosphates are commonly utilized in farming as pesticides, herbicides, and bug sprays. The accumulation of organophosphates in food commodities such as natural products, vegetables, and grains poses potential dangers to human well-being. The presentation of organophosphate buildups has been connected to an extent of well-being dangers, fundamentally influencing the apprehensive and respiratory frameworks (Fu et al., 2022). Organophosphates repress acetylcholinesterase, driving the collection of acetylcholine in nerve neural connections. This disturbance in neurotransmission can result in indications such as cerebral pains, sickness, and in extreme cases, seizures or loss of motion. Ingestion of organophosphate can lead to respiratory issues, trouble breathing, and chest snugness Pre-birth introduction to organophosphates has been related to neurobehavioral shortages and regenerative issues. The inveterate introduction may contribute to cardiovascular illnesses, endocrine disturbance, and certain cancers (Dickey et al., 2021).

Significance of Discovery in Food Commodities

Identifying and measuring organophosphate buildups offer assistance in anticipating the ingestion of sullied nourishment, in this manner lessening the chance of intense and inveterate well-being issues related to introduction. Environmental protection agency (EPA) has set limits for organophosphates in food items. Exact location strategies are fundamental for administrative compliance and dependable location strategies contribute to building buyer certainty within the security of the food supply chain. Buyers are progressively concerned about chemical buildups in their nourishment, and upfront testing methods offer assistance to address these concerns. Exact discovery strategies guarantee food commodities meet the administrative measures of distinctive nations, encouraging smoother exchange relations. Observing and controlling organophosphate buildups in food commodities minimize the harmful effect of pesticide (Ramakrishnan et al.,

2019).

Present Methods and Limitations

The discovery of organophosphate buildups in food commodities is right now performed utilizing different strategies.

Chromatographic Methods

Gas Chromatography

GC is utilized for isolating and analyzing organophosphate compounds. It offers elevated specificity but may require complex test arrangement.

Liquid Chromatography

LC is successful for non-volatile organophosphates. It can be coupled with mass spectrometry for upgraded discovery.

Immunoassays

Procedures such as enzyme-linked immunosorbent test (ELISA) utilize antibodies to identify organophosphate buildups. Immunoassays are quick and cost-effective but may need the specificity of chromatographic strategies.

Mass Spectrometry

Mass spectrometry, especially couple mass spectrometry (MS/MS), is utilized for the evaluation of organophosphates. It requires costly hardware.

Biosensors

Biosensors have been established for their fast reaction. These can offer real-time observing but may endure reproducibility issues.

Nuclear Magnetic Resonance

NMR spectroscopy can give data on the chemical structure of organophosphates. Whereas it could be a non-destructive strategy.

Electrochemical Methods

Electrochemical sensors can offer fast and cost-effective discovery. But they may confront challenges in terms of affectability and selectivity(Chawla et al., 2018).

Limitations of Present Approaches

Accomplishing elevated affectability and specificity at the same time can be challenging. A few strategies may exceed expectations in one angle but compromise the other. Food networks are complex, and different components can meddle with the location of organophosphate (Chadha et al., 2022). Numerous strategies require broad test arrangement, which can be time-consuming. A few methods, such as mass spectrometry, request costly hardware and trained administrators, this indicates that not all strategies are reasonable for real-time checking. The fetching of hardware, reagents, and investigation time can be noteworthy variables, particularly for scheduled testing of extensive test sets (Samadder and Rao, 2023).

Foundation for Nano-biosensors

The advancement and utilization of nano-biosensors for the discovery of organophosphate buildups in food items offer a few compelling points of interest, tending to numerous of the confinements related with conventional location strategies. Nano-biosensors can accomplish momentous affectability, identifying follow sums of organophosphate buildups with tall accuracy. The huge surface zone of nanomaterials permits for expanded intuitive with target analytes, moving forward the sensor's location restrain. Nano-biosensors can be outlined with particular acknowledgment components, such as antibodies or aptamers, guaranteeing tall specificity for the target organophosphates. Nano-biosensors display quick reaction times, empowering real-time checking of organophosphate buildups. This can be pivotal for guaranteeing the convenient discovery of defilement, particularly in perishable food items. Nano-biosensors can be miniaturized, allowing for versatile and field-deployable gadgets. Usually profitable for on-site testing, decreasing the require for test transportation and empowering speedy choices in different settings (Mitra et al., 2022).

Characteristics of Nano-biosensors

Nano-biosensors join different nanomaterials, such as nanoparticles, nanotubes, or nanocomposites. These materials show special properties, counting huge surface area-to-volume proportion, quantum impacts, and improved conductivity, which contribute to progressed affectability. The organic components in nano-biosensors play a pivotal part in giving specificity to the discovery prepare. These components can be proteins, antibodies, aptamers, or indeed entirety cells, depending on the target analyte. They specifically tie to the analyte, starting a flag transduction instrument. Nano-biosensors regularly depend on a transduction instrument to change over the official occasion into a quantifiable flag. This may include

changes in electrical, optical, or mechanical properties of the nanomaterials, permitting for the location and measurement of the target analyte. The combination of nanomaterials and organic components comes about in nano-biosensors with elevated affectability and selectivity. The nanoscale measurements improve the interaction between the sensor and analyte, whereas the natural components guarantee specificity for the target particle (Huang et al., 2021).

Benefits over Conventional Discovery Methods

Nano-biosensors offer a few focal points over routine discovery strategies, particularly when connected to the discovery of organophosphate buildups in nourishment commodities. These focal points contribute to the enhancement of generally food security measures. Nano-biosensors use the interesting properties of nanomaterials, such as huge surface zone and quantum impacts, to improve affectability. This permits for the discovery of lower concentrations of organophosphate buildups, which may go undetected by ordinary strategies. Consolidating organic components, nano-biosensors guarantee high specificity. This minimizes the chance of wrong positives. Nano-biosensors regularly give quick reaction times, empowering real-time monitoring of organophosphate. This is pivotal for convenient intercessions in circumstances where quick discovery is essential, such as in perishable food items. The little measure of nanomaterials permits for the miniaturization of sensor components, making nano-biosensors compact and convenient. This highlight is profitable for on-site testing and reduce the require for test transportation (Sahu and Kashaw, 2023).

Types of Nano-biosensors

Nanomaterials used in Biosensors

Nanoparticles, such as gold nanoparticles and silver nanoparticles are commonly utilized in nano-biosensors. They offer huge surface zones for functionalization with natural components. Carbon nanotubes and nanowires have amazing electrical conductivity and are utilized to build electrochemical nano-biosensors. They give a stage for immobilizing organic particles and show affectability to changes in electrical properties upon analyte authority. Quantum dabs are semiconductor nanocrystals with special optical properties, counting size-tunable fluorescence. They are utilized in fluorescence-based nano-biosensors for multiplexed discovery (Christopher et al., 2020). For illustration, a nanocomposite may consolidate nanoparticles and nanotubes to improve both electrical and basic perspectives of the nano-biosensor. Graphene and its subsidiaries, such as graphene oxide, are known for their great electrical conductivity and expansive surface region. They are utilized in different nano-biosensors, especially those including electrochemical discovery (Stephanie et al., 2021).

Biological Mechanisms in Nano-biosensors

Proteins are broadly utilized in nano-biosensors. They catalyze particular responses with the target analyte, driving to distinguishable changes within the sensor's properties. Antibodies are safe proteins that show high specificity for specific antigens. Immobilizing antibodies on nanomaterials permits for specific authoritative to target analytes, shaping the premise for immunosensors. Aptamers are brief, single-stranded DNA or RNA particles chosen to tie particularly to a target. They offer an elective to antibodies and can be utilized as components in aptamer-based nano-biosensors. A few nano-biosensors consolidate whole cells, such as microscopic organisms or yeast, as the organic acknowledgment component. These living cells can react to the particular analytes, producing signals that are recognizable by the sensor. DNA and RNA can serve as acknowledgment components in nano-biosensors. Other than proteins and antibodies, other proteins can be utilized in nano-biosensors, either for coordinate official to analytes or as components in flag transduction pathways. MIPs are engineered polymers outlined to specifically recognize and tie to particular target particles. These molecularly engraved materials can be coordinates into nano-biosensors for engraving the shape of the target analyte (Bhattacharya et al., 2022).

Principles of Organophosphate Recognition

Molecular Interface with Nano-biosensors

The discovery of organophosphate utilizing nano-biosensors depends on particular atomic intuitive between the target analyte (organophosphates) and the detecting components coordinates into the nano-biosensor. The primary step includes the particular acknowledgment of organophosphate by the natural components immobilized on the nanomaterial surface. The choice of components, such as chemicals, antibodies, aptamers, or molecularly engraved polymers is pivotal in guaranteeing specificity for organophosphates. For chemicals and antibodies, this includes particular official destinations that show partiality for the chemical structure of organophosphates (Uniyal and Sharma, 2018). The nanomaterial utilized within the nano-biosensor plays a basic part in improving the atomic intuitive. The huge surface region of nanomaterials, such as nanoparticles gives adequate destinations for the immobilization of organic acknowledgment components, guaranteeing the next likelihood of intuitive with organophosphates (Chugh et al., 2023).

Indication Transduction Mechanisms

Streamer transduction in nano-biosensors includes the transformation of the atomic interaction between the target analyte (organophosphates) and the binding components into a quantifiable flag. Different nanomaterials and transduction instruments are utilized to realize this change. Nanomaterials such as nanotubes or nanowires may show changes in electrical resistance or conductance upon authority with organophosphates. This will be measured to evaluate the analyte concentration. FET-based nano-biosensors utilize changes within the conductance of the transistor channel upon authority,

giving a coordinate electrical readout (Hashem et al., 2021). Quantum specks can be consolidated into nano-biosensors. Authoritative organophosphates can actuate changes in fluorescence escalated, wavelength, or lifetime, which are recognized optically. Nanomaterials with color-changing properties, such as gold nanoparticles, may experience color changes upon interaction with organophosphates, empowering straightforward visual discovery. Electrochemical nano-biosensors can cause degree changes in current coming about from redox responses related to organophosphate authoritative. This can be commonly achieved through enzymatic responses or coordinate electrochemical oxidation. Changes in anode potential are measured as a result of the official occasion. This will be utilized in ion-selective terminals or other potentiometric sensors. (Sargazi et al., 2022).

Sensitivity and Specificity

The performance of nano biosensors in the detection of organophosphates is often evaluated based on two important parameters: sensitivity and specificity. These factors determine the reliability and accuracy of the sensor in identifying and quantifying organophosphate residues in foods. Sensitivity refers to the ability of a nano biosensor to detect and quantify low concentrations of organophosphate residues. Highly sensitive sensors ensure that even traces of target analytes can be detected(Dincer et al., 2019). Certain nanomaterials, such as quantum dots may provide higher sensitivity due to their unique properties. The chosen transduction method can also have a significant impact on sensitivity, with some mechanisms resulting in greater signal amplification. Appropriate functionalization of nanomaterials with fitting components improves the capacity of the sensor to capture and connected with organophosphates. Specificity alludes to the capacity of a nano biosensor to recognize the target analyte (organophosphate) from other substances (Che Sulaiman et al., 2020).

Nano-biosensor Technologies and Surface-improved Spectroscopy

Surface-enhanced Raman spectroscopy (SERS) may be a capable and advanced analytical strategy that's picking up significance within the field of nano biosensors due to its high specificity. SERS combines the standards of Raman spectroscopy with nanomaterials to increase the Raman flag of atoms, permitting location of follow sums of analytes (Tripathi and Bonilla-Cruz, 2023). Metal nanoparticles such as gold and silver are broadly utilized in SERS-based nano biosensors. These nanoparticles create a localized surface plasmon resonance (LSPR) impact and intensify the Raman signals of neighboring particles. Coordination metal nanoparticles with graphene or other 2D materials improves the SERS impact, makes strides steadiness, and gives a bigger surface zone for interaction with analytes. Functionalization of metal nanoparticles with atomic tests such as aptamers or particular ligands moves forward the selectivity of SERS-based nano biosensors toward organophosphate targets. Tuning the surface properties of nanomaterials through chemical alterations can offer assistance optimize the interaction between sensor components and organophosphates. SERS-based nano biosensors can be planned for multiplexed discovery, permitting concurrent examination of different organophosphates (Serafinelli et al., 2022).

Quantum Dots- based Biosensors

Quantum specks are semiconductor nanocrystals with interesting optical and electronic properties, making them great candidates for creating progressed nano biosensors. Quantum dot-based biosensors have made noteworthy advances in the discovery of different analytes, particularly those containing organophosphate buildups. (Meliana et al., 2024).

Detecting Mechanism

Quantum specks can be combined with other fluorescent colors or quenchers through Fuss, permitting delicate location based on changes in fluorescence concentrated upon interaction with organophosphates. Quantum dabs can take an interest in charge exchange forms when collaboration with organophosphates, causing a alter in their electronic state. This alter can be measured to distinguish the analytes. Integration of proteins and quantum dabs increase the specificity and catalytic action of biosensors. Multicolor quantum specks permit discovery of numerous analytes or distinctive shapes of organophosphates. This highlight encourages multiplexed examination and moves forward sensor execution (Willner and Vikesland, 2018).

Enzyme Improved Nanomaterials

Enzyme-modified nanomaterials play a critical part within the advancement of nano biosensors, upgrading their catalytic movement and specificity for the location of different analytes, counting organophosphates. Later progresses in enzyme-modified nanomaterials for organophosphate discovery incorporate: Proteins such as acetylcholinesterase and organophosphate hydrolase are combined with nanoparticles to make enzyme-nanoparticle crossovers. Enzyme-modified nanoparticles can catalyze responses that result in flag intensification, permitting location of lower concentrations of organophosphates. Chemicals typified in nanomaterials such as liposomes have expanded soundness and are superior secured from natural influences. This epitome guarantees the life span of chemical movement within the capture prepare. The utilize of biocompatible nanomaterials for protein epitome increments the compatibility of enzyme-modified nano biosensors with organic frameworks (Kumar and Madhuri, 2022). Proteins can be immobilized on graphene surfaces to make graphene-enzyme cross breeds that combine graphene's great conductivity and enzymatic action to move forward detecting execution. Proteins can be implanted in nanocomposites containing different nanomaterials. This synergistic approach

combines the special properties of each component to make a multifunctional stage for organophosphate location. Consolidation of proteins into nanocomposites empowers biocatalytic responses that increase the flag, contributing to the affectability and selectivity of nano biosensors. Nanozymes are nanomaterials that display interesting enzyme-like exercises. These materials, such as metal oxide nanoparticles, imitate the catalytic properties of proteins and can be custom fitted for particular discovery of organophosphates. Nanozymes regularly have made strides solidness and reproducibility compared to normal proteins, addressing some of the challenges related with enzyme-based sensors. Enzyme-modified nano biosensors progressively incorporate biodegradable nanomaterials. This eco-friendly approach guarantees that the nanomaterials utilized within the sensor have negligible natural affect (Aggas and Guiseppi-Elie, 2020).

Fabrication and Strategy Distresses and Collection of Nanomaterials

The choice of nanomaterial impacts the affectability, selectivity, and generally execution of the sensor. Consider the special properties of nanomaterials such as conductivity, optical properties, and surface region. These properties must coordinate the specified capture instrument and transmission strategy. Guarantee that the chosen nanomaterials are biocompatible to maintain a strategic distance from antagonistic impacts when association with natural components. Biocompatibility is exceptionally critical for applications including living beings (Mahmoudpour et al., 2022). Select nanomaterials that are steady and solid so that they can keep up their detecting properties over time. Select nanomaterials that can be effectively functionalized with organic components (proteins, antibodies, aptamers, etc.). Functionalization increases the specificity of the sensor for the discovery of organophosphates. (Xu et al., 2021).

Arrangement of Organic Elements

Effective integration of organic components is basic for the specificity and selectivity of nano biosensors. Natural components such as antibodies play an imperative part for detecting organophosphate buildups. Components should be selected with high partiality and specificity for organophosphates (Naresh and Lee, 2021). Depending on the sensor necessities, proteins, antibodies, and aptamers are commonly utilized components. Utilize fitting immobilization methods to guarantee steady connection of natural components to the nanomaterial surface. This may incorporate physical adsorption or covalent holding. Protecting the common structure and work of proteins and antibodies is basic for precise and dependable location (Kozitsina et al., 2018)

Optimization of Detecting Limitations

Optimization of sensor parameters is imperative to realize the required execution characteristics of nano biosensors. Optimize pH and temperature conditions to guarantee solidness and movement of organic components. Decide the ideal brooding time for the sensor to associate with the test. For real-time applications, it is vital to adjust adequate interaction time with the require for fast location. Fine-tune sensor parameters to lower discovery limits, particularly for follow sums of organophosphate buildups. This increases the affectability of the nano biosensor. Build up a strong calibration convention to relate the sensor reaction with known concentrations of organophosphate. Standard calibration guarantees the exactness and unwavering quality of place originates approximately (Kulkarni et al., 2022).

Reduction and Suitability

The miniaturization of nano biosensors is of extraordinary significance for field and point-of-care applications. We plan a nano-biosensor with a compact and coordinates engineering to play down the general gadget measure. The compact plan makes it simple to utilize in different situations. Optimizes sensor control utilization to empower battery operation. Coordinated a little readout framework consistent with the measure of the sensor. This may incorporate on-chip hardware or remote communications for information exchange. Guaranteeing the robustness of the nano-biosensor plan to resist natural conditions and taking care of amid field utilize. The vigorous sensor is appropriate for field applications. We plan the nano biosensor for user-friendly operation and negligible preparing necessities. Real-time information collection helps in opportune decision-making in applications such as food security review (Yildirim-Tirgil, 2023).

Discovery in Fruits and Vegetables and in other Food Commodities

Nano biosensors are utilized in different applications to guarantee the security and quality of natural products and vegetables by recognizing organophosphates. Nano biosensors can be utilized for pre-harvest checking to survey the organophosphate buildups in crops. This permits proactive measures to be taken to play down defilement some time recently collect. The use of nano biosensors at the post-harvest arrange encourages fast quality control assessment. Real-time discovery permits opportune assurance of whether natural products and vegetables are appropriate for utilization. Nano biosensors can offer assistance in screening particular natural products and vegetables.(Mukherjee et al., 2022).

Detecting in Grains and Cereals

Nano biosensors play an imperative part in checking grains for organophosphate tending to food security issues in staple crops. Nano biosensors can be utilized to screen organophosphate levels amid grain and grain capacity and transportation. This guarantees the security of put away food. When analyzing food commodities including cereals or grains, nano biosensors can offer assistance evaluate the relocation of organophosphate buildups. Nano biosensor integration underpins supply chain traceability by giving data on organophosphate defilement status at distinctive stages of the grain

generation (Singh et al., 2024).

Evaluation in Meat and Dairy Products

Nano biosensors are important instruments for surveying organophosphate buildups in meat and dairy items, contributing to the security and quality affirmation. Applications incorporate the utilize of nano biosensors to screen organophosphate defilement in animals bolster (Wahab et al., 2024). This approach makes a difference in anticipating buildup exchange from nourish to creature items. Versatile nano-biosensors encourage on-site testing in meat and dairy handling plants, permitting quick location of organophosphate buildups in crude materials and wrapped up items. Nano biosensors contribute to drain quality control by measuring organophosphate substance. (Bhattacharya et al., 2022).

Experiments in Multiple Food Situations

In spite of propels in nano biosensor innovation, challenges stay when working with complex nourishment frameworks. The complex frameworks such as fats, proteins, and sugars in food commodity can influence the discovery of organophosphate. The improvement of productive and standardized test planning strategies is critical to extricate and concentrate organophosphates from complex nourishment lattices. Cross-reactivity with other compounds display in nourishment lattices postures a challenge to the specificity of nano biosensors, and potential bewildering variables ought to be altogether tried to guarantee precise discovery. There's. Comprehensive approval and compliance with administrative rules are required to guarantee that nano biosensors meet administrative measures and are acknowledged by the nourishment industry. The advancement of cost-effective and scalable fabricating forms will contribute to the commercialization of these sensors within the nourishment industry (Choudhary and Kumar, 2018).

Enactment Assessment and Validation and Evaluation with Traditional Methods

We approve the execution of our nano biosensor in comparison with set up reference strategies for organophosphate discovery. These may incorporate chromatographic procedures, mass spectrometry, or enzyme-linked immunosorbent tests (ELISA). A relationship think about is performed to decide the relationship coefficient between the nano biosensor comes about and the conventional strategy comes about. The solid relationship demonstrates the unwavering quality of the nano biosensor. The most advantage is the quick reaction of nano biosensors. Assess the compatibility of nano biosensors with complex nourishment networks in comparison with conventional strategies. Determine the sensor's capacity to supply precise comes about within the nearness of different nourishment components (Mukherjee et al., 2022).

Field Testing and Existing Biosphere uses

Conduct on-site testing in real-world situations, counting, a cultivate or nourishment handling plant. Assess the execution of the nano biosensor beneath field conditions. Test your nano-biosensor employing an assortment of nourishment tests, counting natural products, vegetables, grains, cereals, meat, and dairy items. Assess the strength of the nano biosensor by uncovering it to changes in natural conditions such as temperature. Guarantees sensor usefulness in different situations. Examine the long-term soundness of the nano biosensor with broad field testing. Meet all lawful necessities and illustrate that your sensor complies with set up rules. Assemble input from conclusion clients such as nourishment reviewers, ranchers, and nourishment industry specialists on the ease of use and viability of nano biosensors (Sharma et al., 2021).

Monitoring Opinions and Compliance with Food Safety Values

Guarantee that usefulness of the nano biosensor complies with existing nourishment security controls and measures built up by administrative specialists such as the Nourishment and Medicate Organization (FDA), or the European Nourishment Security Specialist (EFSA), if you don't mind affirm. Approve the execution of the nano biosensor against the set-up limits of organophosphate buildups in nourishments. Compliance with these limits is basic for sensor acknowledgment and usage within the nourishment industry. Meets exactness and precision prerequisites set by administrative benchmarks. Take after standardized conventions for approval and testing suggested by administrative specialists. This incorporates rules for test arrangement, calibration, and execution assessment to guarantee consistency of comes about. Comprehensive documentation of nano biosensor approval considers, counting affectability, specificity, and comparisons with conventional strategies (Olawore et al., 2024).

Approval Procedures for Nano Biosensors

Pre-submission discourses with administrative specialists to get direction on the nano biosensor endorsement handle. Early dialogs can offer assistance adjust desires and address potential concerns. Get ready and yield a comprehensive information bundle counting execution information, and prove of security and adequacy of the nano biosensor. This format will serve as the premise for your formal appraisal. Conduct an intensive evaluation considering the conceivable dangers related with the utilize of nano biosensors within the nourishment industry. Address security concerns and give chance moderation procedures as portion of your administrative proposition accommodation (Upadhyay et al., 2022). Guarantee that the nano-biosensor fabricating prepare complies with Great Fabricating Hones (GMP). GMP compliance is fundamental to preserve item quality, consistency, and traceability. Set up a post-market observation instrument to screen nano biosensor execution and security after administrative endorsement. These nonstop observing guarantees that any issues that emerge

are tended to instantly (Noor Hasnan et al., 2022).

Experiments and Upcoming Controlling Developments

We address the challenge of standardizing testing conventions for nano biosensors, particularly considering the nonappearance of broadly acknowledged benchmarks. Work with controllers and industry partners to construct agreement on testing strategies. We emphasize intrigue collaboration between researchers, and administrative specialists to address the complexities of nanotechnology in biosensor improvement. Joint endeavors will empower a comprehensive understanding of security and adequacy perspectives. Administrative offices may have to be overhaul their rules and assessment criteria to reflect propels in nano biosensor plan and usefulness. We value data transparency and effective communication throughout the regulatory process. Providing clear and easy-to-understand information will help regulatory authorities understand the properties of nano biosensors and facilitate decision-making. We advocate international harmonization of regulatory standards to create a consistent regulatory environment for nano biosensors. Harmonization reduces barriers to accessing global markets and optimizes approval processes. Recognize the ethical and social implications associated with nano biosensor applications (Kose et al., 2022).

Impending Instructions and Experiments and Developing Technologies

We explore the use of novel nanomaterials with improved properties for nano biosensors. Advances in nanotechnology have introduced materials with superior sensitivity, stability, and biocompatibility, improving the overall performance of sensors. Integrate machine learning and artificial intelligence algorithms into nano biosensor systems to improve data analysis and interpretation. These technologies can improve the accuracy of detection, especially in complex food matrices. Explore the fusion of nanotechnology with other emerging fields such as synthetic biology and 3D printing to create multifunctional nano-biosensors with advanced features. This empowers real-time observing of nourishment quality and security amid capacity and transportation, giving moment data to buyers and partners (Chauhan et al., 2021).

Addressing Sensitivity and Selectivity Substances

Create and optimize acknowledgment components such as aptamers and molecularly engraved polymers with expanded liking and specificity for organophosphates. Fine-tuning these variables can address affectability and selectivity challenges. Coordination distinctive detecting implies, such as optical and electrochemical, increments the by and large affectability and gives complementary data. Methods such as nanomaterial-based intensification and catalysis can increase signals in reaction to organophosphate official. Ceaseless checking gives more comprehensive understanding into transient varieties and presentation designs (Mahmoudpour et al., 2022).

Conclusion

Creating new small biosensors that can find harmful chemicals in food is a big step forward in making sure food is safe to eat and keeping people healthy. Finding a problem early helps us to act quickly and make it less severe. Old ways to find Organophosphate are less efficient and take too much time. Nano biosensors are a good option to help with these problems. Nano biosensors can detect organophosphate residues very quickly and accurately. New technologies like SERS, quantum dot-based biosensors, and graphene-based nano biosensors are making it easier to detect things. Tiny materials that have been changed by enzymes can help substances to react faster and more specifically. This can be a useful way to find and measure organophosphates. Important for making nano biosensors work well: picking the right nanomaterial, combining it with biological elements, adjusting the sensor settings, and making it portable. The new nano biosensor technology will help make sure that food is safe to eat all around the world. This will make it easier to trade food between different countries and keep safety standards the same everywhere. Tiny biosensors may change how we check if our food is safe to eat. The scientific community can make sure that our food is safe by dealing with problems, coming up with new ideas, and working together

REFERENCES

Aggas, J. R., and Guiseppi-Elie, A. (2020). Responsive polymers in the fabrication of enzyme-based biosensors. In *Biomaterials Science* (pp. 1267–1286). Elsevier.

Bhattacharya, M., Paul, I. D., Jayachandran, L., Halder, S., and Banerjee, S. (2022). Nanobiosensors: Principles, techniques, and innovation in nanobiosensors. In *Biosensors in Food Safety and Quality* (pp. 85–110). CRC Press.

Chadha, U., Bhardwaj, P., Agarwal, R., Rawat, P., Agarwal, R., Gupta, I., Panjwani, M., Singh, S., Ahuja, C., and Selvaraj, S. K. (2022). Recent progress and growth in biosensors technology: A critical review. *Journal of Industrial and Engineering Chemistry*, *109*, 21–51.

Chauhan, N., Saxena, K., Tikadar, M., and Jain, U. (2021). Recent advances in the design of biosensors based on novel nanomaterials: An insight. *Nanotechnology and Precision Engineering (NPE)*, *4*(4).

Chawla, P., Kaushik, R., Swaraj, V. J. S., and Kumar, N. (2018). Organophosphorus pesticides residues in food and their colorimetric detection. *Environmental Nanotechnology, Monitoring and Management*, *10*, 292–307.

Che Sulaiman, I. S., Chieng, B. W., Osman, M. J., Ong, K. K., Rashid, J. I. A., Wan Yunus, W. M. Z., Noor, S. A. M., Kasim, N. A. M., Halim, N. A., and Mohamad, A. (2020). A review on colorimetric methods for determination of organophosphate pesticides using gold and silver nanoparticles. *Microchimica Acta*, *187*(2). https://doi.org/10.1007/S00604-019-3893-8

Choudhary, D., and Kumar, S. (2018). Nanotechnology applications in agricultural and biological engineering. In *Sustainable Biological Systems for Agriculture* (pp. 21–54). Apple Academic Press.

Christopher, F. C., Kumar, P. S., Christopher, F. J., Joshiba, G. J., and Madhesh, P. (2020). Recent advancements in rapid analysis of pesticides using nano biosensors: a present and future perspective. *Journal of Cleaner Production*, *269*, 122356.

Chugh, V., Basu, A., Pudake, R. N., Saha, R., and Basu, A. K. (2023). Recent progress in aptamer-based smart detection techniques for agriculture. *Impedance Spectroscopy and Its Application in Biological Detection*, 223–244.

Dickey, B., Madhu, L. N., and Shetty, A. K. (2021). Gulf War illness: mechanisms underlying brain dysfunction and promising therapeutic strategies. *Pharmacology and Therapeutics*, *220*, 107716.

Dincer, C., Bruch, R., Costa-Rama, E., Fernández-Abedul, M. T., Merkoçi, A., Manz, A., Urban, G. A., and Güder, F. (2019). Disposable Sensors in Diagnostics, Food, and Environmental Monitoring. *Advanced Materials*, *31*(30). https://doi.org/10.1002/adma.201806739

Fu, H., Tan, P., Wang, R., Li, S., Liu, H., Yang, Y., and Wu, Z. (2022). Advances in organophosphorus pesticides pollution: Current status and challenges in ecotoxicological, sustainable agriculture, and degradation strategies. *Journal of Hazardous Materials*, *424*(PB), 127494. https://doi.org/10.1016/j.jhazmat.2021.127494

Hashem, A., Hossain, M. A. M., Al Mamun, M., Simarani, K., and Johan, M. R. (2021). Nanomaterials based electrochemical nucleic acid biosensors for environmental monitoring: A review. *Applied Surface Science Advances*, *4*, 100064.

Huang, X., Zhu, Y., and Kianfar, E. (2021). Nano biosensors: properties, applications and electrochemical techniques. *Journal of Materials Research and Technology*, *12*, 1649–1672.

Kose, U., Prasath, V. B. S., Mondal, M. R. H., Podder, P., and Bharati, S. (2022). *Artificial Intelligence and Smart Agriculture Applications*. CRC Press.

Kozitsina, A. N., Svalova, T. S., Malysheva, N. N., Okhokhonin, A. V, Vidrevich, M. B., and Brainina, K. Z. (2018). Sensors based on bio and biomimetic receptors in medical diagnostic, environment, and food analysis. *Biosensors*, *8*(2), 35.

Kulkarni, M. B., Ayachit, N. H., and Aminabhavi, T. M. (2022). Recent Advancements in Nanobiosensors: Current Trends, Challenges, Applications, and Future Scope. *Biosensors*, *12*(10). https://doi.org/10.3390/bios12100892

Kumar, S., and Madhuri, R. (2022). Integrated Biosensors for Rapid and Point-of-Care Biomedical Diagnosis. In *Advanced Microfluidics Based Point-of-Care Diagnostics* (pp. 167–190). CRC Press.

Mahmoudpour, M., Karimzadeh, Z., Ebrahimi, G., Hasanzadeh, M., and Ezzati Nazhad Dolatabadi, J. (2022). Synergizing functional nanomaterials with aptamers based on electrochemical strategies for pesticide detection: current status and perspectives. *Critical Reviews in Analytical Chemistry*, *52*(8), 1818–1845.

Meliana, C., Liu, J., Show, P. L., and Low, S. S. (2024). Biosensor in smart food traceability system for food safety and security. *Bioengineered*, *15*(1), 2310908.

Mitra, T., Sahoo, S. K., Banerjee, A., Upadhyay, A. K., and Hasan, K. N. (2022). Potential of Nanobiosensors for Environmental Pollution Detection: Nanotechnology Combined with Enzymes, Antibodies, and Microorganisms. In *Nanotechnology for Environmental Pollution Decontamination* (pp. 189–218). Apple Academic Press.

Mukherjee, S., Ghosh, K., Bhattacharyya, S., Behera, B. K., Singh, O. K., and Pal, S. (2022a). A review on recent trends in advancement of bio-sensory techniques toward pesticide detection. *Food Analytical Methods*, *15*(12), 3416–3434.

Mukherjee, S., Ghosh, K., Bhattacharyya, S., Behera, B. K., Singh, O. K., and Pal, S. (2022b). We approve the execution of our nano biosensor in comparison with set up reference strategies for organophosphate discovery. *Food Analytical Methods*, *15*(12), 3416–3434.

Naresh, V., and Lee, N. (2021). A review on biosensors and recent development of nanostructured materials-enabled biosensors. *Sensors (Switzerland)*, *21*(4), 1–35. https://doi.org/10.3390/s21041109

Noor Hasnan, N. Z., Basha, R. K., Amin, N. A. M., Ramli, S. H. M., Tang, J. Y. H., and Aziz, N. A. (2022). Analysis of the most frequent nonconformance aspects related to Good Manufacturing Practices (GMP) among small and medium enterprises (SMEs) in the food industry and their main factors. *Food Control*, *141*, 109205. https://doi.org/https://doi.org/10.1016/j.foodcont.2022.109205

Olawore, O., Ogunmola, M., and Desai, S. (2024). Engineered Nanomaterial Coatings for Food Packaging: Design, Manufacturing, Regulatory, and Sustainability Implications. *Micromachines*, *15*(2), 245.

Ramakrishnan, B., Venkateswarlu, K., Sethunathan, N., and Megharaj, M. (2019). Local applications but global implications: Can pesticides drive microorganisms to develop antimicrobial resistance? *Science of the Total Environment*, *654*, 177–189.

Sahu, P., and Kashaw, S. K. (2023). Polymeric Nanocomposites-Based Agricultural Delivery: Recent Developments, Challenges, and Perspectives. *Agricultural and Environmental Nanotechnology: Novel Technologies and Their Ecological Impact*, 287–313.

Samadder, S., and Rao, D. (2023). Chapter-13 Role and Importance of ICT in Agricultural Extension. *Recent Trends in Agriculture*, 199.

Sargazi, S., Fatima, I., Kiani, M. H., Mohammadzadeh, V., Arshad, R., Bilal, M., Rahdar, A., Díez-Pascual, A. M., and Behzadmehr, R. (2022). Fluorescent-based nanosensors for selective detection of a wide range of biological macromolecules: A comprehensive review. *International Journal of Biological Macromolecules*, *206*, 115–147.

Serafinelli, C., Fantoni, A., Alegria, E. C. B. A., and Vieira, M. (2022). Plasmonic metal nanoparticles hybridized with 2D nanomaterials for SERS detection: A review. *Biosensors*, *12*(4), 225.

Sharma, P., Pandey, V., Sharma, M. M. M., Patra, A., Singh, B., Mehta, S., and Husen, A. (2021). A Review on Biosensors and Nanosensors Application in Agroecosystems. *Nanoscale Research Letters*, *16*(1). https://doi.org/10.1186/s11671-021-03593-0

Singh, A., Rajput, V. D., Varshney, A., Sharma, R., Ghazaryan, K., Minkina, T., Alexiou, A., and El-Ramady, H. (2024). Revolutionizing Crop Production: Nanoscale Wonders-Current Applications, Advances, and Future Frontiers. *Egyptian Journal of Soil Science*, *64*(1).

Stephanie, R., Kim, M. W., Kim, S. H., Kim, J.-K., Park, C. Y., and Park, T. J. (2021). Recent advances of bimetallic nanomaterials and its nanocomposites for biosensing applications. *TrAC Trends in Analytical Chemistry*, *135*, 116159.

Tripathi, A., and Bonilla-Cruz, J. (2023). Review on healthcare biosensing nanomaterials. *ACS Applied Nano Materials*, *6*(7), 5042–5074.

Uniyal, S., and Sharma, R. K. (2018). Technological advancement in electrochemical biosensor based detection of Organophosphate pesticide chlorpyrifos in the environment: A review of status and prospects. *Biosensors and Bioelectronics*, *116*, 37–50.

Upadhyay, S. K., Kumar, S., Rout, C., Vashistha, G., and Aggarwal, D. (2022). *Risks and Concerns of Use of Nanoparticles in Agriculture BT - The Role of Nanoparticles in Plant Nutrition under Soil Pollution: Nanoscience in Nutrient Use Efficiency* (V. D. Rajput, K. K. Verma, N. Sharma, and T. Minkina (eds.); pp. 371–394). Springer International Publishing. https://doi.org/10.1007/978-3-030-97389-6_16

Wahab, A., Muhammad, M., Ullah, S., Abdi, G., Shah, G. M., Zaman, W., and Ayaz, A. (2024). Agriculture and environmental management through nanotechnology: Eco-friendly nanomaterial synthesis for soil-plant systems, food safety, and sustainability. *Science of The Total Environment*, 171862.

Willner, M. R., and Vikesland, P. J. (2018). Nanomaterial enabled sensors for environmental contaminants. *Journal of Nanobiotechnology*, *16*, 1–16.

Xu, W., He, W., Du, Z., Zhu, L., Huang, K., Lu, Y., and Luo, Y. (2021). Functional nucleic acid nanomaterials: development, properties, and applications. *Angewandte Chemie International Edition*, *60*(13), 6890–6918.

Yildirim-Tirgil, N. (2023). Flexible Nanobiosensors in Biomolecular Detection and Point of Care Testing. In *Handbook of Nanobioelectrochemistry: Application in Devices and Biomolecular Sensing* (pp. 175–198). Springer

Chapter 44

Pharmacological Importance of Ketamine Loaded Nanoparticles

Asmara[1*], Laiba Fatima[2], Vishah Fatima[3], Maham Ahmed Butt[4], Anam Ghos[5], Muhammad Saleem[6], Muzammil Zaman Khan[7], Saad Hassan Qadir[8] and Muhammad Sikander Afzaal[9]

[1]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
[2]Department of Pharmacy, Faculty of Pharmacy, University of Lahore, Pakistan
[3]Department of Biochemistry, University of Agriculture Faisalabad, Pakistan
[4]Department of Pharmacy, Faculty of Pharmacy, University of Lahore, Pakistan
[5]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[6]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad Pakistan
[7]Department of Pharmacy, University of Agriculture Faisalabad, Pakistan
[8]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Superior University, Lahore, Pakistan
[9]Department of Pharmacy, Faculty of Pharmacy, University of Lahore, Pakistan
*Corresponding Author: asmarashahid005@gmail.com

ABSTRACT

Ketamine is an anesthetic that is utilized to enhance analgesia with a strong opioid-sparing effect in sub -anesthetic dosages and it's a latent treatment option. The brief in vivo elimination half-life of ketamine is an insufficiency. Therefore, our target was to improve ketamine-loaded polyethylene glycol (PEG)-(poly lactic-co-glycolic acid (PLGA) nanoparticles for sustained release that are both biocompatible and biodegradable. Our research exhibits that high drug loading and a sustained release profile are possible with ketamine-loaded PEG-PLGA nanoparticles produced using this novel nanoprecipitation method. Our conclusions show high ketamine encapsulation efficiency in the extended-release KSL preparation with continued release observed in mice consequently systematic management of doses that necessitates future investigation.

KEYWORDS
ketamine, analgesic, PEG-PLGA nanoparticles, Biocompatibility, Sustained release, High drug loading, Drug-loaded nanoparticles, Sustained release lipid particles

Received: 11-Jun-2024
Revised: 04-Jul-2024
Accepted: 11-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Asmara, Fatima L, Fatima V, Butt MA, Ghos A, Saleem M, Khan MZ, Qadir SH and Afzaal MS, 2024. Pharmacological importance of ketamine loaded nanoparticles. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 383-390. https://doi.org/10.47278/book.CAM/2024.470

INTRODUCTION

A. Overview of Ketamine

Ketamine serves as a powerful antagonist of the N-Methyl-D-aspartate (NMDA) receptor that is given in complicated patients associated with moderate to severe cancer pain and utilized as an analgesic adjuvant through a neuropathic constituent. Preclinical studies have presented that comparatively ketamine easily allows it to pass across the Central nervous system barrier. In another study involving laboratory animals, antagonizing NMDA receptors of ketamine decreased resistance to the pain-relieving properties of narcotic medications, which resulted in reducing pain in combination with opioids. Still, in vivo, ketamine has a brief duration of time or lifespan where it is effectiveness increased as a prolonged analgesic therapy. Ketamine loaded-nanoparticles (NPs) were formed according to our new method. Briefly, ketamine hydrogen chlorid (HCl) was altered to the ketamine-free base form by regulating the pH to ~10 by adding 2 M NaOH dropwise (Riccardi et al., 2023).

B. Nanoparticle Drug Delivery Systems

During the last two years, drug delivery systems designed as Lipid-based have extensively developed with increasing achievement from liposomal and semi-solid lipid systems. Liposomes are made of phospholipids that spherical bilayer vesicles that are similar to human cell membrane structure. Another way is solid lipid systems may be sphere-shaped but then their composition can be unequal surfaces and various kinds of lipids with a neutral state, positive and negative charged, or zwitter ionic (Barkat et al., 2020). In contrast with the ketamine-loaded poly(lactic-co-glycolic acid)-based extended-release pharmaceutical delivery systems, the KSL system accomplished a loading of more than 70% drug concentration that system resolved the low loading downside in our earlier designed prolonged-release polymer-based ketamine preparations.

This system thoroughly recognized that the poor chemical stability of various liposomal drug delivery systems is a significant restriction, as disaggregation and substance or medication leakage are more giving rise because of bond hydrolysis. In settlement with others, we also have established a deprived relationship among laboratory and living organism behaviors of our lipid vesicle medicated drug delivery organism. In the physiological condition, a lipid membrane sink may be present which would temporarily limit the movement of the free drug and in vitro drug release process that is unlikely to be simulated effectively (Ezike et al., 2023).

Pharmacokinetics of Ketamine

A. Absorption, Distribution, Metabolism, and Excretion (ADME)

The pharmacokinetic parameters of ketamine or ketamine-loaded NPs. Ketamine administered intravenously was quickly reduced in ~30 min elimination of half-life and plasma absorptions of ketamine decreasing to under the lower limit of quantification as a result of 24 hrs post-dosing. The correlated systemic exposure (AUC 0-inf_obs) was 14.1 μg/mL h. These pharmacokinetic parameters for intravenous ketamine in mice are similar to those described by others (Han et al., 2020). By contrast, for ketamine-loaded PEG-PLGA nanoparticles or PEG-PLGA: SH nanoparticles, the elimination half-life was markedly longer at ~103 h and ~80 h respectively for released ketamine. Furthermore, in comparison to the same dose of i.v. ketamine itself, the systemic exposure (AUC0-inf_obs) values were approximately 10-fold higher at ~162 and ~137 μg/mL h. By extending the elimination half-life, boosting systemic exposure, and reducing clearance in contrast to the same dose of I.V. ketamine administered alone, the incorporation of ketamine into NPs improves its pharmacokinetic profile. When compared with the PEG-PLGA: SH nanoparticle, the elimination half-life and the systemic exposure of ketamine released from the PEGPLGA nanoparticles were longer (~20 h) and larger (~20%) respectively (Glue et al., 2021).

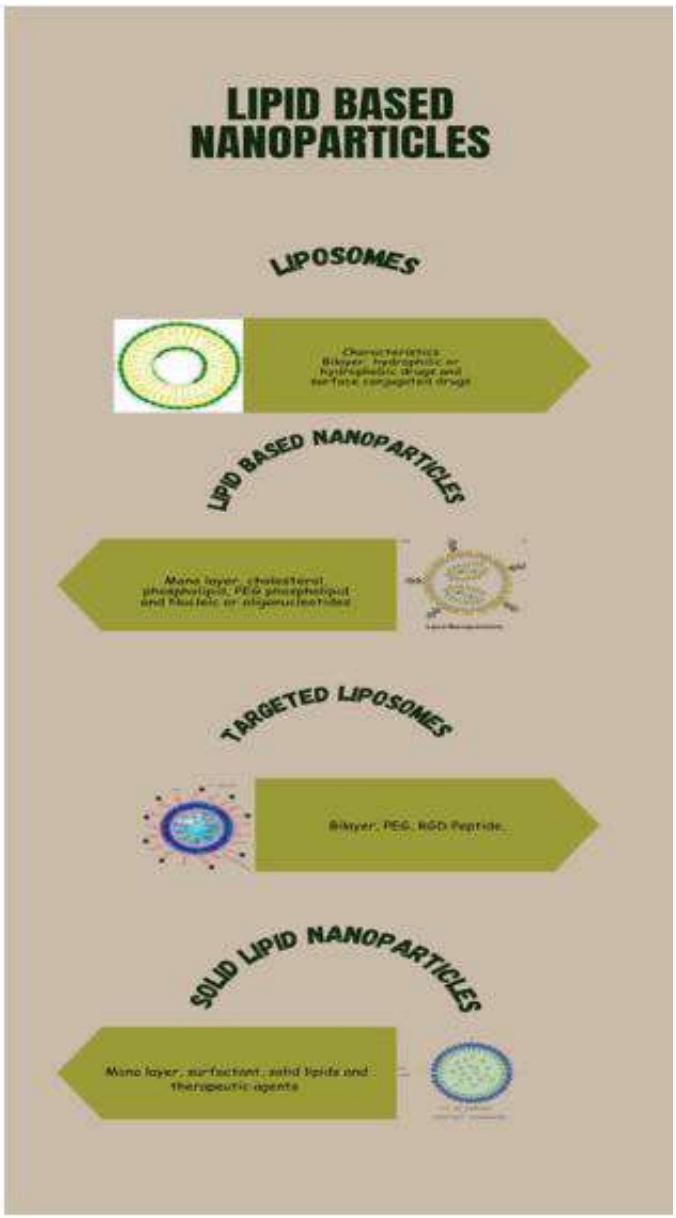


Fig. 1: lipid-based nanoparticles, (polyethylene glycol (PEG), arginine-glycine-aspartic acid (RGD))

B. Limitations of Conventional Ketamine Administration

With traditionally, these limitations improved the dissociative effects of acute Ketamine that give information about intranasal Ketamine 50mg in conjunction. For the treatment of treatment-resistant depression in combination through a conventional antidepressant, an enantiomer of racemic ketamine, was approved by the FDA. Furthermore, we developed hydromorphone-loaded PLGA-based sustained-release micro-particles. We also demonstrated that the concomitant of ketamine and the stout opioid analgesic by intrathecal, PLGA-based sustained-release microparticles show latent to enhance the liberation of else uncontrollable tumor-associated pain. Nonetheless, ketamine loading of these micro-particles was a shortage. On the way to account for such limitations, we offered that a superior outcome can produced by long-term relief of a liposomal-based delivery system and this revision was established to analyze our suggestion (Jelen and Stone, 2021).

Table 1: Types of Nanoparticles and their subtypes

Sr.	Hybrid NPs	Organic NPs	Inorganic NPs	References
1.	Hybrid NPs combine the characteristics of various NPs, including Lipid-polymer nanoparticles, Organic and inorganic nanoparticles, and Cell membrane-coated nanoparticles	This type of NPs contains Liposome-based NPs, Polymer-based nanoparticles including polymeric nanoparticles and polymeric micelles Dendrimers	These NPs contain Gold nanoparticles (Au NPs), Carbon nanotubes, Silica nanoparticles, Magnetic nanoparticles, and Quantum dots	(Yao et al., 2020) (Dristant et al., 2023b)

Nanoparticle Drug Delivery Systems

B. Advantages of Nanoparticle Delivery

In the treatment of disorders such as Cancer, optimal pharmacokinetics, accurate targeting of the tumor cells with reduced adverse reactions, and drug tolerance. NP-enhanced pharmaceutical delivery methods have clearly presented several advantages. The clinical management of various forms of cancer types includes various types i.e. organic and inorganic NPs. That has been thoroughly used as a priority during the process. As compared to conventional drugs with better PK parameters, tumor targeting, and bio-compatibility with stability. The Nano particles-based delivery systems have played a vital role in the significant reduction of systemic toxicity. They also have noticeable effects on drug resistance. These prominent characteristics of the NP-based drug delivery systems make them extensively capable of being applied for chemotherapy, Radiotherapy, gene therapy, hypothermia, and targeted therapy. Furthermore, drug resistance mechanisms including efflux transporters over NPs provide a better platform for combination therapy, which helps according to various methods or systems of multidrug tolerance (Raj et al., 2021). NPs contain a range of targeting and cytotoxic agents to overawed the issues correlated with drug resistance. In the recent few decades, NPs have been proven successful in diagnostics, procurement, and tumor targeting safely and effectively. They also have played a vital role in precise drug targeting with good Pharmacokinetics along with a significant decrease in adverse reactions as well as a reduction in drug tolerance. NP-based systems are designed and tailored based on the size and characteristics of tumors corresponding to their pathophysiology (Gavas et al., 2021).

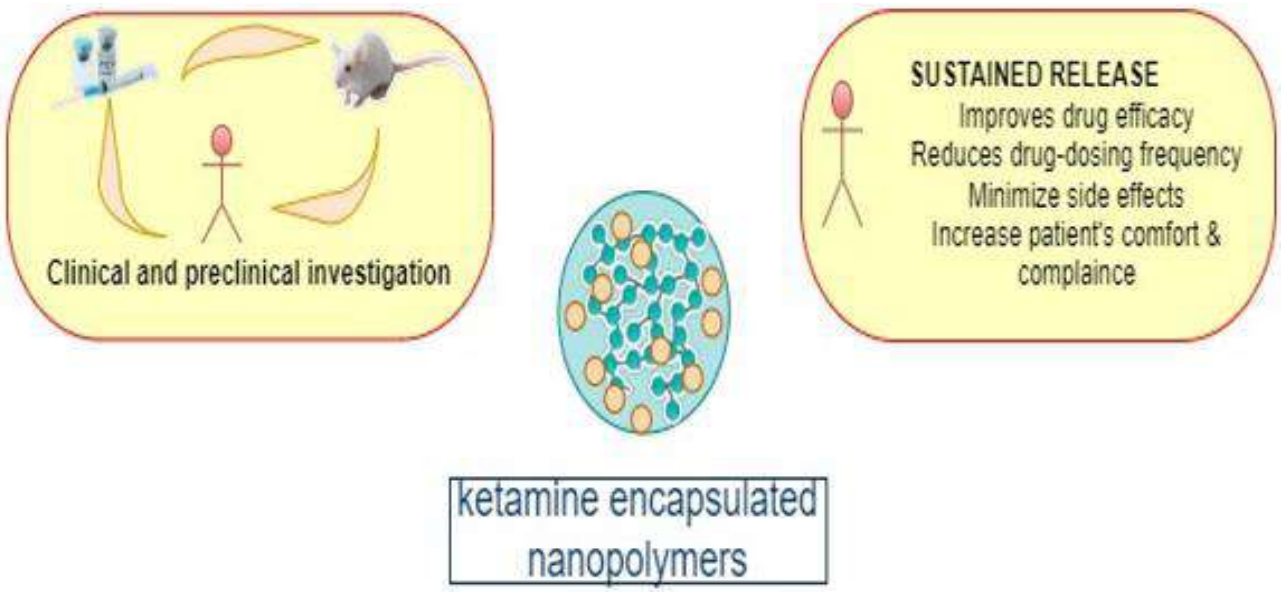


Fig. 2: Ketamine encapsulated nanopolymers that were injected into rats to investigate their sustainability releases

Formulation and Characterization of Ketamine Loaded Nanoparticles

A. Selection of Nanoparticle Carrier

Multi-lamellar liposomes were opted for the requirement of specific large doses. Similar to some homogenous natural membranes, the stability of the liposomal structure helps in increasing the bilayer vigor by the use of cholesterol as well as restricted to poor-cholesterol spheres of bilayer organisms this one is unblended as well as interdigitated (Hallan et al., 2021). One description for such an anomaly is that bulky groups or certainly uniform more agglomerates are formed outside of the hydro-shell, diminish most of the bright signs, also condensed particles are not represented in the particle size distribution data [30–32]. TEM observed the characteristics of Nano-sized particles like shape and structure. We formed round particles that are prospective to be sphere-shaped in 3D astronomical. TEM recommends a size alteration that is more protruding compared with the mean Zeta score with standard deviation demonstrated and in arrangement using the high Power Distance Index. This existence of multi-lamellar liposomes is indicated by the variation of the proportion between 800 nm and 2 μm (Beaumont et al., 2021).

B. Ketamine Encapsulation Techniques

By a Shimadzu UV-2450 (Shimadzu Scientific Instruments, Columbia, MD) with concentration at λ max (268 nm), the ketamine concentrations were calculated by UV–visible spectroscopy (UV–Vis) and interpolated against a standard curve consisting of 8 concentrations (0–20 μg/mL) in triplicate.

The formula for calculating the Drug encapsulation efficiency (EE) was:

EE [weight (drug added) weight (drug un encapsulated)] = / [weight (drug added) based on PEG-PLGA, the small molecule, ketamine, can be successfully encapsulated at high drug loading (41.8%) into biodegradable NPs. Our results are aligned with previous findings by others demonstrating that PLGA in combination with PEG can improve drug release profiles. It is commonly known that by dissolving both drug and polymer in a suitable solvent, many small molecules can be encapsulated and then by using either emulsification methods or nanoprecipitation methods, drug-loaded polymeric nanoparticles are formed. Nonetheless, the drug loading is often very low (less than 5–10%) (Han et al., 2020). Our present work is novel in that by using our approach we have formed polymeric nanoparticles with high ketamine loading. Our data also demonstrate that ketamine-loaded PEG-PLGA and PEGPLGA: SH nanoparticles are appropriate for sustained release for approximately 21 days in vitro and 5 days in vivo. It has been reported the kinetics of medicine release, the particle size, shape, and type of polymers and their degradability all affect considerably. Furthermore, for better-sustained release, particle size and surface characteristics can be improved. Our PEG-PLGA and PEGPLGA: SH nanoparticles are around 100 nm in diameter. Because of their large surface area per unit volume, commonly small-size NPs would be predicted, they show a rapid release profile assisting an increased rate of water permeation and medium dissolution compared with larger particles. Nonetheless, the distribution of drugs and effects of drug release in the polymer matrix from NPs. As the encapsulated drug needs to diffuse through the polymer matrix, our method's unique drug-core polymer-shell structure produced a sustained release profile (Weng et al., 2020). Our hematological data were within the normal ranges for mice, which is consistent with the established safety profiles of the polymers utilized herein. Our method offers a simple way to increase the elimination half-life, the attainment of increased ketamine loading, and a sustained release profile is further confirmed and in this case of ketamine, the systemic exposure of drugs of interest markedly increases (Bernard et al., 2018).

C. Physicochemical Characterization Methods

NPs utilized in pharmaceutical delivery systems are typically intended or selected conventional on their size and physical properties to effectively target the pathology of tumors (Raj et al., 2021). Involuntarily, for the treatment of cancer (Dristant et al., 2023a), Nano-carriers are designed to target tumor cells over the transporter result of nanoparticles and the locating effect of the targeting material once immersed. Following, the drug is discharged to tumor cells to prompt killing. Medications placed with conventional antineoplastic drugs and genetic materials are contained within nanocarriers, this demonstrates their potential part in both cytotoxic and gene treatment (Amreddy et al., 2018). Meanwhile, for some drugs with low solubility, NPs provide a policy for certain drugs with low solubility, thereby facilitating their condensation and their distribution of drugs into blood circulation. Nanocarriers can enhance drug half-life and promote their growth within cancerous tissues also their purpose is to improve drug permeability and retention as a result of the size and surface features of NPs, Nano-carriers can proliferate the half-life of drugs and prompt their growth into tumor tissues (Shinde et al., 2021). In addition, the targeting system defends healthy cells against the cytotoxic effects of drugs; and reduces the negative side effects associated with cancer treatment. For instance, PEGylated liposomes containing doxorubicin effectively condensed cardiotoxicity associated with the free form of doxorubicin (D. Singh and Pahwa, 2020). In addition, nanoparticle albumin-bound paclitaxel demonstrated decreased adverse drug effects and permitted greater tolerated dosages compared to solvent-based Texans. Now accumulation to Chemotherapeutic and genetic therapies, different research has described the use of nanoparticle drugs in the field of immunotherapy and surgical procedure involving the removal of tissue for cancer (Gavas et al., 2021).

Pharmacological Importance of Ketamine Loaded Nanoparticles

A. Enhanced Bioavailability and Stability

Various liposomes in formulation sorts are offered, predominantly the capability to attain long-lasting release of the enclosed medication of concern short of conceding bioavailability invivo. This analysis shows that sustained-release

liposomes containing ketamine were formed effectively used for the initial expending the liable thin-film layer method. In mice, a 5-day post-administration duration was completed, in a continue-release profile the KSL preparation ensued in the systemic circulation along with a sort of muscles. As concerns the PK, the KSL preparation produced in a 27-folding proliferation in lethal half-life, a three-fold propagation in systemic exposure (AUC0−∞), and a three-fold reduction in clearance related through the consistent PK for an equal i.v dosage administered as per an aqueous solution of ketamine HCl. By using procedures planned somewhere else for the preparation of KSL in which the thin-film deposition procedure was utilized (Sharma et al., 2022). Low cholesterol-contented liposomes are preferred for improved consistency, a glycerol phospholipid (DSPC) and for the preparation of a raw lipid solution using cholesterol in a molar ratio containing 90%:10% was liquefied in 10 mL of ethanol by adequate shaky, the KSL system that one possibly will have reduced stability, therefore the lipids rapidly split and distributed, settled their drug content. Typically, one of the main limits is their poor chemical stability for many liposomal drug delivery systems, as a result of bond hydrolysis provides increased disintegration and drug percolation (Kaur et al., 2018).

B. Prolonged Therapeutic Effect

A wide variety of Nano carriers like lipid-based, polymeric, and inorganic the co-organization of these molecules and the distribution of drug therapies like chemotherapy and immunotherapy in similar organisms. To conclude, their is an affinity to the usage of biologically stimulated as well as resultant Nano carriers. In that analysis, we identify the different Nano systems in the field of immunotherapy that are recommended via sorts including polymeric and lipid-based Nano systems, metallic and inorganic Nano systems, and lastly, biologically stimulated and derivative nanovacc in the modern improvement (Y. Zhang et al., 2020). In recent decades, the utilization in nanotechnology have been improved the delivery of therapeutics, furthermore used in the treatment of diseases like cancer, by the improvement of various Nano carriers used for drug delivery applications (Raj et al., 2021). The purpose to develop an effective drug delivery system (DDS) is to concentrate on ensuring a larger insignificant circulation of the therapeutic agent to the target site or affected body part then eliminating minor distribution to non-targeted sites within the body. Various determinations have been dedicated to the development of Nano carriers that are capable of co-delivering chemotherapy drugs, cytokines, and antibodies. The usage of Nano carriers intended for drug delivery, particularly in the enlargement of dual therapeutic DDS is required after in two of these approaches for check-point inhibitors and other vaccines. The compensations derivative with the use of Nano carriers that are capability of the targeted delivery of therapeutic compounds such as the tumor microenvironment or the immune system cells, additionally, the immune stimulatory loading compounds in particulate carriers significantly develop their safety profile, consenting, in certain circumstances, an increase in the quantity of nanocarrier; to conclude, Nano carriers can serve as an adjuvant, decreasing the requirement for co-administration of adjuvants and antigens (Yetisgin et al., 2020).

C. Targeted Drug Delivery

Targeting of nanoparticle appliances can lead to enhancement in reversing multidrug resistance. Mechanisms of tumor drug resistance are more exposed, and NPs are greatly established for targeting these mechanics. Scientists are in progress for investigating the part of NPs in immunotherapy, which has a significant role in the treatment of cancer. NPs and hybrid-based nanoparticles have intended part for the delivery of drugs in chemotherapy, immunotherapy and targeted therapy have defined the nanoparticles-based targeting mechanisms of drug delivery and function in depressive drug resistance. In recent days, the cumulative number of tiny therapeutic drugs has gained entry in different clinical stages. Clinical trials of phase 1 are utilized for targeting the nanoparticles that are based on a system for delivery of small interfering RNA in the patients that have cancer shown in 2010. Testification of different clinical studies has great efficiency in the treatment of tumors by dynamically targeting the polymeric types nanoparticles comprising of chemotherapeutic docetaxel, associated with the solvent that based on DTXL Preparation (C. Zhang et al., 2022).

D. Reduced Side Effects and Toxicity

The nanoparticles that bind with albumin paclitaxel showed minor adverse effects, permitting the dose with a higher tolerance than that based on solvent Texans (Ghasemii et al., 2022). In addition to the chemotherapeutics and therapy of genes, different examinations had stated the implementation of the drugs with nanoparticles in immunotherapeutics and erosion of cancer treatment. When we combine immunotherapeutics and chemotherapeutics, this can treat cancer. Once examination shows that when co-directing the agents of chemotherapy based on the outline 3a and GM-CSF cytokine in the spearmint showed the modification of nanoparticles leading to the enhanced propagation of cytotoxic CDs(+) T cells and restoring the response of immune, directing the tumor necrosis and evading the cell of immune toxic. The combination of chemotherapeutics and immunotherapeutics includes the delivery of chemotherapy and monoclonal antibodies into the pores of nanoparticles of silicon (Chao et al., 2019).

D. Clinical Applications and Future Perspectives

Dependence is a significant barrier that delays the broader clinical use of KA as an antidepressant. Our research shows that nanotechnology-based drug delivery systems are essential for complex kinds of brain-related diseases. When predesigning the design of Nano carriers intended for drug delivery, we must primarily concentrate on two things: one simplifies the delivery of drugs to the specific brain sites related to the disease, while the other reduces the potential for

drugs to reach brain sites related to side effects. The current investigation, we applied a combination of mesoporous calcium-doped silica core, enzyme-responsive hyaluronic acid collaboration, receptor-mediated camouflage, and functional peptide tagging in the nanostructure. All of these approaches confirm that KA is efficiently inserted and transported within the brain. The best optimal of brain targeting spots is vital, with a focus on areas associated with diseases while slightly taking place in other unaffected regions. In our analysis, the N Methyl D Aspartate Receptor (NMDAR) was preferred as a targeting site due to its more occurrence in the hippocampus and prefrontal cortex compared to the VTA and NC, which is extremely associated with addiction or habit behavior. Peptide Con-G was preferred as the designated peptide for targeting as well as concentrating the multifunctional nanoparticles at the NMDAR site in the hippocampus and prefrontal cortex, whereas evading the VTA and NAc parts. Particularly, it is necessary to consider the synergistic outcome of all strategies on the nanostructure while raising Nanocarriers. If only a portion of the strategy is utilized, the recovery efficiency of depressed mice may be inadequate. After simple treatment with our nanoparticles, their activities and cognitive function displayed a significant improvement in the depressed mice that were almost nearly to a normal level. The effects of clinical studies have revealed that enhancement in cognitive function and antidepressant effects can last for approximately two weeks subsequently multiple series of repeated injections of KA over a 2–3 week period. In the future, our target is to regulate the duration for which these developed behaviors and cognitive functions can last following the implementation of the lateswhilet treatment using Nano carrier (Hanif et al., 2021).

Safety and Toxicity Considerations

A. Biocompatibility of Nanoparticles

Nanoparticles play a substantial role as a drug delivery system for the treatment of cancer. Nanoparticle-based drug delivery system has various benefits, similar to conventional drugs, including good solidity and enhanced biocompatibility, improved permeability and improved retention, and targeted delivery. The development and scope of hybrid nanoparticles, which include the collective characteristics of various NPs, have directed this particular drug delivery system to the above grade. Moreover, NPs utilized in pharmaceutical formulations serve a significant purpose in addressing drug resistance encountered in cancer chemotherapy. Polymer-based NPs are a different type of NP with specific structural arrangements for drug carriers designed by various monomers. Poly Lactic-co-glycolic acid (PLGA), a common polymeric nanoparticle, incorporates the co-polymerization of glycolic acid and lactic acid. PLGA is extensively used as a carrier for drug delivery due to its improved biocompatibility, stability, and biodegradation, as well as the EPR effect (Ibrahim and Abdellatif, 2021).

B. Potential Adverse Effects of Ketamine

In vivo, ketamine (KA) is broadly recognized for its short half-life. Frequently repetitive KA administration is essential to retain enhanced and long-lasting treatment outcomes. Still, the total amount of KA may repeatedly surpass the onset for harmless usage, causing potential impacts, including dissociative illusions, dependency, addiction, and cognitive diminishing. As a result of anxieties concerning its potential side effects, the FDA has authorized the use of KA exclusively in the treatment of treatment-resistant depression (TRD) or else main depressive disorder (MDD) in cases of severe thoughts of suicide or self-harm. Until now, the dosage of the antidepressant was insignificant. It is recognized that the effectiveness of antidepressant outcomes is mightily correlated to the dose and frequency at which patients follow them. A comprehensive and quantitative evaluate the efficiency of antidepressants and their impact on cognitive function retrieval depression in mice models. In this study, we tried to incorporate the results of individual behavior experiments into a merged index to estimate the efficacy of antidepressants and the recovery efficacy of cognitive function (Highland et al., 2019).

C. Long-term Safety and Efficacy Studies

Finding innovative and new cancer treatments is a main challenge throughout the globe. With the proliferation of various methodologies for cancer treatment and the conception of modified therapy approaches, the effectiveness of treatment for certain types of malignant tumors has significantly developed. SNPs are widely considered as a highly effective option for drug delivery as a result of their enhanced pharmacokinetic, and therapeutic efficiency, as such as high constancy. Furthermore, porous silicon nanoparticles have greatly exposed latent in the field of immunotherapy as a result of their immune adjuvant characteristics, containing the ability to promote antigen cross-presentation, facilitate lymphocyte polarization, and stimulate the secretion of interferon-γ (IFN-γ) (S. Singh et al., 2021). Both organic and inorganic nanoparticles have their unique benefits and drawbacks, the combination of the twofold in a hybrid-based drug delivery system provides a versatile carrier through enhanced biological characteristics; this can improve treatment efficiency and decrease drug resistance (Shi et al., 2020). Specially Targeting tumor cells is a vigorous property of nano-carriers used for pharmaceutical delivery systems, this one improves the efficiency of therapy whereas protects healthy cells from toxic side effects. While NC and non-natural antigen-presenting cells (APCs) have proved enhanced effectiveness than traditional immunotherapy, additional studies are needed to evaluate the clinical efficiency and patient tolerance of these innovative treatment methods. Furthermore, the development of NPs loaded with immunomodulatory factors might increase the efficacy of vaccines in immunotherapy. Consequently, there is a superior understanding of the tumor microenvironment (TME) and additional research on the relations between nanoparticle-based drug delivery systems and tumor immunity to improve drug strategy and manipulation (Lôbo et al., 2021).

Conclusion

Numerous kinds of nanoparticles, containing organic and inorganic nanoparticles, have previously been extensively utilized in clinical cancer-related types of treatment. Related to conventional drugs, the use of nanoparticles as a base of drug delivery systems is linked with enhanced PK, biocompatibility, cancer targeting, and consistency, even though instantaneously serves a major part in decreasing systemic toxicity and to overcome the challenge of antimicrobial tolerance. These benefits permit nanoparticle-based drug delivery to be broadly utilized in chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy. Moreover, Nano carrier delivery systems arrange for upgraded stages used for combination treatment and also help overcome the resistance of drug mechanism, containing efflux carrier overexpression, malfunctioning apoptotic pathway, and hypoxia lump microenvironment. Based on several applications of multiple drug resistance (MDR), NPs loaded with various combinations of targeting agents and cytotoxic agents have been achieved to overcome the resistance of the drug. Through accumulative research, different types of hybrid nanoparticles have presented enhanced developments for delivery purpose and stimulated more consideration. Advanced research proceeding the biological properties of distinct cancers will result in more accurate drug research information. The main reasons influencing the interfaces between nanoparticles (NPs) and the immune system are the size, shape, composition, and surface characteristics of nanoparticles. While Nano vaccines as well as simulated APCs have established enhanced efficiency associated with traditional immunotherapy, further studies required in these new approaches for the treatment are insufficient in clinical efficiency, safety, and tolerance. Furthermore, increasing immunomodulatory factor-loaded NPs can increase the efficacy of vaccines intended for immunotherapy. Liposomes suggest various desired features in formulation, particularly concentrating on the capability to attain continuous release of the enclosed drug, deprived of conceding its effectiveness in the body. In this study, ketamine was effectively formed in liposomes expanding the standard thin-film coating system for the 1st time. The study demonstrated that the encapsulation and loading of medication in KSL achieved effectiveness rates of 65.6% and 72.4%, respectively . When inserted intravenously in mice, the KSL preparation ensued a prolonged-release profile in the systemic circulation, and various tissues of mice concluded for a period of 5 days after dosing. As regards the pharmacokinetics (PK), the KSL formulation produced a significant proliferation in terminal half-life, systemic exposure (AUC0−∞), and reduction in clearance related to the consistent PK of ketamine (KET) hydrochloric acid administered i.v. as a solution that has been dissolved in water for an equivalent dose. The tissue disposition information indicated that in elevation absorptions of KET were observed in the liver and brain as a result of 5 days following a single administration of the KSL preparation however not the ketamine HCl aqueous solution. Our prospective effort will concentrate on acquiring a better consideration of the production of this lipid particle to improve sensitivity into the detachment between the quick in vitro KET release and the elongated release from the KSL preparation in vivo.

REFERENCES

Amreddy, N., Babu, A., Muralidharan, R., Panneerselvam, J., Srivastava, A., Ahmed, R., Mehta, M., Munshi, A., and Ramesh, R. (2018). Recent advances in nanoparticle-based cancer drug and gene delivery. *Advances in Cancer Research*, *137*, 115–170.

Barkat, M. A., Das, S. S., Pottoo, F. H., Beg, S., and Rahman, Z. (2020). Lipid-based nanosystem as intelligent carriers for versatile drug delivery applications. *Current Pharmaceutical Design*, *26*(11), 1167–1180.

Beaumont, P., Courtois, A., Richard, T., Krisa, S., and Faure, C. (2021). Encapsulation of ε-viniferin into multi-lamellar liposomes: development of a rapid, easy and cost-efficient separation method to determine the encapsulation efficiency. *Pharmaceutics*, *13*(4), 566.

Bernard, M., Jubeli, E., Pungente, M. D., and Yagoubi, N. (2018). Biocompatibility of polymer-based biomaterials and medical devices–regulations, in vitro screening and risk-management. *Biomaterials Science*, *6*(8), 2025–2053.

Chao, J., Chow, W., Koczywas, M., Koehler, S., and Kim, H. (2019). Age-Related Changes in Nanoparticle Albumin Bound (nab) Paclitaxel Pharmacokinetics and Pharmacodynamics. *IRB*, *7157*(07/22), 19.

Dristant, U., Mukherjee, K., Saha, S., and Maity, D. (2023a). An overview of polymeric nanoparticles-based drug delivery system in cancer treatment. *Technology in Cancer Research and Treatment*, *22*, 15330338231152084.

Dristant, U., Mukherjee, K., Saha, S., and Maity, D. (2023b). An Overview of Polymeric Nanoparticles-Based Drug Delivery System in Cancer Treatment. *Technology in Cancer Research and Treatment*, *22*. https://doi.org/10.1177/15330338231152083

Ezike, T. C., Okpala, U. S., Onoja, U. L., Nwike, P. C., Ezeako, E. C., Okpara, J. O., Okoroafor, C. C., Eze, S. C., Kalu, O. L., and Odoh, E. C. (2023). Advances in drug delivery systems, challenges and future directions. *Heliyon*.

Gavas, S., Quazi, S., and Karpiński, T. M. (2021). Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale Research Letters*, *16*(1), 173.

Ghasemii, K., Darroudi, M., Rahimmanesh, I., Ghomi, M., Hassanpour, M., Sharifi, E., Yousefiasl, S., Ahmadi, S., Zarrabi, A., and Borzacchiello, A. (2022). Advances in aptamer-based drug delivery vehicles for cancer therapy. *Biomaterials Advances*, *140*, 213077.

Glue, P., Russell, B., and Medlicott, N. J. (2021). Influence of formulation and route of administration on ketamine's safety and tolerability: systematic review. *European Journal of Clinical Pharmacology*, *77*, 671–676.

Hallan, S. S., Sguizzato, M., Esposito, E., and Cortesi, R. (2021). Challenges in the physical characterization of lipid nanoparticles. *Pharmaceutics*, *13*(4), 549.

Han, F. Y., Liu, Y., Kumar, V., Xu, W., Yang, G., Zhao, C.-X., Woodruff, T. M., Whittaker, A. K., and Smith, M. T. (2020). Sustained-release ketamine-loaded nanoparticles fabricated by sequential nanoprecipitation. *International Journal of Pharmaceutics*, *581*, 119291.

Hanif, S., Muhammad, P., Niu, Z., Ismail, M., Morsch, M., Zhang, X., Li, M., and Shi, B. (2021). Nanotechnology-based strategies for early diagnosis of central nervous system disorders. *Advanced NanoBiomed Research*, *1*(10), 2100008.

Highland, J. N., Morris, P. J., Zanos, P., Lovett, J., Ghosh, S., Wang, A. Q., Zarate Jr, C. A., Thomas, C. J., Moaddel, R., and Gould, T. D. (2019). Mouse, rat, and dog bioavailability and mouse oral antidepressant efficacy of (2R, 6R)-hydroxynorketamine. *Journal of Psychopharmacology*, *33*(1), 12–24.

Ibrahim, M. A., and Abdellatif, A. A. H. (2021). Applications of nanopharmaceuticals in delivery and targeting. *Nanopharmaceuticals: Principles and Applications Vol. 1*, 73–114.

Jelen, L. A., and Stone, J. M. (2021). Ketamine for depression. *International Review of Psychiatry*, *33*(3), 207–228. https://doi.org/10.1080/09540261.2020.1854194

Kaur, G., Grewal, J., Jyoti, K., Jain, U. K., Chandra, R., and Madan, J. (2018). Oral controlled and sustained drug delivery systems: Concepts, advances, preclinical, and clinical status. In *Drug Targeting and Stimuli Sensitive Drug Delivery Systems* (pp. 567–626). Elsevier.

Lôbo, G. C. N. B., Paiva, K. L. R., Silva, A. L. G., Simões, M. M., Radicchi, M. A., and Báo, S. N. (2021). Nanocarriers used in drug delivery to enhance immune system in cancer therapy. *Pharmaceutics*, *13*(8), 1167.

Raj, S., Khurana, S., Choudhari, R., Kesari, K. K., Kamal, M. A., Garg, N., Ruokolainen, J., Das, B. C., and Kumar, D. (2021). Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. *Seminars in Cancer Biology*, *69*, 166–177.

Riccardi, A., Guarino, M., Serra, S., Spampinato, M. D., Vanni, S., Shiffer, D., Voza, A., Fabbri, A., and De Iaco, F. (2023). Narrative review: low-dose ketamine for Pain Management. *Journal of Clinical Medicine*, *12*(9), 3256.

Sharma, A., Verma, N., Chaturvedi, S., Prasad, N., and Rastogi, V. (2022). A Review on Polymeric Invasive and Non-Invasive Nanocarriers Assisted Transdermal Drug Delivery for Improved Penetration and Bioavailability. *Drug Delivery Letters*, *12*(1), 19–34.

Shi, Z., Zhou, Y., Fan, T., Lin, Y., Zhang, H., and Mei, L. (2020). Inorganic nano-carriers based smart drug delivery systems for tumor therapy. *Smart Materials in Medicine*, *1*, 32–47.

Shinde, A. S., Shinde, P. S., and Santra, T. S. (2021). Nanomaterials: versatile drug carriers for nanomedicine. *Nanomaterials and Their Biomedical Applications*, 253–296.

Singh, D., and Pahwa, S. (2020). A review on physico-chemical parameters of liposomal doxorubicin. *International Journal Applied Pharmacy*, *12*(2), 1–5.

Singh, S., Kumar, A., and Mittal, G. (2021). Ketamine-polymer based drug delivery system for prolonged analgesia: recent advances, challenges and future prospects. *Expert Opinion on Drug Delivery*, *18*(8), 1117–1130.

Wang, S., Duan, Y., Zhang, Q., Komarla, A., Gong, H., Gao, W., and Zhang, L. (2020). Drug Targeting via Platelet Membrane–Coated Nanoparticles. *Small Structures*, *1*(1), 1–15. https://doi.org/10.1002/sstr.202000018

Weng, J., Tong, H. H. Y., and Chow, S. F. (2020). In vitro release study of the polymeric drug nanoparticles: development and validation of a novel method. *Pharmaceutics*, *12*(8), 732.

Yao, Y., Zhou, Y., Liu, L., Xu, Y., Chen, Q., Wang, Y., Wu, S., Deng, Y., Zhang, J., and Shao, A. (2020). Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. In *Frontiers in Molecular Biosciences* (Vol. 7, p. 193). https://doi.org/10.3389/fmolb.2020.00193

Yetisgin, A. A., Cetinel, S., Zuvin, M., Kosar, A., and Kutlu, O. (2020). Therapeutic nanoparticles and their targeted delivery applications. *Molecules*, *25*(9), 2193.

Zhang, C., Xie, H., Zhang, Z., Wen, B., Cao, H., Bai, Y., Che, Q., Guo, J., and Su, Z. (2022). Applications and biocompatibility of mesoporous silica nanocarriers in the field of medicine. *Frontiers in Pharmacology*, *13*, 829796.

Zhang, Y., Liu, Y., and Liu, Y. (2020). Cyclodextrin-based multistimuli-responsive supramolecular assemblies and their biological functions. *Advanced Materials*, *32*(3), 1806158.

Chapter 45

Pharmacological Importance of Biomimetic Polymeric Nanoparticles

Sidra Altaf1

[1]Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: sidra.altaf@uaf.edu.pk

ABSTRACT

Biomimetic polymeric nanoparticles are an innovative approach to drug delivery that combines the flexibility of polymeric materials with biomimetic precision. This book chapter investigates the importance of biomimetic polymer nanoparticles in pharmacology and covers their design, synthesis, and application in various therapeutic fields. Biomimetic approaches involve mimicking biological structures and processes to allow nanoparticles to interact more harmoniously with their biological environment. Polymeric nanoparticles are a major drug delivery system that allows controlled release and targeted delivery. The aim of biomimetic designs is to increase biocompatibility, reduce immunogenicity, and overcome biological barriers. Biomimetic polymer nanoparticles contain lipids, proteins, and cell membrane fragments to enhance their biomimetic properties. Nanoparticle synthesis and fabrication techniques such as emulsion/solvent evaporation and surface functionalization are important to customize nanoparticles for specific applications. Biomimetic properties increase the therapeutic efficacy of these nanoparticles by mimicking biological barriers and using targeted strategies and responsive delivery systems. Biomimetic polymer nanoparticles have shown promise in pharmacology in cancers, infectious diseases, and neurological disorders. These enable targeted drug delivery, combination therapy, and effective penetration of the blood-brain barrier. In the future, regulations should be improved collaboratively, which requires the joint efforts of researchers, industry, and regulators. Safety is our top priority, and we focus on biocompatibility studies, toxicity evaluations, and long-term effects evaluations. Addressing the scalability and production challenges of biomimetic polymer nanoparticles requires innovative solutions that integrate advanced bioprocessing technologies and sustainable practices. Emerging trends include advanced targeting, in vivo imaging, responsive drug release, and personalized nanomedicine, paving the way for the transformation of medical nanoparticles. Biomimetic polymer nanoparticles have the potential to revolutionize drug delivery and shape the future of pharmaceuticals and patient transport.

KEYWORDS
Biomimetic nanoparticles; Polymeric drug delivery; Targeted therapy; Nanomedicine; Drug delivery systems; Biocompatible polymers

Received: 15-Jun-2024
Revised: 22-Jul-2024
Accepted: 10-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Altaf S, 2024. Pharmacological importance of biomimetic polymeric nanoparticles. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 391-402. https://doi.org/10.47278/book.CAM/2024.471

INTRODUCTION

Overview of Nanoparticles in Drug Delivery

Nanoparticles have developed as promising carriers for medicate conveyance due to their special properties and flexibility. Among the different sorts of nanoparticles, biomimetic polymeric nanoparticles have picked up noteworthy consideration within the field of pharmacology. These nanoparticles are planned to imitate natural structures and forms, giving a few points of interest for sedate conveyance. In this setting, the pharmacological significance of biomimetic polymeric nanoparticles can be highlighted through different viewpoints. Biomimetic polymeric nanoparticles are outlined to closely take after natural structures, making them inalienably more biocompatible than manufactured options (Umair et al., 2022).

This improves their compatibility with natural frameworks, decreasing the chance of resistant reactions or poisonous quality. By consolidating biomimetic highlights, such as cell films or particular ligands, these nanoparticles can accomplish progress focusing on specificity. This allows for the conveyance of drugs specifically to the required tissues or cells, minimizing off-target impacts and improving helpful viability. Biomimetic polymeric nanoparticles can be designed to overcome organic boundaries, such as blood-brain obstruction, which regularly limits the conveyance of drugs to certain tissues. Their likeness to characteristic structures encourages a more effective entrance of these boundaries, empowering drugs to reach their target destinations (Iqbal, et al., 2024).

The polymeric nature of these nanoparticles permits the embodiment of drugs in a controlled way. This comes about in

maintained and controlled discharge energy, dragging out the helpful impact and lessening the required requirement for visit dosing. Biomimetic polymeric nanoparticles display made strides in soundness in organic situations and delayed circulation times within the circulatory system. This amplified circulation upgrades the chances of the nanoparticles coming to their target destinations and increases the general adequacy of medicate conveyance. Targeted drug delivery and controlled discharge contribute to minimizing side impacts related to conventional medicate conveyance strategies. This can be especially imperative in moving forward with persistent compliance and by and large treatment results. The plan adaptability of biomimetic polymeric nanoparticles permits customization based on the particular prerequisites of diverse drugs and illnesses. This flexibility makes them reasonable for a wide extent of pharmacological applications (Fatima et al., 2023).

Significance of Biomimetic Approach in Nanoparticle Design

The biomimetic approach in nanoparticle plans holds critical significance, particularly within the setting of sedate conveyance frameworks. This approach includes mirroring normal biological structures and forms to make nanoparticles with upgraded usefulness. Biomimetic nanoparticles closely take after common natural substances, making them more consistent with living tissues and diminishing the chance of immunogenic reactions. Typically, pivotal for their secure and compelling integration into organic frameworks. By joining components that imitate particular highlights of cells or tissues, biomimetic nanoparticles can accomplish a predominant focusing on capacities. This upgrades their capacity to specifically convey drugs to infected tissues or cells, making strides in helpful viability while minimizing off-target impacts(Altaf et al., 2024).

Numerous sedate delivery challenges emerge from organic obstructions, such as the blood-brain boundary. Biomimetic nanoparticles can be planned to imitate the intelligence that normal substances utilize to navigate these boundaries, encouraging effective medicate conveyance to already block off locales. Biomimetic nanoparticles can abuse cellular take-up instruments, such as endocytosis, by mirroring the surface characteristics of cells. This advances the productive internalization of nanoparticles by target cells, guaranteeing the payload comes to its planning goal. The biomimetic approach permits the joining of atomic acknowledgment components, such as ligands or antibodies, on the nanoparticle surface. This empowers particular officials to receptors on target cells, encouraging exactly medicate conveyance and minimizing non-specific intuitive. Biomimetic nanoparticles can connected synergistically with organic frameworks, imitating the behavior of characteristic substances (Altaf and Iqbal, 2023).

This improves the in general integration of nanoparticles with physiological forms, moving forward their usefulness and decreasing the probability of antagonistic responses. Biomimetic nanoparticles can be built to reply to particular physiological jolts, such as pH, proteins, or temperature changes. This permits on-demand sedate discharge at the target location, giving a more controlled and responsive medicate conveyance framework. The utilization of biomimetic materials and structures tends to result in nanoparticles with decreased immunogenicity and poisonous quality. Usually significant for guaranteeing the security of nanoparticle-based sedate conveyance frameworks, particularly for incessant medicines. The biomimetic approach gives a flexible stage for nanoparticle plans. Analysts can draw motivation from a wide run of natural structures and forms, permitting the customization of nanoparticles for different restorative applications. Nature has advanced profoundly productive frameworks over time. By imitating these frameworks, biomimetic nanoparticles can advantage of the developmental optimization that has happened in organic substances, driving to made strides in usefulness and execution (Humaira et al., 2023).

Table 1: The characteristics and pharmacological importance of biomimetic polymeric nanoparticles

Sr. No.	Characteristics of biomimetic polymeric nanoparticles	Pharmacological Importance	References
1	Biomimetic Design	Improved Biocompatibility, Enhanced Targeting, Reduced Immunogenicity	(Kutner et al., 2021)
2	Polymeric Material Composition	Tunable Properties, Controlled Drug Release, Versatile Drug Loading	(Lai et al., 2020)
3	Key Components	Lipids, Proteins, Cell Membrane Fragments,	(Luchini and Vitiello, 2020)
4	Synthesis and Fabrication	Emulsion/Solvent Evaporation, Surface Functionalization	(Ali et al., 2021)
5	Biomimetic Properties	Mimicking Biological Barriers, Targeted Drug Delivery, Responsive Release Systems	(Rahamim and Azagury, 2021)
6	Pharmacological Applications	Cancer Therapeutics: Targeted Drug Delivery, Combination Therapy. Infectious Diseases: Antimicrobial Drug Delivery, Vaccine Delivery, Neurological Disorders: Blood-Brain Barrier Penetration, Neuroprotective Strategies	(Yetisgin et al., 2020)

Biomimetic Polymeric Nanoparticles

Definition and Characteristics of Biomimetic Nanoparticles

Biomimetic polymeric nanoparticles speak to a lesson of nanoscale sedate conveyance frameworks outlined to imitate natural structures and forms. These nanoparticles combine the points of interest of both biomimicry and polymer science to make flexible carriers for restorative agents. b Biomimetic polymeric nanoparticles are nanosized carriers for drugs or helpful operators that are designed to reproduce the basic and useful highlights of natural substances. These nanoparticles

coordinated polymeric materials with bioinspired components to upgrade their biocompatibility, focusing on capacities, and in general execution in medicate conveyance applications (Saqib et al., 2023).

Characteristics

Biomimetic nanoparticles are built utilizing polymers as the framework fabric. Polymeric lattices give a steady and biocompatible stage for medicate embodiment and discharge. Common polymers utilized incorporate manufactured polymers e.g., poly (lactic-co-glycolic corrosive) - PLGA, polyethylene glycol - PEG) and common polymers (e.g., chitosan, egg whites). These nanoparticles consolidate biomimetic highlights propelled by organic substances, such as cell films, proteins, or peptides. This biomimicry improves their interaction with organic frameworks, empowering particular focusing on, cellular take-up, and avoidance of the resistant framework (Altaf, Khan, et al., 2023).

Biomimetic polymeric nanoparticles regularly carry focusing on ligands on their surface, imitating the atomic acknowledgment and authoritative capabilities found in natural frameworks. These ligands can incorporate antibodies, peptides, or other particular moieties that recognize and tie to receptors on target cells. A few biomimetic polymeric nanoparticles are planned to display responsive behavior within the nearness of particular physiological jolts. This responsiveness can be activated by variables such as pH, chemicals, or temperature changes, driving to control medicate discharge at the target location. The biomimetic plan permits these nanoparticles to explore through natural obstructions more productively. Whether mirroring cell layers or utilizing particular transport instruments, biomimetic polymeric nanoparticles can overcome deterrents such as the blood-brain boundary, encouraging sedate conveyance to something else challenging anatomical areas (Saleem et al., 2023).

The polymeric nature of these nanoparticles permits for the controlled and supported release of therapeutic specialists. This can be vital for optimizing medicate pharmacokinetics and accomplishing a delayed restorative impact. Biomimetic polymeric nanoparticles exhibit reduced immunogenicity and poisonous quality compared to a few engineered partners. This can be ascribed to the utilization of biocompatible polymeric materials and the integration of biomimetic highlights that improve their compatibility with natural frameworks. The biomimetic approach gives a flexible plan stage, permitting the consolidation of different polymers, and biomimetic components, and focusing on ligands. This flexibility empowers the customization of nanoparticles to suit particular helpful applications (T. Iqbal et al., 2023).

Importance of Polymeric Nanoparticles in Drug Delivery

Polymeric nanoparticles play a vital part in sedate conveyance, advertising a few preferences that contribute to their centrality within the field. These nanoparticles, composed of manufactured or common polymers, give a flexible stage for the epitome and focus on the discharge of helpful specialists. Polymeric nanoparticles can typify hydrophobic drugs, making strides in their solubility and bioavailability. Typically, especially vital for drugs with destitute water dissolvability, as nanoparticles can upgrade their solidness and encourage superior assimilation. The polymeric network of nanoparticles permits the controlled and supported discharge of drugs. This controlled discharge profile can make strides in helpful adequacy, diminish side impacts, and minimize the requirement for visit dosing (Salma et al., 2023).

Functionalization of polymeric nanoparticles with focusing on ligands enables site-specific sedate conveyance. This focused-on approach increments medicate concentration at the specified area, moving forward treatment results while minimizing systemic presentation and side impacts. Numerous polymeric materials utilized in nanoparticle details, such as poly (lactic-co-glycolic corrosive) (PLGA) and polyethylene glycol (PEG), are biocompatible and biodegradable. This upgrades the security profile of polymeric nanoparticles, decreasing the chance of antagonistic responses and harmfulness. Polymeric nanoparticles give a defensive environment for labile drugs, protecting them from corruption due to natural components or enzymatic forms. This defensive impact contributes to the solidness of the sedate amid capacity and transportation (Gulnaz et al., 2023).

Polymeric nanoparticles can abuse the upgraded porousness and maintenance (EPR) impact, which permits them to construct up">to construct up especially in tumor tissues with cracked vasculature. This detached focus on the instrument improves medicate conveyance to cancerous tissues. Polymeric nanoparticles offer flexibility in terms of definition. Analysts can tailor the estimate, surface charge, and composition of nanoparticles based on the particular characteristics of the medicate and the planning mode of conveyance. Polymeric nanoparticles can be effectively stacked with imaging operators, permitting concurrent medicate conveyance and demonstrative imaging (Altaf et al., 2023).

This double usefulness is especially important in theragnostic, where treatment and diagnostics are coordinated. Polymeric nanoparticles empower the co-delivery of numerous drugs or restorative specialists, encouraging combination treatment. This approach can upgrade treatment adequacy by focusing on different pathways or tending to distinctive viewpoints of an illness at the same time. The generation of polymeric nanoparticles is frequently versatile, making them reasonable for large-scale fabricating. This ease of generation is fundamental for deciphering nanoparticle-based medicate conveyance frameworks from inquiry to clinical applications (Iqbal et al., 2024).

Rationale for Biomimetic Design in Drug Delivery Systems

The basis for biomimetic plans in medicates conveyance frameworks is grounded in the thought of imitating nature's standards to upgrade the adequacy, specificity, and biocompatibility of medicate conveyance stages. By consolidating biomimetic components into the plan of sedate conveyance frameworks, analysts point to address different challenges and

optimize helpful results. Biomimetic plan includes utilizing materials and structures that closely take after characteristic substances, lessening the hazard of resistant reactions, and improving the by and large biocompatibility of drug delivery frameworks (Iqbal and Altaf, 2024).

This is often basic for the secure and successful integration of these frameworks into natural situations. Normal boundaries, such as the blood-brain boundary or mucosal boundaries, can hinder the effective conveyance of drugs to target destinations. The biomimetic plan permits sedate conveyance frameworks to imitate the intelligence and instruments utilized by natural substances to explore and overcome these boundaries, progressing sedate entrance and dissemination. Biomimetic medicate conveyance frameworks regularly consolidate focusing on ligands that mirror the atomic acknowledgment and authoritative highlights found in organic frameworks. This empowers exactly focusing on particular cells or tissues, upgrading sedate conveyance to the expected location whereas minimizing off-target impacts (Kar, 2021).

Mirroring the surface characteristics of cells or infections permits biomimetic sedate conveyance frameworks to misuse characteristic cellular take-up instruments. This encourages effective internalization of the sedate carriers by target cells, advancing effective drug conveyance intracellularly. Biomimetic medicate conveyance frameworks can be built to reply to particular physiological prompts, such as pH, proteins, or temperature changes. This responsiveness empowers on-demand sedate discharge at the target location, moving forward the exactness and viability of the restorative intercession. The biomimetic approach permits the optimization of sedate pharmacokinetics by duplicating normal forms. This incorporates the plan of sedate carriers that imitate the behavior of endogenous particles, driving delayed circulation times and moving forward sedate bioavailability. Biomimetic medicate conveyance systems, by the ethicalness of their likeness to characteristic structures, regularly display decreased immunogenicity and poisonous quality (Hussain, 2022).

Typically, significant for minimizing antagonistic responses and guaranteeing the security of the conveyed restorative specialists. The biomimetic plan cultivates a synergistic interaction between medicate conveyance frameworks and natural substances. This interaction permits for superior integration with physiological forms, driving to move forward usefulness and minimizing disturbances to ordinary cellular capacities. Nature has experienced broad developmental optimization to create proficient and viable frameworks. Biomimetic medicate conveyance frameworks draw motivation from these normally advanced structures and forms, coming about in stages that advantage of millions of long times of organic refinement. The biomimetic approach gives a flexible plan stage, permitting customization based on the particular necessities of distinctive drugs and infections. This versatility makes biomimetic sedate conveyance frameworks appropriate for a wide extend of helpful applications (Elshafei et al., 2021).

Key Components of Biomimetic Polymeric Nanoparticles

Biomimetic polymeric nanoparticles are advanced medicate conveyance frameworks that consolidate different components to imitate and upgrade characteristic organic capacities. The polymeric network shapes the auxiliary spine of biomimetic polymeric nanoparticles. Polymers can be engineered, characteristic, or a combination of both. Common engineered polymers incorporate poly (lactic-co-glycolic corrosive) (PLGA) and polyethylene glycol (PEG), whereas chitosan and egg whites are illustrations of characteristic polymers. The choice of polymer impacts the soundness, biocompatibility, and medicate discharge characteristics of the nanoparticles. Biomimetic polymeric nanoparticles join highlights motivated by natural substances. This will incorporate the integration of cell films, proteins, or peptides on the nanoparticle surface to imitate common structures and capacities (Poko et al., 2024).

These biomimetic components upgrade intuitive with natural frameworks, advancing particular focusing on cellular take-up. Focusing on ligands are atoms joined to the surface of biomimetic polymeric nanoparticles to encourage particular authority to receptors on target cells. These ligands can be antibodies, peptides, or other moieties that recognize and tie to cell surface receptors, empowering focused on medicate conveyance. Surface alterations, such as the joining of polyethylene glycol (PEGylation), can improve the soundness and circulation time of biomimetic polymeric nanoparticles within the circulatory system. PEGylation decreases nonspecific intuition with blood components and improves the stealth properties of the nanoparticles. The drug payload is the helpful specialist typified inside the polymeric network of the nanoparticles. This could include small-molecule drugs, proteins, nucleic acids, or other bioactive compounds. The choice of sedate depends on the restorative application and the required mode of activity. A few biomimetic polymeric nanoparticles are designed to reply to particular physiological jolts (Konstantinidis et al., 2023).

Responsive components, such as pH-sensitive polymers or enzyme-responsive linkers, empower controlled drug discharge in reaction to changes within the neighborhood microenvironment, moving forward the exactness of sedate conveyance. Methods for typifying drugs inside the polymeric lattice play a significant part in the plan of biomimetic polymeric nanoparticles. Common strategies incorporate dissolvable vanishing, emulsion procedures, and nanoprecipitation, which permit the proficient embodiment of different sorts of drugs. In biomimetic polymeric nanoparticles motivated by cell films, lipids or lipid-like materials may be consolidated to imitate the lipid bilayer structure (Adhikari, 2021).

This upgrades the nanoparticles' biocompatibility and cellular take-up, closely taking after normal cell intelligence. Stabilizers and surfactants are regularly utilized amid the nanoparticle definition preparation to avoid molecule conglomeration and stabilize the emulsion or suspension. These operators contribute to the consistency and steadiness of biomimetic polymeric nanoparticles. Biomimetic polymeric nanoparticles can be outlined to carry imaging operators for demonstrative purposes. These imaging specialists may incorporate fluorescent colors, attractive nanoparticles, or other differentiated specialists, permitting concurrent imaging and medicate conveyance (Guan et al., 2022).

Synthesis and Fabrication of Biomimetic Polymeric Nanoparticles

Polymer Selection and Characteristics

The blend and manufacture of biomimetic polymeric nanoparticles include cautious determination of polymers and thought of their characteristics to attain the required properties for medicate conveyance applications. The choice of polymers impacts biocompatibility, sedate embodiment effectiveness, and the discharge profile of the nanoparticles. Polymers used in biomimetic polymeric nanoparticles must show tall biocompatibility to play down safe reactions and poisonous quality. Common biocompatible polymers incorporate polyethylene glycol (PEG), poly(lactic-co-glycolic corrosive) (PLGA), chitosan, and egg whites. Biodegradable polymers are favored to guarantee the continuous breakdown of the nanoparticles in vivo, decreasing the hazard of long-term amassing. PLGA, polylactic corrosive (PLA), and poly-caprolactone (PCL) are illustrations of biodegradable polymers commonly utilized in nanoparticle definitions. The chosen polymer ought to be congruous with the physicochemical properties of the medicate to be typified. For hydrophobic drugs, polymers with hydrophobic sections, such as PLGA, are appropriate, whereas hydrophilic drugs may require polymers with hydrophilic properties, such as PEG (Mwiiri & Daniels, 2020).

The steadiness and solvency of the polymer within the chosen dissolvable or scattering medium are vital for the manufacture preparation. The polymer ought to frame steady nanoparticles with the specified characteristics amid the union handle. Polymers ought to permit simple surface adjustment to present biomimetic highlights or useful bunches. This incorporates the joining of focusing on ligands, imaging specialists, or other biomimetic components to improve the nanoparticle's organic interactions. Polymers with tunable corruption rates and controlled discharge properties are alluring for accomplishing supported and controlled sedate discharge. PLGA, for occasion, can be custom fitted to debase over particular time periods, affecting the discharge energy. The chosen polymer ought to be agreeable to the chosen nanoparticle manufacturing method. Common manufacturing strategies incorporate dissolvable vanishing, emulsion techniques, and nanoprecipitation (Alipanah et al., 2023).

The polymer's characteristics ought to permit the arrangement of nanoparticles with a steady estimate and morphology. To improve the nanoparticles' circulation time within the circulation system and diminish clearance by the safe framework, polymers with stealth properties, such as PEG, are frequently utilized. This "PEGylation" gives a hydrophilic and steric obstruction on the nanoparticle surface, anticipating acknowledgment by macrophages. Depending on the application, polymers with temperature or pH-sensitive properties can be invaluable. These polymers empower the plan of stimuli-responsive nanoparticles that discharge drugs in reaction to particular natural cues. For biomimetic polymeric nanoparticles motivated by cell films, lipid-like materials may be included. These materials ought to display membrane-mimicking characteristics, permitting the nanoparticles to be associated with cells in a way comparable to common cellular components. Thought ought to be given to the versatility of the chosen polymer for large-scale nanoparticle generation. Polymers that can be synthesized or gotten in bulk with reliable quality are ideal for down-to-earth applications (Tenchov et al., 2023).

Techniques for Nanoparticle Fabrication

This procedure includes the arrangement of a steady emulsion by blending a water-immiscible natural stage containing the polymer and a water stage containing a surfactant or stabilizer. The organic solvent is then evaporated, leading to the formation of nanoparticles. Dissolve the polymer and drug (if applicable) in an organic solvent. Form an emulsion by adding this organic phase to an aqueous phase containing a surfactant. Stir to create a stable emulsion, where the organic phase is dispersed in tiny droplets in the aqueous phase. Evaporate the organic solvent, leading to the formation of solid nanoparticles. Versatile and widely used. Allows for the encapsulation of hydrophobic drugs. Achieves controlled release by modifying polymer composition (Zembyla et al., 2020).

Nanoprecipitation

Nanoprecipitation involves the rapid precipitation of a polymer from a solution by adding a non-solvent. This results in the formation of nanoparticles due to the reduced solubility of the polymer in the non-solvent. Dissolve the polymer and drug (if applicable) in a water-miscible organic solvent. Inject this solution into a non-solvent under constant stirring. Rapid precipitation of the polymer occurs, leading to nanoparticle formation. Remove residual solvents through purification steps. Simplicity and reproducibility. Suitable for thermolabile drugs. Allows for control over particle size and drug loading (Lavino et al., 2021).

Self-assembly involves the spontaneous organization of molecules into nanoparticles through non-covalent interactions such as hydrogen bonding, hydrophobic interactions, or electrostatic forces. Use amphiphilic block copolymers or surfactants that can self-assemble in aqueous solutions. The formation of micelles or vesicles occurs due to the arrangement of hydrophobic and hydrophilic segments. Encapsulation of drugs within the hydrophobic core of these structures. The self-assembled nanoparticles can be stabilized by cross-linking or additional modifications. Avoids the need for organic solvents. Enables controlled drug release through modulation of self-assembly parameters. Well-suited for encapsulating hydrophobic drugs (Q. Li et al., 2020).

Surface Functionalization and Modification of Biomimetic Polymeric Nanoparticles

Surface functionalization and modification play a crucial role in tailoring the properties of biomimetic polymeric nanoparticles for specific drug delivery applications. These forms include the presentation of useful bunches, ligands, or biomimetic components onto the nanoparticle surface to improve biocompatibility, accomplish focus on sedate conveyance,

and move forward intelligence with natural frameworks. A few methodologies are utilized for surface functionalization and alteration. Polyethylene glycol (PEG) is commonly utilized to adjust the surface of nanoparticles in a handle known as PEGylation. PEGylation gives a hydrophilic and steric obstruction to the nanoparticle surface, lessening opsonization, and drawing out circulation time within the bloodstream. Increased stealth properties, minimized safe reaction, and upgraded bioavailability. Biomimetic polymeric nanoparticles are regularly functionalized with focusing on ligands such as antibodies, peptides, or aptamers (Shi et al., 2021).

These ligands advance particular intuition with receptors on target cells, encouraging focus on medicate delivery. Improved selectivity, improved cellular take-up, and decreased off-target impacts. Mirroring the characteristic cell film, nanoparticles can be coated with parts or vesicles determined from cell films. This surface adjustment improves biocompatibility and permits for intelligent cells in a way comparative to normal cell-cell intuitive. Made strides in biocompatibility, decreased safe reaction, and improved cellular take-up. Nanoparticles can be coated with polymers that react to changes in pH, such as poly(2-(diisopropylamino)ethyl methacrylate) (PDPA). This permits pH-triggered sedate discharge in particular physiological situations. Controlled sedate discharge at target destinations with shifting pH, such as tumor microenvironments (Gao et al., 2020).

Nanoparticles can be planted with coatings that react to particular chemicals shown in infected tissues. For this case, peptide groupings delicate to proteins like lattice metalloproteinases (MMPs) can be consolidated to empower enzyme-triggered sedate discharge(T. Iqbal, Altaf, Salma, et al., 2024). Upgraded sedate discharge at illness locales with overexpressed proteins, focusing on treatment. Changing the surface charge of nanoparticles through the expansion of charged polymers or surfactants can impact their intelligence with cells and organic components. Cationic or anionic coatings can be applied based on the desired effect. Improved cellular uptake, reduced clearance by the immune system, and controlled interactions with biological systems. Nanoparticles can be functionalized with imaging agents, such as fluorophores, radiotracers, or magnetic nanoparticles, to enable simultaneous imaging and drug delivery (theragnostic). Real-time monitoring of drug delivery, improved diagnosis, and personalized treatment approaches. Combining multiple functionalization strategies, such as incorporating targeting ligands and imaging agents simultaneously, can result in multi-functional nanoparticles with enhanced therapeutic and diagnostic capabilities. Comprehensive and synergistic functionalities for optimized drug delivery (Makvandi et al., 2021).

Biomimetic Properties in Polymeric Nanoparticles

Mimicking Biological Barriers

Blood-Brain Barrier (BBB)

The BBB is a highly selective barrier that regulates the passage of substances from the bloodstream into the brain. Overcoming the BBB is a significant challenge in drug delivery for the treatment of central nervous system disorders. Surface modification with ligands that interact with receptors overexpressed on BBB endothelial cells (e.g., transferrin receptors) facilitates receptor-mediated transcytosis. Coating nanoparticles with fragments of cell membranes, such as those from red blood cells or brain cells, can mimic natural interactions and enhance BBB penetration(Altaf et al., 2021)(Altaf & Alkheraije, 2023). Designing nanoparticles with sizes within the optimal range (typically below 200nm) can enhance their ability to pass through the tight junctions of BBB endothelial cells. Improved drug delivery to the brain, enhanced therapeutic efficacy for neurological disorders, and reduced systemic side effects (Wu et al., 2023).

Mucosal Barriers

Mucosal barriers, including those in the gastrointestinal tract, respiratory tract, and genitourinary tract, present challenges for effective drug delivery due to mucus secretion and rapid clearance mechanisms. Surface modification with mucoadhesive polymers, such as chitosan or poly (acrylic acid), facilitates prolonged contact with mucosal surfaces, improving drug retention and absorption. Planning nanoparticles with surface adjustments that decrease attachment to bodily fluid components and upgrade infiltration through bodily fluid layers can move forward mucosal medicate conveyance. Presenting pH or enzyme-responsive coatings empowers controlled medicate discharge in particular mucosal situations, optimizing helpful results. Upgraded mucosal grip, delayed medicate maintenance, moved forward assimilation and focused on the conveyance for mucosal maladies or immunization (Cavalu et al., 2020).

Targeting Strategies

Ligand conjugation includes connecting particular focusing on ligands to the surface of polymeric nanoparticles. These ligands can be antibodies, peptides, aptamers, or other moieties that recognize and tie to receptors overexpressed on the surface of target cells. Ligands selectively bind to receptors on the target cell surface. Upon binding, the ligand-receptor complex is internalized through endocytosis. The nanoparticle, along with the encapsulated drug, is released inside the target cell. Ligand conjugation improves the specificity of drug delivery to target cells or tissues. Minimizes non-specific interactions and off-target effects. Facilitates efficient internalization by target cells (Yan et al., 2024).

Active targeting involves exploiting physiological characteristics or processes to enhance the accumulation of polymeric nanoparticles at specific target sites. This can include targeting diseased tissues, inflamed areas, or sites with specific physiological features. Passive targeting by leveraging the leaky vasculature in tumor tissues allows nanoparticles to accumulate selectively. Designing nanoparticles to respond to specific stimuli in the target microenvironment (e.g., pH,

enzymes) for controlled drug release. Mimicking cellular internalization processes, such as endocytosis, for efficient uptake by target cells (Kang et al., 2020).

Responsive Release Systems and pH-Sensitive Nanoparticles

pH-sensitive nanoparticles are planned to discharge their payload in reaction to changes in pH inside the target microenvironment. This procedure is especially valuable for sedate conveyance to particular physiological compartments with changing causticity, such as tumor tissues or intracellular endosomes. Polymers with pH-responsive bunches e.g., poly (acrylic corrosive), poly (histidine) experience ionization or protonation changes in reaction to pH varieties. pH-induced changes lead to changes within the polymer structure, causing the nanoparticles to swell or recoil. c. Swelling uncovered the typified medication to the encompassing environment, encouraging controlled discharge (Ding et al., 2022)(Altaf, Iqbal, et al., 2023).

Allows for drug release at sites with specific pH conditions. Optimizes drug release in response to the physiological characteristics of target tissues. Minimizes off-target release in normal physiological environments. Enzyme-triggered release systems exploit the presence of specific enzymes in diseased tissues to induce drug release. This approach is particularly relevant for diseases characterized by overexpression of certain enzymes, such as cancers and inflammatory conditions. Incorporating enzyme-cleavable linkers within the polymeric matrix of nanoparticles(T. Iqbal et al., 2023). Enzymes present in the target tissue selectively cleave the linkers. Cleavage of linkers results in the release of the encapsulated drug. Enables drug release specifically in the presence of disease-associated enzymes. Reduces off-target release in healthy tissues. Optimizes therapeutic effects in diseased tissues while sparing normal tissues (X. Li et al., 2021).

Pharmacological Applications of Biomimetic Polymeric Nanoparticles

Cancer Therapeutics and Targeted Drug Delivery

Targeted drug delivery using biomimetic polymeric nanoparticles is a promising strategy in cancer therapeutics to enhance the specificity and efficacy of anticancer drugs while minimizing systemic side effects. Surface modification with targeting ligands (e.g., antibodies, peptides) for specific recognition of cancer cells. Passive targeting exploits the leaky vasculature and impaired lymphatic drainage in tumor tissues. pH-sensitive or enzyme-triggered nanoparticles for selective drug release within the tumor microenvironment. Increased drug concentration in tumor tissues. Minimized impact on healthy tissues (Beh et al., 2021).

Enhanced targeting precision for effective cancer treatment. Combination therapy involves the simultaneous delivery of multiple therapeutic agents using biomimetic polymeric nanoparticles. This approach aims to target multiple pathways or address different aspects of cancer biology for improved treatment outcomes. Encapsulation and simultaneous release of multiple drugs within the same nanoparticle. Combining drugs with complementary mechanisms of action for enhanced anticancer effects. Tailoring the combination of drugs based on the specific characteristics of the cancer type. Improved therapeutic effects through synergistic drug interactions. Targeting multiple pathways can help overcome resistance mechanisms. Achieving therapeutic efficacy with lower individual drug doses, minimizing adverse effects (Wang et al., 2022).

Infectious Diseases

Biomimetic polymeric nanoparticles can be employed for targeted and controlled delivery of antimicrobial active substances to combat infectious diseases caused by bacteria, viruses, fungi, or parasites(M. U. Iqbal et al., 2024)(T. Iqbal, Altaf, Fatima, et al., 2024).

Ligand-functionalized nanoparticles for particular acknowledgment and authority to microbial pathogens. Custom fitted for discharge in particular contamination locales with shifting pH or protein expression. Synchronous conveyance of different antimicrobial specialists for synergistic impacts. Focusing on microbial pathogens with ligand-functionalized nanoparticles (Ibrahim et al., 2021).

Minimizing the effect on cells through a focus on conveyance. Combating microbial resistance through combination treatment. Biomimetic polymeric nanoparticles offer a promising stage for effective and focused antibody conveyance, giving upgraded safe reactions and security against irresistible maladies. Loading nanoparticles with antigens from pathogens to stimulate an immune response. Surface modification with ligands to enhance uptake by antigen-presenting cells (APCs). Co-delivery of immune-stimulating adjuvants for enhanced vaccine efficacy. Enhancing the immune response against specific pathogens. Facilitating antigen presentation for a robust immune response (Ferreira et al., 2020).

Neurological Disorders

Biomimetic polymeric nanoparticles can be utilized for neuroprotective strategies aimed at preserving neuronal function and preventing or mitigating damage associated with neurological disorders. Loading nanoparticles with antioxidants to combat oxidative stress, is a common feature in neurological disorders. Delivery of anti-inflammatory drugs to reduce neuroinflammation and protect neurons. Encapsulation and controlled release of neurotrophic factors to support neuronal survival and regeneration. Mitigating damage and supporting the survival of neurons. Addressing underlying mechanisms contributing to neurodegeneration. Prolonged and controlled release for sustained neuroprotection (Fukuta et al., 2022).

Biocompatibility and Safety Considerations

In vitro and In vivo Biocompatibility Studies

In vitro studies assess the compatibility of biomimetic polymeric nanoparticles with biological systems at the cellular and molecular levels before proceeding to in vivo evaluations. Evaluate the impact of nanoparticles on the viability of cultured cells using assays like MTT or Alamar Blue. Assess the potential of nanoparticles to induce cell death or adverse effects on cellular morphology. Measure the release of inflammatory markers or cytokines from exposed cells. Investigate interactions with blood components to assess the risk of hemolysis or clotting. Exposure of relevant cell lines to varying concentrations of nanoparticles. Microscopy to observe cellular morphology and interactions. Quantification of cell viability, cytotoxicity, and inflammatory responses. Identification of nanoparticle concentrations that are well-tolerated by cells. Insights into potential cytotoxic effects or inflammatory responses (Kenry et al., 2020).

In vivo Biocompatibility Studies

In vivo studies evaluate the biocompatibility, biodistribution, and safety of biomimetic polymeric nanoparticles in living organisms, providing insights into their systemic effects. Examine the distribution of nanoparticles in major organs to understand their systemic behavior. Assess tissue morphology and identify potential signs of inflammation or damage. Evaluate changes in blood parameters, liver enzymes, and other markers of organ function. Look at safe cell enactment and reactions to nanoparticle introduction. Utilize important creature models (e.g., mice, rats) to imitate physiological conditions. Analyze the nearness of nanoparticles in different organs over time. Assess tissue segments for variations from the norm or signs of poisonous quality. Evaluate blood tests for changes in hematological and biochemical parameters. Affirmation of the by and large security and tolerability of nanoparticles. Discovery of any signs of poisonous quality, aggravation, or organ harm. Experiences into alterations required for moved forward security (Marshall et al., 2022).

Toxicological Assessment

Toxicological appraisal may be a basic component of assessing the security of biomimetic polymeric nanoparticles. It includes a comprehensive investigation of potential poisonous impacts at the atomic, cellular, and systemic levels. The objective is to distinguish and get any unfavorable responses or dangers related to the utilize of these nanoparticles. Toxicological appraisal envelops a run of studies, both in vitro and in vivo, to supply a careful understanding of the security profile of the nanoparticles. Evaluate the potential poisonous impacts of biomimetic polymeric nanoparticles on cells and cellular forms. Decide the effect on the development and survival of refined cells (Biswas et al., 2022).

Assess potential harm to cellular DNA. Degree oxidative push initiated by nanoparticles. Survey the discharge of incendiary go-betweens and cytokines. Introduction of important cell lines to shifting concentrations of nanoparticles. Evaluations utilizing comet measures, micronucleus measures, or other genotoxicity tests. Utilize fluorescent tests or tests to degree intracellular ROS levels. Measure cytokine discharge and other markers of aggravation. Determination of adverse effects on cell viability and proliferation. Insights into potential DNA damage. Understanding the impact on cellular inflammatory pathways. Evaluate the safety of biomimetic polymeric nanoparticles in living organisms, providing a more holistic view of potential systemic toxicity. Examine nanoparticle distribution in major organs to understand systemic behavior. Assess tissue morphology and identify signs of toxicity or damage (Mathios et al., 2021).

Examine blood samples for changes in organ function markers. Evaluate immune system reactions to nanoparticle exposure. Use relevant animal models to mimic physiological conditions. Analyze the presence of nanoparticles in various organs over time. Evaluate tissue sections for abnormalities or signs of toxicity. Assess blood samples for changes in hematological and biochemical parameters. Confirmation of overall safety and tolerability. Detection of any signs of toxicity in specific organs. Understanding how the immune system reacts to nanoparticle exposure (Chen et al., 2020).

Long-term Effects and Biodistribution

Assess the potential chronic effects and persistence of biomimetic polymeric nanoparticles over an extended duration. Evaluate any sustained adverse effects on organs, tissues, or physiological processes. Investigate the potential for nanoparticle-induced carcinogenesis over prolonged exposure. Monitor long-term impact on the function of vital organs. Continued exposure and monitoring of animal models over an extended period. Ongoing assessment of tissue morphology and signs of chronic toxicity. Systematic evaluation of the potential for nanoparticle-induced cancer development. Understanding the persistence of any toxic effects. Assessment of the nanoparticles' safety over extended exposure (Ben-Akiva et al., 2020).

Evaluation of any potential carcinogenic effects. Investigate the distribution and accumulation of biomimetic polymeric nanoparticles in various organs and tissues. Quantify the presence of nanoparticles in major organs. Assess the rate at which nanoparticles are cleared from the body. Determine the extent of nanoparticle accumulation in specific target tissues. The biodistribution of nanoparticles. Utilize imaging modalities like MRI, CT, or fluorescence for real-time visualization. Extricate tissues at different times focuses on quantitative examination. Understanding how nanoparticles disseminate inside the body. Data to optimize nanoparticle properties for made strides focusing on. Distinguishing proof of techniques to decrease off-target amassing (Mansouri et al., 2020).

Current Challenges and Future Perspectives

Regulatory Challenges

The administrative endorsement preparation for biomimetic polymeric nanoparticles faces challenges due to the one-of-a-kind nature of these progressed medicate conveyance frameworks. Administrative organizations may not have particular rules custom-made to the endorsement of biomimetic polymeric nanoparticles, driving to instabilities within the assessment preparation. The complex nature of these nanoparticles may pose challenges in standardizing characterization methods, making it troublesome to set up reliable administrative criteria. Collaborative endeavors between analysts, industry, and administrative bodies to create standardized rules for the assessment and endorsement of biomimetic polymeric nanoparticles. Ceaseless communication between partners to guarantee that administrative systems advance in parallel with progressions in nanoparticle innovation (Elmowafy et al., 2023).

The security evaluation of biomimetic polymeric nanoparticles includes special contemplations, and administrative organizations may confront challenges in setting up comprehensive security criteria. Standardizing conventions for the toxicological appraisal of these nanoparticles may be challenging, as their properties can shift broadly. Administrative systems may not be completely prepared to address the long-term impacts and incessant harmfulness of biomimetic polymeric nanoparticles. Advancement of standardized poisonous quality testing conventions particular to biomimetic polymeric nanoparticles, considering their special characteristics. Incorporation of long-term thinks about administrative necessities to survey unremitting impacts and guarantee the security of delayed presentation (Nanda et al., 2024).

Understanding the biodistribution and pharmacokinetics of biomimetic polymeric nanoparticles is vital for administrative endorsement but presents challenges in terms of standardization and consistency. Variability in individual reactions to nanoparticles may complicate endeavors to set up standardized biodistribution designs. Current models may not completely capture the complex intelligence of biomimetic nanoparticles inside the body. Progressions in imaging innovations and modeling approaches to make strides in the consistency of biodistribution. Collaboration between administrative offices, the scholarly community, and industry to refine rules for assessing and detailing biodistribution information (Kenry et al., 2020).

The intriguing nature of biomimetic polymeric nanoparticle inquiry about requires collaboration between researchers, clinicians, and administrative specialists, which can be challenging to execute consistently. The need for effective communication between analysts and administrative specialists can result in errors or delays within the endorsement preparation. Administrative offices may confront challenges in enlisting and holding specialists with intriguing information of nanoparticle innovation. Advancement of collaborative stages and activities that encourage exchange and information exchange among analysts, clinicians, and administrative specialists. Advancement of preparing programs and instructive assets to improve administrative skills within the assessment of progressed nanomedicines (Fondaj et al., 2023).

Scalability and Manufacturing Concerns

The complex nature of biomimetic polymeric nanoparticles may pose challenges in accomplishing large-scale generation and reproducibility. Complex details may result in varieties between bunches, affecting consistency in medicate conveyance execution. Deciphering laboratory-scale details to versatile fabricating forms can be troublesome due to expanded complexity. Selection of quality-by-design (QbD) standards within the improvement handle to get it and control basic parameters influencing versatility. Usage of progressed explanatory procedures to screen and control fabricating forms in real-time (Fabozzi et al., 2021).

Consolidating biomimetic components into the fabricating preparation includes complexity and requires imaginative bioprocessing approaches. Recognizing and sourcing biomimetic components for nanoparticles may pose challenges in terms of accessibility, consistency, and ethical contemplations. Guaranteeing the correct integration of biomimetic components into the fabricating handle without compromising solidness and reproducibility. Advancement of versatile and feasible strategies for sourcing biomimetic components. Integration of progressed bioprocessing advances, such as nonstop fabricating, to upgrade productivity and control (Dalton et al., 2020).

Quality Control and Characterization

Guaranteeing the quality and consistency of biomimetic polymeric nanoparticles at a huge scale requires vigorous quality control measures. Characterizing the complex structure of biomimetic nanoparticles can be challenging, affecting the advancement of standardized quality control strategies. Assembly administrative benchmarks for item quality and consistency may be more complex due to the special highlights of biomimetic definitions. Headways in explanatory procedures for comprehensive characterization of biomimetic nanoparticles (Mehta et al., 2023).

Collaboration between industry and administrative offices to set up standardized quality control conventions for biomimetic definitions. The selection of novel advances for the adaptable generation of biomimetic polymeric nanoparticles may confront challenges in terms of mechanical preparation and optimization. Exchanging imaginative laboratory-scale innovations to large-scale fabricating settings may experience obstacles. Guaranteeing innovations that novel innovation are financially reasonable for a large-scale generation without compromising item quality. Collaborative endeavors between the scholarly world and industry to bridge the hole between novel advances created in investigatinginvestigative settings and their adaptability for fabricating. Venture in investigation and advancement to optimize and adjust novel innovations for large-scale generation (AlAli et al., 2023).

Emerging Trends and Future Directions in Biomimetic Nanoparticles

Advanced Targeting Strategies

Development of ligands with multiple targeting functionalities for improved recognition and binding to specific cells or tissues. Integration of responsive elements that enable on-demand activation of targeting mechanisms in response to specific cues in the microenvironment. Advancements in responsive release systems to achieve spatiotemporal control over drug delivery. Incorporation of external stimuli (e.g., light, magnetic fields) for precise control over drug release. Implementation of feedback mechanisms to adjust drug release in response to real-time physiological changes (Mi et al., 2020).

Continued exploration of innovative strategies to overcome biological barriers, especially the blood-brain barrier. Designing nanoparticles that mimic the properties of exosomes for enhanced transport across biological barriers. Utilizing advanced cell membrane engineering techniques to improve interactions with biological barriers. Development of biomimetic nanoparticles with immunomodulatory properties for enhanced therapeutic outcomes. Designing nanoparticles that evade immune recognition for prolonged circulation. Integration of immunostimulatory components to enhance the immune response against infectious diseases or cancer (Choudhari et al., 2021).

Conclusion

Nanoparticles have unique advantages in drug delivery, and their biomimetic counterparts aim to improve specificity, biocompatibility, and therapeutic efficacy. Biomimetic approaches copy biological structures and processes to improve drug delivery and interaction with biological systems. Polymeric nanoparticles are essential for drug delivery and provide controlled release and targeted delivery. Biomimetic designs in drug delivery systems aim to improve biocompatibility, reduce immunogenicity, increase targeting, and bypass biological barriers. Biomimetic polymer nanoparticles often contain lipids, proteins, and cell membrane fragments that give them biomimetic properties. Using specific polymers and methods such as emulsion/solvent evaporation and surface functionalization, biomimetic polymer nanoparticles can be created precisely. Nanoparticles mimic biological barriers, employ targeting strategies, and use responsive release systems to improve drug delivery efficiency. Biomimetic polymer nanoparticles have shown promise in targeted drug delivery, combination therapy, and blood-brain barrier penetration in cancer, infectious diseases, and neurological disorders. Biomimetic polymeric nanoparticles offer an innovative solution to drug delivery challenges. This field has great potential to revolutionize medical interventions through ongoing research, collaboration, and a commitment to safety and sustainability. Exciting new developments in biomimetic polymer nanoparticles are expected to revolutionize patient care and healthcare innovation in the future.

REFERENCES

Adhikari, C. (2021). Polymer nanoparticles-preparations, applications and future insights: A concise review. Polymer-Plastics Technology and Materials, 60(18), 1996–2024.

AlAli, M., Mattar, Y., Alzaim, M. A., & Beheiry, S. (2023). Applications of biomimicry in architecture, construction and Civil engineering. Biomimetics, 8(2), 202.

Ali, N., Bilal, M., Khan, A., Ali, F., Khan, H., Khan, H. A., & Iqbal, H. M. N. (2021). Fabrication strategies for functionalized nanomaterials. In Nanomaterials: Synthesis, Characterization, Hazards and Safety (pp. 55–95). Elsevier.

Alipanah, Z., Zakerhamidi, M. S., Movla, H., Azizi, B., Musevic, I., & Ranjkesh, A. (2023). Light-powered liquid crystal polymer network actuator using TiO2 nanoparticles as an inorganic ultraviolet-light absorber. ACS Omega, 8(11), 10555–10564.

Altaf, S., & Alkheraije, K. A. (2023). Cell membrane-coated nanoparticles: An emerging antibacterial platform for pathogens of food animals. Frontiers in Veterinary Science, 10(5). https://doi.org/10.3389/fvets.2023.1148964

Altaf, S., & Iqbal, T. (2023). Bee Venom Used for the Treatment of Rheumatoid Arthritis. Biomedical Journal of Scientific & Technical Research, 53(2), 44503–44507.

Altaf, S., Iqbal, T., Majeed, W., Farooq, M. A., Naseer, D., Saleem, M., Babar, S. U. R., & Ikram, M. (2023). Plasma membrane camouflaged nanoparticles: an emerging antibacterial approach. One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, 2, 193–200.

Altaf, S., Iqbal, T., Salma, U., Sajid, M., Basit, I., Sabir, M. Z., Riaz, K., Rasheed, R., Umair, M., & Talha, R. (2024). Gold nanoparticles for the detection of organophosphate. Agrobiological Records 16: 11-18.

Altaf, S., Khan, S., Iqbal, T., Farooq, M. A., & Muzaffar, H. (2023). Potential treatment of anthrax infection. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 576–588.

Altaf, S., Muhammad, F., … B. A.-H. & E., & 2021, undefined. (2021). Cell membrane enveloped polymeric nanosponge for detoxification of chlorpyrifos poison: In vitro and in vivo studies. Journals.Sagepub.Com, 40(8), 1286–1295. https://doi.org/10.1177/0960327121993207

Beh, C. Y., Prajnamitra, R. P., Chen, L.-L., & Hsieh, P. C.-H. (2021). Advances in biomimetic nanoparticles for targeted cancer therapy and diagnosis. Molecules, 26(16), 5052.

Ben-Akiva, E., Meyer, R. A., Yu, H., Smith, J. T., Pardoll, D. M., & Green, J. J. (2020). Biomimetic anisotropic polymeric nanoparticles coated with red blood cell membranes for enhanced circulation and toxin removal. Science Advances, 6(16), eaay9035.

Biswas, R., Alam, M., Sarkar, A., Haque, M. I., Hasan, M. M., & Hoque, M. (2022). Application of nanotechnology in food: processing, preservation, packaging and safety assessment. Heliyon, 8(11).

Cavalu, S., Antoniac, I. V., Mohan, A., Bodog, F., Doicin, C., Mates, I., Ulmeanu, M., Murzac, R., & Semenescu, A. (2020). Nanoparticles and nanostructured surface fabrication for innovative cranial and maxillofacial surgery. Materials, 13(23), 5391.

Chen, Y., Zheng, Y., Yu, Y., Wang, Y., Huang, Q., Qian, F., Sun, L., Song, Z., Chen, Z., & Feng, J. (2020). Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. The EMBO Journal, 39(24), e105896.

Choudhari, M., Hejmady, S., Saha, R. N., Damle, S., Singhvi, G., Alexander, A., Kesharwani, P., & Dubey, S. K. (2021). Evolving new-age strategies to transport therapeutics across the blood-brain-barrier. International Journal of Pharmaceutics, 599, 120351.

Dalton, P. D., Woodfield, T. B. F., Mironov, V., & Groll, J. (2020). Advances in hybrid fabrication toward hierarchical tissue constructs. Advanced Science, 7(11), 1902953.

Ding, H., Tan, P., Fu, S., Tian, X., Zhang, H., Ma, X., Gu, Z., & Luo, K. (2022). Preparation and application of pH-responsive drug delivery systems. Journal of Controlled Release, 348, 206–238.

Elmowafy, M., Shalaby, K., Elkomy, M. H., Alsaidan, O. A., Gomaa, H. A. M., Abdelgawad, M. A., & Mostafa, E. M. (2023). Polymeric nanoparticles for delivery of natural bioactive agents: recent advances and challenges. Polymers, 15(5), 1123.

Elshafei, G., Vilčeková, S., Zeleňáková, M., & Negm, A. M. (2021). An extensive study for a wide utilization of green architecture parameters in built environment based on genetic schemes. Buildings, 11(11), 507.

Fabozzi, A., Della Sala, F., di Gennaro, M., Solimando, N., Pagliuca, M., & Borzacchiello, A. (2021). Polymer based nanoparticles for biomedical applications by microfluidic techniques: from design to biological evaluation. Polymer Chemistry, 12(46), 6667–6687.

Fatima, M., Iqbal, T., Shaheen, L., Salma, U., Siddique, R., Ali, R., Rehman, A. U., & Usman, S. (2023). Transmission dynamics of rabies virus. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 386–397.

Ferreira, J. J. M., Fernandes, C. I., & Ferreira, F. A. F. (2020). Technology transfer, climate change mitigation, and environmental patent impact on sustainability and economic growth: A comparison of European countries. Technological Forecasting and Social Change, 150, 119770.

Fondaj, D., Arduino, I., Lopedota, A. A., Denora, N., & Iacobazzi, R. M. (2023). Exploring the microfluidic production of biomimetic hybrid nanoparticles and their pharmaceutical applications. Pharmaceutics, 15(7), 1953.

Fukuta, T., Oku, N., & Kogure, K. (2022). Application and utility of liposomal neuroprotective agents and biomimetic nanoparticles for the treatment of ischemic stroke. Pharmaceutics, 14(2), 361.

Gao, J., Wu, P., Fernandez, A., Zhuang, J., & Thayumanavan, S. (2020). Cellular AND gates: Synergistic recognition to boost selective uptake of polymeric nanoassemblies. Angewandte Chemie, 132(26), 10542–10546.

Guan, W., Ma, Y., Ding, S., Liu, Y., Song, Z., Liu, X., Tang, L., & Wang, Y. (2022). The technology for improving stability of nanosuspensions in drug delivery. Journal of Nanoparticle Research, 24(1), 14.

Gulnaz, R., Saqib, M., Saleem, M., Fatima, M., Iqbal, T., & Arif, Z. (2023). Outbreak of the ebola virus. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 359–373.

Humaira, H. A., Iqbal, T., Habib, I., & Aman, Z. (2023). Vaccine strategies for dengue fever. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 561–575.

Hussain, S. (2022). Biomimetic 3D scaffolds for regenerative medicine: Opportunities and challenges. Brac University.

Ibrahim, U. H., Devnarain, N., & Govender, T. (2021). Biomimetic strategies for enhancing synthesis and delivery of antibacterial nanosystems. International Journal of Pharmaceutics, 596, 120276.

Iqbal, M. U., Altaf, S., Naeem, M. A., Aufy, M., Alfuraydi, A. A., Iqbal, T., Hussein, A. M., Maksoud, M. A. A., & Malik, A. (2024). Amelioration of Organophosphate Poisoning Using Red Blood Cell Membrane-Cloaked Oil Nano-Sponge. Journal of Biological Regulators and Homeostatic Agents, 5753–5767. https://doi.org/10.23812/J.BIOL.REGUL.HOMEOST.AGENTS.20243808.462

Iqbal, T., Ahmad, A., Naveed, M. T., Ali, A., & Ahmad, M. (2023). Potential Role of Zoonoses in Bioterrorism. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 1, 499–512.

Iqbal, T., & Altaf, S. (2024). Nigella Sativa use for the Treatment of Cancer. https://doi.org/10.26717/BJSTR.2024.55.008660

Iqbal, T., Altaf, S., Fatima, M., Rasheed, R., Laraib, K., Azam, M., Karamat, M., Salma, U., & Usman, S. (2024). A narrative review on effective use of medicinal plants for the treatment of parasitic foodborne diseases. Agrobiological Records 16: 79-92.

Iqbal, T., Altaf, S., Salma, U., Fatima, M., Khan, M. N., Farooq, S., Abrar, M., Tasleem, M., & Afzal, A. (2024). Cell membrane coated polymeric nanocarriers: a novel drug delivery approach for the targeted therapy of rheumatoid arthritis. Agrobiological Records 15: 91-102.

Kang, H., Rho, S., Stiles, W. R., Hu, S., Baek, Y., Hwang, D. W., Kashiwagi, S., Kim, M. S., & Choi, H. S. (2020). Size-dependent EPR effect of polymeric nanoparticles on tumor targeting. Advanced Healthcare Materials, 9(1), 1901223.

Kar, N. R. (2021). A Review on Targeting of Drugs to Brain. Indian Journal of Natural Sciences, 11, 64.

Kenry, Yeo, T., Manghnani, P. N., Middha, E., Pan, Y., Chen, H., Lim, C. T., & Liu, B. (2020). Mechanistic understanding of the biological responses to polymeric nanoparticles. ACS Nano, 14(4), 4509–4522.

Konstantinidis, F. K., Myrillas, N., Tsintotas, K. A., Mouroutsos, S. G., & Gasteratos, A. (2023). A technology maturity assessment framework for industry 5.0 machine vision systems based on systematic literature review in automotive manufacturing.

International Journal of Production Research, 1–37.

Kutner, N., Kunduru, K. R., Rizik, L., & Farah, S. (2021). Recent advances for improving functionality, biocompatibility, and longevity of implantable medical devices and deliverable drug delivery systems. Advanced Functional Materials, 31(44), 2010929.

Lai, Y., Zhu, Y., Xu, Z., Hu, X., Saeed, M., Yu, H., Chen, X., Liu, J., & Zhang, W. (2020). Engineering versatile nanoparticles for near-infrared light-tunable drug release and photothermal degradation of amyloid β. Advanced Functional Materials, 30(11), 1908473.

Lavino, A. D., Ferrari, M., Barresi, A. A., & Marchisio, D. (2021). Effect of different good solvents in flash nano-precipitation via multi-scale population balance modeling-CFD coupling approach. Chemical Engineering Science, 245, 116833.

Li, Q., Li, X., & Zhao, C. (2020). Strategies to obtain encapsulation and controlled release of small hydrophilic molecules. Frontiers in Bioengineering and Biotechnology, 8, 437.

Li, X., Ramadori, P., Pfister, D., Seehawer, M., Zender, L., & Heikenwalder, M. (2021). The immunological and metabolic landscape in primary and metastatic liver cancer. Nature Reviews Cancer, 21(9), 541–557.

Luchini, A., & Vitiello, G. (2020). Mimicking the mammalian plasma membrane: An overview of lipid membrane models for biophysical studies. Biomimetics, 6(1), 3.

Makvandi, P., Josic, U., Delfi, M., Pinelli, F., Jahed, V., Kaya, E., Ashrafizadeh, M., Zarepour, A., Rossi, F., & Zarrabi, A. (2021). Drug delivery (nano) platforms for oral and dental applications: tissue regeneration, infection control, and cancer management. Advanced Science, 8(8), 2004014.

Mansouri, K., Rasoulpoor, S., Daneshkhah, A., Abolfathi, S., Salari, N., Mohammadi, M., Rasoulpoor, S., & Shabani, S. (2020). Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC Cancer, 20, 1–11.

Marshall, S. K., Angsantikul, P., Pang, Z., Nasongkla, N., Hussen, R. S. D., & Thamphiwatana, S. D. (2022). Biomimetic targeted theranostic nanoparticles for breast cancer treatment. Molecules, 27(19), 6473.

Mathios, D., Johansen, J. S., Cristiano, S., Medina, J. E., Phallen, J., Larsen, K. R., Bruhm, D. C., Niknafs, N., Ferreira, L., & Adleff, V. (2021). Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nature Communications, 12(1), 5060.

Mehta, M., Bui, T. A., Yang, X., Aksoy, Y., Goldys, E. M., & Deng, W. (2023). Lipid-based nanoparticles for drug/gene delivery: an overview of the production techniques and difficulties encountered in their industrial development. ACS Materials Au, 3(6), 600–619.

Mi, P., Cabral, H., & Kataoka, K. (2020). Ligand-installed nanocarriers toward precision therapy. Advanced Materials, 32(13), 1902604.

Mwiiri, F. K., & Daniels, R. (2020). Electrospun nanofibers for biomedical applications. In Delivery of drugs (pp. 53–74). Elsevier.

Nanda, A., Pandey, P., Rajinikanth, P. S., & Singh, N. (2024). Revolution of nanotechnology in food packaging: Harnessing electrospun zein nanofibers for improved preservation-A review. International Journal of Biological Macromolecules, 129416.

Poko, A., Gun, G., & Babuc, E. (2024). TECHNOLOGY OF PREPARATION OF MICROENCAPSULATED FORMS FOR SUSTAINED RELEASE USING BIODEGRADABLE POLY LACTIC-CO-GLYCOLIC ACID (PLGA) POLYMER–REVIEW. World, 3(2).

Rahamim, V., & Azagury, A. (2021). Bioengineered biomimetic and bioinspired noninvasive drug delivery systems. Advanced Functional Materials, 31(44), 2102033.

Saleem, F., Atiq, A., Altaf, S., Habib, M., & Iqbal, T. (2023). Etiology, treatment and complications of dengue fever: a systematic analysis. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 551–560.

Salma, U., Nawaz, H., Farooq, M., & Iqbal, T. (2023). Management, control and treatment of monkeypox disease. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 666–675.

Saqib, M., Iqbal, K. J., Khan, S., Gulnaz, R., Iqbal, T., Mankga, L. T., & Fatima, K. (2023). Immune boosters to combat zoonotic viral diseases. Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, 3, 344–358.

Shi, L., Zhang, J., Zhao, M., Tang, S., Cheng, X., Zhang, W., Li, W., Liu, X., Peng, H., & Wang, Q. (2021). Effects of polyethylene glycol on the surface of nanoparticles for targeted drug delivery. Nanoscale, 13(24), 10748–10764.

Tenchov, R., Sasso, J. M., & Zhou, Q. A. (2023). PEGylated lipid nanoparticle formulations: immunological safety and efficiency perspective. Bioconjugate Chemistry, 34(6), 941–960.

Umair, M., Altaf, S., Muzaffar, H., Iftikhar, A., Ali, A., Batool, N., Iqbal, T., & Saif-ur-Rehman, B. S. R. (2022). Green nanotechnology mediated silver and iron oxide nanoparticles: Potential antimicrobials. Agrobiol Rec, 10, 35–41.

Wang, Z., Rich, J., Hao, N., Gu, Y., Chen, C., Yang, S., Zhang, P., & Huang, T. J. (2022). Acoustofluidics for simultaneous nanoparticle-based drug loading and exosome encapsulation. Microsystems & Nanoengineering, 8(1), 45.

Wu, D., Chen, Q., Chen, X., Han, F., Chen, Z., & Wang, Y. (2023). The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy, 8(1), 217.

Yan, S., Na, J., Liu, X., & Wu, P. (2024). Different Targeting Ligands-Mediated Drug Delivery Systems for Tumor Therapy. Pharmaceutics, 16(2), 248.

Yetisgin, A. A., Cetinel, S., Zuvin, M., Kosar, A., & Kutlu, O. (2020). Therapeutic nanoparticles and their targeted delivery applications. Molecules, 25(9), 2193.

Zembyla, M., Murray, B. S., & Sarkar, A. (2020). Water-in-oil emulsions stabilized by surfactants, biopolymers and/or particles: A review. Trends in Food Science & Technology, 104, 49–59.

Chapter 46

Antimalarial Activity of Metallic Nanoparticles

Huma Fatima*[1], Nargis Shaheen[2], Sumbal Haleem[3], Asma Ashraf[4], Attiya Iqbal [2] and Shawana Qayyum[1]

[1]Department of Zoology, Women University Mardan, KPK, Pakistan
[2]Department of Zoology, Quaid e Azam University Islamabad, Pakistan
[3]Department of Zoology, Shaheed Benazir Bhutto Women University, Peshawar, Khyber Pakhtunkhwa, Pakistan
[4]Department of Zoology. Education University Lahore, Jauharabad Campus, Punjab, Pakistan
*Corresponding author: drhumafatima@wumardan.edu.pk; fhuma26@yahoo.com

ABSTRACT

One of the most severe infectious diseases is malaria, which is characterized by high fever, severe anemia, and neurological sequelae including coma and stroke. *Plasmodium* species are the source of malaria, a parasitic disease that infects people when female *Anopheles* mosquitoes bite them. Metal NPs were primarily evaluated for their ability to kill bacteria and viruses. Nanoparticles can be made by different methods i.e. physical, chemical and biological methods. The most protective and environmental friendly method of nanoparticle synthesis is by using biological materials that is known as green synthesis. Diverse biological materials can be used for the production of nanoparticles i.e. leaves, seeds, flowers, stem, fruits etc. Different nanoparticles are synthesized by combining plant extract with mill molar and molar solutions of salts of different metals mixed in different ratios. The indication of nanoparticle formation was marked by a color change observed within 10-150 minutes. Confirmation of nanoparticle formation was achieved through ultraviolet spectroscopy, which revealed characteristics of plasmon vibrations. Characterization can be done by XRD, FTIR, SEMS and TEMS. Results of different articles showed that green-produced nanoparticles exhibited no cytotoxicity when applied to normal cells and affectively reduced malarial infection. So the green synthesized Nanoparticles can be the effectively reduced malarial infection further studies are required to enhance these findings.

KEYWORDS
Antimalarial activity, Characterization of nanoparticles, Cytotoxicity, Green synthesis, Metallic nanoparticles

Received: 15-Jun-2024
Revised: 22-Jul-2024
Accepted: 10-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Fatima H, Shaheen N, Haleem S, Ashraf A, Iqbal A and Qayyum S, 2024. Antimalarial activity of metallic nanoparticles. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 403-412. https://doi.org/10.47278/book.CAM/2024.477

INTRODUCTION

One of the most severe infectious diseases is malaria, which is characterized by recurrent high fever, severe anemia, convulsions, and neurological sequelae including coma and stroke. An estimated 608,000 fatalities worldwide were attributed to malaria in 2022, with a mortality rate of 14·3 deaths per 100,000 people. According to the reported death rate, the following four nations accounted for 50% of all deaths: Nigeria (31%), the Democratic Republic of the Congo (12%), Niger (6%), and Tanzania (4%) (WHO, 2022).

Plasmodium protozoans are the source of malaria, a parasitic disease that infects people when female Anopheles mosquitoes bite those (White et al., 2014). Malaria badly affects economic growth and development in sub-Saharan Africa. Malaria remains a serious public health concern. In 2017, there were 219 million cases of malaria worldwide, and the disease was projected to have caused 435,000 fatalities. Ninety-two percent of these cases were from sub-Saharan Africa (Ta et al., 2014).

The world malaria report identified that the total cases reported in 2022 was expressively higher when compared to the pandemic situation in 2019. However, in nineteen year i.e. 2000 to 2019, there is a decrease in 10 million cases globally i.e. from 243 million to 233 million. But unfortunately, 11 million cases increased in 2020. No change was observed in 2021, however in 2022 there is an increase of 5 million cases in 2022, for a total of about 249 million cases (WHO, 2022).

There was also increase in a number of global malaria deaths in 2022 when compared to the death rate (864 000) in 2019. After that, there has been a decline in the Malaria deaths since 2000, 864 000 to 576,000. After the pandemic situation, the number of deaths increased from 55,000 in 2020, to 631,000 (WHO, 2022).

The most common parasite is *Plasmodium vivax*, but the most lethal is *Plasmodium falciparum*. Several species infect in humans, including *Plasmodium malariae, Plasmodium ovale, Plasmodium cynomolgi* and *Plasmodium knowlesi,* (White et al., 2014; WHO, 2018 and Ta et al., 2014). Despite substantial global initiatives to combat malaria, involving increased financing to support research and development, provision, and expedite its control (The 2020 malaria morbidity and mortality targets set by the Global Technical Strategy (GTS) are still far from being reached by adequate diagnosis, prevention measures, and effective treatment) (WHO, 2018).

Resistance to Current Malarial Drugs

The malaria parasite has developed resistance to nearly all existing drugs, posing a significant obstacle to global malaria control efforts. Combination therapy of artemisinin-based (ACT), the most potent treatment option, which played a vital role in recent advancements in malaria control (White et al., 2014; WHO, 2018 and Ta et al., 2014). Strains of *P. falciparum* that are resistant to artemisinin have been documented from the Subregion of the Greater Mekong (GMS), Western Cambodia, and China's South (WHO, 2017; Dama et al., 2017 and Noedl et al., 2008). Treatment of malaria patients and efforts to control the disease in impacted areas have been severely hampered by the presence of artemisinin (ART) resistant parasites in addition to resistance to partner medication in ACT. The existence of ART-resistant parasites has been linked in multiple studies to increased rates of treatment adherence in patients with ACT (Fairhurst and dondrop, 2016; Tilley et al., 2016 and Woodrow and White, 2017). Kelch (K13) gene identified inside *P.falciparum* propeller domain, appears to be positive selection occurring on the artemisinin resistance pattern (Cheeseman, 2012, Miotto et al., 2013 and Takala-Harrison et al., 2013). This indicates that the specific genes responsible for delayed clearance or contributing to resistance to artemisinin has not been identified conclusively, however, 13 non-nonsynonymous variants have been identified as relevant markers (WHO, 2017; Dondorp et al.,2009; Witkowski et al.,2013, Ashley et al.,2014; Takala-Harrison et al.,2015; Ariey et al.,2014 and Straimer et al.,2015). The appearance or dissemination resistance to artemisinin from Asia to Africa mirrors previous occurrences with older anti-malarial medications such as Chloroquine and sulfadoxine-pyrimethamine (Trape, 2001; Trape et al., 2002 and Wongsrichanalai and Sibley, 2013), It would have a catastrophic impact on global malaria eradication initiatives. Despite widespread concern about the possible emergencies or dissemination of K13 mutations associated with artemisinin – resistance in Africa, the mutations identified thus for or infrequent and distinct from k13 polymorphism linked to diminished susceptibility in Asia (WHO, 2017; Djaman et al., 2017; Kamau et al., 2015; Murugan et al., 2017; Borrmann et al., 2013; Torrentino-Madamet et al., 2014; Cooper et al., 2015; Ouattara et al., 2015; Menard et al., 2016 and Taylor et al., 2015).

Alternative Source for the Treatment of Malaria by Nanoparticle

Therefore, provided the circumstances and the fact that many antimalarial treatments are supported by governments, non-profit organizations, and other entities, the ability of research and development to provide the next generation of anti-malarial drugs will determine the success of malaria control and global eradication (Tse et al., 2019). If the project fails, it may seriously impair the chances of successfully managing and eliminating malaria, particularly in Africa as outlined in the worldwide Technical Strategy 2016-2030 (WHO, 2022). Keeping in view of the above-mentioned problem in GMC nanotechnology seems to be the alternate treatment of malaria.

Nano products and metal nanoparticles offer significant utility and are inherently safe, finding a wide array of applications in renewable energies, biomedical devices, and health care catalysis, cosmetics, food, electronics, and environmental cleanup (Ealia and Saravanakumar, 2017; Gahlawat and Choudhury, 2019; Ahmed et al., 2016 and Khandel and Shahi, 2016).

Metallic Nanoparticles

In nanotechnology metallic nanoparticles have much important medical importance. Various approaches are available for creating new anti-malarial medication, with some originating from living organisms. The process of creating metal nanoparticles essentially included combining three components: the capping agent, the reducing agents, and the metal supply (usually noble metals like silver, gold, palladium, and titanium salt) (Ealia and Saravanakumar, 2017). Metal NPs were primarily evaluated for their ability to kill bacteria (Maiti et al., 2014; Patra and Baek, 2016 and Patra and Baek, 2017), fungi (Mallmann et al., 2015 and Arciniegas-Grijalba et al., 2017), and viruses (Narasimha, 2013 and Broglie et al., 2015). There is limited information available regarding the anti-plasmodial capabilities of metal nanoparticles (Dauda et al., 2017).

Methods for the Formulation of Metallic Nanoparticles

They can be prepared by using three methods, chemicals, physical, and biological. In nanotechnology metallic nanoparticles have much important medical importance. They can be prepared by using three methods, chemicals, physical, and Biological (Fig 1). Chemicals and physical methods pose challenges due to their expense, time intensiveness, and reliance on environmentally harmful reagents (Ealia and Saravanakumar, 2017 and Gahlawat and Choudhury, 2019).

Green Synthesis as Cost – an Efficient and Environmentally Friendly Method

In response to this, innovative methods for synthesizing nanoparticles, known as Green synthesis, that use biological material. Green synthesis involves producing metal nanoparticles by harnessing the natural capping and reducing abilities of biomolecules derived from living things like microbes and plants**.** This approach is straightforward, cost–efficient, and environmentally friendly (Barabadi et al., 2019; Moher et al., 2009; Panneerselvam et al., 2011; Ponarulselvam et al., 2012 and Mishra et al., 2013). However extensive efforts are required to maintain the cultures of microorganisms so plant source is the best option for the formulation of Nanoparticles.

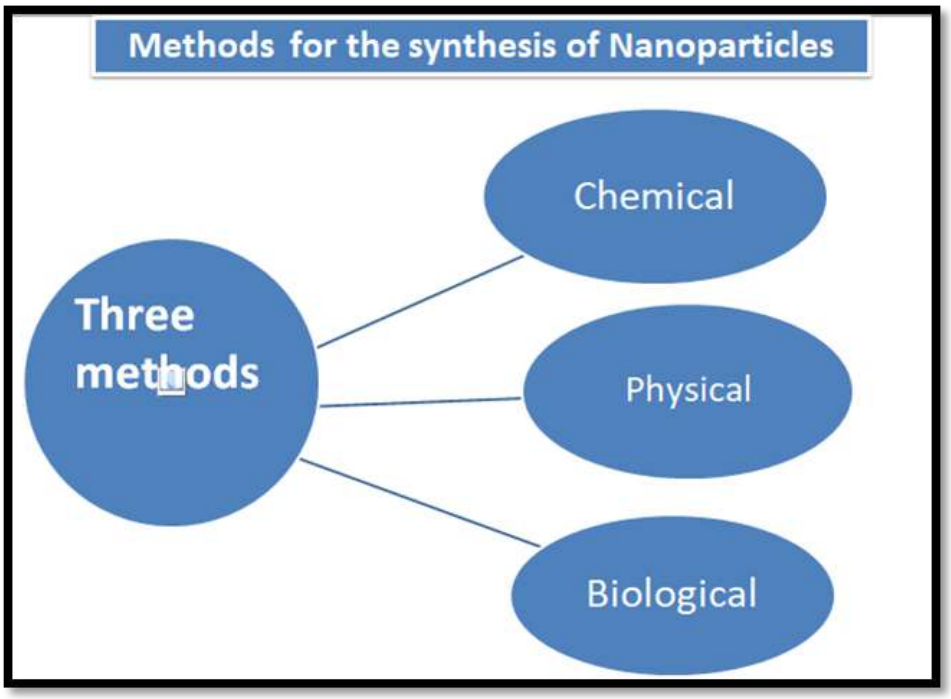


Fig. 1: Methods for the synthesis of metallic Nanoparticle

Different Biological Material that can be used for the Synthesis of Nanoparticles

Diverse biological materials can be used to produce nanoparticles i.e. leaves, seeds, flowers, stem, peels of fruits, fruits, etc. (Fig. 2). A summary of different plant materials used is given in Table 1. Leaves as the biological materials for the synthesis of metal NPs. Flowers, seeds, and barks were among the additional plant parts (Panneerselvam et al., 2015; Subramaniam et al., 2016 and Dutta et al., 2017).

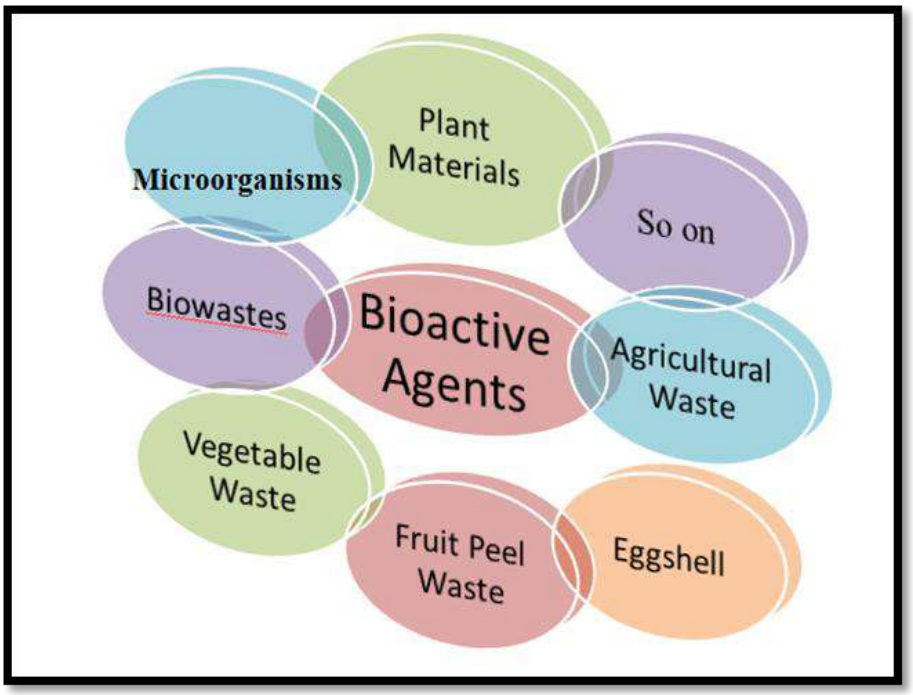


Fig. 2: Different biological materials used for the production of Nanoparticles

Table 1: Summary of different plant materials utilized in the production of Nanoparticles

Plant Source	References
Leaves	(Panneerselvam et al., 2011; Ponarulselvam et al., 2012; Mishra et al., 2013; Panneerselvam et al., 2015; Murugan et al., 2015; Subramaniam et al., 2016; Dutta et al., 2017; Sardana et al., 2018; Gandhi et al., 2018 and Rotimi et al., 2019
Flowers	(Subramaniam et al., 2016)
Seeds	(Murugan et al., 2016 and Rotimi et al., 2019)
Barks	(Dutta et al., 2017)

Preparation of Plant Extracts

The selected plant material is air-dried at room temperature. Subsequently, the dried plant material is finely ground using a mechanical blender. By using different quantities of plant material and deionized water extract can be made by simple method or by using Soxhlet extraction method by using Soxhlet Apparatus. By simple boiling and decantation method. Whatman no 1 filter paper is used to filter the resultant mixture. The filtrate obtained underwent lyophilization to produce a dry powder, which is stored in a covered centrifuge tube in the refrigerator at 4°C until needed for nanoparticle synthesis.

In the literature, the authors mostly used a simple method to create aqueous extracts, which needed to be combined with a material's predecessor to synthesize Nanoparticles. After thorough washing with double-distilled water and cutting, biological material (4-10g) was cooked. The mixture was then dripped out and filtered via Whatman N°1 filter paper utilizing water as the preferred extraction solvent.

Stock Solution of different Salts of different Metals

Millimolar and molar solutions of salts of different metals are prepared.

Synthesis of Nanoparticles

Different nanoparticles are synthesized by combining plant extract with mill molar and molar solutions of salts of different metals mixed in different ratios. Then the mixture underwent an incubation period with continuous stirring for different durations, in darkness to avoid photochemical reactions. The indication of nanoparticle formation was marked by a color change observed within 10-150 minutes following the mixing of the metal precursor and plant extracts.

After that mixture was centrifuged at different rpm for different time durations at room temperature. The resulting pellet is washed twice with double distilled water, air-dried, and utilized for subsequent assays (Panneerselvam et al.,2011; Ponarulselvam et al.,2012; Mishra et al.,2013; Panneerselvam et al.,2015; Rajakumar et al.,2015; Murugun et al.,2015; Subramaniam et al.,2016; Panneerselvam et al.,2016; Murugan et al.,2016; Dutta et al.,2017; Sardana et al.,2018; Gandhi et al.,2018; Rotimi et al.,2019; Karthik et al.,2013; Jaganathan et al.,2016; and Murugan et al.,2017).

Methods used for the Characterization of Nanoparticles

The research investigated the physical properties of metal nanoparticles across several dimensions: shape, size, and variability, as well as their chemical composition, in structural stability (refer to Table 4). Confirmation of nanoparticle formation was achieved through ultraviolet spectroscopy (UV -VIS), which revealed characteristics of plasmon vibrations. To determine the morphology and dimension of nanoparticles, Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) were suggested. Elemental mapping based on atomic composition was made easier by CEM in conjunction with energy-dispersive X-ray spectroscopy (EDX, EDS), and crystallographic planes were exposed by TEM in conjunction with selected area electron diffraction (SAED). Using molecular vibrations, FTIR was utilized to investigate the interface between NPs and secondary metabolites. X-ray diffraction (XRD) offers information about crystallinity, nature, and additional aspects such as size and shape determination. Size distributions and terms of hydrodynamic radius were obtained by dynamic light scattering (DLS); some research concentrated on spectroscopy (AAS) (Subramaniam et al.,2016; Dutta et al.,2017; Gandhi et al.,2018 and Karthik et al.,2013) (Fig. 3).

Different Metals used for the Synthesis of Metallic Nanoparticles

Silver nitrate (AgNO3) served as a primary metal precursor for producing nanoparticles related to plants. Additionally, other noble metals such as gold, palladium, and titanium were utilized in nanoparticle synthesis (Rajakumar et al.,2015; Subramaniam et al.,2016; Dutta et al.,2017; Gandhi et al.,2018 and Karthik et al.,2013). The indication of nanoparticle formation was marked by a color change observed within 10-15 minutes following the mixing of the metal precursor and plant extracts characteristic and characterization of some metallic nanoparticles that were synthesized previously for antimalarial activity is summarized in Table 2 and Table 3.

Characterization Techniques used for Identification of Nanoparticles in Previous Studies

UV – VIS spectroscopy emerged as a pivotal method for examining nanoparticle behavior, including their formation, evolution, or aggregation.

The characteristics of plasmon vibration arise from the unrestricted movement of electrons on the surface of metallic materials. In the case of silver, these vibrations occur within the range of 400-450 nm (Panneerselvam et al.,2011; Ponarulselvam et al.,2012; Mishra et al., 2013; Panneerselvam et al., 2015; Murugan et al.,2015; Panneerselvam et al.,2016; Murugan et al.,2016; Dutta et al.,2017 and Sardana et al.,2018), while for gold, they occur around 540 and 560 nm (Rajakumar et al.,2015 and Karthik et al.,2013) and 8360 nm for titanium dioxide (Gandhi et al., 2018), most studies observed the formation of spherical- shaped Nanoparticles (Table 3). Globally, these nanoparticles ranged in size from 4 to 65 nm, and some research observed aggregation phenomena throughout production (Mishra et al., 2013 and Murugan et al., 2016). Additionally, certain research revealed the existence of other Bragg peaks (Ponarulselvam et al., 2012; Mishra et al., 2013; Panneerselvam et al., 2015 and Murugan et al., 2016). Signals related to oxygen or carbon atoms were detected using energy-dispersive X-ray analysis (Rajakumar et al., 2015 and Murugan et al., 2016), whole

additional Signals associated with chlorine were occasionally observed as well (Panneerselvam et al., 2016). The resultant nanoparticles' crystallographic planes and diffraction patterns were discovered by selected area electron diffraction (SAED) (Dutta et al., 2017).

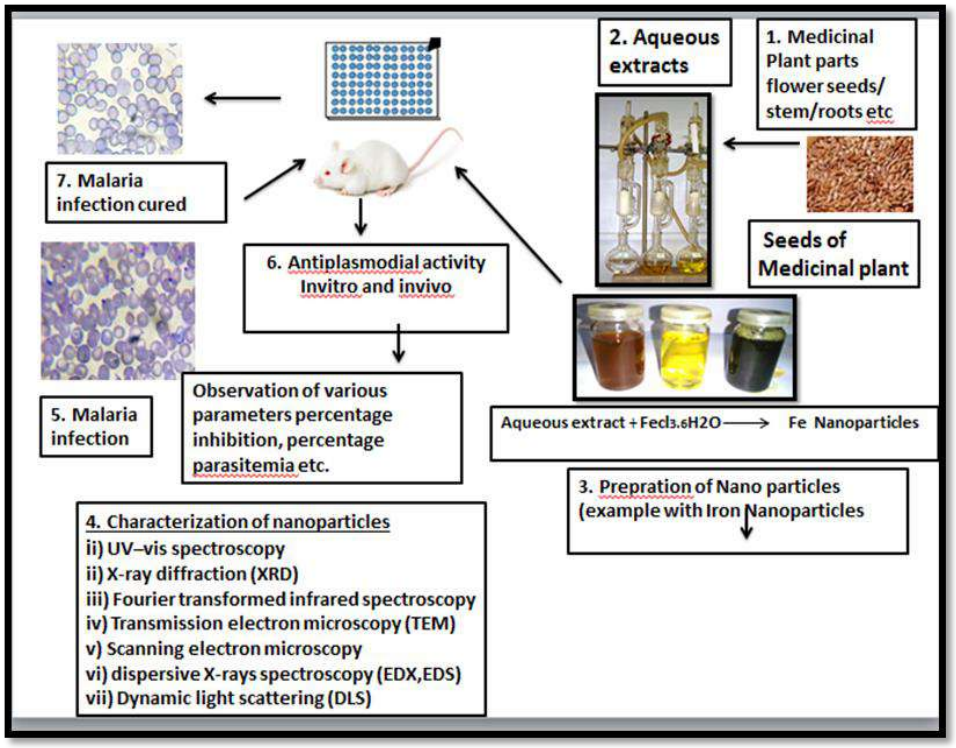


Fig. 3: Schematic diagram for synthesis, characterization, *In vivo* and *In vitro* antiplasmodial activity of metallic nanoparticles

Power X-ray diffraction is a noteworthy characterization method in solid-state chemistry (Das et al., 2014), used to evaluate nanoparticles generated from biological extracts like plants or earthworms and identify the crystalline phases. The anti-plasmodial properties were more extensively evaluated with Nano silver (57%) and Nano gold (29%). The analysis was made easier by contrasting the acquired patterns with those in the Giant Committee on Powder Diffraction Standards (JSPDS) database, which was originally known as the International Center for Diffraction Data (ICDD). While biosynthesis typically yields pure palladium, gold, or titanium dioxide NPs, the case differs for silver, where the outcomes may include Nano silver, silver chloride, Nano crystallites, or their mixture (Ahmed et al.,2016; Khandel and shahi, 2016 and Broglie et al.,2015).

Table 2: Summary of Physio-chemical characterization of NPs reported in the literature

Physio-chemical characteristic	Characterization method used	References
Plasmon resonance	UV-Vis	(Panneerselvam et al., 2011; Ponarulselvam et al., 2012; Panneerselvam et al., 2015; Rajakumar et al., 2015; Murugan et al., 2015; Subramaniam et al., 2016; Panneerselvam et al., 2016; Murugan et al., 2016; Dutta et al., 2017; Sardana et al., 2018; Gandhi et al., 2018; Rotimi et al., 2019; Karthik et al., 2013; Jaganathan et al., 2016; Murugan et al., 2017)
Shape, size and Size distribution	FESEM/SEM, EDX, EDAX	(Panneerselvam et al., 2011; Ponarulselvam et al., 2012; Panneerselvam et al., 2015; Rajakumar et al., 2015; Murugan et al., 2015; Subramaniam et al., 2016; Panneerselvam et al., 2016; Murugan et al., 2016; Rotimi et al., 2019; Karthik et al., 2013; Jaganathan et al., 2016 and Murugan et al., 2017)
	HRTEM/TEM, SAED	(Mishra et al., 2013; Rajakumar et al., 2015; Dutta et al., 2017; Sardana et al., 2018; Gandhi et al., 2018; Rotimi et al., 2019; Karthik et al., 2013 and Murugan et al., 2017)
Silver content	AAS	(Mishra et al., 2013)
Interface NPs-metabolites	FTIR	(Mishra et al., 2013; Rajakumar et al.,2015; Murugan et al., 2015; Subramaniam et al., 2016; Murugan et al.,2016; Dutta et al., 2017; Gandhi et al., 2018; Rotimi et al., 2019; Jaganathan et al., 2016 and Murugan et al., 2017)
Size distribution	DLS	(Mishra et al., 2013 and Gandhi et al., 2018)
Crystallinity of the structure	XRD	(Panneerselvam et al.,2011; Mishra et al., 2013;Panneerselvam et al., 2015; Rajakumar et al., 2015; Murugan et al., 2015; Subramaniam et al., 2016; Panneerselvam et al., 2016; Murugan et al., 2016; Dutta et al., 2017 and Karthik et al., 2013)
Stability	Zeta potential	(Panneerselvam et al., 2011; Rajakumar et al., 2015; Subramaniam et al., 2016 and Murugan et al., 2016)

Table 3: Summary of some characteristics of metallic NPs reported in the literature

Characteristics	Detail	References
Metal source	AgNO3	(Panneerselvam et al.,2011; Ponarulselvam et al.,2012; Mishra et al.,2013; Panneerselvam et al.,2015; Murugan et al.,2015; Panneerselvam et al.,2016; Murugan et al.,2016; Dutta et al.,2017; Sardana et al.,2018; Karthik et al.,2013 and Murugan et al.,2017)
	HAuCl4	(Subramaniam et al.,2016; Dutta et al.,2017; Rotimi et al.,2019 and Karthik et al.,2013)
	Pd (OAc)2	(Rajakumar et al.,2015)
	TiCl4	(Gandhi et al.,2018)
Production time	< 30 min	(Panneerselvam et al.,2015; Sardana et al.,2018; Gandhi et al.,2018 and Karthik et al.,2013)
	>30 min	(Panneerselvam et al.,2011; Mishra et al.,2013; Rajakumar et al.,2015; Subramaniam et al.,2016; Panneerselvam et al.,2016 and Murugan et al.,2016)
Shape	Spherical or mainly Spherical	(Panneerselvam et al.,2011; Ponarulselvam et al.,2012; Mishra et al.,2013; Panneerselvam et al.,2015; Rajakumar et al.,2015; Panneerselvam et al.,2016; Murugan et al.,2016; Dutta et al.,2017; Sardana et al.,2018; Gandhi et al.,2018 and Jaganathan et al.,2016)
	Other shapes (cubical, polygonal, triangular, oval, ellipsoid, rectangular)	(Panneerselvam et al.,2015; Rajakumar et al.,2015; Murugan et al.,2015; Subramaniam et al.,2016; Murugan et al.,2016; Dutta et al.,2017; Sardana et al.,2018; Gandhi et al.,2018 and Karthik et al.,2013)
NPs aggregation Phenomenon	Yes	(Mishra et al.,2013 and Murugan et al.,2016)

FTIR analysis was conducted to examine biomolecule extracts at the interfaces of silver, gold, palladium, and titanium metal oxides. Using this technique, molecular vibrations within or on the surface of artificial nanoparticles can be observed. The results of spectroscopic research showed that the absorption frequencies closely matched the known molecular properties. Alcohols are present, i.e. when O-H (stretch, H-bonded) is present at 3200-3600 and C-O (stretch) is present at 1050-1150. Alkanes show C-H (bending) at 1350-1480 and C-H (stretch) at 2860-3000. Comparably, C=C (stretch) is found in alkanes at 1620-1680 and N-H (stretch) and N-H (bending) are found in amines at 83300-3500 and 1600, respectively, along with C-N (stretch) at 0180-1360. Carbonyls show C=O (stretch) at 1670-1820, whereas aromatics show C-H (stretch) at 3000-3100 and C=C (stretch) at 1400-1600 (Hanson, 2013).

Anti-plasmodial Activity of Nanoparticles

The experiments primarily focused on in vitro setups, although a few also involved in vivo studies (Rajakumar et al.,2015 and Gandhi et al., 2018), or a combination of both (Murugan et al.,2016 and Murugan et al.,2017). Chloroquine was used as a positive control in most of these studies to evaluate exposure to different laboratory strains of Plasmodium falciparum, including INDO (CQ-resistant), 3D7 (CQ-sensitive), FcB1/Colombia (CQ-sensitive), and Dd2 (CQ-sensitive) (Table 3). Control groups included distilled water, uninfected or maybe infected erythrocytes, or culture medium. P. falciparum field strains were collected by some research from patients in healthcare facilities (Panneerselvam et al.,2016; Murugan et al.,2016 and Dutta et al., 2017). P. berghei served as the model organism and studies involving animal models to evaluate malarial susceptibility and NPs were given intraperitoneally (Karthik et al., 2013) or orally (Murugan et al., 2016). To assess the anti-plasmodial activity of nanoparticles, the 50% inhibitory concentration (IC50) and the percentage of suppressed parasite development were used as endpoints. Panneerselvam et al., (2015), Observed a decrease in parasite growth rate ranging from 26% to 83% at doses of 25µg/mL and 100µg/mL, respectively. Murugan et al. (2016) Reported reduced action against Plasmodial ranging from 6.4% to 42.8%. Results based on IC50 varied among studies but usually fell into one of three groups: (I) The results showed that nanoparticles outperformed the positive control (Murugan et al., 2015; Subramaniam et al., 2016; Panneerselvam et al., 2016 and Murugan et al., 2016), (II) that they outperformed plant extracts (Mishra et al., 2013; Rajakumar et al., 2015; Murugan et al., 2016 and Dutta et al., 2017), and (III) that they underperformed both the positive control (Chloroquine) and the plant extract (Subramaniam et al., 2016; Panneerselvam et al., 2016; Murugan et al., 2016 and Dutta et al., 2017). Using chloroquine as a reference, metal nanoparticles were found to be more effective in 9 out of 11 investigations (Mishra et al., 2013; Rajakumar et al., 2015; Murugan et al., 2015; Subramaniam et al., 2016; Panneerselvam et al., 2016; Murugan et al., 2016; Jaganathan et al., 2016 and Murugan et al., 2017). For example, Gajanathan et al., observed that their NPs had IC50 values of 49.3µg/mL and 55.5µg/mL against the chloroquine-sensitive-strain of P.falciparum 3D7 and the chloroquine-resistant strain of INDO, respectively, in comparison to 81.5µg/mL and 86.5µg/mL, respectively, of chloroquine (Jaganathan et al.,2016). According to Murugan et al., (2016) nanoparticles had IC50 values of 63.18µg/mL and 69.24µg/mL against 3D7 and INDO strains, respectively, whereas extracts had IC50 values of 82.41µg/mL and 86.12 µg/ml. This suggests that nanoparticles have greater anti-plasmodial activity

than plant extracts. The current investigation assessed the antimalarial activity of Silver NPs produced from crude extracts of the marine seaweed S. tenerrimum (Ag-ST), in vivo as well as in vitro studies. With IC_{50} values of 7.71 ± 0.39 µg/mL and 23.93 ± 2.27 µg/mL against Plasmodium falciparum and Plasmodium berghei, respectively, the result demonstrated that Ag-ST NPs had excellent anti-plasmodial action (Veeragoni et al., 2023).

Using an IC_{50} value of 3.41 µg/mL, it was discovered that the produced ZnO NPs exhibited good anti-plasmodial properties. According to the results of this study, ZnO NPs showed excellent anti-plasmodial activity. These findings may be applied to future in vivo investigations to develop anti-plasmodial drugs (Najoom et al., 2021).

Cytotoxicity of Nanoparticles

Out of 17 studies, 7 conducted cytotoxicity assessments of the synthesized nanoparticles (Mishra et al., 2013; Rajakumar et al., 2015 and Karthik et al., 2013). Among the seven investigations, four concluded that the nanoparticles had little to no negative effect on the cell lines that were investigated (Mishra et al.,2013; Panneerselvam et al., 2015; Dutta et al., 2017 and Gandhi et al., 2018). The remaining three studies, on the other hand, documented severe side effects that included apoptosis (Jaganathan et al., 2016), necrosis, cytopathic effects (Rajakumar et al., 2015), behavioral changes, physical appearance changes, and mortality of laboratory animals (Karthik et al., 2013). PBMCs are readily available, round-nucleated cells extracted from buffy coats or blood. Systemic toxicity and medication resistance are the two main side effects of chemotherapy medications. Because human PBMCs are susceptible to novel medications and toxins, they are frequently utilized in cytotoxicity testing (Bendale et al., 2017). Using the MTT test, the cytotoxic effect of Iron oxide nanoparticles on PBMCs was thus assessed. We observed that the cell viability of PBMCs treated with varying concentrations of FeO NPs (5,10,15,20, and 25 µg/mL) did not significantly change. Conversely, it was shown that as the concentration of FeO NPs was raised, after PBMCs were treated with them, the cell viability decreased. The cell viability percentage in relation to various concentrations (Figure 4). FeO nanoparticles were successful in achieving 78% viability on PBMCs at 25 µg/mL. According to ISO 10993-5:2009, If cell viability exceeds 70%, Iron Oxide nanoparticle activity is considered non-toxic (López-Badillo et al., 2021). Therefore, it is possible to classify the produced FeO NPs as non-toxic. Our results are corroborated by other investigations that found that green-produced nanoparticles exhibited no cytotoxicity when applied to normal cells (Zangeneh et al., 2020). FeO NPs' lack of toxicity gives them greater stability for use in applications related to drugs and other medicines.

REFERENCES

Ahmed, S., Ahmad, M., Swami, B. L., and Ikram, S. (2016). A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: a green expertise. *Journal of Advanced Research*, *7*(1), 17-28.

Arciniegas-Grijalba, P. A., Patiño-Portela, M. C., Mosquera-Sánchez, L. P., Guerrero-Vargas, J. A., and Rodríguez-Páez, J. E. (2017). ZnO nanoparticles (ZnO-NPs) and their antifungal activity against coffee fungus Erythricium salmonicolor. *Applied Nanoscience*, *7*, 225-241.

Ariey, F., Witkowski, B., Amaratunga, C., Beghain, J., Langlois, A. C., Khim, N., and Ménard, D. (2014). A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. *Nature*, *505*(7481), 50-55.

Ashley, E. A., Dhorda, M., Fairhurst, R. M., Amaratunga, C., Lim, P., Suon, S., and White, N. J. (2014). Spread of artemisinin resistance in Plasmodium falciparum malaria. *New England Journal of Medicine*, *371*(5), 411-423.

Barabadi, H., Alizadeh, Z., Rahimi, M. T., Barac, A., Maraolo, A. E., Robertson, L. J., and Ahmadpour, E. (2019). Nanobiotechnology as an emerging approach to combat malaria: a systematic review. *Nanomedicine: Nanotechnology, Biology and Medicine*, *18*, 221-233.

Bendale, Y., Bendale, V., and Paul, S. (2017). Evaluation of cytotoxic activity of platinum nanoparticles against normal and cancer cells and its anticancer potential through induction of apoptosis. *Integrative Medicine Research*, *6*(2), 141-148.

Borrmann, S., Straimer, J., Mwai, L., Abdi, A., Rippert, A., Okombo, J., and Clark, T. G. (2013). Genome-wide screen identifies new candidate genes associated with artemisinin susceptibility in Plasmodium falciparum in Kenya. *Scientific Reports*, *3*(1), 3318.

Broglie, J. J., Alston, B., Yang, C., Ma, L., Adcock, A. F., Chen, W., and Yang, L. (2015). Antiviral activity of gold/copper sulfide core/shell nanoparticles against human norovirus virus-like particles. *PloS one*, *10*(10), e0141050.

Cheeseman, I. H., Miller, B. A., Nair, S., Nkhoma, S., Tan, A., Tan, J. C., and Anderson, T. J. (2012). A major genome region underlying artemisinin resistance in malaria. *Science*, *336*(6077), 79-82.

Cooper, R. A., Conrad, M. D., Watson, Q. D., Huezo, S. J., Ninsiima, H., Tumwebaze, P., and Rosenthal, P. J. (2015). Lack of artemisinin resistance in Plasmodium falciparum in Uganda based on parasitological and molecular assays. *Antimicrobial Agents and Chemotherapy*, *59*(8), 5061-5064.

Dama, S., Djimde, A. A., and Doumbo, O. K. (2017). Methods for monitoring artemisinin-based combination therapies efficacy. *Clinical Reviews and Opinions*, *8*(1), 1-13.

Das, R., Ali, E., and Abd Hamid, S. B. (2014). CURRENT APPLICATIONS OF X-RAY POWDER DIFFRACTION-A REVIEW. *Reviews on Advanced Materials Science*, *38*(2).

Dauda, K., Busari, Z., Morenikeji, O., Afolayan, F., Oyeyemi, O., Meena, J., and Panda, A. (2017). Poly (D, L-lactic-co-glycolic acid)-based artesunate nanoparticles: formulation, antimalarial and toxicity assessments. *Journal of Zhejiang University.*

Science. B, *18*(11), 977.

Djaman, J. A., Olefongo, D., Ako, A. B., Roman, J., Ngane, V. F., Basco, L. K., and Tahar, R. (2017). Molecular epidemiology of malaria in cameroon and cote d'ivoire. xxxi. kelch 13 propeller sequences in plasmodium falciparum isolates before and after implementation of artemisinin-based combination therapy. *The American Journal of Tropical Medicine and Hygiene*, *97*(1), 222.

Dondorp, A. M., Nosten, F., Yi, P., Das, D., Phyo, A. P., Tarning, J., and White, N. J. (2009). Artemisinin resistance in Plasmodium falciparum malaria. *New England Journal of Medicine*, *361*(5), 455-467.

Dutta, P. P., Bordoloi, M., Gogoi, K., Roy, S., Narzary, B., Bhattacharyya, D. R., and Mazumder, B. (2017). Antimalarial silver and gold nanoparticles: Green synthesis, characterization and in vitro study. *Biomedicine and Pharmacotherapy*, *91*, 567-580.

Ealia, S. A. M., and Saravanakumar, M. P. (2017, November). A review on the classification, characterisation, synthesis of nanoparticles and their application. In *IOP Conference Series: Materials Science and Engineering* (Vol. 263, No. 3, p. 032019). IOP Publishing.

Faculty of Hanson.(2013) Introduction to structure determination infrared: characteristic frequencies.. p. 1–4.

Fairhurst, R. M., and Dondorp, A. M. (2016). Artemisinin-resistant Plasmodium falciparum malaria. *Microbiology Spectrum*, *4*(3), 10-1128.

Gahlawat, G., and Choudhury, A. R. (2019). A review on the biosynthesis of metal and metal salt nanoparticles by microbes. *RSC Advances*, *9*(23), 12944-12967.

Gandhi, P. R., Jayaseelan, C., Kamaraj, C., Rajasree, S. R., and Mary, R. R. (2018). In vitro antimalarial activity of synthesized TiO2 nanoparticles using Momordica charantia leaf extract against Plasmodium falciparum. *Journal of Applied Biomedicine*, *16*(4), 378-386.

Jaganathan, A., Murugan, K., Panneerselvam, C., Madhiyazhagan, P., Dinesh, D., Vadivalagan, C., and Benelli, G. (2016). Earthworm-mediated synthesis of silver nanoparticles: A potent tool against hepatocellular carcinoma, Plasmodium falciparum parasites and malaria mosquitoes. *Parasitology International*, *65*(3), 276-284.

Kamau, E., Campino, S., Amenga-Etego, L., Drury, E., Ishengoma, D., Johnson, K., and Djimde, A. A. (2015). K13-propeller polymorphisms in Plasmodium falciparum parasites from sub-Saharan Africa. *The Journal of Infectious Diseases*, *211*(8), 1352-1355.

Karthik, L., Kumar, G., Keswani, T., Bhattacharyya, A., Reddy, B. P., and Rao, K. B. (2013). Marine actinobacterial mediated gold nanoparticles synthesis and their antimalarial activity. *Nanomedicine: Nanotechnology, Biology and Medicine*, *9*(7), 951-960.

Khandel, P., and Shahi, S. K. (2016). Microbes mediated synthesis of metal nanoparticles: current status and future prospects. *Internatinal Journal Nanomater Biostruct*, *6*(1), 1-24.

López-Badillo, C. M., Hernández-González, M., Hernández-Centeno, F., Olivas-Armendáriz, I., Rodríguez-González, C. A., Múzquiz-Ramos, E. M., and López-De la Peña, H. Y. (2021). Antibacterial activity and in vitro cytotoxicity studies of Ag-doped CaO nanoparticles. *Materials Letters*, *283*, 128741. https://www.sciencedirect.com/science/article/abs/pii/S0167577X20314488

Maiti, S., Krishnan, D., Barman, G., Ghosh, S. K., and Laha, J. K. (2014). Antimicrobial activities of silver nanoparticles synthesized from Lycopersicon esculentum extract. *Journal of Analytical Science and Technology*, *5*, 1-7.

Mallmann, E. J. J., Cunha, F. A., Castro, B. N., Maciel, A. M., Menezes, E. A., and Fechine, P. B. A. (2015). Antifungal activity of silver nanoparticles obtained by green synthesis. *Revista do instituto de Medicina Tropical de sao Paulo*, *57*(2), 165-167.

Menard, S., Tchoufack, J. N., Maffo, C. N., Nsango, S. E., Iriart, X., Abate, L., and Berry, A. (2016). Insight into k13-propeller gene polymorphism and ex vivo DHA-response profiles from Cameroonian isolates. *Malaria Journal*, *15*, 1-7.

Miotto, O., Almagro-Garcia, J., Manske, M., MacInnis, B., Campino, S., Rockett, K. A., and Kwiatkowski, D. P. (2013). Multiple populations of artemisinin-resistant Plasmodium falciparum in Cambodia. *Nature Genetics*, *45*(6), 648-655.

Mishra, A., Kaushik, N. K., Sardar, M., and Sahal, D. (2013). Evaluation of antiplasmodial activity of green synthesized silver nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *111*, 713-718.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and PRISMA Group*, T. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264-269.

Murugan, K., Anitha, J., Suresh, U., Rajaganesh, R., Panneerselvam, C., Aziz, A. T., and Hwang, J. S. (2017). Chitosan-fabricated Ag nanoparticles and larvivorous fishes: a novel route to control the coastal malaria vector Anopheles sundaicus?. *Hydrobiologia*, *797*, 335-350.

Murugan, K., Panneerselvam, C., Samidoss, C. M., Madhiyazhagan, P., Suresh, U., Roni, M., and Benelli, G. (2016). In vivo and in vitro effectiveness of Azadirachta indica-synthesized silver nanocrystals against Plasmodium berghei and Plasmodium falciparum, and their potential against malaria mosquitoes. *Research in Veterinary Science*, *106*, 14-22.

Murugan, K., Panneerselvam, C., Subramaniam, J., Madhiyazhagan, P., Hwang, J. S., Wang, L., and Benelli, G. (2016). Eco-friendly drugs from the marine environment: spongeweed-synthesized silver nanoparticles are highly effective on Plasmodium falciparum and its vector Anopheles stephensi, with little non-target effects on predatory copepods. *Environmental Science and Pollution Research*, *23*, 16671-16685.

Murugan, K., Samidoss, C. M., Panneerselvam, C., Higuchi, A., Roni, M., Suresh, U., and Benelli, G. (2015). Seaweed-synthesized silver nanoparticles: an eco-friendly tool in the fight against Plasmodium falciparum and its vector

Anopheles stephensi?. *Parasitology Research*, *114*, 4087-4097.

Murugan, K., Wei, J., Alsalhi, M. S., Nicoletti, M., Paulpandi, M., Samidoss, C. M., and Benelli, G. (2017). Magnetic nanoparticles are highly toxic to chloroquine-resistant Plasmodium falciparum, dengue virus (DEN-2), and their mosquito vectors. *Parasitology Research*, *116*, 495-502.

Najoom, S., Fozia, F., Ahmad, I., Wahab, A., Ahmad, N., Ullah, R., and Khan, A. A. (2021). Effective antiplasmodial and cytotoxic activities of synthesized zinc oxide nanoparticles using Rhazya stricta leaf extract. *Evidence-Based Complementary and Alternative Medicine*, *2021*(1), 5586740.

Narasimha, G. (2013). Virucidal properties of silver nanoparticles synthesized from white button mushrooms (Agaricus bisporus), 181-184 https://www.sid.ir/EN/VEWSSID/J_pdf/1010420130302.pdf

Noedl, H., Se, Y., Schaecher, K., Smith, B. L., Socheat, D., and Fukuda, M. M. (2008). Evidence of artemisinin-resistant malaria in western Cambodia. *New England Journal of Medicine*, *359*(24), 2619-2620.

Ouattara, A., Kone, A., Adams, M., Fofana, B., Maiga, A. W., Hampton, S., and Djimde, A. A. (2015). Polymorphisms in the K13-propeller gene in artemisinin-susceptible Plasmodium falciparum parasites from Bougoula-Hameau and Bandiagara, Mali. *The American Journal of Tropical Medicine and Hygiene*, *92*(6), 1202.

Panneerselvam, C., Murugan, K., and Amerasan, D. (2015). Biosynthesis of silver nanoparticles using plant extract and its anti-plasmodial property. *Advanced Materials Research*, *1086*, 11-30.

Panneerselvam, C., Murugan, K., Roni, M., Aziz, A. T., Suresh, U., Rajaganesh, R., and Benelli, G. (2016). Fern-synthesized nanoparticles in the fight against malaria: LC/MS analysis of Pteridium aquilinum leaf extract and biosynthesis of silver nanoparticles with high mosquitocidal and antiplasmodial activity. *Parasitology Research*, *115*, 997-1013.

Panneerselvam, C., Ponarulselvam, S., and Murugan, K. (2011). Potential anti-plasmodial activity of synthesized silver nanoparticle using Andrographis paniculata Nees (Acanthaceae). *Archive Applied Science Research*, *3*(6), 208-217.

Patra, J. K., and Baek, K. H. (2016). Biosynthesis of silver nanoparticles using aqueous extract of silky hairs of corn and investigation of its antibacterial and anticandidal synergistic activity and antioxidant potential. *IET Nanobiotechnology*, *10*(5), 326-333.

Patra, J. K., and Baek, K. H. (2017). Antibacterial activity and synergistic antibacterial potential of biosynthesized silver nanoparticles against foodborne pathogenic bacteria along with its anticandidal and antioxidant effects. *Frontiers in Microbiology*, *8*, 167.

Ponarulselvam, S., Panneerselvam, C., Murugan, K., Aarthi, N., Kalimuthu, K., and Thangamani, S. (2012). Synthesis of silver nanoparticles using leaves of Catharanthus roseus Linn. G. Don and their antiplasmodial activities. *Asian Pacific Journal of Tropical Biomedicine*, *2*(7), 574-580.

Rajakumar, G., Rahuman, A. A., Chung, I. M., Kirthi, A. V., Marimuthu, S., and Anbarasan, K. (2015). Antiplasmodial activity of eco-friendly synthesized palladium nanoparticles using Eclipta prostrata extract against Plasmodium berghei in Swiss albino mice. *Parasitology Research*, *114*, 1397-1406.

Rotimi, L., Ojemaye, M. O., Okoh, O. O., Sadimenko, A., and Okoh, A. I. (2019). Synthesis, characterization, antimalarial, antitrypanocidal and antimicrobial properties of gold nanoparticle. *Green Chemistry Letters and Reviews*, *12*(1), 61-68.

Sardana, M., Agarwal, V., Pant, A., Kapoor, V., Pandey, K. C., and Kumar, S. (2018). Antiplasmodial activity of silver nanoparticles: A novel green synthesis approach. *Asian Pacific Journal of Tropical Biomedicine*, *8*(5), 268-272.

Straimer, J., Gnädig, N. F., Witkowski, B., Amaratunga, C., Duru, V., Ramadani, A. P., and Fidock, D. A. (2015). K13-propeller mutations confer artemisinin resistance in Plasmodium falciparum clinical isolates. *Science*, *347*(6220), 428-431.

Subramaniam, J., Murugan, K., Panneerselvam, C., Kovendan, K., Madhiyazhagan, P., Dinesh, D., and Benelli, G. (2016). Multipurpose effectiveness of Couroupita guianensis-synthesized gold nanoparticles: high antiplasmodial potential, field efficacy against malaria vectors and synergy with Aplocheilus lineatus predators. *Environmental Science and Pollution Research*, *23*, 7543-7558.

Ta, T. H., Hisam, S., Lanza, M., Jiram, A. I., Ismail, N., and Rubio, J. M. (2014). First case of a naturally acquired human infection with Plasmodium cynomolgi. *Malaria Journal*, *13*, 1-7.

Takala-Harrison, S., Clark, T. G., Jacob, C. G., Cummings, M. P., Miotto, O., Dondorp, A. M., and Plowe, C. V. (2013). Genetic loci associated with delayed clearance of Plasmodium falciparum following artemisinin treatment in Southeast Asia. *Proceedings of the National Academy of Sciences*, *110*(1), 240-245.

Takala-Harrison, S., Jacob, C. G., Arze, C., Cummings, M. P., Silva, J. C., Dondorp, A. M., and Plowe, C. V. (2015). Independent emergence of artemisinin resistance mutations among Plasmodium falciparum in Southeast Asia. *The Journal of Infectious Diseases*, *211*(5), 670-679.

Taylor, S. M., Parobek, C. M., DeConti, D. K., Kayentao, K., Coulibaly, S. O., Greenwood, B. M., and Juliano, J. J. (2015). Absence of putative artemisinin resistance mutations among Plasmodium falciparum in sub-Saharan Africa: a molecular epidemiologic study. *The Journal of Infectious Diseases*, *211*(5), 680-688.

Tilley, L., Straimer, J., Gnädig, N. F., Ralph, S. A., and Fidock, D. A. (2016). Artemisinin action and resistance in Plasmodium falciparum. *Trends in Parasitology*, *32*(9), 682-696.

Torrentino-Madamet, M., Fall, B., Benoit, N., Camara, C., Amalvict, R., Fall, M., and Pradines, B. (2014). Limited polymorphisms in k13 gene in Plasmodium falciparum isolates from Dakar, Senegal in 2012–2013. *Malaria Journal*, *13*, 1-5.

Trape, J. F. (2001). The public health impact of chloroquine resistance in Africa. *The Intolerable Burden of Malaria: A New*

Look at the Numbers: Supplement to Volume 64 (1) of the American Journal of Tropical Medicine and Hygiene.

Trape, J. F., Pison, G., Spiegel, A., Enel, C., and Rogier, C. (2002). Combating malaria in Africa. *Trends in Parasitology*, *18*(5), 224-230.

Tse, E. G., Korsik, M., and Todd, M. H. (2019). The past, present and future of anti-malarial medicines. *Malaria Journal*, *18*(1), 93.

Veeragoni, D., Deshpande, S. S., Singh, V., Misra, S., and Mutheneni, S. R. (2023). In vitro and in vivo antimalarial activity of green synthesized silver nanoparticles using Sargassum tenerrimum-a marine seaweed. *Acta Tropica*, *245*, 106982. https://www.sciencedirect.com/science/article/abs/pii/S0001706X23001699

White, N.J., Pukrittayakamee, S., Tinh Hien, T., Abul Faiz, M., Mokuolu, O.A., and Dondorp, A.M. (2014) Malaria. Lancet.391:1608–21.

WHO (2022). World malaria report. Geneva: World Health Organization; 2022. http://www.who.int.

WHO. (2017) Status report on artemisinin and ACT resistance.WHO/ Htm/Gmp/20179. 2017:11. http://www.who.int/malaria/publications/ atoz/artemisinin-resistance-april2017/en/.

WHO (2018) World malaria report. Geneva: World Health Organization; 2018. http://www.who.int.

Witkowski, B., Amaratunga, C., Khim, N., Sreng, S., Chim, P., Kim, S., and Menard, D. (2013). Novel phenotypic assays for the detection of artemisinin-resistant Plasmodium falciparum malaria in Cambodia: in-vitro and ex-vivo drug-response studies. *The Lancet Infectious Diseases*, *13*(12), 1043-1049.

Wongsrichanalai, C., and Sibley, C. H. (2013). Fighting drug-resistant Plasmodium falciparum: the challenge of artemisinin resistance. *Clinical Microbiology and Infection*, *19*(10), 908-916.

Woodrow, C. J., and White, N. J. (2017). The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. *FEMS Microbiology Reviews*, *41*(1), 34-48.

Zangeneh, A., Zangeneh, M. M., and Moradi, R. (2020). Ethnomedicinal plant-extract-assisted green synthesis of iron nanoparticles using Allium saralicum extract, and their antioxidant, cytotoxicity, antibacterial, antifungal and cutaneous wound-healing activities. *Applied Organometallic Chemistry*, *34*(1), e5247

Chapter 47

Application of Nanoparticles and Nanomaterials in Animal Health and Performance

Aneela Amin[1], Sadaf Faiz[1], Muhammad Asmat Ullah Saleem[2], Muhammad Usman[1], Muhammad Abdullah Arshad[1], Muhammad Asad Ali[1], Muhammad Bilal[1], Ali Haider[1] and Aisha Khatoon[1*]

[1]Department of Pathology, University of Agriculture, Faisalabad, Pakistan
[2]College of Veterinary Medicine Northeast Agricultural University, Harbin, China
*Corresponding author: aisha.khatoon@uaf.edu.pk

ABSTRACT

Nanotechnology is one of the fastest-growing industries in the world. It has a wide application in almost all fields from agriculture to food systems, thus crucial in overcoming future food scarcity in the world. This technology has all the characteristics, features, and potential to solve all the problems related to animal health and production. This chapter is mainly related to the production of different types of nanoparticles, their preparation methods, characterization, and potential use of nanoparticles in the veterinary field. In animal health, nanoparticles have a significant impact on diagnostics, therapeutic, vaccinology, and drug delivery as drugs delivered through this technology have maximum outputs in controlling the disease and improving the animal health and minimal toxicity. Nanoparticles also have a crucial role as a feed additive in animal production system as a very small amount of additive is used for maximum outputs. By reviewing all the miracles of nanotechnology in terms of cost and available resources in veterinary medicines, the main purpose of this chapter is to discuss briefly the uses of nanoparticles in the improvement of animal health and production and lastly, the main discussion will be on future potential and use of nanomaterials in the veterinary field.

KEYWORDS
Nanoparticles, Diagnostics, Therapeutic, Immunization, Animal Health and Production

Received: 22-Jun-2024
Revised: 10-Jul-2024
Accepted: 21-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Amin A, Faiz S, Saleem MAU, Usman M, Arshad MA, Ali MA, Bilal M, Haider A and Khatoon A, 2024. Application of nanoparticles and nanomaterials in animal health and performance. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 413-420. https://doi.org/10.47278/book.CAM/2024.490

INTRODUCTION

Nanotechnology has become a part of our daily lives in recent years (Nasrollahzadeh et al., 2019). Therapeutic application of nanoparticles in veterinary field has played a significant role. This field of modern science focuses on the design, preparation of NPs, and alteration of particle structures ranging in size from 1-100 nm. Nanotechnology involves utilizing materials with at least one dimension at the nanometer scale to create products, tools, or structures with new or significantly improved properties (Kargoza et al., 2018). These nanomaterials have greater potential than traditional sources, allowing for reduced but effective quantities to be used. Nanoparticles have unique physiochemical properties including bioavailability, large surface area, controlled particle size, increased reactivity with pathogens, stability of the compound, controlled drug release property, and targeting to the specific site (Thakur and Thakur, 2022).

Nanomedicine is widely used in the livestock industry for diagnosis, monitoring, treatment, and prevention of disease. This field involves using nano-sized materials, such as biocompatible nanoparticles, within living organisms. The quantity and quality of dairy and poultry products are enhanced by using nanocomposites (Prasad et al., 2021).

Nanoparticles possess antimicrobial properties and can reduce antibiotic residues in livestock and poultry, making them potential candidates for combating antibiotic-resistant bacteria. For the early detection of livestock and poultry diseases nanoparticles prove to be a very cost-effective, unique, and rapid tool for accurate diagnosis of disease (Mekonnen, 2021). Nanomaterials has made a significant impact on veterinary medicine across various areas, integrating treatment, diagnostics, tissue engineering, vaccine production, and disinfectants. Nanoparticles have unique properties of targeting specific sites so, low dosage medicine is used that leads to a deceased withdrawal period of medicine (Ulucan-Karnak et al., 2023).

Nanoparticles (NPs) can effectively eliminate a variety of animal pathogens, including those responsible for persistent infections, intracellular pathogens, and blood parasites. Nanocomposites offers novel approaches to addressing significant challenges faced by veterinarians, such as tuberculosis, foot and mouth disease, brucellosis, and methicillin-resistant

Staphylococcus aureus (MRSA), as well as intracellular and blood pathogen infections (Osama et al., 2020). Consequently, researchers have been actively seeking new solutions, with metal NPs emerging as the most suitable agents. Ag NPs, Cu NPs, and AgCu-NPs on pathogen species were also assessed. There is also a great use of nanocomposites in the poultry sector. Copper, zinc, zinc oxide, selenium, chitosan, and chromium nanoparticles are being used at a larger scale in the poultry industry. These NPs used in diagnostic procedures, vaccine development, antimicrobials, disinfectants, immunomodulatory, and anti-mycotoxin agents (Hernández-Díaz et al., 2021). However, it is also worth emphasizing the term nanotoxicology because nanoparticles at high doses and administration for longer periods cause toxicity in animals. Considering the above information, this chapter intends to discuss the types, preparation methods, modes of action, and various applications of NPs as well as their safety and hazardous effects in the poultry and livestock industry.

Classification of Nanoparticles

Nanoparticles are classified into different types on the basis of their size, shape, application, surface modification, composition, and nature (Harish et al., 2023).

Based on Form

NPs have different types such as liposomes, fibers, dendrimers, nanotubes, carbon tubes, nanoclusters, and micelles based on form.

Based on Size

NPs have a size in the range between 1- 100nm. Particles of smaller size exhibit a large surface area.

Based on Shape

Different types of NPs based on shapes are there which include spheres, cubes, stars, tubes, plates wires, hooks, helices, plates, zigzags, and triangular.

Based on Application

Based on application nanoparticles have therapeutic and diagnostic properties. NPs also used in vaccine production and as feed additives in animals.

Based on Surface Modifications

Positive and negative charge nanoparticles are produced on the basis of surface modification.

Based on Composition

Nanomaterial may be synthesized only from one material (single material) and produced from at least two materials (composites or hybrid).

Based on Nature

NPs are organic, inorganic, and carbon NPs on the basis of nature. The details of these nanoparticles is described below.

(a) Organic NPs

Ferritin, liposomes, fibers, dendrimers, etc., are also known as organic NPs. Such NPs are nontoxic and biodegradable and certain particles like liposomes and the micelle have a hollow core known as nano-capsules and are prone to light and heat radiation, and one can efficiently use them for drug delivery. Along with their typical principles like size, structure, sugar morphology, etc. (Niknam et al., 2024) The organic NPs' field of application use depends on their drug-carrying power, stability, and delivery ways whether it is a trapped drug system or absorbed drug system. Organic NPs are used in the field of medicine since an efficient drug delivery system is safe to use, and also one can inject at a specific site (Ajith et al., 2023).

(b) Inorganic NPs

Metals and metal oxide are incorporated into inorganic type of nanomaterials and their significant characteristics are described below.

Metal-based

The nanoparticles based on metals are very commonly used and are prepared by different methods such as constructive and destructive. Common metals used in synthesizing nanoparticles include Ag, Au, Cu, Iron, Co, Al, and Hg (Shabatina et al., 2023). Almost all the metals may be transformed into nanoparticles. In addition to this coating of one type of nanoparticles to another may also be prepared and in this way, their efficacy may also be increased by several folds (Zang et al., 2023).

Metal Oxide based

In addition to the metal-based nanoparticles, their oxides can also equally be used for the preparation of nanoparticles (Carrapiço et al., 2023).

(c) Carbon-based Nanoparticles

In this type of nanoparticle, the main element from which the nanoparticles are prepared is carbon and this category can be classified as fullerenes, and carbon compounds like graphite, carbon tubes, carbon nanofibers, nanocarbon, and black carbon are of chief importance (Manimegalai et al., 2023).

Nanoparticles Synthesis

Particles that have a size of less than 100 nm in different dimensions are known as nanoparticles. Nanoparticles can be prepared in the lab by following different techniques like bottom-up techniques and top-down approaches in addition to nanoparticles in nature like in soil particles, ashes, and biomolecules (Nie et al., 2023).

Different factors are responsible for the synthesis of nanoparticles such as temperature, time, pressure, size and shape of particle, pore size of the material, and cost of the production of nanoparticles (Molaei et al., 2023)

Approaches for the Synthesis of Nanoparticles

Broadly two types of approaches are used in the synthesis of nanoparticles which are discussed as follows.

a) Top-down approach

The main purpose of these types of techniques is to decrease the size of larger size particles into smaller type particles and this can be achieved by a sequence of operations applied over them for the decrease in size (Table 1). This type of system uses large-scale machinery and a large amount of labor work. This type of system is very expensive and cannot be used on the industrial scale production of nanoparticles in a laboratory. The main principle of this type of method is to grinding of large-size materials (Abid et al., 2022).

b) Bottom-up Approach

The bottom-up technique can also be used for the preparation of nanoparticles in which the material size is reduced to the subatomic level with additional protocols to sensitize the NPs (Table 1). The basic principle of this method is uniting all the physical forces into a larger stable one and knowing the molecular recognition of materials used in the preparation of nanoparticles. These types of techniques are under-processed and innovative and have just started to be used at the commercial level for the production of nanoparticles (Jiang et al., 2022).

Table 1: Approaches for synthesis of nanoparticles

Methods in top-down approach	Methods in a bottom-up approach
• Physical vapor deposition.	• Sol-gel synthesis
• Ion implantation	• Colloidal precipitation
• Electron beam lithography	• Hydrothermal synthesis
• Chemical vapor deposition	• Organometallic chemical route
• X-ray lithography	• Electrodeposition

Methods of Synthesis of Nanoparticles

There are three kinds of approaches to produce nanoparticles (Table 2) (Joudeh and Linke, 2022).

1. Physical Methods
2. Chemical Methods
3. Biological Methods

Physical Methods

There are different methods used in the preparation of NPs, one of them is a physical method which uses evaporation and condensation by using a tube furnace at atmospheric pressure. The main purpose of this technique is to reduce particle size to the desired level and this can be achieved by employing radiation and speed in addition to certain chemicals. Limitations of this method are that a very small amount of product is achieved at the cost of high energy in addition to this contamination with different solvents used in this procedure may also be observed. Physical elements used in the reduction of particle size include mechanical pressure, high-energy waves, radiation, and thermal energy (Islam et al., 2022).

Chemical Methods

Chemical methods use different chemicals for the reduction of particle size. They mostly used the mixing of precursor and reducing agents while having the composition equal to the operating systems at which the reaction is carried out. The very small amount of surfactant is used for reciprocal aggregation.

The reducing reagents are mainly responsible for the sizing of the NPs i.e., stronger reagents produce the smaller size of particles and vice versa. Certain stabilizers such as acetates, amines, phosphines, thiols, and carbon monoxide generally monitor particle size preparation and reduce the clumping of these NPs. One of the common limitations of this type of chemical method is that this holds significant toxicity issues such as hazardous chemicals are the main players of this method (Pracht et al., 2020).

Biological Methods

Many chemicals like surfactants and reductants are toxic to humans and animals and proved to be dangerous for the environment. Efforts have been made to introduce a green synthesis process that is non-harmful and eco-friendly. Microbial synthesis of nanoparticles makes a connection between nanotechnology and microbial biotechnology. Biosynthesis of gold, silver, gold–silver nanocomposites, silica palladium, selenium, uraninite, platinum, tellurium, quantum dots, titanium, zirconia, and magnetite NPs by bacteria, viruses, yeast, fungi, and actinomycetes have been recorded. Utilizing naturally occurring non-toxic environmentally friendly reductants, microorganisms such as fungi, and algae, plant extracts containing plant active molecules, proteins, template supports like DNA (often referred to as "greener synthesis"), and other biological materials (such as ferritin) are used in biological methods for NP synthesis. A wide range of mineral NPs, including zinc, silver, palladium, selenium, gold, silver, cadmium, and titanium, have been created biologically utilizing various plant elements (Samrot et al., 2021).

Table 2: Methods for synthesis of nanoparticles

Physical method	Chemical method	Biological method
Mechanical Method	Sol-gel method	Synthesis using microorganisms
Pulse Laser Ablation	Sonochemical synthesis	Synthesis using plant extracts
Pulsed Wire Discharge Method	Co-precipitation method	Synthesis using algae
Chemical Vapor Deposition	The inert gas condensation method	
Laser Pyrolysis	Hydrothermal synthesis	
Ionized Cluster Beam Deposition		
(Dhand et al., 2015).		

Nanoparticle Characterization

Different techniques are used for the characterization of NPs**.** Size and shape affect the function and properties of nanoparticles (Zang et al., 2023).

- Particle size distribution
- Zeta potential
- Scanning electron microscopy
- Transmission electron microscope (TEM)
- X-ray diffraction (XRD)
- Infrared Spectroscopy (IR)
- Fourier Transform Infrared Spectroscopy (FTIR**)**

Modes of Actions of NPs

Size, charge, and solubility affect the mechanism of action of nanoparticles. For higher interaction with the pathogen's surface proper size and charge of NPs should be required.

- Nanoparticles have a high surface area that can increase their contact with pathogens.
- Due to their small size, they can easily penetrate through membranes of bacteria, viruses, and fungi.
- Nanoparticles trigger the production of excessive reactive oxygen species (ROS) which produces stress on the bacterial cells that leads to damage to DNA and RNA decreases membrane activity and produces peroxide (Pikula et al., 2020)

Applications of Nanoparticles in Veterinary Medicine

Nanotechnology presents veterinarians with similar opportunities as physicians, such as in therapy, diagnostics, tissue engineering, vaccine manufacturing, and the development of disinfectants. Nanotechnology is already being utilized in animal health, production, husbandry practices, reproduction, and nutrition of animals (Zhao et al., 2022). While nanoparticles have long been employed in human medicine for diagnosis and treatment, their use in veterinary medicine and animal processing is a recent development (Morena et al., 2022).

Nanoparticles used against different Infectious Diseases

Nanoparticles are used against various types of animal pathogens that cause chronic infections such as Hemiparasite, and intracellular pathogens. Nanomaterial helps veterinarians to deal with severe infectious diseases such as bovine TB, foot and mouth disease, brucellosis, and methicillin-resistant *Staphylococcus (S.) aureus*. Mastitis is a very serious issue in livestock production, pathogens that cause this disease have antibiotic resistance, therefore, researchers developed new

solutions, to overcome these issues. In this regard, metal NPs gain attention (Morena et al., 2022). CuNPs, AgNPs, and composite of Cu and Ag nanoparticles against pathogens species (e.g., *S. aureus* and *E. coli*) that are involved in inflammation of the udder of mastitis cow (Yu et al., 2024). Nanoparticles of appropriate size and properties did not show any lethal effect on the mammary glands of the animals and decreased the viability of pathogens. Silver nanoparticles were used against multiple drug-resistant strains of *Pseudomonas* (P.) *aeruginosa* and *S. aureus* in goats infected with mastitis (Bruna et al., 2021).

Nanoparticles as an Alternative to Antibiotics

In the livestock industry, antibiotics are mainly used as growth promoters, but these antibiotics have greater microbial antibiotic resistance. Alternative to these antibiotics, nanoparticles are being used as antimicrobials to fulfill the demand of the livestock industry (Singh et al., 2020). Nanoteparticles plays a very important role in the veterinary field. Nanocomposites helped to establish antimicrobial agents that are non-toxic and decreased antibiotic resistance against various pathogens that cause chronic animal diseases, like *Brucella*, *Mycobacterium bovis, Streptococcus,* and *Rhodococcus equi* (Mubeen et al., 2021).

Nanoparticles used in Vaccine Preparation

Nanoparticles are widely used in vaccine production for veterinary use. Nanoparticles have immune-modulatory property that enhances the immune response. Nanoparticles increase peptide cross-linkage and activate antigen-presenting cells resulting in targeting the lymph nodes. NPs also act as adjuvant to make the slow release of antigens that enhance vaccine efficacy (Kheirollahpour et al., 2020). The IBV vaccine coated with chitosan nanoparticles was used alone or in combination with the live attenuated vaccine by ocular and nasal route in broiler birds causing both humoral and cell-mediated immune response and protecting the chicks against IBV (Renu et al., 2020). Nano-based vaccines such as recombinant B. anthracis, bovine para influenza type III vaccine, influenza vaccines, *Bordetella pertussis* vaccine, tetanus toxoid, and C. Recombinant Leishmania SOD vaccine loaded with chitosan nanoparticles are being used in veterinary practice. Gold nanoparticles-based vaccines are also being used against FMD (Maina et al., 2020)

Nanoparticles in Animal Nutrition

In animal nutrition, nanoparticles play a very important role in processing nanominerals that are being used in veterinary practices. These nanowires decrease intestinal mineral antagonism, excretion, and environmental decontamination. Feeding of nanoparticles increases the intentional digestive capability, and immune status of animals (Prasad et al., 2022). Scientists managed to process food, meat, and milk that contains high levels of minerals contents to enhance the flavor, taste, appearance, and long-term storage of food. Nanoparticles are used as a feed additive in micro and macro-nanoparticle forms to increase their digestibility in animals. Contaminated-free meat and meat products are synthesized by use of nanomaterial. Micro and macro nanoparticles are inexpensive, used in low amounts, and act as growth-promoting and immune stimulators. These nanomaterials also manipulate pathogens present in the feed and the fermentation process in the rumen is improved by nanoparticles (Osama et al., 2020). ZnO NPs are one of the most used nano minerals to enhance the growth and immune response of the animals. Nano zinc is also used in cows suffering from mastitis and leads to decreased somatic cell counts. Mycotoxicosis is a very serious issue in both humans and animals (Reda et al., 2021). SiO2 and MgO nanoparticles are the best nanoantimycotoxin against toxins and inactivate them. Chitosan nanoparticles also get attention in this regard to use against aflatoxin (Jogee et al., 2020).

Nanoparticle in Animal Reproduction

In animal reproduction, nanomaterials are used as cryo-preservatives for embryos, sperm, oocytes, and gonadal tissues. To facilitate fertilization from a single dose to conceive more than one female, nanoparticles are used to potentiate fertilization efficiency. By using nano-purification of the semen, damaged sperm can be differentiated from healthy, undamaged sperm (Ajdary et al., 2021). A nano-purified bull's spermatozoa showed conception levels equal to un-purified semen without any negative effects. Several applications of nanocomposites have been developed for diagnosing and treating reproductive problems, detecting estrus, freezing sperm, and interfering with the calving process. Further, many issues related to the reproductive health of the animals such as retained placenta can be cured by the use of nanoparticles. Additionally, nanoparticles have a great effect on protecting and managing the release of reproduction hormones like steroid and gonadotropic hormones. Nano-sensors are also used in reproduction with a cell probe. These probes are used for the diagnosis of reproductive disorders, illness, metabolic and hormonal issues, and the detection of heat in animals. Metallic nanoparticles like cadmium lead to toxicity in animals so sterilized nanoparticles can be used in appropriate doses (Fard et al., 2023).

Application of Nanoparticles in Drug Delivery Systems

In the field of pharmacology, nanoparticles are used ideal in drug delivery that protect animals from bacterial, viral, and parasitic infection but are also helpful in wound healing and decrease pain. NPs deliver drugs to specific sites of tissue and organs. These frameworks may affect the rate at which drugs or other substances are absorbed, digested, and released from the body. They may also allow for the monitoring of drug dynamics, the acquisition of a therapeutic effect, the

assurance of bioavailability and stability, the extension of the duration of movement, the reduction of the frequency of doses necessary to maintain therapeutic responses, and the mitigation of toxicity (Onugwu et al., 2023).

Nanoparticles and Pet Care

Nanoparticles are also used in pet care. These are used as surface refreshing and disinfects due to their unique physiochemical properties. Different nanoparticles like silver nanoparticles added in the shampoo for tropical use in the pet (Yavuz et al., 2023).

Applications of NPs in the Poultry Industry

Nanoparticles also gained attention in the field of poultry. Copper, zinc, zinc oxide, chitosan and chromium and selenium nanoparticles are being used at a larger scale. These NPs used in diagnostic procedures, and vaccine development as immunomodulatory agents, antimicrobials, disinfectants, and anti-mycotoxin agents (Younas et al., 2023). The administration of chitosan nanoparticle-based vaccine against salmonellosis in birds enhanced the level of T helper cell 1 and 2 cytokines, mRNA expression and increases the levels of antibodies (IgYand IgA) (Renu et al., 2020). DNA-based vaccine encapsulated with $AgSiO_2$ used against ND in chickens that results in protective mucosal immunity. Vaccines prepared aluminum NPs have been shown to produce high and long-lasting antibody titers after a single immunization. AgNPs are used to reduce microbial load, proper disinfection of eggs and hatcheries, and protection for longer periods as antibacterial and antiviral during the incubation of eggs (Salesa et al., 2023). NPs are used as feed additives in poultry and administration of NPs in poultry is via oral, inhalation, injection, and topical. Feed additives contain minerals (micro and macro) in nano forms (nano zinc, nano copper, nano selenium) that act as growth promoters in poultry. NPs specially the metallic act as antibacterial against different diseases in poultry like Aeromonas, Flavobacterium, Escherichia, Klebsiella spp Bacillus, *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Salmonella Enteritidis*. Gold nanoparticles and green synthesized Ag exhibit antiviral properties and may be used as a delivery system for immunomodulatory drugs. ZnO NPs have the potential to be used as antiviral agent against different antiviral infections in poultry like H1N1 influenza virus infection Gold NPs used as anti-parasitic agent in different parasitic diseases (Fatima et al., 2024). Ag NPs and chitosan showed measurable harm, growth retardation, and cytotoxic effects against a variety of parasites, including plasmodium, Giardia, helminths, Toxoplasma and Leishmania. Different NPs used as antifungal agent against different various strains of Aspergillus and Candida spp. Chitosan NPs have the great adsorption capability against different mycotoxin such as AF, OTA, DON and FUM when compared with antifungal drugs like nystatin (Pawariya et al., 2023).

Nanoparticle Related Safety and Hazardous Concern

In animals and poultry, safe delivery of nanoparticles depends upon intercellular, biological interaction and function of the nanoparticles. Previous studies revealed that NPs are eco-friendly, and non-toxic but recent studies showed that NPs have adverse effects on animals. Concentration, size, and charge affect the toxicity of NPs. Accumulation of NPs in organs like the liver and kidney and effects on the immune systems are seen due to prolonged exposure to nanoparticles. Nanoparticles are water soluble, so their aggregation is harmful to some beneficial bacteria therefore their concentration should be monitored before being in to feed of animals (Chen et al., 2023).

Conclusion

Nanotechnology is one of the fastest-growing industries in the world and has a wide application in almost all fields from agriculture to food systems. By the use of nanomaterial in food and feed the production performance of livestock and poultry can be enhanced. One of the fine aspects of nanotechnology is the use of nanomaterials in vaccine development against new emerging diseases. It is a need of time to use nanoparticles for the well-being of humanity in terms of modernization of diagnostics, development of new tools for early disease detection, and increase production both in agriculture and animal so we can overcome future problems ailing humanity.

REFERENCES

Abid, N., Khan, A. M., Shujait, S., Chaudhary, K., Ikram, M., Imran, M., and Maqbool, M. (2022). Synthesis of nanomaterials using various top-down and bottom-up approaches, influencing factors, advantages, and disadvantages: A review. *Advances in Colloid and Interface Science*, *300,* 102597.

Ajdary, M., Keyhanfar, F., Moosavi, M. A., Shabani, R., Mehdizadeh, M., and Varma, R. S. (2021). Potential toxicity of nanoparticles on the reproductive system animal models: A review. *Journal of Reproductive Immunology*, *148*, 103384.

Ajith, S., Almomani, F., Elhissi, A., and Husseini, G. (2023). Nanoparticle-based materials in anticancer drug delivery: Current and future prospects. *Heliyon*.

Bruna, T., Maldonado-Bravo, F., Jara, P., and Caro, N. (2021). Silver nanoparticles and their antibacterial applications. *International Journal of Molecular Sciences*, *22*(13), 7202.

Chen, J., Guo, Y., Zhang, X., Liu, J., Gong, P., Su, Z., and Li, G. (2023). Emerging nanoparticles in food: sources, application, and safety. *Journal of Agricultural and Food Chemistry*, *71*(8), 3564-3582.

Carrapiço, A., Martins, M. R., Caldeira, A. T., Mirão, J., and Dias, L. (2023). Biosynthesis of metal and metal oxide

nanoparticles using microbial cultures: Mechanisms, antimicrobial activity and applications to cultural heritage. *Microorganisms*, *11*(2), 378.

Dhand, C., Dwivedi, N., Loh, X. J., Ying, A. N. J., Verma, N. K., Beuerman, R. W., and Ramakrishna, S. (2015). Methods and strategies for the synthesis of diverse nanoparticles and their applications: a comprehensive overview. *Rsc Advances*, *5*(127), 105003-105037.

Fard, N. J. H., Mohammadi, M. J., and Jahedi, F. (2023). Effects of nano and microplastics on the reproduction system: In vitro and in vivo studies review. *Food and Chemical Toxicology*, 113938.

Fatima, A., Zaheer, T., Pal, K., Abbas, R. Z., Akhtar, T., Ali, S., and Mahmood, M. S. (2024). Zinc oxide nanoparticles significant role in poultry and novel toxicological mechanisms. *Biological Trace Element Research*, *202*(1), 268-290.

Harish, V., Ansari, M. M., Tewari, D., Yadav, A. B., Sharma, N., Bawarig, S., and Barhoum, A. (2023). Cutting-edge advances in tailoring size, shape, and functionality of nanoparticles and nanostructures: A review. *Journal of the Taiwan Institute of Chemical Engineers*, *149*, 105010.

Hernández-Díaz, J. A., Garza-García, J. J., Zamudio-Ojeda, A., León-Morales, J. M., López-Velázquez, J. C., and García-Morales, S. (2021). Plant-mediated synthesis of nanoparticles and their antimicrobial activity against phytopathogens. *Journal of the Science of Food and Agriculture*, *101*(4), 1270-1287.

Islam, F., Shohag, S., Uddin, M. J., Islam, M. R., Nafady, M. H., Akter, A., and Cavalu, S. (2022). Exploring the journey of zinc oxide nanoparticles (ZnO-NPs) toward biomedical applications. *Materials*, *15*(6), 2160.

Jiang, Z., Li, L., Huang, H., He, W., and Ming, W. (2022). Progress in laser ablation and biological synthesis processes:"Top-Down" and "Bottom-Up" approaches for the green synthesis of Au/Ag nanoparticles. *International Journal of Molecular Sciences*, *23*(23), 14658.

Jogee, P., and Rai, M. (2020). Application of nanoparticles in inhibition of mycotoxin-producing fungi. *Nanomycotoxicology*, 18 (1), 239-250.

Joudeh, N., and Linke, D. (2022). Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *Journal of Nanobiotechnology*, *20*(1), 262.

Kargozar, S., and Mozafari, M. (2018). Nanotechnology and Nanomedicine: Start small, think big. *Materials Today: Proceedings*, *5*(7), 15492-15500.

Kheirollahpour, M., Mehrabi, M., Dounighi, N. M., Mohammadi, M., and Masoudi, A. (2020). Nanoparticles and vaccine development. *Pharmaceutical Nanotechnology*, *8*(1), 6-21.

Maina, T. W., Grego, E. A., Boggiatto, P. M., Sacco, R. E., Narasimhan, B., and McGill, J. L. (2020). Applications of nanovaccines for disease prevention in cattle. *Frontiers in Bioengineering and Biotechnology*, *8*, 608050.

Mekonnen, G. (2021). Review of the application of nanotechnology in animal health and production. *Journal Nanomedicine Nanotechnology*, *12*, 559.

Molaei, S., Hamidpour, M., Shirani, H., and Sabet, M. (2023). Investigation of factors affecting removal of arsenic from polluted water using iron-based particles: Taguchi optimization design. *Revista Internacional de Contaminación Ambiental*, *39*.

Manimegalai, P., Selvam, K., Loganathan, S., Kirubakaran, D., Shivakumar, M. S., Govindasamy, M., and Bahajjaj, A. A. A. (2023). Green synthesis of zinc oxide (ZnO) nanoparticles using aqueous leaf extract of Hardwickia binata: their characterizations and biological applications. *Biomass Conversion and Biorefinery*, 1-16.

Morena, A. G., Bassegoda, A., Natan, M., Jacobi, G., Banin, E., and Tzanov, T. (2022). Antibacterial properties and mechanisms of action of sonoenzymatically synthesized lignin-based nanoparticles. *ACS Applied Materials and Interfaces*, *14*(33), 37270-37279.

Mubeen, B., Ansar, A. N., Rasool, R., Ullah, I., Imam, S. S., Alshehri, S., and Kazmi, I. (2021). Nanotechnology as a novel approach in combating microbes providing an alternative to antibiotics. *Antibiotics*, *10*(12), 1473.

Nasrollahzadeh, M., Sajadi, S. M., Sajjadi, M., and Issaabadi, Z. (2019). Applications of nanotechnology in daily life. *Interface Science and Technology*, *28*, 113-143.

Nie, P., Zhao, Y., and Xu, H. (2023). Synthesis, applications, toxicity and toxicity mechanisms of silver nanoparticles: A review. *Ecotoxicology and Environmental Safety*, *253*, 114636.

Niknam, Z., Zadeh, F. H., Toosi, S., Shoreh, N. K. H., Rasmi, Y., and Saleem, I. (2024). Organic-based nanomaterials for regenerative medicine. In *Handbook of Nanomaterials, Volume 2* (pp. 359-400). Elsevier.

Onugwu, A. L., Nwagwu, C. S., Onugwu, O. S., Echezona, A. C., Agbo, C. P., Ihim, S. A., and Khutoryanskiy, V. V. (2023). Nanotechnology based drug delivery systems for the treatment of anterior segment eye diseases. *Journal of Controlled Release*, *354*, 465-488.

Osama, E., El-Sheikh, S. M., Khairy, M. H., and Galal, A. A. (2020). Nanoparticles and their potential applications in veterinary medicine. *Journal of Advanced Veterinary Research*, *10*(4), 268-273.

Pawariya, V., De, S., and Dutta, J. (2023). Chitosan-based Schiff bases: Promising materials for biomedical and industrial applications. *Carbohydrate Polymers*, 121395.

Pikula, K., Mintcheva, N., Kulinich, S. A., Zakharenko, A., Markina, Z., Chaika, V., and Golokhvast, K. (2020). Aquatic toxicity and mode of action of CdS and ZnS nanoparticles in four microalgae species. *Environmental Research*, *186*, 109513.

Pracht, P., Bohle, F., and Grimme, S. (2020). Automated exploration of the low-energy chemical space with fast quantum chemical methods. *Physical Chemistry Chemical Physics*, *22*(14), 7169-7192.

Prasad, R. D., Charmode, N., Shrivastav, O. P., Prasad, S. R., Moghe, A., Sarvalkar, P. D., and Prasad, N. R. (2021). A review on concept of nanotechnology in veterinary medicine. *ES Food and Agroforestry*, *4*, 28-60.

Prasad, R. D., Sahoo, A. K., Shrivastav, O. P., Charmode, N., Kamat, R., Kajave, N. G., and Prasad, N. R. (2022). A review on aspects of nanotechnology in food science and animal nutrition. *ES Food and Agroforestry*, *8*, 12-46.

Reda, F. M., El-Saadony, M. T., El-Rayes, T. K., Attia, A. I., El-Sayed, S. A., Ahmed, S. Y., and Alagawany, M. (2021). Use of biological nano zinc as a feed additive in quail nutrition: biosynthesis, antimicrobial activity and its effect on growth, feed utilisation, blood metabolites and intestinal microbiota. *Italian Journal of Animal Science*, *20*(1), 324-335.

Renu, S., and Renukaradhya, G. J. (2020). Chitosan nanoparticle based mucosal vaccines delivered against infectious diseases of poultry and pigs. *Frontiers in Bioengineering and Biotechnology*, *8*, 558349.

Salesa, B., Ferrús-Manzano, P., Tuñón-Molina, A., Cano-Vicent, A., Assis, M., Andrés, J., and Serrano-Aroca, Á. (2023). Study of biological properties of gold nanoparticles: Low toxicity, no proliferative activity, no ability to induce cell gene expression and no antiviral activity. *Chemico-Biological Interactions*, *382*, 110646.

Samrot, A. V., Sahithya, C. S., Selvarani, J., Purayil, S. K., and Ponnaiah, P. (2021). A review on synthesis, characterization and potential biological applications of superparamagnetic iron oxide nanoparticles. *Current Research in Green and Sustainable Chemistry*, *4*, 100042.

Shabatina, T. I., Vernaya, O. I., Shimanovskiy, N. L., and Melnikov, M. Y. (2023). Metal and metal oxides nanoparticles and nanosystems in anticancer and antiviral theragnostic agents. *Pharmaceutics*, *15*(4), 1181.

Singh, A., Gautam, P. K., Verma, A., Singh, V., Shivapriya, P. M., Shivalkar, S., and Samanta, S. K. (2020). Green synthesis of metallic nanoparticles as effective alternatives to treat antibiotics resistant bacterial infections: A review. *Biotechnology Reports*, *25*, e00427.

Thakur, P., and Thakur, A. (2022). Introduction to nanotechnology. *Synthesis and Applications of Nanoparticles*, 1-17.

Ulucan-Karnak, F., Kuru, C. İ., Türkcan, C., and Kulabhusan, P. K. (2023). Potential application of nanobiotechnology for creating various diagnostic approaches for diseases in livestock. In *Nanobiotechnology for the Livestock Industry* (pp. 157-174). Elsevier.

Yavuz, G., Yilmaz, E., Halvaci, E., Catal, C., İrem, T. Ü. R. K., Maran, F. N., ... and Fatih, Ş. E. N. (2023). Nanotechnology In Medical Applications: Recent Developments In Devices And Materials. *Journal of Scientific Reports-C*, (005), 1-32.

Younas, Z., Mashwani, Z. U. R., Ahmad, I., Khan, M., Zaman, S., Sawati, L., and Sohail. (2023). Mechanistic approaches to the application of nano-zinc in the poultry and biomedical industries: A comprehensive review of future perspectives and challenges. *Molecules*, *28*(3), 1064.

Yu, R., Chen, H., He, J., Zhang, Z., Zhou, J., Zheng, Q., and Zhang, X. (2024). Engineering antimicrobial metal–phenolic network nanoparticles with high biocompatibility for wound healing. *Advanced Materials*, *36*(6), 2307680.

Zhao, R., Xiang, J., Wang, B., Chen, L., and Tan, S. (2022). Recent advances in the development of noble metal NPs for cancer therapy. *Bioinorganic Chemistry and Applications*, *2022*.

Zang, Y., Zhang, Y., Wei, R., Xue, H., and Jiang, J. (2023). Difunctional molecularly imprinted polymers and heterostructured CdS nanoparticle-sensitized ZnO nanorod arrays for antibody-free photoelectrochemical alpha-fetoprotein sensor. *Journal of Electroanalytical Chemistry*, *944*, 117631