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

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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.

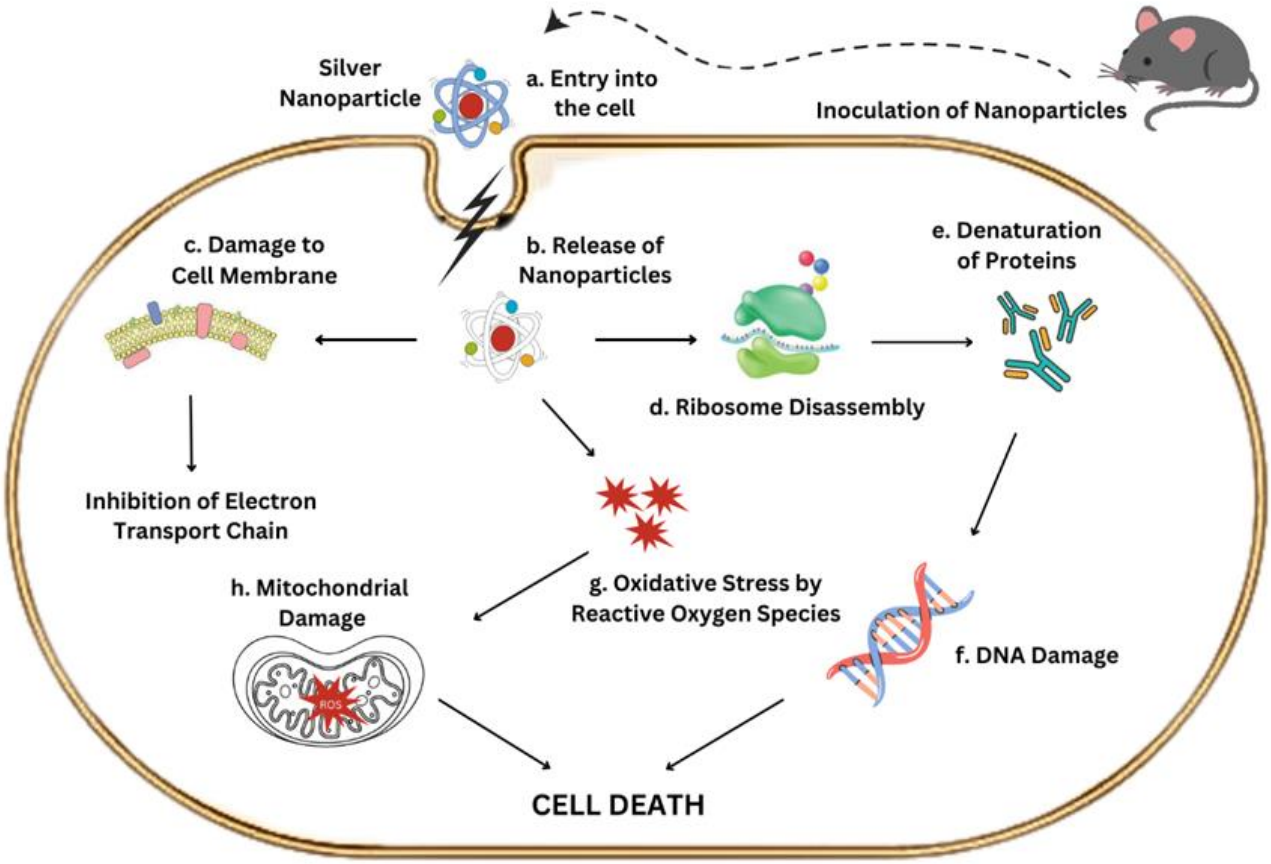

Fig. 1: Nanoparticles general mechanism of action against parasitic infections

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).

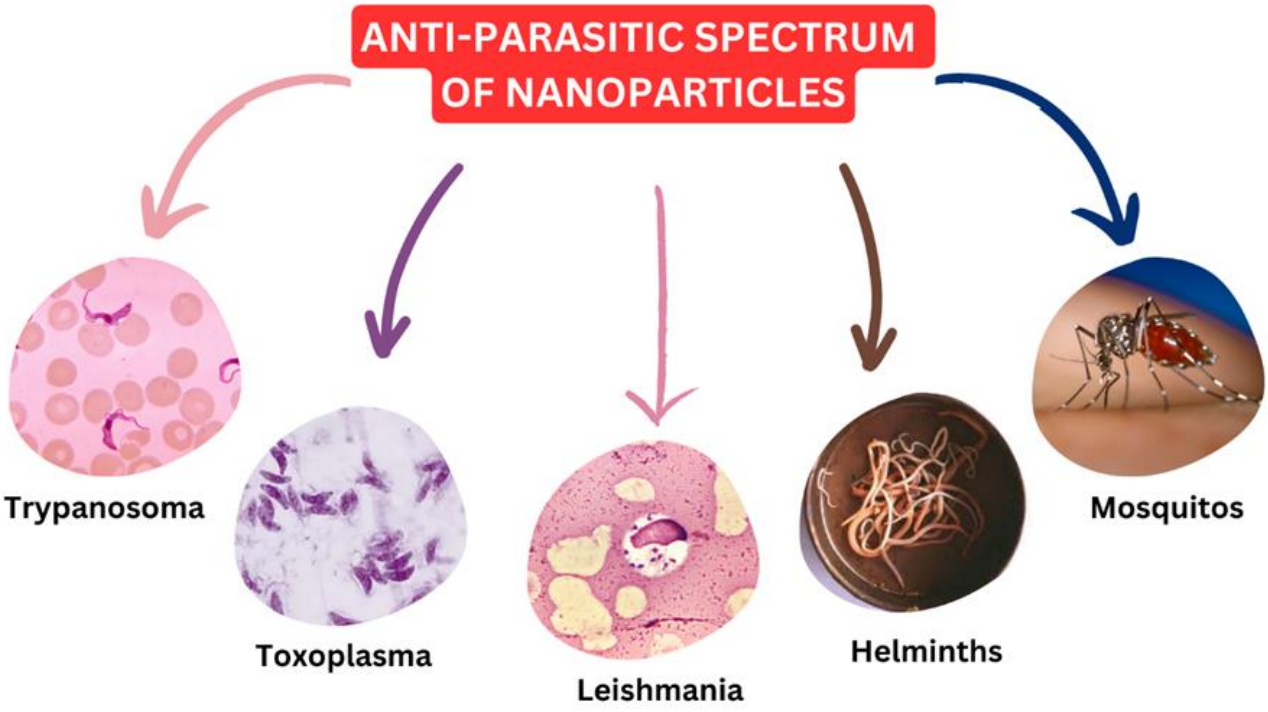

Fig. 2: Antiparasitic spectrum of nanoparticles

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.

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