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.

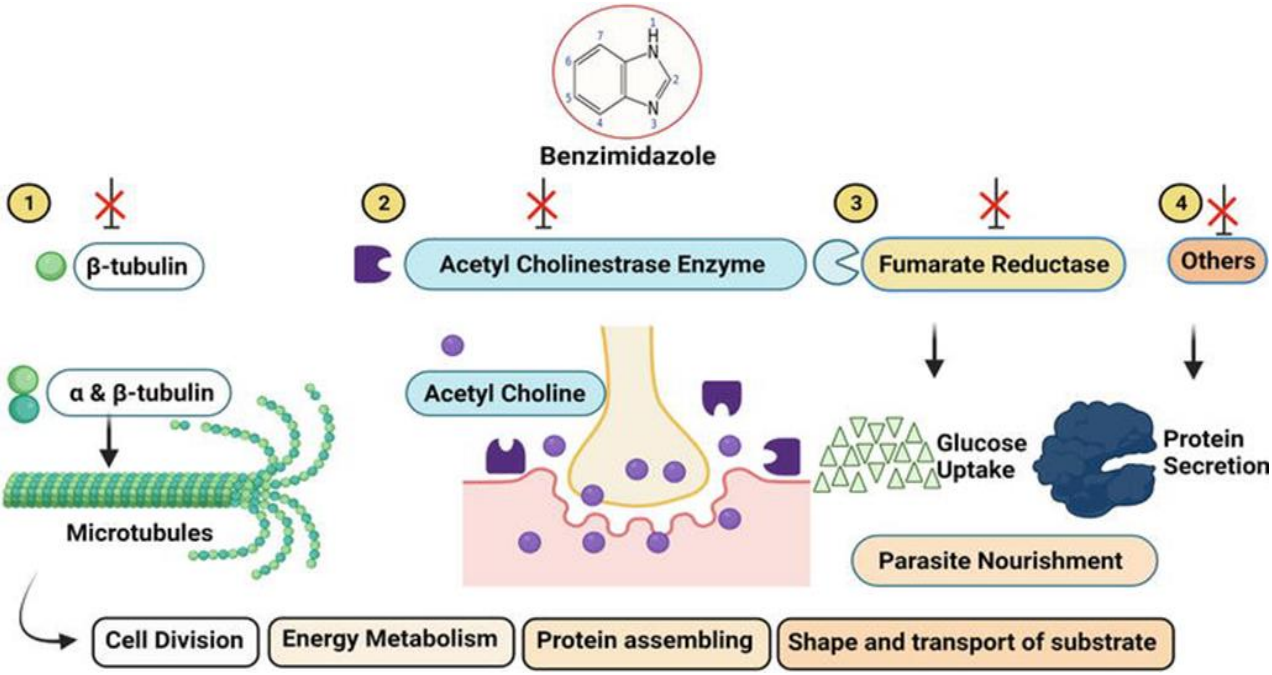


Fig. (a): Mechanism of Resistance against anthelmintic

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).

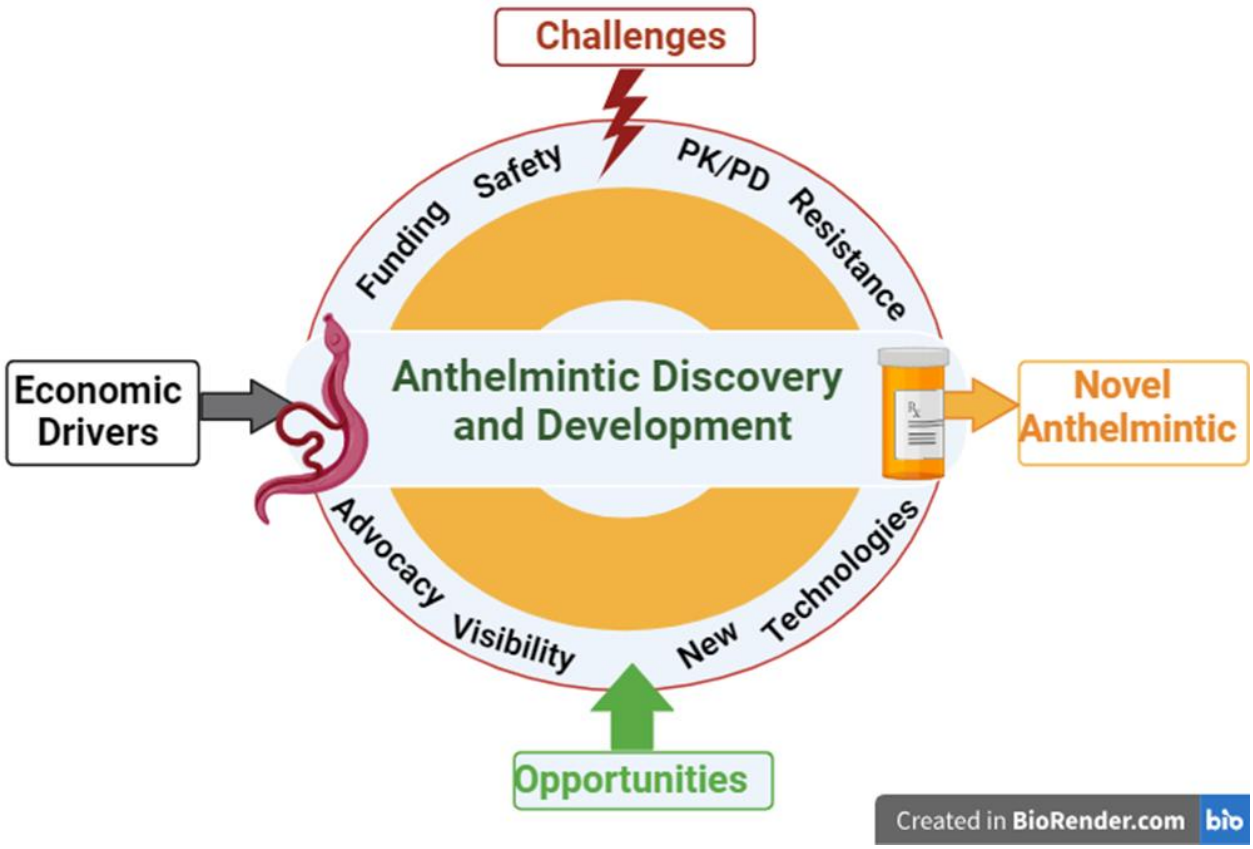


Fig. (b): Hurdles and challenges in the way of new anthelmintic development

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).

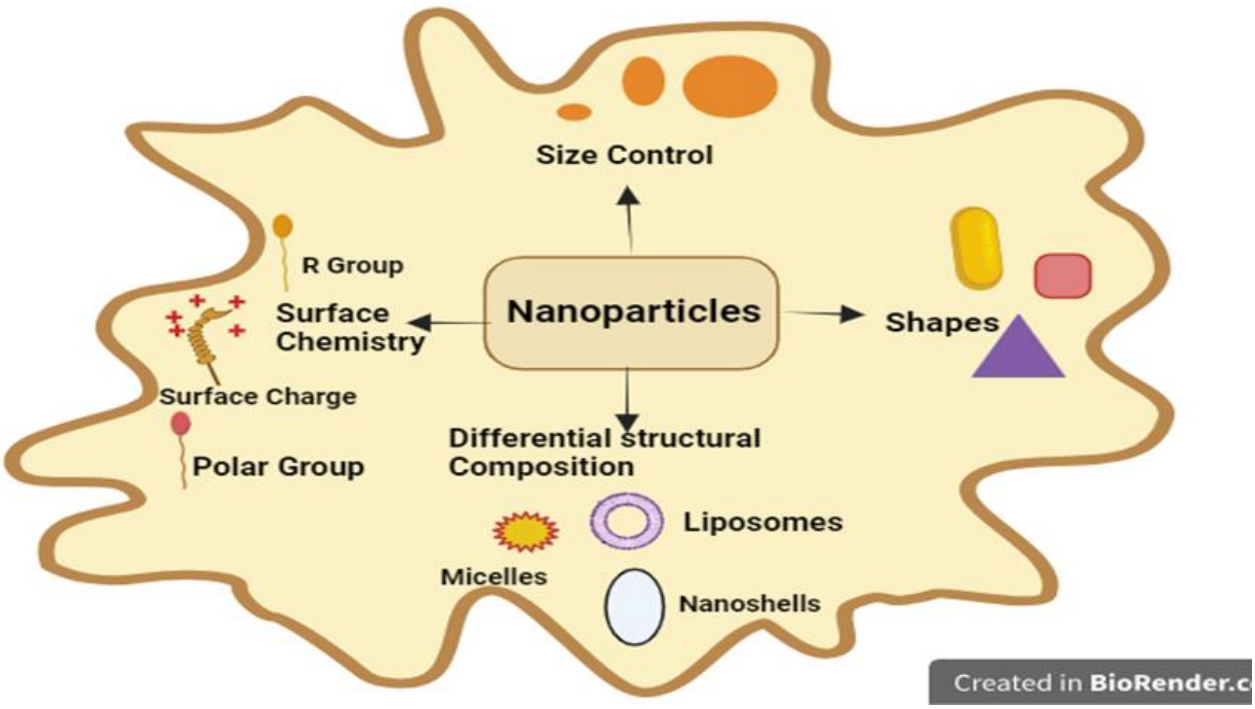
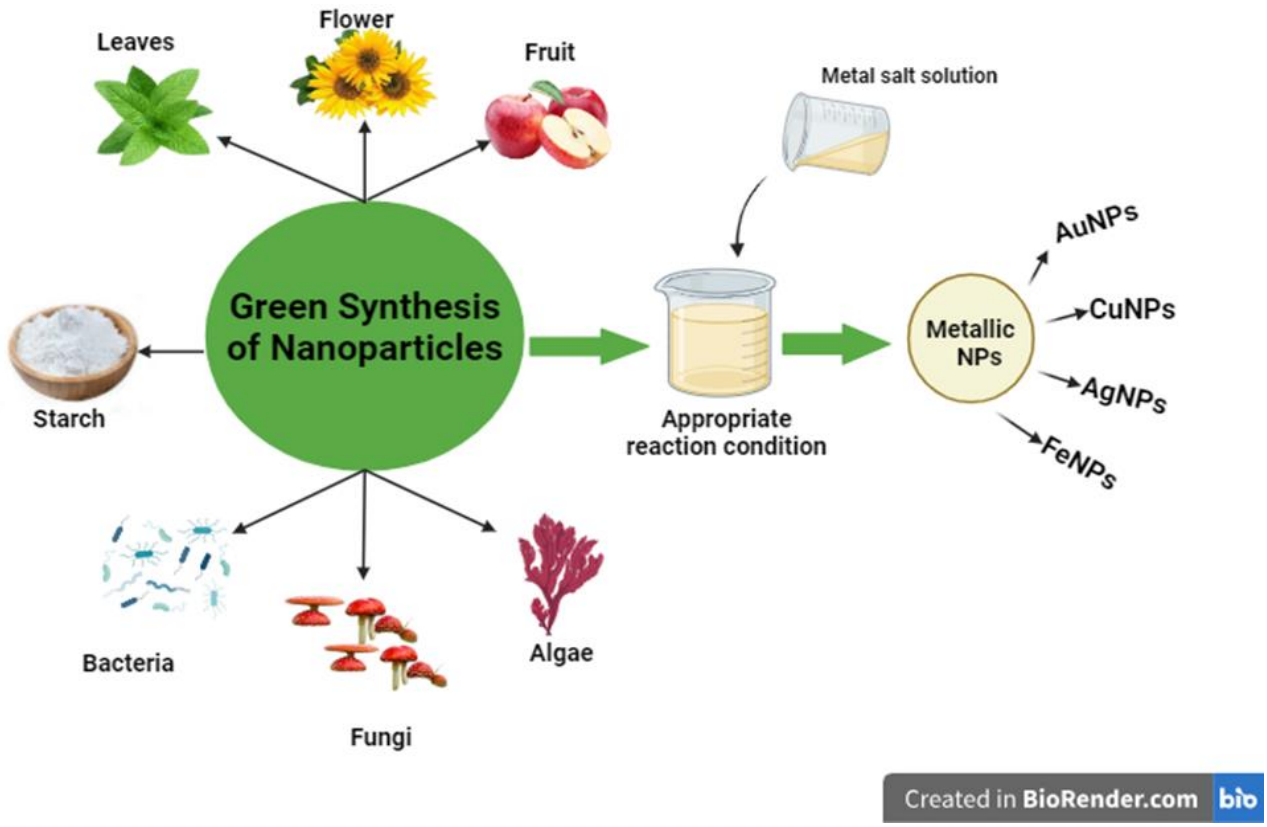


Fig. (c): Role of Nanoparticles in Drug delivery



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.

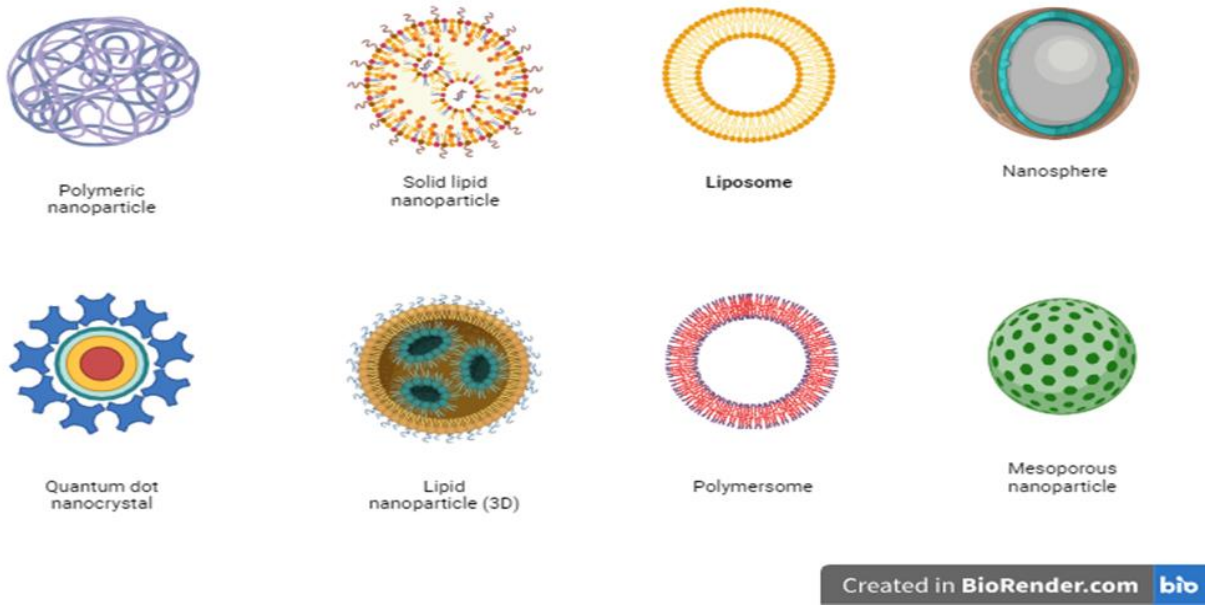


Fig. (e): Different type of nanoparticle used to assist drug.

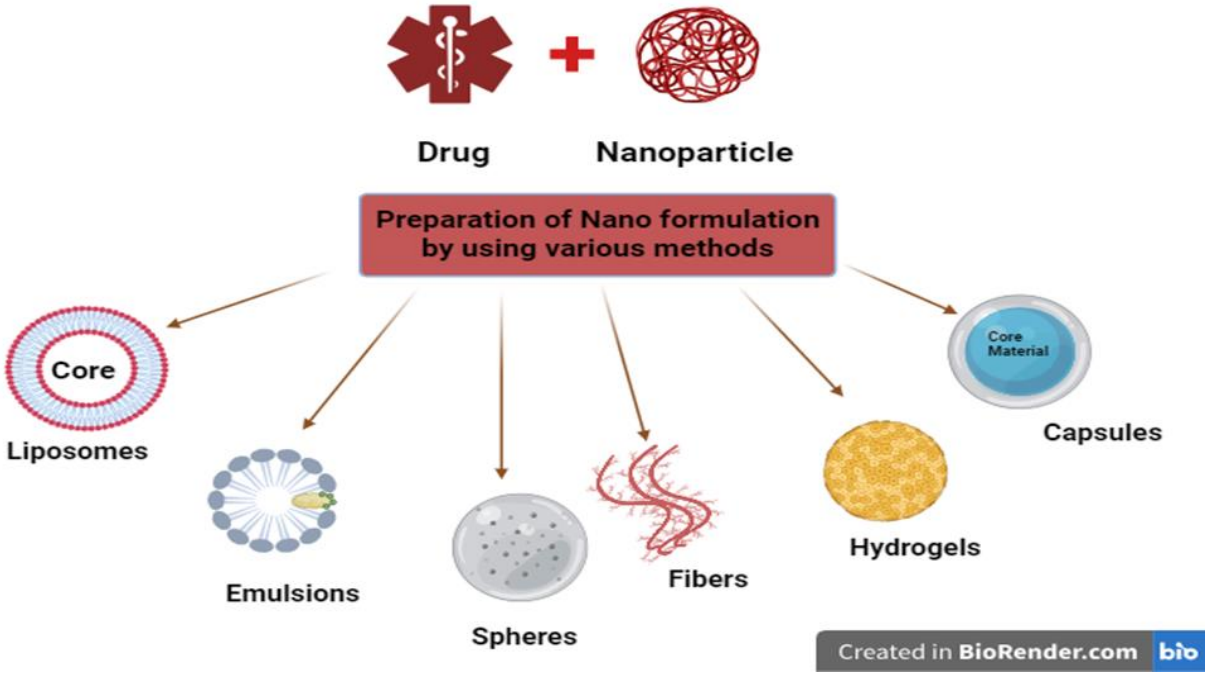


Fig. (F): Encapsulated drug with nanoparticles

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	Pensel (2014)
Albendazole			against cysts.	
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