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Review

An Insight into the Global Problem of Gastrointestinal Helminth Infections amongst Livestock: Does Nanotechnology Provide an Alternative?

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Abstract: Helminth parasitic infections are a considerable constraint to the livestock industries worldwide. Nematode parasites cause the major proportion of harm to livestock. The infections caused are accountable for severe economic losses in cattle, goat and sheep farming industries. Morbidity and mortality in livestock due to parasitic diseases are increasing alarmingly. Also, their zoonotic influence on human health is considered significant. Anthelmintic drugs have been developed occasionally to curb this disease and prevent major losses. But the development of resistance against these drugs has put another constraint on this flourishing industry. Helminth parasites have developed resistance against three main classes of anthelmintics: benzimidazoles, macrocyclic lactones and nicotinic agonists. With the intensification of resistance, various screening and confirmatory tests have been developed for the speedy introduction of newer drugs in the livestock industry. At the same time, designing and launching novel anthelmintics is time-consuming and economically restrained. Phytochemicals attract much attention because of their pharmacotherapeutic potential, least toxic profile and low environmental hazards. A lot of work is going on plant-based anthelmintic drugs throughout the world. Plants possessing anthelmintic activity have been found efficacious against gastrointestinal parasites. Nevertheless, these herbal medicines have various drawbacks, which include poor efficacy and the absence of target selectivity. These problems are now being taken care of with the help of nanotechnology. Nanoparticles improve the drug's effectiveness, enhance drug delivery, and target selectivity at specific sites. A comprehensive literature survey was carried out via electronic searches of Google Scholar, PubMed, MEDLINE, Science Direct, Scopus and Cochrane Library databases and based on inclusion and exclusion criteria; articles were selected for this review. The review aims at providing a comprehensive overview of plant-based nanoparticles as therapeutic alternatives over conventional synthetic anthelmintic drugs. It also encompasses the methods of detection of resistance and the ways to overcome this menace. The effectiveness of various organic and inorganic nanoparticles against helminthes is also discussed in this review.

Keywords: nematode parasites; livestock; zoonosis; anthelmintic resistance; phytochemicals; nanoparticles

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1. Introduction

Livestock plays an undeniable role in the human life cycle and ecosystem balance. In traditional and contemporary agriculture, cattle are a valuable blessing, providing meat, milk, skin, wool, hides, manure and draught power. Moreover, in a traditional society, they are a quintessential part of the social structure, depicting a family asset, and they are appraised as a survival tool by the nomads. Compared to the distribution of land, the distribution of animal assets is significantly more egalitarian [1]. Worldwide, livestock has

a significant impact on improving rural economies. Livestock has the potential to create jobs, particularly for small farmers and landless peasants [2]. Thus, livestock contributes to equitable revenue distribution by alleviating regional and societal poverty [2,3]. Livestock animals can become infected with harmful pathogens just like humans. Gastrointestinal helminthosis is a substantial obstacle in breeding for goats, sheep and cattle [4]. It is defined as a disease caused by the presence of helminth parasites like cestodes (tapeworms), trematodes (flukes) or nematodes (roundworms) in the gastrointestinal tract (GIT) of an animal. Almost all animal species can be infected with helminth parasites, but the infection often is far more severe in very young and old or immunosuppressed animals. Certain adult animals can flourish satisfactorily despite being infected with a low parasite load. Helminth parasitism is responsible for the loss of economy in many ways which sometimes go unnoticed to the proprietor, such as decreased fertility, decreased milk yield, reduced work capacity, lack of appetite, diarrhoea, anorexia, anaemia, decreased growth rate, and mortality and morbidity of heavily parasitized animals [5]. Helminth parasitic infections significantly hinder ruminants' sound and satisfactory productive efficacies [6]. Occasional ruminant mortality due to parasitic diseases probably may not be considered panicking. Still, its indirect effects on livestock productivity and their zoonotic impact on human beings are considered alarmingly significant [7,8]. Losses indirectly about nematode infections involve the decreasing potential of productivity due to weight loss, diarrhoea, decreased growth rate, anorexia, and anaemia [5]. Considering the effect of certain groups and species of GIT parasites on cattle populations at risk, the economic losses were estimated to be $7107.97 million in 2011. The potential financial losses caused in 2011 by the significant five ectoparasites and GIT parasites of cattle in Brazil was a surprising amount of $13.9 billion. [9]. Therefore, the effective management and control of parasitic helminth diseases are critical in increasing livestock production yield from a diminishing foundation of natural resources to fulfil the necessities of an upsurging world population nutritionally and dietarily more demanding [10].

The annual integrated cost of the three helminth infections in 18 countries participating in COMBAR (2020) (Combatting Anthelmintic Resistance in ruminants) was estimated to be €1.8 billion [€1.0–2.7 billion] [11]. Nearly 81% of this cost (€1.46 billion [€0.84–2.10 billion]) comprised of charges owing to production losses and 19% (€0.35 billion [€0.14−0.57 billion]) accredited to treatment costs. Currently, known public expenditure in research on controlling helminth infections is approximately 0.15% of the annual expenses for parasitic diseases [11]. The severity of this disease and the drop off of production depends on the severity of the infection and nutritional position [12]. Pregnant females and young animals are susceptible to a greater extent to helminthosis than adult ones because of their intricate nutritional condition and abject degree of immunity [13]. Animal diseases will remain a significant threat to livestock productivity if not taken care of in time and rationally. Hence, a major economic profit can be made in the agricultural sector by strengthening the control of various crucial parasitic diseases [14].

Despite the advantages of these synthetic drugs in treating and eradicating diseases, they may have adverse effects on various non-target species when released into the environment. Due to the increased production pressure, more medications are being administered to animals, raising the environmental risks of these potential chemical pollutants [15]. A considerable rise in synthetic antihelmintic drug usage worldwide has led to the build-up of drug residues in animal body organs, rendering the life of consumers at risk, especially children, the most vulnerable risk group in the population [16]. Various hazards include embryotoxicity, teratogenicity, and other harmful consequences of benzimidazoles in many animal species [17]. Increased concentrations of levamisole have proven to cause hematological problems in people consuming foods containing its residues for more extended periods [18]. This review provides a comprehensive overview of plant-based nanoparticles and their role as therapeutic alternatives to conventional synthetic anthelmintic drugs.

2. Methodology

A comprehensive literature survey was carried out via electronic searches of Google Scholar, PubMed, MEDLINE, Science Direct, Scopus and Cochrane Library databases by using different search terms like "helminthosis, anthelmintics, anthelmintic drug resistance, herbal anthelmintics, plant-based anthelmintics, the anthelmintic activity of nanomaterials nanotechnology, nanoparticles, nanomedicine" in the title as well as keywords. Research papers published in the English language related to this topic were considered.

Inclusion Criteria: All the articles that described related knowledge as the primary source of the study were included in the review. The record of references from published items was attentively noticed, and correlated papers were searched and downloaded. Original research papers in the English language on nanoparticles used to treat helminthiasis, assays and efficacy of nanoparticles, metal and biopolymer nanomaterials, and nano-encapsulated phytochemicals tested against helminthic infections were all included in the study. Other relevant papers were also incorporated to support the findings as mentioned above. A total of 200 (n = 200) research items were downloaded. One hundred eighty-five (n = 185) articles were included based on inclusion criteria.

Exclusion Criteria: All the articles that appeared either irrelevant or duplicate, articles on nanoparticles treating diseases other than helminthiasis, chemical/synthetic drugs besides nanoparticles, where nanoparticles were utilized as carriers for vaccines and papers other than the English language were excluded. Fifteen articles were excluded from the study based on exclusion criteria.

3. Anthelmintic Drugs and Resistance

Vaccines are used to prevent a disease rather than cure it. EG95 is a vaccine designed against the zoonotic disease echinococcosis or hydatid cyst [19]. Various other vaccines are being developed, such as TSOL-18 against neurocysticercosis [20] caused by *Taenia solium* and Hc-23 against *Haemonchus contortus* [21], but there are still many other parasitic diseases, where vaccines have not been developed, or their development is in the infancy. Their treatment broadly relies on chemotherapy. However, these chemotherapeutic agents are prone to resistance. Anthelmintic resistance is losing sensitivity to the parasitic populations previously sensitive to the drug. It is a heritable change because it is genetically transmitted, which makes it even worse [22]. Anthelmintic resistance has become a prevalent issue. It is noticed in the field ordinarily when helminthic control policies collapse. Anthelmintic resistance (AR) is thought to have appeared due to parasitic or management and handling factors. Genetic divergence is also considered an element in drug resistance development. Many reports suggest resistant alleles are present before the primary anthelmintic dosing [23]. The first case of anthelmintic resistance appeared in mid- 1950 in sheep kept at a research centre in Kentucky, USA, where in the treatment of haemonchosis, phenothiazine failed as a drug [24]. The occurrence of resistance against most of the pre-eminent marketed anthelmintic drugs has become a grievous problem globally [25]. Resistance against all of the three broad spectrum families, the benzimidazoles, ivermectin and imidathiazoles, has been recorded worldwide [26]. Resistance against drugs of a narrow spectrum of activity, like salicylanilides, has also been observed [27]. An intensifying spread of AR has been confirmed by the latest investigations that have illustrated predominantly in nematode populations of livestock animals [26–31]. AR has acquired economic and clinical gravity in certain parts of the globe, especially in trichostrongyle species infecting sheep and goat populations. The problem seemingly has reached more significant levels coupled with the occurrence and expansion of multi-drug resistant species in small ruminants [30]. The evident discrepancy between the soaring evidence of AR, on the one hand, in the field, and unpredictability regarding the authentic status of the helminth population in any particular group of animals, on the other hand, is a problem that requires redressal.

Factors related to the management include repeated use of a single drug or a congener drug belonging to the same category repeatedly, mass treatments of all farm animals as a prophylactic measure, inappropriate dosing and under or over-dosing [31]. According to

Andrew C Kotze and co-workers [32], AR might be induced by various factors like deletion or mutation of any amino acids in the gene of the target or a reduction in the total number of receptors, decreased affinity of receptors for the target drugs, and absence of enzymes required in the process. The time of resistance development against an introduced anthelmintic drug has shrunk to less than 10 years [33]. AR has developed against various groups of anthelmintic drugs on many continents [34]. The most commonly used three classes of anthelmintic drugs in small ruminants include macrocyclic lactones (MLs), benzimidazoles (BZs), and cholinergic agonists (especially levamisole; LVM). The most accepted mechanism of resistance is that of BZ; however, the mechanisms of resistance of some other anthelmintics have not been well understood [35]. Resistance against LVM, ML and BZ among ruminants was recorded in *Cooperia* sp. *Haemonchus* sp., *Teladorsagia circumcincta*, *Trichostrongylus* sp. and *Ostertagia ostertagi* [36]. Hamed [37], highlighted the development of resistance against ivermectin of the GIT parasites, specifically of *Trichostrongylus* sp., *Ascaris* sp., *Trichuris* sp. and *Moniezia* sp. in camel hosts. Mphahlele and coworkers [38] successfully measured the effective resistance of BZ and LVM in ruminant nematode species. Bartley and Co-workers [39] successfully measured the resistance against monpental in *H. contortus*, *T. circumcincta* and *T. axei*, Coles and co-workers [40] detected resistance against BZ. In contrast, Dolinska and co-workers [41] reported resistance against Ivermectin in livestock nematodes. A study by Mickiewicz and coworkers [42] showed the existence of AR against BZ, LEV and ML in Polish goat farms, where the resistance was extensive against BZ and ML but comparatively low against LEV. Potarinche and co-workers [43] studied the resistance of GIT nematodes in goats against BZs and MLs, in Romania. Van den Brome and co-workers [44] revealed the occurrence of AR against the newest groups of anthelmintic drugs by *Haemonchus contortus* against monepantel C and an amino acetonitrile derivative. Studies have shown that AR develops briefly after the drug is launched. In certain countries, unfortunately, various goat and sheep farms have been closed down because of the increasing anthelmintic resistance [45]. In sheep, AR against tetrahydro pyrimidines, imidazothiazoles, and avermectin/milbemycins, developed in three to nine years. The severity and the range of this problem, especially concerning the multi-drug resistant (MDR) nematode population, is predicted to upsurge further [33]. Various researchers have outlined the ubiquitous occurrence of MDR populations of *H. contortus*, *Trichostrongylus* and *Teladorsagia* against imidazothiazoles, benzimidazoles, and macrocyclic lactones in the European sheep populations [46].

Macrocyclic lactone (MLs) resistance was found to have developed in trichostrongyle species of cattle in Europe [47]. The same results also appeared in South and North America [28,48]. Two studies reported multi-drug resistance against ML and BZ [28,49]. Resistance is frequently found in small strongyle species of horses against BZs and, to a considerably lesser extent, against pyrantel (PYR) [50]. Despite these alarming discoveries, it is to be ascertained that these anthelmintics still perform adequately in a considerable percentage of stables [51,52]. Table 1 outlines the different classes of anthelmintic drugs and their drug action and resistance mechanisms.

Table 1. Various classes of anthelmintic drugs with their mechanism of action and drug resistance.

Anthelmintic Standard Drug	Mechanism of Action	Mechanism of Resistance	References
Benzimidazoles	Inhibition of Polymerization of microtubule subunits leading to disarrangement of microtubules.	Changes in the β tubulin isotype 1 target site in the nematode parasite. Continued polymerization of microtubules.	[53,54]
Macrocyclic Lactones	Modulating the glutamate-gated chloride channel.	Mutation in glutamate-gated chloride channel or gamma-aminobutyric acid receptor gene.	[54,55]
Imidazothiazole	Agonists of nicotinergic acetylcholine receptor	Altered Nicotinic acetylcholine receptor.	[54]
Monepantel	Act on Nicotinic acetylcholine receptor genes.	Increased expression of P-glycoproteins. Mutation in Hco-des-2H, Hco-acr-23H, Hco-MPTL-1 genes	[54]

4. Factors Leading to Drug Resistance

The rate of the development of AR is affected by several factors, which include:

Anthelmintic dosage rates: Incorrect, inappropriate and indiscriminate administration of anthelmintic drugs is one of the leading causes of resistance. Visually estimating the weight is one of the most commonly applied methods used to estimate the optimum dosage of anthelmintics in veterinary medicine, which often is disproportionate and leads to underdosing. This dosing, in turn, permits the existence of heterozygous resistant worms, leading to the preference for resistant strains [56].

Frequency of Treatment: It determines the rate of development of resistance. When an anthelmintic agent is administered customarily, the progression of AR is faster. This is because treatment provides advantages for reproduction and replication to the surviving parasites compared to the susceptible ones for about 22 days after administering the anthelmintic drug [57].

Genetics: In the parasitic populations' resistance is pre-existing and anthelmintic resistance is presently accepted as a pre-adaptive event. The continuous usage of anthelmintic drugs offers resistant parasites an advantage of survival, giving them a chance to reproduce quickly compared to susceptible worms. This results in the upsurge of worms with resistant phenotypes in the population. This frequency ultimately advances to a point where AR is assumed to have developed. Only homozygous parasites endure a given anthelmintic drug when AR is a recessive trait in worm populations. The anthelmintic drug kills heterozygous parasites [58].

Mass treatment: It is now proven that administrating mass prophylactic treatment leads to the upsurge of AR in parasitic worms. It is thought to obstruct the development of AR by treating 80% of the flock [59].

5. Plant-Based Drugs as an Alternative to Combat Anthelmintic Drug Resistance

Using chemical control methods in the past may no longer be a successful strategy, as has been shown. The control techniques relying solely on anthelmintics must be replaced with other viable ones considering immunological, chemical, and environmental controls. Scientists and researchers have been challenged in recent years to develop novel, sustainable treatments for gastrointestinal nematodes that infect small ruminants due to the occurrence of anthelmintic resistance as well as farmers' growing awareness of the need for residue-free, non-toxic animal products. One significant and innovative move is using medicinal plants as a saviour, often known as "green dewormer", which is readily available, environmentally benign, biodegradable, and nontoxic to the host [60,61].

Parasitic diseases in farm animals may lead to economic losses and severely affect food production worldwide. To curb this loss, billions of dollars are spent annually on chemotherapeutic agents. World Health Organization (WHO) officially recommended evaluating plant-derived products in 2000. Medicinal herbs are deemed safe, and they provide a source of efficient anthelmintic treatments [62]. Increased instances of resistance necessitate the discovery and development of new anthelmintic drugs.

Since the dawn of human civilization, medicinal plants have been used extensively in medicine and produce many modern medications [63]. These plants are used far more frequently than contemporary medicine, which can be ascribed to their cultural acceptance, economic accessibility, and effectiveness against some types of ailments. In many indigenous tribes, especially those in Africa, plants have been crucial in treating numerous human and animal diseases. "Medicinal plants" refers to various ovarioles employed in herbalism with medicinal properties. These medicinal plants are regarded as rich sources of components for the creation and synthesis of necessary medications. Additionally, these plants are essential to the growth of human cultures worldwide [64]. Traditional medicine, defined by WHO [59], is the entire body of knowledge and practices that can be formally explained or used in the prevention and elimination of physical, mental, or social imbalance and rely solely on real-world experience and observation passed down from generation to generation, whether verbally or in writing [60]. Many valuable chemicals and drugs are

derived from medicinal plants. In European countries, over 1300 medicinal plants are used, with 90% coming from wild sources. According to the International Union for Conservation of Nature (IUCN) and World Wildlife Fund, approximately 50,000–80,000 flowering plants are used for medicinal purposes [65]. Phytochemicals are attracting attention because of their pharmacotherapeutic potential [66]. Medicinal plants demonstrated for anthelmintic activity are increasingly crucial nowadays [67,68]. The plant-based bioactive components like, alkaloids, flavonoids, saponins, terpenoids and phenolic compounds have the potential to destroy gastrointestinal helminths, opening doors for a promising solution for the problem of anthelmintic resistance among ruminants [69]. Further research must be carried out on a large scale, engaging many animals, utilizing suitable doses, standardizing those and conducting toxicity checks to develop therapeutically effective drugs.

Nanoparticles improve the drug's efficacy, enhance drug delivery, and target selectivity at specific sites [70]. Coupled with the advantages of the nanoparticles, the enriched herbal preparation can effectively inhibit the hatching of nematode eggs regardless of low doses. Moreover, nanoformulations are used to enhance the solubility of herbal medicines alongside advocating the targeting of Phyto molecules to a specific location [71].

6. Nanomedicine & Anthelmintics

Nanotechnology is defined as a field of study that refers to structures roughly 1–100 nm in size in one dimension at least. Nanomaterials possess a large surface area to volume ratio and other properties, like friction and interaction with other molecules, distinguishing them from equivalent materials on a larger scale [72]. The typical application of nanotechnology in the medical field is developing novel therapeutic modalities that can beat and win over contemporary technology in these areas. [73]. Nanomaterials are used in various medical, biological and environmental grounds due to their exceptional physical and chemical properties. Different types of nanoparticles (including their synthesis) are extensively studied in parasitology and other fields of research and development. These studies have shown promising results, from techniques for disease detection to drug development against a broad range of helminths of concern [74]. Figure 1 shows the advantages of nano-based drug delivery systems over conventional drugs.

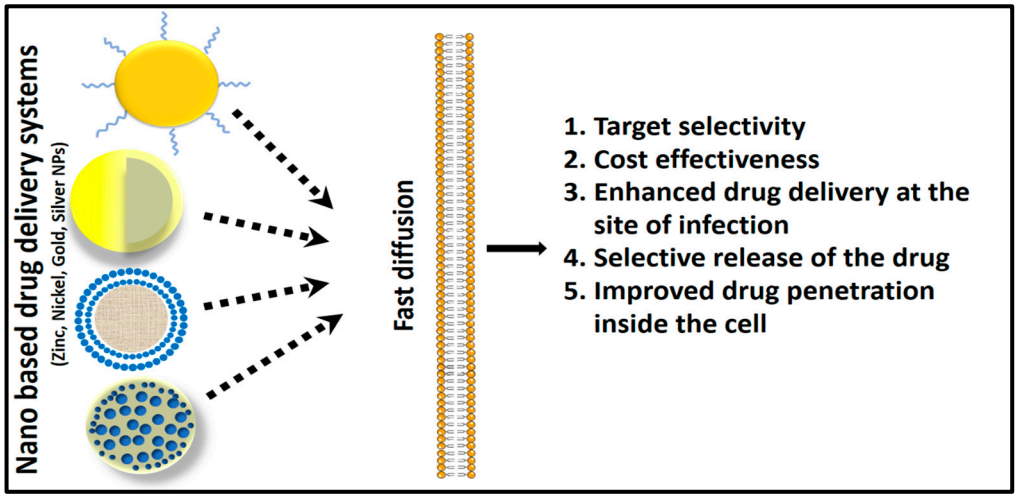

Figure 1. Illustrating various advantages of nano-based drug delivery systems.

6.1. Inorganic Nano Particle (NP)

6.1.1. Gold Nanoparticles

Gold nanoparticles (Au NPs) are implemented in parasitology's varied orbit of domains. They exhibit high toxicity on cestodes and trematodes. They are also toxic to *Cryptosporidium*, *Plasmodium*, *Toxoplasma*, *Trypanosoma*, *Leishmania*, and other microsporidian parasites. The bioactivity of Au NPs was investigated on various species of economic concern. This nanomaterials category shows encouraging applications in detection techniques and the development

of drugs, targeting a broad range of species of public health concern. Kar and co-workers [75] focused on producing Nanogold with anthelmintic efficacy using a green chemistry approach. They utilized a filtrate obtained from the *Nigrospora oryzae* phytopathogen fungus to assemble Au NPs, ranging in size from 6 to 18 nm in diameter. The fabricated Au NPs functioned as vermifuge agents targeting the cestode *Raillietina* sp. (Davaineidae), an intestinal parasite found in domestic fowl. The paralytic state onset in the parasite was accomplished relatively quickly compared to that of the standard reference drug [75].

The treatment of schistosomiasis (caused by a trematode helminth parasite *Schistosoma*) mainly depends on certain drugs like praziquantel. Still, these drugs exhibit various limitations along with the development of resistance [76]. Au NPs of this drug have been introduced as a highly assuring and effective treatment strategy and to develop new diagnostic assays [77].

Barabadi and co-workers [78] carried out the green synthesis of AuNPs using green mycelia-free culture filtrate of *Penicillium aculeatum* against the scolicidal activity of hydatid cyst protoscolices of *Echinococcus granulosus* (a carnivore tapeworm). Their study revealed that the increased concentrations of AuNPs increased the elimination of protoscolex of the parasite. The treated worms showed loss of turgidity in the soma region and damage to the tegument. At its usual dosage, Albendazole sulfoxide, the drug of choice for protoscolices, elevated the liver enzymes [79]. Barabadi and co-workers concluded that biosynthesized AuNPs effectively functioned as potential scolicidal agents. It was also noted that the concentration of AuNPs and time of exposure played a notable role, as a slight rise in exposure time elevated the protoscolex elimination rate under laboratory conditions.

6.1.2. Silver Nanoparticles

In the past few years, silver nanoparticles (AgNPs) have emerged as a rapidly developing material because of their high specific surface area, small size and distinctive physical, chemical and biological properties. Biobased silver nanoparticles (AgNPs) possessing anthelmintic activity are among the best-studied metal nanoparticles [80]. In recent years, nanoparticles showing antiparasitic properties, mostly silver nanoparticles, are gaining much consciousness in this field by offering a contrasting approach [81,82].

Green synthesis of Ag-NPs was carried out by Rashid and co-workers [83] using the fruit extract of *Momordica charantia* L. (bitter melon). Using Albendazole as the standard reference drug, they tested it against adult earthworms, *Pheretima posthuma*. The integrated anthelmintic activity of *M. charantia* with AgNPs was observed to be more compared to their independent effects. When the extract was capped on Ag nanoparticles, a strong wormicidal effect was seen. The experimental data generated from this study demonstrated that Ag Extract NPs developed in a cost-effective, safe, simple and eco-friendly way possess excellent wormicidal activity against *P. posthuma*. This study ultimately paved the way for designing a new anthelmintic drug from the combination *of M. charantia* and AgNP.

The anthelmintic effect of biologically synthesized silver nanoparticles (AgNPs) was studied on a predominant amphistome parasite, *Gigantocotyle explanatum*, which infects the liver of Indian water buffalo. The AgNPs demonstrated ROS-mediated biochemical changes in the treated worms. The study showed that these nanoparticles damaged the DNA and altered the parasite's polypeptide profile. AgNPs critically deranged the tegument causing a strong anthelmintic effect [84].

AgNPs using *Azadirachta indica* (neem) leaf extract were studied for their in vitro anthelmintic potential against *H. contortus*. An increased mortality rate of adult parasites using AgNPs treatment, compared to aqueous *A. indica* leaf extract treatment, has been attributed to the exceptionally small size of the nanoparticles, i.e., 15–25 nm, which certainly permit transcuticular absorption of AgNPs by the target parasite [85].

Non-electrolytic chemicals usually enter nematodes through transcuticular diffusion. Contrary to oral intake, it has been stated that this method expressively is the predominant route for the uptake of broad-spectrum anthelmintics. The external cuticular covering of the helminths can be penetrated more easily by hydrophobic (lipophilic) anthelmintics like albendazole than

by their hydrophilic counterparts [86,87]. To assess the anthelmintic (adulticidal and ovicidal) activities of biologically produced Silver Nanoparticles (AgNPs) and *Azadirachta indica* leaf extract, Charitha [88] showed that AgNPs were extremely efficient with a rapid commencement of activity and paralysed or killed *Haemonchus contortus* worms at various doses in a better way than aqueous extracts of *Azadirachta indica*. Mombrini and co-workers [89], while determining the anthelmintic activity of silver nanoparticles (AgNPs) synthesised using the extract of nematophagous fungus; *Duddingtonia flagrans*, on infecting *Ancylostoma caninum* larvae (L3 stage) discovered that chemically synthesised AgNPs did not kill all of the larvae compared to AgNP combined with *D. flagrans*. The reduced silver was not the sole cause of larval death; the efficacy of the AgNP (*D. flagrans*) was attributed to the absorption of *D. flagrans* proteins on the surface of the AgNPs. Silva and co-workers [90] demonstrated that chitinase is the protein found on the surface of the AgNP synthesised from the fungus *D. flagrans*. This protein aided the penetration of nanoparticles inside the nematode. It was also discovered that when the larvae were exposed to anthelmintics such as levamisole and ivermectin, no visual changes in the nematode's cuticle were observed, as these drugs acted on GABAergic receptors and caused spastic paralysis of the target nematodes. As a result, neither drug affects the parasite's cuticle. No morphological changes in the nematode cuticle were observed after the larvae were treated with $AgNO_3$ solution and chemically synthesised AgNP. However, larvae treated with AgNP (*D. flagrans*) showed significant morphological changes in the cuticle. The *D. flagrans* solution, ivermectin, levamisole, and chemical synthesis all produced less satisfactory outcomes than AgNPs (*D. flagrans*), which also demonstrated to be the only material to cause integumentary alterations in the *A. caninum* larvae [89].

Kumar [91] conducted another study with albendazole as the standard and various concentrations of silver nanoparticles and an aqueous extract of *Azadirachta indica* (Neem) as the test substance. The colloidal solution of silver nanoparticles demonstrated more significant anthelmintic activity than the aqueous extract against adult earthworms *Eudrilus eugeniae* and *Eisenia fetida* in a concentration-dependent manner. Compared to the standard, the neem leaf-assisted green synthesized silver nanoparticles demonstrated significant anthelminthic activity.

The extracts of Vallarai chooranam, a polyherbal made up of ten different herbs, including *Myristica fragrans*, *Centella asiatica*, *Eletteria cardamomum*, *Syzgium aromaticum*, *Quercus infectoris*, *Taxus beccata*, *Emblica ofcinalis*, *Terminalia belerica* and *Terminalia chebula* [92] were used to prepare silver nanoparticles. Sathiyaraj and co-workers investigated the toxicity of Vallarai chooranam Nanoparticles (VC-AgNPs) on the earthworm *Pheretima posthumua* using different silver nanoparticle concentrations. Upon treatment, all individuals showed morphological abnormalities such as body lifting, curling and coiling. When compared to controls, the exposed worms remained ineffective. Earthworms exposed to nanoparticles developed visible surface lesions. Coelomic fluid oozed from the body due to bloody lesions on the posterior part of the body, leading to their death. Histopathological examination revealed a significant disintegration of the tissue arrangement, the development of excess glandular epithelium and the loss of ectodermal tissues [93].

Preet and Tomar [94], for the first time, biofabricated AgNPs using aqueous leaf extracts of *Ziziphus jujube* (Jujuba) on adult *Haemonchus contortus* worms obtained from the abomasum of freshly slaughtered goats with albendazole as a reference drug. They concluded this could be used as an antihelmintic and an ovicidal medication.

Toxocara vitulorum is a common gastrointestinal nematode that infects cattle and buffaloes, primarily young calves and causes Toxocariasis. Adult worms are typically treated with pyrantel, piperazine, oxfendazole, and febantel [95]. The parasite has developed resistance to several commonly used pharmaceuticals. As a result of increasing drug resistance and unfavourable side effects, there is a need to develop novel alternative effective anthelmintic drugs against *T. vitulorum* [96]. Venjakob and Ahmad, along with their co-workers [97,98], investigated the anthelmintic effects of AgNPs on male and female *T. vitulorum*, in vitro. A silver nitrate base with lemon juice as a reducing agent was used to biosynthesize silver nanoparticles. Light and scanning electron microscope (SEM)

demonstrated the changes in morphological characteristics. Additionally, oxidative stress markers were investigated to confirm its potential use as an anthelmintic drug. Both male and female *T. vitulorum* worms showed cuticular changes in the form of wrinkles, swellings and swollen hypodermis along with vacuolizations triggering complete disruption of the outer cuticle and the inner muscle layer; however, AgNPs induced more distortion and disintegration in the body wall structure of female worms compared to their male counterparts. Ilavarashi and co-workers [99] assessed the effectiveness of aqueous *Moringa oleifera* seed extract and biosynthesized silver nanoparticles as anthelmintics against strongyle nematodes of small ruminants. Both the extract and the AgNPs significantly inhibited the hatching of the eggs, but the AgNPs-based preparation showed better results than the aqueous extract. This difference may be explained by the fact that the phytochemicals and the nanoparticles work better together to inhibit the hatching of strongyle eggs.

Dicrocoelium dendriticum; a parasite that causes the food-borne disease dicrocoeliasis, affects both humans and herbivores. The condition severely alters the liver and bile systems pathologically, and there are only a few effective therapy alternatives [100,101]. Additionally, a significant barrier in treating this disease is problems with drug delivery. Arbabi [102] determined the anthelmintic activity of silver oxide nanoparticles (AgO) as a new technique in treating dicrocoeliasis. He employed a variety of concentrations of AgO nanoparticles in vitro. A synthetic anthelmintic medication, Closantel, was used in this nanoformulation. The sensory papillae of worms treated with AgO were destroyed, and no apparent network structures or tegument vesicles were seen. AgO NPs had an anthelmintic impact, and the mortality rate increased with time and concentration.

6.1.3. Zinc Oxide and Iron Oxide Nanoparticles

ZnO-NPs and FeO-NPs have attracted much attention for diagnostic uses due to their easy preparation, non-toxicity and cost-effectiveness. Zinc, a crucial component for humans but toxic to microbes [103], is present as zinc oxide (ZnO) in zincite mineral, which is now gaining popularity due to its safety and compatibility with the human body [104].

Toxocara vitulorum, a nematode of small intestines of Asian water buffalos (*Bubalis bubalis*) and cattle (*Bos indicus*, *Bos taurus*), causes global economic loss due to consequent weight loss and anorexia or even death [105,106]. ZnO and FeO nanoparticles have shown a significant increase in worm mortality rate, decreased mobility, and high nitric oxide (NO) and malondialdehyde (MDA) content compared to the control group in a time- and concentration-dependent manner. These nanoparticles showed their anthelmintic effects through the induction of oxidative/nitrosative stress [107].

Another study used biocompatible zinc oxide nanoparticles (ZnO NPs) made from egg albumin (*Gigantocotyle explanatum* infection of *Bubalis bubalis)* in varied concentrations vitro. This resulted in oxidative stress and ROS generation leading to cell death of the parasitic worm. Since the quantity of intracellular ROS often increases in response to the usage of nanoparticles, the flukes mount a survival effort by increasing the activity of numerous antioxidant enzymes, such as Superoxide dismutase (SOD) and Glutathione S transferase (GST), to scavenge the ensuing ROS created in response to ZnO NPs treatment [108]. ROS levels alter the electron transport system of the parasite, which eventually inhibits the synthesis of ATP and affects the target parasite's ability to contract [109]. Surface topographic and histopathologic evaluation shows damaged tegumental papillae. The tegumental abnormalities make it easier for nanoparticles to enter the sub-tegumental sections of the worms, where they can cause more severe lesions. In a study, treatment of *G. explanatum* with ZnO NPs resulted in significant suppression of SOD and GST activity, raised levels of malanodialdehyde (MDA), suppression and digestion, permanent failure of motility, and disruption of tegument, indicating a potent anthelmintic action of nanoparticles [110].

Hosain and Islam examined the properties of ZnO nanoparticles, including their anthelmintic activity in the target worm, using the reference standard medicine albendazole. ZnO nanoparticles exhibited exceptional anthelmintic activity against *Pheretima posthuma*,

causing dose-dependent paralysis, ranging from the loss of mobility to the loss of reaction to outside stimuli, progressively leading to death [111].

Hosain and colleagues [112] demonstrated that modifying ZnO NPs synthesised using Ag doped ZnO nanoparticles (ZnO: Ag NPs) exhibited anthelmintic activity against *Pheretima posthuman*. Zinc oxide nanoparticles (ZnO NPs) were made using a sonochemical technique and precipitation. The worms were treated with Albendazole (standard), ZnO nanoparticles and ZnO: Ag nanoparticles in different concentrations. Compared to albendazole, all the synthesised ZnO and ZnO: Ag NPs displayed more excellent anthelmintic activity, attributed to the nano formulation's particle size.

One of the most prevalent and significant nematodes found in the abomasums of small ruminants is *Haemonchus contortus*. Often called "Wire Worm" or "Barber Pole Worm," it is most frequently seen in tropical and subtropical regions of the world and is responsible for significant monetary losses [113,114]. Esmaeilnejad and co-workers demonstrated the extraordinary anthelmintic action of ZnO-NPs on *H. contortus* by inducing the oxidative/nitrosative destruction of the target worm's biomolecules [115]. The worm sustained general DNA damage, which an alkaline comet test detected. The vitality and motility of the parasite were noticeably reduced over time and at different concentrations. The antioxidant enzymes catalase (CAT), SOD, and glutathione peroxidase (GSH-Px) showed contentious changes in activity when *H. contortus* was exposed to various doses of ZnO-NPs in an in vitro experimental setup. These enzymes have a dual nature that neutralises oxidant molecules produced spontaneously by the parasite or the host, ensuring the parasite's survival. Baghbani and Esmaeilnejad, in their study, concluded that ZNO-NPs exerted significant anthelmintic activity against *T. circumcincta* by induction of oxidative and nitro stative damages to the worm's biomolecules. It also exhibited genotoxic effects (damage to DNA by affecting enzymes) on the parasite, leading to its death. The anthelmintic effects were concentration-dependent, and the highest concentration critically repressed the antioxidant enzyme system of worms and damaged the biomolecules, including lipids and proteins [116].

Horses, zebras, and donkeys are the hosts of harm intestinal parasite *Parascaris equorum* [117]. The World Health Organization (WHO) promoted management programmes and periodic anthelmintic treatment. However, encounter resistance against this tiny strongyle, which harms the horse populations [118]. Morsy and co-workers [119] studied the in vitro anthelmintic potential of *P. equorum* using biocompatible zinc oxide employing a Scanning Electron Microscope (SEM). Because of the metal's absorption and interaction with the treated worm's body, the entire body was seen to be critically wrinkled from the cephalic region to the vulva and tail when compared to the control group. The surface images of the ZnO NPs-treated worms profoundly showed severe cuticle destruction, gravely injured areas, and cuticle layer bursting in some body regions. This is attributed to the ZnO NPs causing the generation of hydroxyl ions and reactive oxygen species (ROS), which causes membrane disruption [120]. Another finding in this study was that the specific arrangement and position of pre and postanal papillae were damaged in treated male worms compared to the control group. The alimentary system is the primary route of NP uptake into the nematode body, where the worms actively ingest NPs while feeding [121]. During the exposure time, the NPs passively diffuse into the cuticle, anus, vulva, and excretory pore [122]. The outermost layer of the nematode cuticle comprises glycoproteins, which have a negative surface charge and interact electrostatically with nanoparticles, resulting in the adsorption of positively charged NPs on the cuticle's surface. Morsy and co-workers [119] demonstrated that ZnO NPs at environmentally appropriate concentrations have substantial anthelminthic potential against *P. equorum*.

Puttaraju and co-workers used dragon fruit for the green synthesis of ZnO NPs against Indian Earthworms in their study [123]. Smaller quantities of ZnO (25 mg/mL) required a long time to kill the target worms, whereas higher concentrations of ZnO NPs (100 mg/mL) paralysed them in 5 min. When examined at 62 min, death was similar to that caused by piperazine citrate. It was inferred that ZnO NPs biosynthesized using the green method should be used as a simple, non-poisonous, and low-cost technique [123].

A study by Oasis and co-workers [124] demonstrated that ZnO and FeO nanoparticles are effective anthelmintics against *Fasciola*, as evidenced by decreased worm mobility and increased mortality rate over time and concentration. FeO nanoparticles were found to be more potent than ZnO nanoparticles. The reason is that each nanoparticle has unique properties [125]. ZnO and FeO nanoparticles at concentrations of 0.004 percent and 0.012 percent resulted in the widening of the ventral sucker and roughness in the tegument, as well as disruptions, sloughing and complete loss of spines, with 0.012 percent conc they were being more efficacious. SEM images revealed wrinkled lips, weathered cuticles, irregular denticles, cuticle bursts, disrupted surface annulations, and damaged male surface papillae around the cloaca opening. They concluded that because of their effective fasciocidal pursuit, ZnO and FeO nanoparticles could be used to treat fascioliasis. They are a valuable tool to control the disease, especially when drug resistance is increasing.

Praziquantel (PZQ), the drug of choice for treating schistosomiasis, is no exception to the growing problem of drug resistance [76]. Khalil and co-workers investigated the effect of iron nanoparticles (Fe NPs) in vitro on *Schistosoma mansoni* and *Biomphalaria alexandrina*. They studied the mortality rate of adult worms after 48 h of exposure. After 3 h, 30 mg/L of iron nanoparticle exposure resulted in 20% mortality, and 60 mg/L resulted in 77% mortality. Surface ultrastructural images revealed blebs, erosion, cracks, incomplete fusion of some tubercles, and the loss of most spines and a perforated tegument [126].

6.1.4. Nickel Oxide Nanoparticles

A. Ullah and co-workers reported that the anthelmintic activity of Nickel oxide nanoparticles derived from *Pinus roxburghii* was greater than *Ficus carica* and *Toona ciliata* against *Pheretima posthuma* using Albendazole as a reference drug. In a concentration-dependent manner, plant extract-based nickel oxide nanoparticles caused worm paralysis and death in less time than plant extracts alone. Because of the wormicidal activity, nickel oxide nanoparticles can form an effective treatment against parasitic infections in humans [127].

6.2. Organic Nanoparticles

Chitosan Nanoparticles

Chitosan, a cationic polysaccharide derived naturally from chitin, is used in various applications because it is inexpensive, potent, easy to use, and well-suited for various medical applications [128]. *Haemonchus contortus*, a major gastrointestinal nematode of sheep and goats, is widely regarded as a significant hazard to the livestock industry worldwide [129]. Because of their indiscriminate use, Anthelmintic drugs, which were earlier effective, gave rise to multi-drug resistant nematode populations in some areas [130]. Weibson and co-workers [131] concentrated on the utilization of essential oils and their bioactive compounds, such as 4–6 Carvacrol (2-methyl-5-(1-methyl ethyl) phenol) (CV), a phenolic compound of essential oils from Lamiaceae plants [132] and Carvacryl acetate (CVA); an acetylated derivative of carvacrol. CV and CVA exhibited anthelmintic activity [133]. They nano-encapsulated CV and CVA using chitosan, with NPs ranging from 100 to 800 nm. Nanoencapsulated CVA was found to have significant anthelmintic activity against GIT nematodes in sheep and goats.

Lyeverton and co-workers [134] carried out a study to evaluate the activity of Carvacryl acetate (CVA), and Nano encapsulated CVA (nCVA) against GIT nematode parasites of sheep. Chitosan/gum Arabic was used to Nano encapsulate CVA. The efficacies of nCVA and CVA were quite similar. Both reduced the worm burden caused by *Haemonchus* spp. in the sheep host. The properties of CVA against *Haemonchus* spp. were enhanced by the encapsulation with chitosan, which included increased bioavailability of CVA, sustained release in acidic pH, and ultimately enhancing its anthelmintic efficacy.

Wasso and co-workers [135] conducted a study to show that oral administration of chitosan-encapsulated bromelain derived from pineapple, up to a dose of 30 mg/kg, had no adverse clinical side effects. They found that Nano encapsulated bromelain was more active than plain bromelain. Thus, the encapsulation process improves bromelain efficacy.

They used *H. contortus* for in vitro experiments and the goat for in vivo studies. Bromelain encapsulation with chitosan increased its anthelmintic activity both in vitro and *in vivo*, suggesting that it could be an essential supplement for chemically synthesized anthelmintic drugs, particularly in areas where anthelmintic resistance has occurred. Conversely, Albendazole outperformed Nano encapsulated and plain bromelain in vitro [135].

Ascaridia columbae is the main gut parasite of pigeons [136]. It not only affects the pigeon's health but also the droppings of the infected pigeons put the surrounding environment at risk, increasing the danger of the spread of parasitic infection to other avian or animal species [137]. Anthelmintics like levamisole, piperazine citrate, ivermectin, fenbendazole and albendazole treat this infection in pigeons [138]. But these synthetic drugs are unaffordable to small pigeon farm owners. Chitosan nanoparticle therapy efficiently alleviated *A. columbae* in vitro and in vivo. It showed nematicidal efficacy. Chitosan nanoparticles brought about the shrinkage in the mouth parts of the worms as well as induction of damage to the worm body. In the examined pigeons, mitigation of severe clinical signs was achieved. Mortalities were decreased, and intestinal tissue repair in the pigeons was observed.

In tropical regions, haemonchosis has been causing enormous livestock and economic losses [139]. Because of the extensive spread of drug-resistant strains of *H. contortus* [140], plant-derived products, like bromelain, were suggested as potent anthelmintics [141]. Hunduza and coworkers [142] evaluated the in vitro ovicidal, larvicidal, and adult mortality properties of Chitosan encapsulated bromelain against *Haemonchus contortus*. Bromelain obtained from ripe pineapple (*Ananas comosus* L. *Merr*.) encapsulated in methyl cellulose-chitosan (for control release and activity) nanocarriers were evaluated for in vitro ovicidal, larvicidal and adult mortalities using albendazole as the positive control and compared with commercially available bromelain and extracted bromelain. Nano-encapsulated bromelain exhibited potent anthelmintic activity on various developmental stages (eggs, larvae, as well as adult worms) of the life cycle of *H. contortus*, which could be credited to the fact that nanoencapsulation stabilizes the bromelain protein structure hence enhances its activity. Wasso and coworkers [135] evaluated the anthelmintic property using bromelain nano encapsulated in chitosan against *Haemonchus* spp. in the GIT of Small East African goats in Kenya. They showed that chitosan-encapsulated bromelain was safe but had lower potency against GIT strongyle nematode parasites when treated with a single dose. They also observed that this treatment was effective against other parasitic nematodes such as *Ostertagia* spp. They were living in the large intestines of the host.

Observing the anthelmintic effects of *Eucalyptus staigeriana* essential oil nano encapsulated with 4% chitosan on sheep infected with *Trichostrongylus* spp., *Haemonchus* spp., and *Oesophagostomum* spp. was the goal of a study conducted by de Aquino Mesquita and co-workers [143]. The most severely harmed of the three worms was *H. contortus*. Along with a decrease in the parasite burden on the host small intestine of 22.3%, a drop in the load of 83.7% of the *H. contortus* parasite was noted.

Essential oils have been shown to disrupt the metabolism of helminths by causing the target worm to become disorganised and unable to carry out essential duties, even in the early stages of development. They have also demonstrated a worsened deregulation of the nematode's nervous system, inhibiting their motility [144]. Citral is the primary ingredient in *Cymbopogon citratus* (family Poaceae/Gramineae) and is a naturally occurring mixture of two isomeric aldehydes, geranial (*trans-citral*) and neral (*cis-citral*). Together, they account for about 65–85% of the plant's overall oil composition, giving the herb its anthelmintic properties.

Biological features of *Cymbopogon citratus* Essential Oil (CcEO) have been described in studies by Macedo and co-workers [145], including anthelmintic activity against *Haemonchus contortus.* CcEO, which contains 97.7% citral, decreased the parasite burden in *Meriones unguiculatus*, which had been experimentally infected with *H. contortus*, by roughly 38.6%. The anthelmintic potential of the *C. citratus* essential oil nanoemulsion (CcEOn) was also examined in this work. CcEO and CcEOn effectively reduced the adult

worm load of *H. contortus* by 66.4 and 83.1%, respectively. CcEO and CcEOn prevented larvae from hatching in the egg hatch test by 98.4% and 97.1%, respectively. The treatment groups' total worm load and faecal egg count were identical to those of the negative control group. They came concluded CcEOn acts as a nanoencapsulation to increase anthelmintic efficacy against *H. contortus*.

By nanoencapsulation *Eucalyptus staigeriana* and *Eucalyptus citriodora* essential oils with 1% chitosan, Ribeiro and co-workers [146] found that the suppression of hatching larvae of several sheep GIT nematodes was increased.

Macedo and coworkers [147] suggested that the use of the essential oil derived from *Cymbopogon citratus* in free as well as nanostructured forms, and its important component, terpinen-4-ol, inhibited the hatching and migration of *H. contortus* larvae. It was observed that the same could be used in in-vivo studies, which presents an optimistic research scenario in treating GIT helminth infections.

7. Conclusion and Future Prospectives

Infections with helminths can be fatal and catastrophic to the livestock sector and are bound to have economic implications. Existing anthelmintic medications are currently losing effectiveness owing to the emergence of resistant forms. Thus presently, many helminth parasites are immune to the available anthelmintic drugs. Plant-based anthelmintics are being developed to tackle this problem. Herbs and nanoparticles offer good prospects in several biomedical disciplines, including helminthosis. Nanoparticles have proven to be a viable source for new anthelmintic medications with lesser emergence of resistance. The majority of in vitro studies have confirmed the effectiveness of anthelmintic nanoparticles. However, more research is required to understand, assess and describe the molecular effects of nano-encapsulated substances.

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