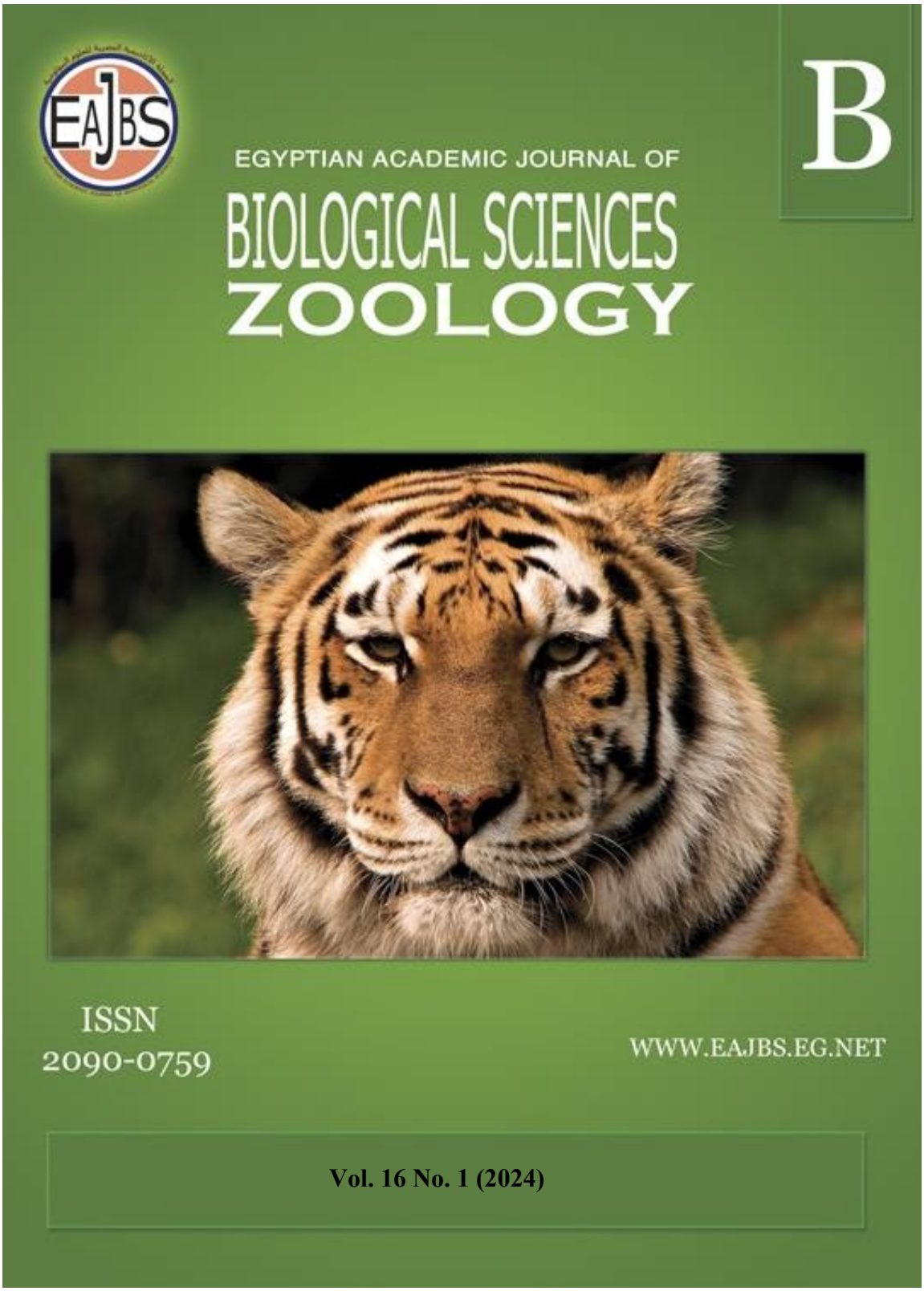

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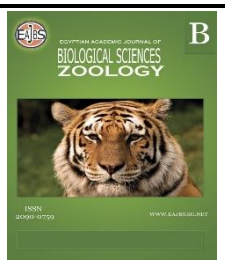

A mini Review of New Potential Therapeutic Strategies Against Trichinellosis

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ABSTRACT

Trichinella spiralis is a parasitic nematode transmitted through the consumption of contaminated meat. The study aims to provide comprehensive information on various aspects of trichinellosis, including its manifestations, conventional treatment methods, and emerging anti-trichinellosis strategies using nanoparticles is a promising approach to overcoming the challenges posed by conventional trichinellosis treatments. The infection begins when a host ingests meat containing infective larvae of *T. spiralis*. The adult worms release newborn larvae (NBL) that enter the bloodstream. These NBL invade striated skeletal muscle cells and establish nurse cell-parasite complexes within the muscle tissue. Trichinella causes a public health impact and economic costs related to pig husbandry and food safety. As the prevalence of trichinellosis remains a concern, continued research, surveillance, and public awareness efforts are essential to mitigate the impact of this parasitic infection on human health and the food industry. Pursuing new and effective treatments for trichinellosis remains imperative, and ongoing research efforts are exploring innovative strategies to address the limitations of existing drugs and enhance their therapeutic outcomes. Several studies highlight the potential of specific antigens for developing vaccines that could offer protective immunity against *T. spiralis* infection, providing valuable insights for future research in parasitology and vaccine development. In conclusion, the integration of nanotechnology and nanoparticles holds promise for revolutionizing drug delivery systems, improving therapeutic outcomes, and offering novel approaches to treat various diseases, including parasitic infections like trichinellosis. Ongoing research in this field is likely to unveil more innovative applications and solutions in the future.

INTRODUCTION

Trichinellosis is a parasitic disease with diverse manifestations, ranging from gastrointestinal symptoms to severe muscle pain and potentially life-threatening complications. Conventional treatment involves anthelmintic medications and supportive care, while new anti-trichinellosis strategies aim to improve treatment outcomes and address emerging challenges associated with the disease.

1.1 Trichinella:

This statement means that nematodes, which are a type of worm-like parasite, are found in many different places and environments, and they have adapted to live in various

ways. These adaptations allow nematodes to occupy different niches or roles within ecosystems, such as living as parasites in animals or plants, or even as free-living organisms in soil or water. Their widespread distribution and ability to adapt to different lifestyles make nematodes significant members of many ecosystems (Tahir Aleem *et al*., 2022). Trichinellosis is a zoonotic disease that is initiated by roundworms of the genus *Trichinella spp.* (Abou Rayia, *et al*., 2022) and worldwide distributed in almost 30% of countries with a record of about 10000 cases/year (Pozio, 2007; Rawla and Sharma, 2022). *Trichinella* is the smallest nematode parasitizing humans with a clinically significant impact (Pozio, 2015). The disease has a substantial public health impact on humans as well as high *economic* cost in terms of pig husbandry and food safety (Nöckler *et al*., 2005) as it results in high rates of morbidity and mortality (Al-Attar *et al*., 2020; Bai *et al*., 2022).

Over 8000 *Trichinella* isolates from all over were identified by the International *Trichinella* Reference Centre (ITRC) (Marucci *et al*., 2022). Seven species of *Trichinella* infesting humans are documented. Three of them have a significant clinical impact on humans as they all have encysted larvae in the muscles; *Trichinella spiralis* is cosmopolitan, and *Trichinella nativa* is found in the Arctic, and sub-Arctic region, However, *Trichinella britovi* is found in Eurasia, and Africa (Gómez-Morales *et al*., 2018). The species, *T. spiralis*, pigeonholed one of the top ten foodborne parasites worldwide (El Temsahy *et al*., 2015). *T. spiralis* can infect more than 100 different species of animals, including mammals, birds, and reptiles (Gottstein *et al*., 2009; Bai *et al*., 2022). Pigs are the main definitive hosts in *T. spiralis'* life cycle (Basso *et al*., 2022). Only in China, more than 400,000 people are in perilous of trichinellosis, as China is one of the highest countries in breeding and consuming pig meats (Chávez-Ruvalcaba *et al*., 2021). By consuming raw or undercooked meat infested with *T. spiralis* larvae, humans get infected. The US Food and Drug Administration (USDA) endorses raising the internal heat of the meat during cooking to 76.7 °C to be enough to kill the larvae (Bacon and Sofos, 2003).

1.2 Manifestation of Trichinellosis:

Trichinella typically possesses two phases within their hosts; the intestinal (enteric) phase for 1-2 weeks and the muscular (parenteral) invasive phase (Darwish *et al.*, 2022). The manifestation of *Trichinella* initiates in the intestine with several gastric symptoms including colic, diarrhea, seasickness, and queasiness (Rawla and Sharma, 2022). In the parenteral phase, *Trichinella* larvae enter striated muscle cells and encyst within it lasting viable for 1 year to several years reliant on *Trichinella* species (Bruschi *et al.*, 2002). At the parenteral phase, malaise, fever, marked eosinophilia, and widespread myalgias for up to 8 weeks are common (Sethi *et al.*, 2010). Myalgia is particularly in the rib cage, mid-abdomen, and face caused by released larvae (Bai *et al*., 2022; Rawla and Sharma, 2022).

The clinical representation of *Trichinella* infection fluctuates from asymptomatic to fatal depending on the number of larvae and site of invasion within the host body (Rosca *et al*., 2021). Generally, the clinical picture of trichinellosis includes fever, inflammation of muscles, fatigue, gastrointestinal symptoms, occasional bleeding in the retina, and decreasing in cognitive ability (Jaiswal *et al*., 2023). Mortality in severe infection is recorded by emitted larvae (Bruschi *et al.*, 2002). Other symptoms encountered include numbness of limbs, depression, low oxygen supply to the brain focal neurologic deficits due to ischemic events due to larval migration and vascular obstruction, and lung inflammation due to helmintho-cytotoxity (Gentilini *et al*., 2011).

1.3 Conventional treatment of Trichinellosis:

There is no absolute effective treatment for the eradication of trichinellosis, as an effective treatment must combat different phases of the disease (Gottstein, *et al*., 2009; Albogami, 2023). Most anti-trichinellosis drugs have synergistic action by limiting inflammation and larval capsule formation (El-Wakil *et al*., 2023). Benzimidazole derivatives such as albendazole, flubendazole, and mebendazole are the foremost

anthelmintic drugs used against trichinellosis (Codina *et al*., 2015). So far, these drugs may have a significant adverse impact on human health causing implication as cancer, encephalitis epilepsy, or even death (Matadamas-Martínez *et al*., 2013; Fahmy and Diab, 2021). In addition, some of these drugs are not advised during pregnancy and are suitable for toddlers (Shalaby *et al*., 2010).

Moreover, the efficiency of these regular drugs fluctuates depending on the phase of infection and time of drug application, the eradication power is more predominant during the early enteric phase as compared to the encysted muscular phase (Siriyasatien *et al*., 2003; Gottstein *et al.* 2009). Although albendazole is the most preferable drug against trichinellosis, it has a low water solubility, bioavailability, and tissue absorption and it shows weakened renitency against the encysted larvae stage (Kalaiselvan *et al*., 2007; Codina *et al*., 2015; Nada *et al*., 2018). Thus, the high demand for new and effective treatments against trichinellosis drugs is mandatory (Shalaby *et al*., 2010; Yadav *et al.*, 2012).

To increase the rate of dissolution and oral bioavailability of albendazole, an assortment of approaches was used. Several therapeutic and alternative active compound strategies were used. This included the use of active compounds to enhance the drug's therapeutic efficacy and combat resistance (Eissa *et al*., 2022). Many studies were applied to enhance the efficacy of albendazole, the novel tested albendazole forms were found to eradicate the intestinal phase of *T. spiralis* infection and subsequently reduce its burden in muscle (García *et al*., 2013). Researchers assessed three new solid microencapsulated formulations of albendazole *in vivo*, aiming to surpass the oral bioavailability of standard albendazole. Two out of the three formulations were found to intensely reduce the parenteral phase measurement of the muscle larval (Codina *et al*., 2015).

Other methods were applied combining the drug into lipid-based drug delivery systems (Will Castro *et al*., 2021); and complexing the drug with cyclodextrin (Kalaiselvan *et al*., 2007 and Eid *et al*., 2020). Essential oils are natural and complex mixtures of compounds from aromatic plant parts, in a study by Lopez et. al., (2022), carvacrol (a phenolic monoterpenoid in lots of essential oils) and albendazole combination were used to enhance the efficacy of albendazole. This strategy allowed to improve the efficacy of the treatment without increasing the administrative doses of albendazole or extending the treatment period which sequentially reduces the incidence of adverse effects (Krolewiecki *et al*., 2022). Another study demonstrated gallic acid in combination with albendazole has a promising antitrichinellosis effect against the muscular phase of *T. spiralis* larvae (Albogami, 2023). Albendazole-β-cyclodextrin citrate (ABZ: C-β-CD) complex also showed antiparasitic activity against *T. spiralis* in the parenteral phase in mice enhancing its efficacy (Codina *et al*., 2015).

1.4. New Anti-Trichinellosis Strategies:

The anti-trichinellosis strategy refers to innovative methods or approaches that are being developed or implemented to prevent, diagnose, or treat trichinellosis, which is an infectious disease caused by the parasite Trichinella. These strategies could include advancements in drug development, vaccine research, improved diagnostic techniques, vector control measures, public health interventions, or any other innovative means aimed at reducing the incidence or severity of trichinellosis infections. The goal is to introduce more effective and efficient methods to combat this parasitic disease and ultimately improve public health outcomes (Fig.1).

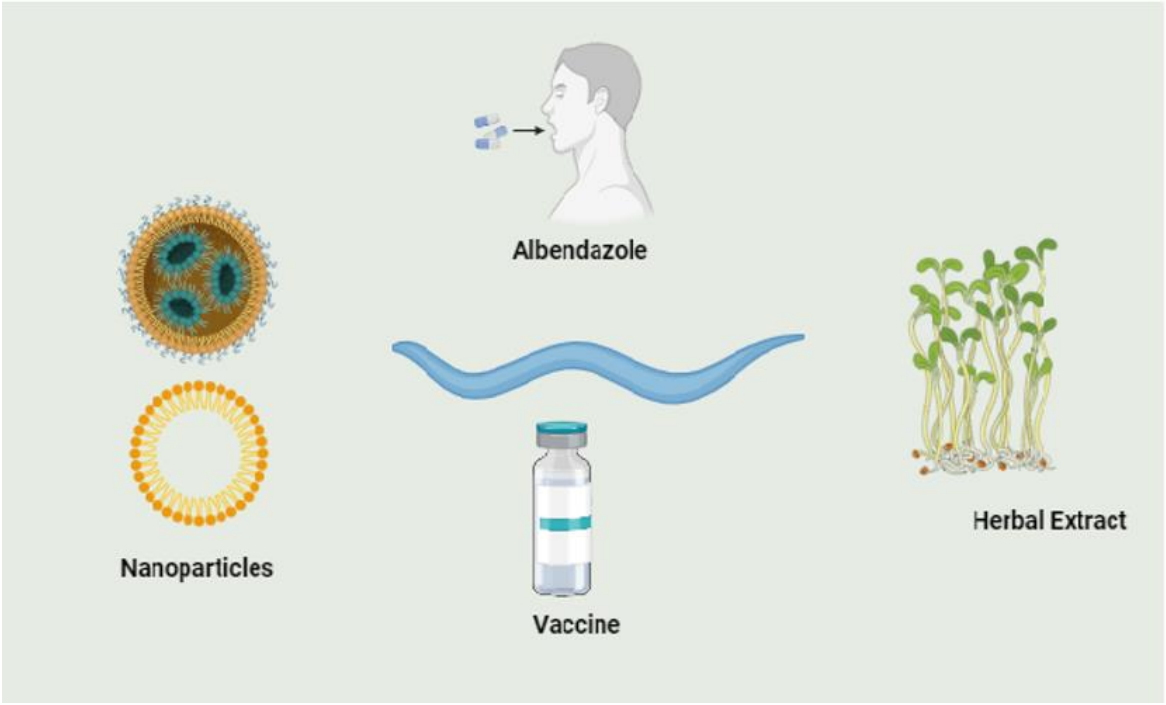

Fig. 1: Potential anti-trichinellosis treatment

1.4.1. Medicinal Plants:

Consequently, many studies have investigated newer anthelminthic drugs derived from medicinal plants or with efficient antioxidant impact and low toxicity and adverse effects **(**Yadav *et al.*, 2012; Attia *et al*., 2015; Seow *et al*., 2021). The effects of myrrh extracted from the aloe-gum resin of *Commiphora molmol* were tested, and the results showed using myrrh for controlling *T. spiralis* could be promising and effective (Basyoni and El-Sabaa, 2013). Abuelenain *et al.* (2022) investigated the phenotypic changes induced by albendazole, Lipidium sativum (garden cress), and Commiphora molmol (myrrh), finding that myrrh surpassed garden cress as an effective complementary agent to albendazole in both *in vivo* and *in vitro* studies.

Punica granatum extract from a fruit commonly known as pomegranate showed anti-inflammatory and antioxidant properties that showed an anti-trichinellosis effect (Al-Megrin, 2017; Dkhil *et al*., 2019). Esmat *et al*. (2021) also stated that the *P. granatum* and amygdalin extracts with cobalamin when combined with albendazole can decrease larval pathology and myositis from *T. spiralis*.

The efficacy of the leaf extract of *Lasia spinosa* against *T. spiralis* was assessed and it was found that the extract decreased *T. spiralis* infections in mice. Therefore, the active ingredient of *L. spinosa* leaves needs to be isolated and tested against different stages of *T. spiralis* in animal models (Yadav *et al*., 2012). Also, the efficacy of *Artemisia annua* extract against trichinellosis was evaluated. The treatment declined *T. spiralis* adult-worm count in infected animals and reestablished the normal intestinal construction and diminished the pathological impact of the infection as edema, inflammation (El-Kady *et al*., 2022). The *Curcuma longa* extract, pomelo peels extract, and their chitosan NPs were used experimentally against trichinellosis in the presence of albendazole. This study mentioned that the NPs of Curcuma and Pomelo have the potential to be employed therapeutically in the treatment of trichinellosis. (El-Hamed *et al*., 2022).

1.4.2. Vaccination:

Long-term therapeutic investigations were conducted targeting *T. spiralis*, utilizing a novel cathepsin B gene (TsCB, GenBank: XP_003379650.1). The study explored the protective immunity induced by immunization with rTsCB in a mouse model. TsCB was

identified in the cuticle and stichosome of the parasite. Vaccination with rTsCB triggered specific IgG and IgE responses, leading to partial immune protection. This was evidenced by a significant reduction in worm burden in the intestines and muscles of vaccinated mice. The humoral immune responses generated by rTsCB immunization impeded intestinal worm growth and compromised its fecundity. These findings suggest that TsCB could be considered a promising molecular target for the development of vaccines against *T. spiralis* infection (Cui *et al*., 2019).

T. spiralis galectin (Tsgal) is a recently discovered protein located on the surface of this nematode. The involvement of recombinant Tsgal (rTsgal) in the invasion of intestinal epithelial cells (IECs) by larvae has been observed, with the invasion process hindered by the presence of anti-rTsgal antibodies (Zhang *et al*., 2024). Vaccination with an oral rTsgal vaccine stimulated a local mucosal sIgA response in the gut, along with a specific systemic Th1/Th2 immune response, demonstrating clear protective immunity against *T. spiralis* challenge. The oral rTsgal vaccine presents a promising approach for controlling *T. spiralis* infection (Xu *et al.*, 2022).

The biological properties of a novel *T. spiralis* trypsin (TsT) against larvae were assessed. TsT gene was recorded at *T. spiralis* lifecycle stages, principally at epicuticle of 5-6 day adult worms, indicating that TsT is a worm somatic antigen and adult-stage specific surface antigen. Inoculating mice with rTsT elicited a noticeable humoral immune response and stimulated the production of cytokines IFN-γ and IL-4. The mice that received the rTsT vaccination demonstrated a significant decrease of 33.17% in adult worms in the intestines and a 37.80% reduction in muscle larvae following larval challenge. These findings suggest that TsT could be regarded as a potential target antigen for developing anti-*T. spiralis* vaccines (Zhang *et al*., 2020).

In a research investigation, a recombinant Lactobacillus plantarum carrying the gene for *T. spiralis* inorganic pyrophosphatase (TsPPase) was utilized to assess its immune protective capabilities against *T. spiralis* infection. The findings revealed that the rTsPPase was successfully expressed on the surface of the recombinant strain, and oral vaccination with rTsPPase triggered elevated levels of specific serum IgG, IgG1, IgG2a, and mucosal secretory IgA (sIgA) in BALB/c mice (Hu *et al*., 2021).

1.4.3. Nanoparticles (NPs):

NPs are small-sized particles (10 to 100 nm) with high surface area to volume ratio, surface charge, crystalline and amorphous structures, shape, and color variety (Ealia *et al*., 2017; Mukherji *et al*., 2019). Nanostructures include polymers, liposomes, dendrimers, liposomes, and metal NPs (Ling *et al*., 2008). Different characterization methods are used to evaluate NPs as ultraviolet-visible (UV–vis) absorption spectroscopy, dynamic light scattering (DLS), Fourier transform infrared spectroscopy (FT-IR), energy dispersive X-ray analysis, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (Boroumand *et al.*, 2019).

Some NPs may be biodegradable, and non-toxic. NPs can be coated with organic particles as micelles and liposomes are known as nanocapsules and are commonly used in drug delivery systems due to their stability and size (Dash *et al*., 2020; Chandrakala *et al*., 2022). NPs can enhance the therapeutic competence of ionized drugs and increase the penetration of water-soluble compounds, proteins, peptides, vaccines, siRNA, miRNA, and DNA (Sperling & Parak, 2010).

The NPs have biomedical and pharmacological uses due to their antioxidant, antimicrobial, antidiabetic, and anticancer effects (Ameen *et al*., 2023; Baran *et al*., 2023; Meliani *et al*., 2023). Drug delivery systems using NPs are improved as compared to traditional forms of drugs (Chandrakala *et al*., 2022). NPs have been used to shield the drug in systemic circulation and limit its release to the selected sites (Yetisgin *et al*., 2020). Thus, the adverse side effects of the drug can be minimized, and the therapeutic efficacy is

increased at lower doses of regular drugs (Zhang *et al*., 2020; Sana *et al*., 2022; Tabakoglu *et al*., 2023).

The efficacy of albendazole with albumin nanocarrier was introduced in two sizes; 10 nm which is extremely effective against tumor growth at low doses and 200 nm which has a good overwhelming ascites (Noorani *et al*., 2015). The oral bioavailability of albendazole was improved as a novel nanocrystalline formulation of the drug by spray-drying albendazole with a triblock copolymer. The new formula significantly enhanced the drug dissolution compared to the commercial product, and the formulation showed a good cyst inhibition effect 3.7-fold greater than that of regular albendazole (Hu *et al*., 2021).

Albendazole-encapsulated polyurethane nanoparticles were developed via the polycondensation technique which improved the shape and size of the drug (Eissa *et al.*, 2022). The study exposed a noteworthy antiproliferative activity of the new nanoformula by apoptosis induction and cell death and the lack of toxicity as an indication of its possible biocompatible nanocarrier for anticancer drugs (Racoviceanu *et al*., 2020). It also assessed solid lipid nanoparticles containing albendazole to enhance cellular penetration and cytotoxicity against U-87 MG glioma cell lines. The findings demonstrated an enhanced efficacy of the drug when delivered through the nanocarrier (Marslin *et al*., 2017).

Elmehy *et al*. (2021) reported that niosomes enhanced the efficacy of oral Ivermectin against various stages of *T. spiralis* infection compared to nano-crystalline Ivermectin. Both niosomes and nano-crystals caused a significant decrease in adult and larval counts with superior activity of niosomal Ivermectin by reduction of inflammation in both jejunal and muscle homogenates. Niosomal form efficacy exceeded the nanocrystalline form in the treatment of different phases of trichinellosis (Elmehy *et al*., 2021).

Nanomedicine is a highly significant application of nanotechnology that is used for the treatment, diagnosis, and control of various parasitic infections (Hasan, 2015; Khurana *et al*., 2019). Metal and metal oxide-based NPs are commonly categorized as inorganic NPs and they also have exceptional physical, chemical, and biological properties when compared to higher scales particles (Yu *et al*., 2021; Nair *et al*., 2022). Metal NPs such as Ag, Au, Ce, Fe, Se, Ti, and Zn possess an important role due to their unique bioactivities in nanoforms (Khurana *et al*., 2019; Malik *et al*., 2023).

The green silver nanoparticles (AgNPs) showed their larvicidal activity against malaria**,** dengue, and filariasis vectors (Elumalai *et al*., 2017). Most trichinellosis drugs showed limited bioavailability, a high degree of resistance, and weak action against encysted larvae (Abou Rayia *et al*., 2022; Khedr *et al*., 2023).

Thus, The utilization of chitosan nanoparticles, either alone or loaded with full and half doses of albendazole, boosted its effectiveness against the muscular phases of *T. spiralis* infection, enhancing its antiparasitic activity (Mohammed *et al*., 2023). Muscle histological changes were also enhanced, and encysted larvae degeneration with minimum pathologic changes of infected skeletal muscles was also seen (Asif *et al*., 2023; Mohammed *et al*., 2023).

Also, the emerging anti-trichinosis using chemical and biosynthesized AgNPs revealed an obvious larvicidal effect against muscular larvae of *Trichinella* affecting their cuticle. The application of AgNPs led to the total suppression of infectivity in treated larvae exposed to sublethal doses of chemically and myrrh-prepared AgNPs before infecting animal models. This marks the inaugural instance where AgNPs synthesized with myrrh have been examined for their anthelminthic efficacy against Trichinella *in vitro* model **(**Abd-Elrahman *et al*., 2021).

Selenoproteins are proteins that can be found in archaea, bacteria, and eukarya There has been renewed interest in selenium NPs (SeNPs) as trichinosis supplements due to their incorporation in antioxidant defense systems–enzymes and proteins as Se-dependent glutathione peroxidase, thioredoxin-reductase, selenoprotein (Gabrashanska *et al*., 2019).

The addition of selenium as a supplement has the potential to hinder the generation of free radicals and the processes of lipid peroxidation in trichinellosis (Gabrashanska *et al.*, 2010). The reduction of muscle larvae after Sel-plex application was 63%. The study indicated that a diet containing selenium may prove advantageous in managing diseases associated with significant oxidative stress, especially parasitic infections (Gabrashanska *et al.*, 2019).

Conclusion

Many studies collectively contribute to a comprehensive understanding of trichinellosis pathogenesis and treatment modalities, paving the way for the development of effective interventions to combat this parasitic infection and alleviate its associated morbidity and mortality. The convergence of research efforts in parasitology, vaccine development, and nanotechnology offers hope for advancing our understanding of trichinellosis and developing more effective strategies for its prevention and treatment. Continued investment in research and innovation in these areas is essential for addressing the challenges posed by *T. spiralis* and other parasitic infections in the future for both humans and animals.

List of Abbreviations:

ABZ: C-β-CD: Albendazole-β-cyclodextrin citrate
DLS: Dynamic light scattering
FT-IR: Fourier transform infrared spectroscopy
ITRC: International *Trichinella* Reference Centre
IECs: Intestinal epithelial cells
NBL: Newborn larvae
NPs: Nanoparticles
SEM: Scanning electron microscopy
SeNPs: Selenium NPs
AgNPs: Silver nanoparticles
TEM: Transmission electron microscopy
Tsgal: *T.* spiralis galectin
UV–vis: Ultraviolet-visible
USDA: US Food and Drug Administration

Declarations:

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Conflicts of Interest: There is no conflict of interest.

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