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Nanoparticles as Potent Agents for Treatment of *Schistosoma* Infections: A Systematic Review

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ABSTRACT

Background: Schistosomiasis is an acute and chronic parasitic disease caused by blood flukes of the genus *Schistosoma*. The current drugs for treating schistosomiasis are associated with some side effects.
Objective: The aim of this systematic study was an overview of the treatment of diseases caused by *Schistosoma* based on nanoparticles.
Methods: In the present systematic research with keywords "*Schistosoma*", "parasitism", "anti-*Schistosoma* activity", "nanoparticles", "metal nanoparticles", "silver nanoparticles", "gold nanoparticles", "polymer nanoparticles", "PLGA nanoparticles", "nanoemulsions", "*in vitro*", and "*in vivo*" from five English-language databases, including ScienceDirect, europePMC, PubMed, Scopus, Ovid, and Cochrane were searched from 2000 to 2022 by 2 researchers.
Results: In the initial search, 250 studies were selected. Based on the inclusion and exclusion criteria, 27 articles were finally selected after removing duplicate, unrelated, and articles containing full text. In present article, the most nanoparticles used against *Schistosoma* were gold nanoparticles (22%).
Conclusions: The results indicate the high potential of various nanoparticles, including metal nanoparticles, against *Schistosoma*. Also, the remarkable anti-schistosomal activity of nanoparticles suggests their use in different fields to eliminate this pathogenic microorganism so that it can be used as an effective candidate in the preparation of anti-schistosomal compounds because these compounds have fewer side effects than chemical drugs. *Ther Res Clin Exp*. 2023; XX:XXX–XXX).

Introduction

Parasitic diseases can be considered among the most common infectious diseases.[1] Schistosomiasis is a parasitic disease of humans and animals that is caused by *Schistosoma* species (also known as the blood flukes). The disease is prevalent in tropical and subtropical regions, particularly in poor peoples with no access to safe drinking water and satisfactory sanitation.[1] Based on World Health Organization data, schistosomiasis causes more than 200,000 deaths annually around the world; at least 251.4 million people needed preventive treatment in 2021.[2] In humans, schisto-

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somiasis occurs mainly in Africa, the Middle East, South America, and the Caribbean islands. In mammalian hosts, female worms lay eggs in the mesenteric vessels, after which the eggs pass through the intestinal tract and are excreted through feces. Under laboratory conditions, *Schistosoma* eggs adhere to endothelial cells and induce cell migration. More than 11% of *Schistosoma* eggs laid in the mesenteric vessels are transported through the portal vein and stored in the liver. Inside the tissues, *Schistosoma* eggs secrete a variety of soluble egg antigens that increase the attachment of the egg to endothelial cells and induce the formation of granuloma through T cells. Granuloma production as an immunological reaction has a protective role.[2,3] Intestinal schistosomiasis is reported by *S mekongi, S japonicum, S intercalatum, S guineensis,* and *S mansoni*, whereas the urogenital schistosomiasis is caused by *S haematobium*.[2] Praziquantel (PZQ) remains the first-line drug against adult *Schistosoma* worms and the smaller stages of schistosomes; however, it displayed some advers side effects, allergic and hypersensitivity responses, and does not prevent reinfection.[4] Therefore, a novel effective and safe antischistosomal agent must be developed.

In recent years, researchers have investigated the effects of nanoparticles and their mechanism of action on parasitic infections to find a suitable alternative to routine drugs.[5,6] Recent studies have investigated the antiparasitic effects of nanoparticles in vivo and in vitro and reported promising results on the effect of nanoparticles in the treatment of parasitic diseases.[7–11] Nanoparticles are finely dispersed particles or solid particles with a size of 10 to 100 nm, which are prepared in different forms. In fact, they are considered biological mimics, nanomachines, can target cells, and extracellular elements to deliver drugs and genetic factors.[12] The aim of this systematic study was to present an overview of the treatment of diseases caused by *Schistosoma* based on nanoparticles.

Methods

Search strategy and selection

The study covered the period from 2000 to 2022 according to the Preferred Reporting Items for Systematic Reviews protocol. Five English-language databases, including ScienceDirect, europePMC, PubMed, Scopus, Ovid, and Cochrane were searched by 2 of the authors. The search was performed using the syntax and specific tags for each of the databases. The words used for the search were Schistosoma, *parasitemia*, Schistosoma *anti-activity nanoparticles*, *metallic nanoparticles*, *silver nanoparticles*, *gold nanoparticles*, *polymeric nanoparticles*, *PLGA nanoparticles*, *nano-emulsions*, *in vitro*, and *in vivo*. Duplicate articles were removed by EndNote software version 9 (Clarivate, London, United Kingdom). The title and abstract of the articles were independently reviewed by 2 of the authors, and in case of disagreement, discrepancies were resolved through discussion.

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria in this study were as follows: studies published in English, studies published in peer-reviewed journals, studies that had clear information to evaluate, studies for which full text was available, and studies that only analyzed the effect of nanoparticles on *Schistosoma.*

Exclusion criteria

The exclusion criteria in this study were as follows: studies for which full text was not available, case reports, case series, systematic reviews, summaries of presentations at seminars and conferences, and studies without clear information to evaluate.

Data extraction

Two authors independently extracted the initial information of the selected articles as follows: author (year), type of nanoparticles, drug, concentration (in micrograms per milliliter), and exposure time.

Results and Discussion

Selected studies

At the beginning of the search, the studies identified through the database search included 240 studies. After removing additional records identified through other sources and duplicates that included 10 studies, 120 studies were left, which included 120 studies, and the remaining cases were 116 studies. Based on the exclusion criteria, 40 more studies were also excluded. Eighty studies remained eligible for evaluation. In the next step, 53 articles that did not have enough information to be included in the study were removed and finally 27 studies were evaluated in the present systematic review (see the Figure). The most used nanoparticles against *Schistosoma* were gold nanoparticles (AuNPs) (22%), followed by liposome (14.8%) and chitosan (14.8%) nanoparticles. Most studies (51%) were performed in vitro and 13 studies (48.1%) were performed in vivo. Other information is described in Tables 1 and 2.

Targeted drug delivery mechanisms in nanoparticles

Nanoparticle drug delivery systems are engineering technologies that use nanoparticles for targeted delivery and production control of therapeutic drugs. A modern form of drug delivery system should minimize side effects and optimize dosage. In recent years, nanoparticles have received attention due to their potential application for effective drug delivery.[41] Nanomaterials offer different chemical and physical properties or biological effects than their larger counterparts, which can be useful for drug delivery systems. Some of the important advantages of nanoparticles are high surface-to-volume ratio, chemical and geometric stimulability, and their ability to interact with biomolecules to facilitate absorption into cell membranes. Nanoparticles include a large family of organic and inorganic materials that have unique tunable properties that can be selectively tailored for specific applications. Despite the many advantages of nanoparticles, there are also several challenges, which include nanotoxicity, biological release, and collection and release of nanoparticles by the human body.[42]

Using nanoparticles to treat parasitic infections

Research on the preparation and use of nanoparticles in the treatment and diagnosis of diseases in nanomedical projects is of primary importance and includes the accurate identification of cells and receptors, depending on specific clinical conditions, and the selection of appropriate nanocarriers to obtain a desired response while minimizing side effects. Mononuclear phagocytes, dendritic cells, endothelial cells, and cancers (tumor cells and neovascular tumors) are key targets of nanoparticle therapy.[43] Parasitic diseases such as malaria, leishmania, and trypanosomiasis are important global issues and due to their intracellular nature, they pose a challenge for researchers aiming to discover and supply drugs. In addition, the small amount of discovery in the field of antiparasitic drugs in the past decades has necessitated effective management to maintain supply.[44] The latest studies in the field of drug development for parasitic diseases are focused on

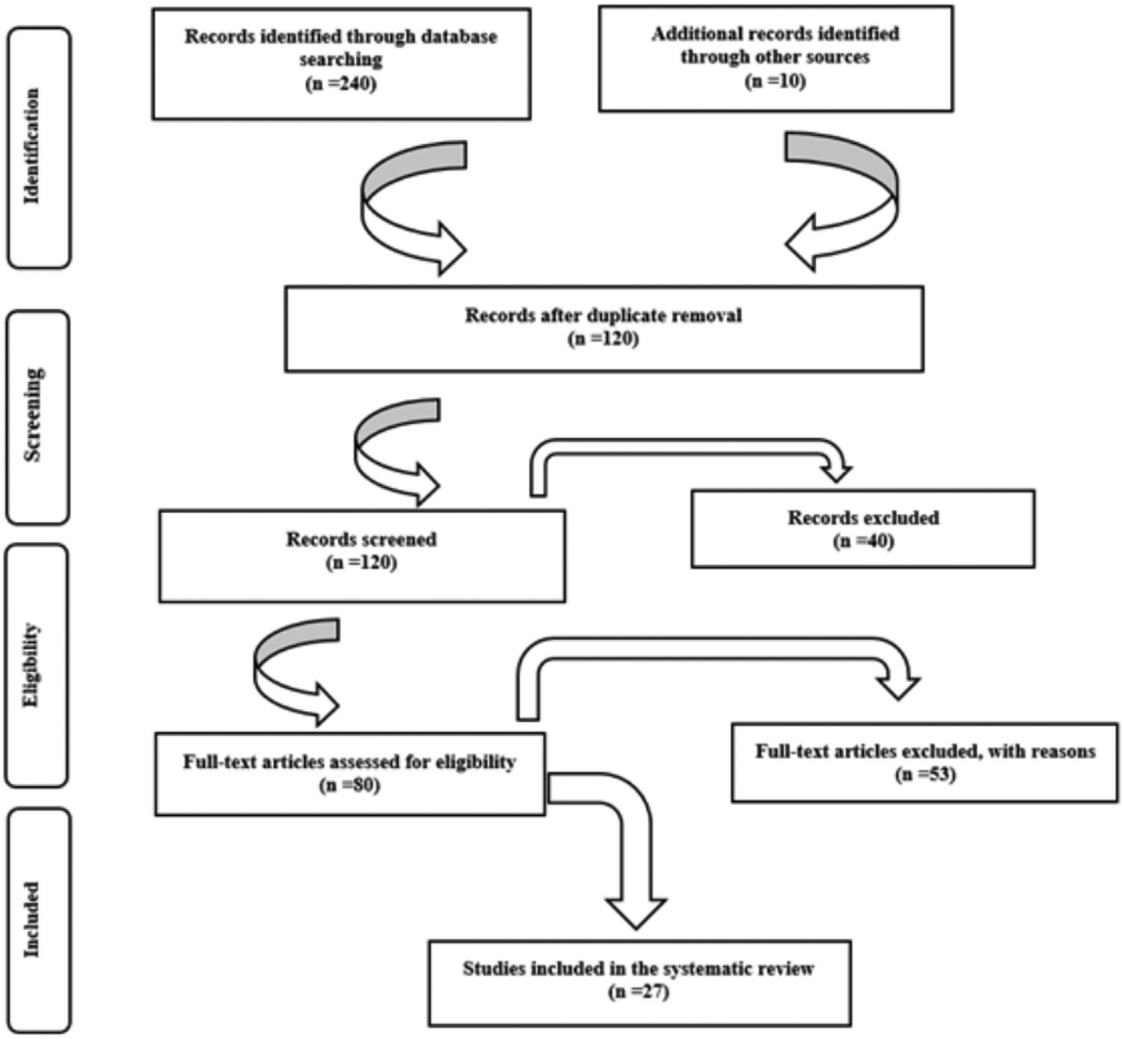

Figure. The flowchart of the process of article selection.

biological and biopharmaceutical issues. The role of colloidal carrier liposomes, polymeric nanoparticles, lipid nanoparticles including lipid-conjugated drugs, and nanoparticles used in optimizing the supply of antimalarial, anti-*Leishmania*, and anti-*Trypanosoma* agents have been studied. Macrophages are excretory cells whose role in diseases is well known.[45] Therefore, macrophages are an effective drug target that provides many opportunities to investigate potential agents that target them.[46] For example, although most microorganisms are killed by macrophages after phagocytosis, many pathogens find ways to survive in macrophages. In certain cases, the lysosomes within the macrophage provide a habitat for pathogens. Examples in this field include *Toxoplasma gondii*, different species of *Leishmania*, *Mycobacterium tuberculosis*, and *Listeria monocytogenes*. Therefore, nanoparticles carrying coated antimicrobial medicinal agents are a logical solution to eliminate pathogens.[47] The endocytic pathway transports nanoparticle carriers to lysosomes where pathogens reside. The breakdown of the carriers by lysosomal enzymes releases the drugs into the phagosome or lysosome vesicle, or this process may occur in the cytoplasm by diffusion and specific transfer depending on the physicochemical nature of the molecules. For the treatment of visceral leishmaniasis or confirmed infections with specific fungal strains, the accepted formulation for use in humans is limited to lipid-based nanosystems with a size of 100 to 200 nm containing amphotericin B. This form of targeting has significantly reduced the effective clinical dose of amphotericin B due to the suboptimal therapeutic concentration of the drug in infected macrophages.[48] In medicine, nanoparticles such as gold and silver have a long history in the treatment of diseases such as rheumatoid arthritis and cancer. However, in recent years, the use of gold derivatives against parasitic diseases or neglected diseases has been noticed. Although limited research has been done in this regard. Therefore, this study reviewed the recent advances and treatment methods that employ nanoparticles as anti-parasitic drugs against *Schistosoma* infections.

The effects of nanoparticles against *Schistosoma*

Silver nanoparticles and AuNPs

AuNPs and silver nanoparticles (AgNPs) have potential antimicrobial properties due to their very small size and large surface area, which increase chemical, biological, and solubility activities, and have attracted the attention of researchers.[49] Moustafa et al[13] investigated the potential effects of AgNPs and AuNPs for use as molluscicides on *Biomphalaria alexandrina* snails and as cercaricides on *S mansoni* and reported that AgNPs and AuNPs with a concentration of 30 µg/mL and 160 µg/mL, respectively, resulted in 100% mortality rate in *B alexandrina* snails, whereas a concentration of 50 µg/mL AgNPs and 100 µg/mL AuNPs caused 100% mortality in *S mansoni* cercariae. By investigating the antioxidant effects of AuNPs on granuloma caused by *S mansoni*, Al-Sherbaghi

Table 1
Details of selected studies that reported the use of nanoparticles (Nps) in the treatment of *Schistosoma* infection based on natural or unknown compounds used in combination with nanoparticles in vitro.

Author (y)	Nps type	Drug	Concentration	Exposure time	Ref.
	Silver Nps			5 min	
Moustafa (2018)	Gold Nps	ND*	3, 5, 10, 25, and 50 µg/mL	30 min	
			5, 10, 25, 50, 75, and 100 µg/mL	45 min	13
				60 min	
El-Shorbagy (2017)	Gold Nps	PZQ[2]	0.1, 0.625, 1.25, 2.5, 5, 10, and 25 µg/mL	7 and 14 days	14
Lotfia (2018)	Iron Nps	ND[1]	30–60 mg/L	30 min	15
				1 h	
				2 h	
				3 h	
				4	
Cheng (2013)	Silver Nps	ND	200–1200 µg/mL	ND	16
El-Nour (2021)	Calcium silicate Nps	PZQ	0.07–10 µg/mL	48 h	17
Zoghroban (2019)			11, 0.5, 0.2, 0.1, 0.01, 0.05, and		
	Niosomes	PZQ	0.001 µg/mL	24 h	18
Radwan (2019)	Solid lipid Nps	PZQ	250, 500, and 1000 mg/kg	24 h	19
Aly (2017)	Nanoemulsion	*Curcuma longa* extract	12.5, 25,	24, 48, and 72 h	20
			50, and 100 µg/mL.		
Kishik (2019)	Chitosan Nps	*Nigella sativa*	10, 20, 40, 60, 80, and 100 µg/mL	24 and 48 h	21
Luz (2012)	Polylactide-co-glycolide acid Nps	Curcumin	50 and 100 µM	24 h	22
Andrade (2020)	Solid lipid Nps	PZQ	0.25, 0.5, 1, and 1.5 µg/mL	72 h	23
Kolenyak-Santos (2015)	Nanostructured lipid carriers	PZQ	25 µg/mL	72 h	24
de Souzaa (2014)	Solid lipid Nps	PZQ	25 and 50 µg/mL	2, 4, 6, 24, 48, and 72 h	25
Amara (2018)	Lipid nanocapsules	PZQ	5 and 25 mg/mL	ND	26
Guimaraes (2014)	Liposome	PZQ	5, 200, 300, and 400 µg/mL	24, 48, 72, 96, and 120 h	27

ND = not determined; PZQ = praziquantel; Ref. = reference number.
* The absence of the required information in the main texts of the article, and despite the participation of a group of authors, the required information could not be extracted.

et al[14] showed a significant decrease in the granuloma index and granulocyte mediators, including hydrogen peroxide and nitric oxide, with a significant increase in tumor necrosis factor.

Cheng et al[16] investigated the effect of AgNPs in inhibiting the infectivity of *S japonicum* cercariae and reported that AgNPs rapidly caused tail shedding, agitated behavior, and a decrease in cercarial secretion in a dose-dependent manner that caused 100% cercariae mortality at AgNPs concentration of 125 µg/L.

Dkhil et al[28] investigated the antioxidant and protective role of AuNPs against hepatic *S monsoni* in mice and reported that AuNPs reduced the inflammatory response by downregulating the messenger RNA expression of interleukin 1β and interleukin 6, improved tumor necrosis factor α, interferon γ and inducible nitric oxide synthase. In another study, Dkhil et al[29] investigated the effect of AuNPs on the brain of mice infected with *S mansoni* and found that in mice treated with AuNPs, the changes in norepinephrine and dopamine content and oxidative brain damage were reduced. In general, AuNPs can reduce neuro-oxidative stress and regulate gene expression.[29] Another study showed that AuNPs treatment reduced the degree of histological disorder and oxidative kidney damage. AuNPs were able to regulate gene expression disrupted by *S mansoni* infection.[30]

By evaluating the effect of nanoselenium and AuNPs against intestinal schistosomiasis in mice, Dkhil et al[31] showed that treating mice with metal nanoparticles reduced oxidative stress and histological disorders in the jejunum tissue. The results showed the protective role of nanoseleniums and AuNPs against jejunum damage in mice infected with *S. mansoni*.

Copper oxide nanoparticles

Due to its remarkable properties, copper oxide (CuO) is among the most important transition metal oxides and has many applications. Recently, CuO has been used as an antimicrobial agent against several bacterial, fungal, and parasitic species.[50,51] Abu Al-Nurba et al[17] investigated the effects of nano calcium silicate containing 5% CuO on *Schistosoma* and reported that nano-calcium silicate incorporating 5% CuO showed excellent anti-schistosome activity in in vitro and in vivo tests for 2 strains of Egyptian schistosome. The strongest effect of CS-5% nano-calcium silicate incorporating 5% CuO was shown after 6 hours at 10 µg/mL with significant activity.

Magnetic nanoparticles

Due to its high biocompatibility, magnetic nanoparticles have many applications in the field of medicine and treatment of diseases.[52] Khalil et al[15] investigated the effects of iron nanoparticles on adult *S mansoni* worms and reported that worms exposed to 30 and 60 mg/L iron nanoparticles showed 20% and 77% mortality after 3 hours, respectively. Younis et al[32] studied the activity of magnetite particles and zero-valent iron nanoparticles against *S mansoni*, and showed that zero-valent nanoparticles had a significant effect in reducing the number of tissue eggs and the size of liver granulomata, whereas magnetic nanoparticles significantly reduced the total burden of female worms, the number of tissue eggs, female fertility, and the number of liver granulomata.

Nano-chitosan

Chitosan contains amine groups in diatomic carbon after deacetylation in the chitin structure. Chitosan is used due to its positive charge and binding power to negatively charged surfaces, as well as its simplicity in creating surface changes to transfer drugs and genes to target cells.[53] Kishik et al[21] investigated the anti-*Schistosoma* effects of *Nigella sativa*-loaded chitosan nanoparticles against adult stage *S mansoni* and reported time-dependent effects on the movement and death of worms so that live worms had poor mobility after 24 hours of incubation and showed 100% mortality after 48 hours. El-Menyawy et al[35] recently investigated the anti-*S. mansoni* activity of thymoquinone chitosan nanopar-

Table 2
Details of the selected studies that reported the use of nanoparticles in the treatment of *Schistosoma* infection based on natural or unknown compounds used in combination with nanoparticles in vivo.

Author (y)	Nanoparticle type	Drug	Animal	Concentration	Mortality percentages/lethal doses	Type of administration	Treatment duration	Ref.
Moustafa (2018)	Silver Nps Gold Nps	ND*	Swiss albino mice	ND	ND	ND	1 h	13
Dkhil (2015)	Gold Nps	ND	CD-1 mice	0.25, 0.5, and 1 mg/kg	0.25 mg/kg	IP	2 times on day 46 and day 49 postinfection	28
Dkhil (2015)	Gold Nps	ND	Swiss albino mice	100 µL, 0.25, 0.5 and 1.0 mg/kg	0.5 mg/kg	IP	2 times/wk (on days 46 and day 49 postinfection)	29
Dkhil (2016)	Gold Nps	PZQ	Swiss albino mice	50, 500, and 1000 µg/kg	1 mg/kg	IP	2 d	30
Dkhil (2019)	Selenium Nps Gold Nps	PZQ	Swiss albino mice	0.5, 1, and 600 mg/kg	0.25 mg/kg	IP	7 d 2 d	31
Younis (2021)	Iron Nps	PZQ	Swiss albino mice	10 mg/kg	0.5 mg/kg	OA	4 d	32
El-Nour (2021)	Calcium silicate Nps	PZQ	Golden hamsters	0/07, 10 µg/mL	1.0 mg/kg	IP	5 d	17
Zoghroban (2019)	Niosomes	PZQ	Swiss albino mice	250 mg/kg	500 µg/kg	OA	4–12 wk	18
Radwan (2019)	Solid lipid nanoparticles	PZQ	Swiss albino mice	5 mg/kg 62/5 mg/kg	1000 µg/kg	OA	ND	19
Amara (2018)	lipid nanocapsules	PZQ Cabrafac Kolliphor Hs 15	Rats	250 mg/kg 30% (w/w) 25% (w/w)	0.5 mg/kg	OA	7 d	26
El Gendy (2019)	Liposomes	PZQ	Swiss albino mice	500 and 1000 mg/kg	50%	IP	7, 30, and 45 d	33
Frezza (2013)	Liposomes	PZQ	Swiss albino mice	47, 60, 250, and 300 mg/kg	10 µg/mL	OA	30 d	34
Frezza (2015)	Liposomes	PZQ	Swiss albino mice	60 and 100 mg/kg	500 mg/kg	OA	A single dose	35
Wahab (2021)	Ginger-derived Nps	PZQ MFQ	Swiss albino mice	2, 5, 10, 500, and 1000 mg/kg	1000 mg/kg	OA	3 d/wk for 5 consecutive wk	36
EL-Derbawy (2019)	Chitosan Nps	Ginger extract	BALB/c mice	500 mg/kg/d	250 mg/kg	OA	3 d/wk for 5 wk	37
El-Menyawy (2021)	Chitosan Nps	*Nigella sativa* Thymoquinone	Swiss albino mice	200 mg/kg	ND	ND	3 times every wk for 4 wk	38
Elawamy (2019)	Chitosan Nps	*Nigella sativa* PZQ	ND	1140 and 500 mg/kg	ND	OA	2 wk	39
AboSheishaa (2019)	Polylactide-co-glycolide acid Nps	PZQ	Swiss albino mice	500 mg/kg/d 600 mg	98.4%	OA	10 wk	40

IP = intraperitonially; MFQ = mefloquine; ND = not determined; Nps = nanoparticles; OA = orally; PZQ = praziquantel; Ref. = reference number.
* The absence of the required information in the main texts of the article, and despite the participation of a group of authors, the required information could not be extracted.

ticles (thymoquionone extracted/purified from *Nigella sativa*) and reported that infected mice treated with thymoquinone chitosan nanoparticles had a significant reduction in the total worm burden, a large reduction in the number of eggs in the intestinal tissue, and a moderate decrease in the liver tissue. Elawamy et al[39] investigated the role of chitosan nanoparticles in *S mansoni*-infected mice and showed a decrease in the diameter and number of granulomata, thus confirming the role of chitosan nanoparticles in reducing liver damage.

Nanoemulsions

Due to their small size, transparency, long-term physical stability, and the need for less surfactant, nanoemulsions cause more absorption of antimicrobial substances by microorganisms. Nanoemulsion production is used for microencapsulation and releases control of various drugs, dyes, essential oils, and vitamins.[54] Aly et al[20] prepared a chlorine nanoemulsion of *Curcuma longa* extract and evaluated its effect on *S mansoni* cercariae and reported that the formulation showed greater solubility and bioavailability compared with the ethanol extract of the plant.

Polyglycolic lactic acid nanoparticles

Polyglycolic lactic acid (PLGA) is a co-polyester consisting of lactic acid and polyglycolic acid. Its hydrolysis leads to the production of lactic acid and glycolic acid monomers. Among the characteristics of these polymers is biocompatibility. Their safety has been pointed out, so this feature has made this polymer be used for the preparation of vaccines.[55] In a study aimed at investigating the anti-schistosomal effect of curcumin loaded in PLGA nanoparticles, Luz et al[22] showed that PLGA nanoparticles loaded with curcumin (50 and 100 μM) caused the death of all worms and separation between 50% and 100% of *S mansoni* couples at 30 μM concentrations. In addition, PLGA nanoparticles loaded with curcumin also reduced locomotor activity and caused slight changes in the tissue of adult worms.[22] Another study that evaluated the effect of PLGA nanoparticles loaded with praziquantel against mice infected with *S mansoni* reported a significant decrease in the total worm load, a decrease in the number of tissue eggs, an increase in serum interleukin 10 levels, and a decrease in serum aspartate transaminase, alanine transaminase, interleukin 4, and interferon γ levels.[41]

Lipid nanoparticles

Lipid nanoparticles are nanostructures of fats that are used as carrier systems to control drug release and increase the chemical stability of drugs introduced into them.[56] Zoghroban et al[18] used niosomes to increase the activity of praziquantel against *S mansoni* and in vitro results showed that niosomes containing PZQ at a concentration of 0.001 μg/mL increased the mortality rate from 30% to 50%, whereas PZQ solution only caused 10% mortality. In vivo results show that niosome-PZQ compared with PZQ solution significantly reduced the number of adult worms, hepatic and intestinal oocyte deposits, and liver granuloma size and number, with a significant decrease in the expression of vascularized endothelial growth factor.[18] Radwan et al[19] evaluated the anti-schistosomal effect of PZQ solid lipid nanoparticles against *S mansoni* infection in mice and reported that compared with market PZQ, PZQ solid lipid nanoparticles showed superior anti-schistosomal-activity with increased bioavailability in all treated groups at low dose levels, in which the 95% effective dose (ED_{95}) of PZQ solid lipid nanoparticles was 5.29-fold lower than that of market PZQ, with significantly greater reductions in liver and intestinal tissue oocyst loads and almost complete disappearance of immature deposited oocysts.

Similarly, Andrade et al[23] also reported that PZQ solid lipid nanoparticles were much more effective in inducing the death of *S mansoni* than PZQ alone. Investigating nanostructured lipid carriers and the in vitro schistosomiasis activity of PZQ, Kolenyak-Santos et al[24] showed that encapsulating PZQ in nanostructured lipid carriers 2 or nanostructured lipid carriers 4 improved the safety profile of the drug against the *S mansoni* Belo Horizonte (BH) strain, whereas the intestinal transport of free PZQ and PZQ- nanostructured lipid carriers 2 was similar. De Souza et al,[25] by evaluating the effect of PZQ solid lipid nanoparticles against *S mansoni* and reported a significant reduction in the intestinal absorption of PZQ loaded in solid lipid nanoparticles compared with free PZQ, which indicates that the slid lipid nanoparticles medium can act as a reservoir system that reduced the time needed to kill the parasite. Amara et al[26] evaluated the anti-*Schistosoma* activity of PZQ-lipid nanocapsules and reported that PZQ-lipid nanocapsules reduced worm burden and improved liver pathology and proposed that the formulation be administered orally as a lower, tolerable PZQ dose for mass therapy with greater effectiveness. The study by Guimaraes et al[27] had synthesized epiisopiloturine-loaded liposomes with different concentrations of lipids and reported that dipalmitoylphosphatidylcholine: cholesterol with a weight ratio of 9:1 had killed all *S mansoni* parasites after 96 hours of incubation, whereas the 8:2 weight ratio required 120 hours of incubation to achieve 100% mortality.

El Gendy et al[33] evaluated the effect of nanoparticles on the therapeutic synergy of PZQ against *S mansoni* in mice and reported that the group that received liposome-encapsulted PZQ had the most significant reduction in the total number of worms eggs per gram of liver and intestinal tissue, the number and diameter of liver granuloma in comparison with the other groups. In another study, Frezza et al[34] reported the effectiveness of liposomal PZQ against *S mansoni* in BH mice after 45 days of infection, and reported that 300 mg/kg of liposomal PZQ had decreased the total number of worms and egg count by 68.8% and 55.5%, respectively, the number of eggs in the intestine by 79%, and the number of hepatic granulomata by 98.4% compared with the untreated control group. In another study, Frezza et al[35] evaluated the effectiveness of combination therapy comprised of liposomal PZQ and hyperbaric oxygen in the experimental treatment of *S mansoni*, and reported that administering 100 mg/kg liposomal PZQ followed by hyperbaric oxygen showed 48% worm count reduction, 83.3% decrease in eggs per gram of feces, and 100% altered oograms (indicating interruption of oviposition) compared with the control group.

Green synthesis of nanoparticles

Synthesis of nanomaterials by an environmentally friendly process using enzymes, microscopic organisms, and plant extracts has been the focus of researchers for biosafety.[57] Abd El Wahab et al[36] investigated the effect of nanoparticles derived from ginger (*Zingiber officinale*) on *S mansoni*-infected mice and reported a significant 50% reduction in therapeutic doses when combined with PZQ or mefloquine. Eldarbawi et al[37] investigated the potential effect of ginger nanoparticles on mice and reported that the worm load and egg density in the liver decreased significantly in the group that received ginger extract loaded on chitosan nanoparticles, in addition to liver tissue improvement marked by significantly decreased alanine aminotransferase and aspartate aminotransferase levels.

Summary of Nanotechnology against *Schistosomiasis*

The use of synthetic drugs in the treatment of parasitic diseases has led to a decrease in the bioavailability of the drug due to its low solubility in water. Therefore, the use of a new strategy; that is, increasing the bioavailability of the drug, leads to a reduction in the treatment period of the disease as well as the dosage regiment of the drug, and consequently, a reduction in the side effects of the drug in patients. Based on the reviewed research, synthetic

and herbal drugs loaded with nanoparticles show more significant effects against the larval and adult forms of *Schistosoma* than the drug alone, which have been clearly demonstrated in vitro studies. However, due to the lack of extensive studies on the toxicity of nanoparticles, therapeutic doses of nanoparticles should be evaluated in larger preclinical and clinical studies, and in vivo studies should be conducted to further investigate the therapeutic effects of nanoparticles. In addition to identifying the toxic concentrations of nanoparticles, it is necessary to investigate the effects of unloaded nanoparticles as well as those loaded with praziquantel and other parasiticidal drugs in the larval and adult stages. Therefore, the use of synergist compounds provides enhanced absorption and solubility and reduced toxicity of administered drugs. However, limitations such as the toxicity of nanoparticles including AuNPs and AgNPs cannot be ignored although their effectiveness against schistosome larval and adult stages has been established.

Conclusions

The findings of this review show that nanoparticles have desirable effects against diseases caused by *Schistosoma* that can be used synergistically as a more effective treatment option for this zoonotic infection. Thus, we recommend further research and the development of more effective, less harmful drugs for the prevention and treatment of other parasitic infections.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Author contributions

P. Shakib and K. Cheraghipour conceptualized and designed the study; A. K. Khalaf, A. Marzban, M. Zivdaria, and M. Ganjalikhani-Hakemi conducted the searches; P. Shakib, H. Mahmoudvand, analyzed and interpreted the data; H. Mahmoudvand and K. Cheraghipour wrote the main manuscript text; and A. Marzban supervised the study. All authors contributed to helpful discussions and read and approved the final manuscript.

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References

1. Mahmoudvand H, Mohebali M, Sharifi I, Keshavarz H, Hajjaran H, Akhoundi B, Jahanbakhsh S, Zarean M, Javadi A. Epidemiological aspects of visceral leishmaniasis in Baft district, Kerman Province, Southeast of Iran. *Iranian journal of parasitology*. 2011;6(1):1.
2. WHO. Schistosomiasis. 2020. Accessed July 1, 2020, https://www.who.int/news-room/fact-sheets/detail/schistosomiasis.
3. Ngaiza JR, Doenhoff MJ, Jaffe EAJJoID. Schistosoma mansoni egg attachment to cultured human umbilical vein endothelial cells: an in vitro model of an early step of parasite egg excretion. *J Infect Dis*. 1993;168(6):1576–1580.
4. de Moraes J. Antischistosomal natural compounds: present challenges for new drug screens. *Curr Topics Trop Med*. 2012:333–358.
5. Kandeel M, Akhtar T, Zaheer T, Ahmad S, Ashraf U, Omar M. Anti-parasitic applications of nanoparticles: a review. *Pakistan Vet J*. 2022 Apr 1;42(2).
6. Zaheer T, Kandeel M, Abbas RZ, Khan SR, Rehman TU, Aqib AI. Acaricidal potential and ecotoxicity of metallic nano-pesticides used against the major life stages of hyalomma ticks. *Life*. 2022;12(7):977.
7. Zaheer T, Ali MM, Abbas RZ, Atta K, Amjad I, Suleman A, Khalid Z, Aqib AI. Insights into nanopesticides for ticks: the superbugs of livestock. *Oxidative Medicine and Cellular Longevity*. 2022:2022.
8. Keyhani A, Ziaali N, Shakibaie M, Kareshk AT, Shojaee S, Asadi-Shekaari M, Sepahvand M, Mahmoudvand H. Biogenic selenium nanoparticles target chronic toxoplasmosis with minimal cytotoxicity in a mouse model. *Journal of Medical Microbiology*. 2020;69(1):104–110.
9. Albalawi AE, Alanazi AD, Baharvand P, Sepahvand M, Mahmoudvand H. High potency of organic and inorganic nanoparticles to treat cystic echinococcosis: an evidence-based review. *Nanomaterials*. 2020;10(12):2538.
10. Ezzatkhah F, Khalaf AK, Mahmoudvand H. Copper nanoparticles: Biosynthesis, characterization, and protoscolicidal effects alone and combined with albendazole against hydatid cyst protoscoleces. *Biomedicine & Pharmacotherapy*. 2021;136:111257.
11. Zaheer T, Abbas RZ, Perveen N, Sparagano OA, Khan SR, Rehman TU, Raza A, Khan MK, Arshad MI. Application of cypermethrin-coated ZnS and ZnO nanoparticles against rhipicephalus ticks. *Pathogens*. 2023;12(6):807.
12. Elmi T, Gholami S, Fakhar M, Azizi FJJoMUoMS. A review on the use of nanoparticles in the treatment. *J Mazandaran Uni Med Sci*. 2013;23(102):126–133.
13. Moustafa M, Mossalem H, Sarhan R, Abdel-Rahman A, Hassan EJPr. The potential effects of silver and gold nanoparticles as molluscicides and cercaricides on *Schistosoma mansoni*. *Parasitol Res*. 2018;117(12):3867–3880.
14. El-Shorbagy A, Gamil IS, Mohey MA, Nady SJNJ. Antioxidant effects of gold nanoparticles on *Schistosoma mansoni*induced granuloma, in vitro. *Nanomed J*. 2019;6(1):19–26.
15. Lm Khalil, Am Azzam, Ha Mohamed, Ah Nigm, Ha Taha, Mijjotesop Soliman. In vitro effects of iron nanoparticles on *Schistosoma mansoni* adult worms and its intermediate host snail. *Biomphalaria alexandrina*. *Journal of the Egyptian Society of Parasitology*. 2018;48(2):363–368.
16. Cheng Y, Chen X, Song W, Kong Z, Li P, Liu YJP. Contribution of silver ions to the inhibition of infectivity of *Schistosoma japonicum cercariae* caused by silver nanoparticles. *Parasitology*. 2013;140(5):617–625.
17. Abou El-Nour MF, Kenawy SH, El-Bassyouni GT, Hamzawy EMAJAPB. A novel treatment of schistosomiasis: nano-calcium silicate incorporating 5% copper oxide. *Advanced Pharmaceutical Bulletin*. 2021;11(1):68.
18. Zoghroban HS, El-Kowrany SI, Aboul Asaad IA, El Maghraby GM, El-Nouby KA, Abd Elazeem MAJPr. Niosomes for enhanced activity of praziquantel against *Schistosoma mansoni*: in vivo and in vitro evaluation. *Parasitology Research*. 2019;118(1):219–234.
19. Radwan A, El-Lakkany NM, William S, El-Feky GS, Al-Shorbagy MY, Saleh S, et al. A novel praziquantel solid lipid nanoparticle formulation shows enhanced bioavailability and antischistosomal efficacy against murine *S. mansoni*infection. *Parasites & vectors*. 2019;12(1):1–12.
20. Aly N, Husseein A, Emam H, Rashed GJPUJ. Curcuma longa extract nanoemulsion preparation and demonstration of its in vitro activity against *Schistosoma mansoni cercariae*, schistosomules and adult stages. *Parasitologists United Journal*. 2017;10(1-2):44–51.
21. Kishik SM, Mohram AF, Nagib MM, Ali HS, Hendawy FFJJoMPR. In vitro effect and scanning electron microscopic changes of *Nigella sativa* loaded chitosan nanoparticles on *Schistosoma mansoni* adult. *Journal of Medicinal Plants Research*. 2019;13(3):66–72.
22. Luz PP, Magalhães LG, Pereira AC, Cunha WR, Rodrigues V, Andrade e Silva MLJPr. Curcumin-loaded into PLGA nanoparticles. *Parasitology Research*. 2012;110(2):593–598.
23. Andrade LN, Marques C, Barbosa T, Santos R, Chaud MV, da Silva CF, et al. Praziquantel-loaded solid lipid nanoparticles: Production, physicochemical characterization, release profile, cytotoxicity and in vitro activity against *Schistosoma mansoni*. *Journal of Drug Delivery Science and Technology*. 2020;58:101784.
24. Kolenyak-Santos F, Garnero C, De Oliveira RN, De Souza AL, Chorilli M, Allegretti SM, et al. Nanostructured lipid carriers as a strategy to improve the in vitro schistosomiasis activity of praziquantel. *Journal of Nanoscience and Nanotechnology*. 2015;15(1):761–772.
25. de Souza ALR, Andreani T, de Oliveira RN, Kiill CP, dos Santos FK, Allegretti SM, et al. In vitro evaluation of permeation, toxicity and effect of praziquantel-loaded solid lipid nanoparticles against *Schistosoma mansoni* as a strategy to improve efficacy of the schistosomiasis treatment. *International journal of pharmaceutics*. 2014;463(1):31–37.
26. Amara RO, Ramadan AA, El-Moslemany RM, Eissa MM, El-Azzouni MZ, El-Khordagui LKJIjon. Praziquantel–lipid nanocapsules: an oral nanotherapeutic with potential *Schistosoma mansoni* tegumental targeting. *International journal of nanomedicine*. 2018;13:4493.
27. Guimaraes MA, Campelo YD, Veras L, Colhone MC, Lima DF, Ciancaglini P, et al. Nanopharmaceutical approach of epiisopiloturine alkaloid carried in liposome system: preparation and in vitro schistosomicidal activity. *Journal of nanoscience and nanotechnology*. 2014;14(6):4519–4528.
28. Dkhil MA, Bauomy AA, Diab MS. Al-Quraishy SJIjon. Antioxidant and hepatoprotective role of gold nanoparticles against murine hepatic schistosomiasis. *International journal of nanomedicine*. 2015;10:7467.
29. Dkhil MA, Bauomy AA, Diab MS, Wahab R, Delic D, Al-Quraishy SJPr. Impact of gold nanoparticles on brain of mice infected with *Schistosoma mansoni*. *Parasitology Research*. 2015;114(10):3711–3719.
30. Dkhil MA, Khalil MF, Bauomy AA, Diab MS, Al-Qura SJB. sciences e. Efficacy of gold nanoparticles against nephrotoxicity induced by *Schistosoma mansoni* infection in mice. *Biomedical and Environmental Sciences*. 2016;29(11):773–781.
31. Dkhil MA, Khalil MF, Diab MS, Bauomy AA, Santourlidis S, Al-Shaebi EM, et al. Evaluation of nanoselenium and nanogold activities against murine in-

testinal schistosomiasis. *Saudi Journal of Biological Sciences*. 2019;26(7):1468–1472.
32. Younis S, Diab R, Eltarahony M, Arafa FJPUJ. The anti-schistosomal activity of magnetite and zero-valent iron nanoparticles on *Schistosoma mansoni*: An in vivo study. *Parasitologists United Journal*. 2021;14(3):269–277.
33. Labib El Gendy AEM, Mohammed FA, Abdel-Rahman SA, Shalaby TIA, Fathy GM, Mohammad SM, El-Shafey MA, Mohammed NA. Effect of nanoparticles on the therapeutic efficacy of praziquantel against Schistosoma mansoni infection in murine models. *Journal of parasitic diseases: official organ of the Indian Society for Parasitology*. 2019;43(3):416–425.
34. Frezza TF, Gremião MPD, Zanotti-Magalhães EM, Magalhães LA, de Souza ALR, Allegretti SMJAt. Liposomal-praziquantel: efficacy against Schistosoma mansoni in a preclinical assay. *Acta Tropica*. 2013;128(1):70–75.
35. Frezza TF, de Souza ALR, Prado CCR, de Oliveira CNF, Gremião MPD, Giorgio S, et al. Effectiveness of hyperbaric oxygen for experimental treatment of schistosomiasis mansoni using praziquantel-free and encapsulated into liposomes: assay in adult worms and oviposition. *Acta Tropica*. 2015;150:182–189.
36. Abd El Wahab WM, El-Badry AA, Mahmoud SS, El-Badry YA, El-Badry MA, Hamdy DAJPNTD. Ginger (Zingiber Officinale)-derived nanoparticles in *Schistosoma mansoni* infected mice: Hepatoprotective and enhancer of etiological treatment. *PLoS Neglected Tropical Diseases*. 2021;15(5):e0009423.
37. EL-DERBAWY MM, EL KHOLY WAEMS, BAIUOMY IR, SALEM HSJJotESoP. A study of the potential therapeutic effect of ginger (*Zingiber Officinale*) loaded nanoparticles on murine schistosomiasis mansoni. *Journal of the Egyptian Society of Parasitology*. 2019;49(1):123–128.
38. El-Menyawy HM, Metwally KM, Aly IR, Abo Elqasem AA, Youssef AAJTEJoHM. The Therapeutic role of Thymoquinone Bioactive Compound as Target Natural Product from *Nigella sativa* Loaded with Chitosan Nanoparticles on Schistosomiasis. *The Egyptian Journal of Hospital Medicine*. 2021;84(1):1818–1826.
39. Elawamy WE, Mohram AF, Naguib MM, Ali HS, Kishik SM, FFJJoMPR Hendawi. Therapeutic role of chitosan nanoparticles in murine schistosomiasis mansoni. *Journal of Medicinal Plants Research*. 2019;13(18):443–451.
40. AboSheishaa GAJEVMSoPJ. Evaluation of Poly lactide-co-glycolide Acid [PLGA] Nanoparticles Loaded with Praziquantel in treatment of experimental murine Schistosomiasis mansoni. *Egyptian Veterinary Medical Society of Parasitology Journal*. 2019;15(1):149–162.
41. Gouveia MJ, Brindley PJ, Gärtner F, Costa JMCD, Vale N. Drug Repurposing for Schistosomiasis: Combinations of Drugs or Biomolecules. *Pharmaceuticals (Basel)*. 2018;11(1):15.
42. Kakkar VA, Wani SU, Gautam SP, Qadrie ZL. Role of microspheres in novel drug delivery systems: preparation methods and applications. *International Journal of Current Pharmaceutical Research*. 2020;12(3):10–15.
43. Langer RJN. Drug delivery and targeting. *Nature*. 1998;392(6679 Suppl):5–10.
44. Date AA, Joshi MD, Patravale VBJAddr. Parasitic diseases: liposomes and polymeric nanoparticles versus lipid nanoparticles. *Advanced Drug Delivery Reviews*. 2007;59(6):505–521.
45. Chatelain E, Ioset J-RJDd. development, therapy. Drug discovery and development for neglected diseases: the DND i model. Drug Design. *Development and Therapy*. 2011:175–181.
46. Allen TM, Cullis PRJS. Drug delivery systems: entering the mainstream. *Science*. 2004;303(5665):1818–1822.
47. Veerareddy PR, Vobalaboina VJDot. Lipid-based formulations of amphotericin B. *Drugs Today (Barc)*. 2004;40(2):133–146.
48. Miller C, Waller E, Klingemann H, Dignani M, Anaissie E, Cagnoni P, et al. Lipid formulations of amphotericin B preserve and stabilize renal function in HSCT recipients. *Bone Marrow Transplant*. 2004;33(5):543–548.
49. Connor EE, Mwamuka J, Gole A, Murphy CJ, Wyatt MDJS. Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity. *Small*. 2005;1(3):325–327.
50. Ebrahimi K, Shiravand S, Mahmoudvand H. Biosynthesis of copper nanoparticles using aqueous extract of Capparis spinosa fruit and investigation of its antibacterial activity. *Marmara Pharmaceutical Journal*. 2017;21(4):866–871.
51. Albalawi AE, Abdel-Shafy S, Khudair Khalaf A, Alanazi AD, Baharvand P, Ebrahimi K, Mahmoudvand H. Therapeutic potential of green synthesized copper nanoparticles alone or combined with meglumine antimoniate (glucantime®) in cutaneous leishmaniasis. *Nanomaterials*. 2021;11(4):891.
52. Albalawi AE, Khalaf AK, Alyousif MS, Alanazi AD, Baharvand P, Shakibaie M, Mahmoudvand H. Fe3O4@ piroctone olamine magnetic nanoparticles: Synthesize and therapeutic potential in cutaneous leishmaniasis. *Biomedicine & Pharmacotherapy*. 2021;139:111566.
53. AlMohammed HI, Khudair Khalaf A, Albalawi A E, Alanazi AD, Baharvand P, Moghaddam A, Mahmoudvand H. Chitosan-based nanomaterials as valuable sources of anti-leishmanial agents: a systematic review. *Nanomaterials*. 2021;11(3):689.
54. Koul O, Walia S, GJBi Dhaliwal. Essential oils as green pesticides: potential and constraints. *Biopestic. Int*. 2008;4(1):63–84.
55. Xiang SD, Scholzen A, Minigo G, David C, Apostolopoulos V, Mottram PL, et al. Pathogen recognition and development of particulate vaccines: does size matter? *Methods*. 2006;40(1):1–9.
56. Lim S-J, Kim C-KJIjop. Formulation parameters determining the physicochemical characteristics of solid lipid nanoparticles loaded with all-trans retinoic acid. *International Journal of Pharmaceutics*. 2002;243(1-2):135–146.
57. Saadatmand M, Al-Awsi GR, Alanazi AD, Sepahvand A, Shakibaie M, Shojaee S, Mohammadi R, Mahmoudvand H. Green synthesis of zinc nanoparticles using Lavandula angustifolia Vera. Extract by microwave method and its prophylactic effects on Toxoplasma gondii infection. *Saudi Journal of Biological Sciences*. 2021;28(11):6454–6460.