Over the last years, nanotechnology has been introduced as a toxicity for treating giardiasis. It is necessary to find new alternatives with high efficacy and low toxicity as combined therapy with some agents [7]. Consequently, it is monotherapy with some effective drugs such as quinacrine as well as metalloids like MTZ, tinidazole, and nitazoxanide is the preferred treatment for giardiasis [5]. However, according to recent reports, these agents are associated with adverse side effects ranging from nausea to possible genotoxicity. The present investigation was designed to systematically review the in vitro, in vivo, and clinical studies about the efficacy of nanoparticles against giardiasis. The study was carried out based on the 06-PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database. The search was performed in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, without time limitation for publications worldwide related to anti-Giardia effects of all organic and inorganic nanoparticles without date limitation in order to identify all the published articles. The searched words and terms were “Giardiasis”, “Giardia lamblia”, “Giardia intestinalis”, “Giardia duodenalis”, “nanoparticles”, “nanomedicine”, “in vitro”, “in vivo”, and “clinical trial”. Out of 312 papers, 10 papers, including 4 in vitro (40.0%), 5 in vivo (50.0%), and 1 in vitro/in vivo (10.0%) up to 2021 met the inclusion criteria for discussion in this systematic review. The most common type of nanoparticles was metal nanoparticles (5 studies, 50.0%) such as silver, gold, etc., followed by organic nanoparticles such as chitosan nanoparticles (4 studies, 40.0%). The results of this review study showed the high efficacy of a wide range of organic and non-organic NPs against giardiasis, indicating that nanoparticles could be considered as an alternative and complementary resource for treating giardiasis, since they have no significant toxicity. However, more studies are required to elucidate this conclusion, especially in clinical systems.

**Keywords**: Giardia lamblia, Giardia intestinalis, Giardia duodenalis, Nanoparticles, Nanomedicine, In vitro, In vivo, Clinical trial

**INTRODUCTION**

*Giardia lamblia* (syn. *Giardia intestinalis*, *Giardia duodenalis*) is a flagellated protozoan parasite that commonly causes giardiasis or acute and watery diarrhea [1]. The disease is considered as one of the main waterborne and foodborne diarrhea around the world, which infects about 280 million people annually [2]. Humans are generally infected through ingestion contaminated water and food, as well as person-to-person transmission. The most people at risk for giardiasis are children in day-care settings, childcare workers, institutionalized individuals, and travelers in endemic areas via ingestion of contaminated or recreational water, immunodeficiency, cystic fibrosis, and oral-anal sex [2, 3]. Although the disease is mostly asymptomatic, a number of clinical symptoms such as diarrhoea, steatorrhea, nausea, abdominal pain, vomiting, and weight loss are present in the infected children [4].

At present, chemotherapy with some drugs such as nitroimidazoles derivatives is the preferred treatment for giardiasis. However, these agents are associated with adverse side effects ranging from nausea to possible genotoxicity. The present investigation was designed to systematically review the in vitro, in vivo, and clinical studies about the efficacy of nanoparticles against giardiasis. The study was carried out based on the 06-PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database. The search was performed in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, without time limitation for publications worldwide related to anti-Giardia effects of all organic and inorganic nanoparticles without date limitation in order to identify all the published articles. The searched words and terms were “Giardiasis”, “Giardia lamblia”, “Giardia intestinalis”, “Giardia duodenalis”, “nanoparticles”, “nanomedicine”, “in vitro”, “in vivo”, and “clinical trial”. Out of 312 papers, 10 papers, including 4 in vitro (40.0%), 5 in vivo (50.0%), and 1 in vitro/in vivo (10.0%) up to 2021 met the inclusion criteria for discussion in this systematic review. The most common type of nanoparticles was metal nanoparticles (5 studies, 50.0%) such as silver, gold, etc., followed by organic nanoparticles such as chitosan nanoparticles (4 studies, 40.0%). The results of this review study showed the high efficacy of a wide range of organic and non-organic NPs against giardiasis, indicating that nanoparticles could be considered as an alternative and complementary resource for treating giardiasis, since they have no significant toxicity. However, more studies are required to elucidate this conclusion, especially in clinical systems.

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At present, chemotherapy with some drugs such as metronidazole (MTZ), tinidazole, and nitazoxanide is the preferred treatment for giardiasis [5]. However, according to recent reports, these agents are associated with adverse side effects ranging from nausea and metallic taste in the mouth to psychosis, carcinogenesis, and possible genotoxicity [6]. In recent years, an alarming increase in resistance to the conventional agents with nitroimidazoles such as MTZ has been reported in various parts of the world. However, the promising strategies for this drug treatment failure are monotherapy with some effective drugs such as quinacrine as well as combined therapy with some agents [7]. Consequently, it is necessary to find new alternatives with high efficacy and low toxicity for treating giardiasis.

Over the last years, nanotechnology has been introduced as a relatively new field of science and technology that deals with nanometer-sized material for medical purposes [8]. This innovative technology has been used in various fields of sciences through a combined approach. Nowadays, an increasing number of applications and products containing nanomaterials have been considered [8].

Use of nanotechnology for medical purposes has been named nanomedicine and is described as applying nanomaterials for diagnosis, monitoring, control, prevention, and treatment of diseases [9]. Although a wide range of in vitro, in vivo, and clinical studies have reported the antimicrobial effects of some inorganic nanoparticles (such as metal and metal oxide) and organic nanoparticles (peptide- and polymer-based nanoparticles such as cationic polymers, chitosan, etc.) [10, 11]; but there is no documented report on the drug resistance of microbes, especially parasites, to nanoparticles. However, broad adoption of nanoparticles for giardiasis is at present hampered by uncertain findings of the investigation, not always sufficiently powered. Our study aimed to systematically review the existing literature (in vitro and in vivo) in the field of nanomedicine for giardiasis treatment.

**MATERIALS AND METHODS**

**Search strategy**

The current study was carried out using 06-PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database [12]. The search was performed in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar without time limitation for publications worldwide related to anti-Giardia effects of organic and inorganic nanoparticles without date limitation in order to identify all the published articles (in vitro, in vivo, and clinical studies). Studies in any language were entered into the search step if they had an English abstract. The words and terms were used as a syntax with specific tags of each database. The searched words and terms were: “Giardiasis”, “Giardia lamblia”, “Giardia intestinalis”, “Giardia duodenalis”, “Nanoparticles”, “Nanomedicine”, “in vitro”, and “in vivo” (fig 1.).
Quality assessment and article selection

First, the studies were imported to EndNote X9 software (Thomson Reuters, New York, NY, USA) and duplicate studies were deleted. Afterwards, three independent authors examined the title and abstract of the studies and the relevant studies were included for further analysis. The same authors carefully read the studies and the eligible studies with adequate inclusion criteria were selected.

Exclusion criteria

The studies with inadequate information, abstracts submitted in congresses without full texts, failure to match methods with results, and the incorrect interpretation of the results was excluded from the current study.

Inclusion criteria

Inclusion criteria of this study were the articles evaluating the effects of nanoparticles on giardiasis, emphasizing the design of various forms of nanoparticles containing drugs and other pharmaceutical formulations against giardiasis.

Data extraction

Three independent authors extracted information from the selected articles and, if needed, the differences were resolved by the corresponding author. The extracted data included nanoparticle type, in combination or loaded with other drugs, type of study, parasite form, condition, concentration, time of use and obtained findings, and references.

RESULTS AND DISCUSSION

Out of 312 papers, 10 papers including 4 in vitro (40.0%), 5 in vivo (50.0%), and 1 in vitro/in vivo (10.0%) up to 2021 met the inclusion criteria for discussion in this systematic review with the data extracted, as presented in Table 1. The most common type of nanoparticles was metal nanoparticles (5 studies, 50.0%) such as silver, gold, etc., followed by organic nanoparticles such as chitosan nanoparticles (4 studies, 40.0%). In this study, we investigated the effect of different nanoparticles on Giardia parasite and giardiasis disease, put the obtained information in a table, and categorized it. According to the nanoparticles mentioned in the table, we classified them into two categories of organic and inorganic nanoparticles and explained their effect on Giardia.

Organic nanoparticles

Chitosan

Chitosan (poly-(b-1/4)-2-amino-2-deoxy-D-glucopyranos) and its derivatives due to having some exceptional properties such as minimum toxicity, biocompatibility, and biodegradability, have been broadly used as an immunomodulatory, anticancer, anti-nociceptive, antioxidant, anti-inflammatory, and antimicrobial agent [23-26]. Today’s, it has been proven that chitosan-based biomedical drugs such as nanoparticles, hydrogels, coatings, suspensions, powders, membranes, films, etc. are able to affect the pharmaceutical and biomedical effects of these agents [27, 28]. In recent years, several studies have reported the antimicrobial effects of chitosan and its derivatives against a broad spectrum of pathogenic viruses, bacteria, fungi, as well as helminthic and protozoan parasites [29-31]. Yarahmadi et al. (2016) demonstrated the considerable chitosan nanoparticles (CNPs) synthesized by Penicillium viridicatum and P. aurantiogriseum at the doses of 50, 100, 200, and 400 µg/ml on Giardia cysts, whereas CNPs at the dose of 400 µg/ml and after 180 min exposure killed 100% Giardia cysts [13].

In addition, Chabra et al. (2019) reported that chitosan and nano-chitosan at the concentrations of 100, 200, and 400 µg/ml significantly reduced the G. lamblia trophozoite, ranging from 89 to 100, after 3 h exposure in vitro. The findings also showed that the oral administration of chitosan and nano-chitosan at the dose of 100 µg/kg significantly reduced the mean percentage of excrated cysts up to 10 times in the infected BALB/C mice G. lamblia [14].

In the study conducted by Elmi et al. (2020), CNPs synthesized by Penicillium fungi at the dose of 50 µg/ml after 180 min exposure eliminated 31.3% of G. lamblia cysts [19]. Said et al. (2012) also showed that synthesized CNPs prepared by ionic crosslinking of chitosan solution at the dose of 5 ppm for 8 d significantly reduced the number of Giardia cysts in the stool and trophozoites in intestinal sections of rats with giardiasis [16].

Recently, El-Gendy et al. (2021) demonstrated that oral administration of CNPs at the dose of 50µghamster/day for 7 consecutive days alone and especially in combination with MTZ in Syrian hamsters infected with G. lamblia significantly reduced the cysts and trophozoites counts by 63.64-94.69%. They also reported significant healing of intestinal mucosa in the infected hamsters after treatment with MTZ+CsNPs [15].
### Table 1: A list of studies on effects of nanoparticles against giardiasis

| Nanoparticle                  | Preparation method                  | Condition | Parasite form | Dose                  | Time                  | Outcome                                                                                           | Ref      |
|-------------------------------|-------------------------------------|-----------|---------------|-----------------------|-----------------------|---------------------------------------------------------------------------------------------------|----------|
| Chitosan nanoparticles        | -                                   | In vitro  | Cysts         | 50, 100, 200 and 400 µg/ml | 10, 30, 60 and 180 min | CNPs synthesized by *Penicillium viridicatum* and *P. aurantiogriseum* at the doses of 50, 100, 200, and 400 µg/ml on Giardia cysts; whereas CNPs at the dose of 400 µg/ml and after 180 min exposure killed 100% Giardia cysts | [13]     |
| Chitosan and nanochitosan (CNPs) | Ionic gelation method               | In vitro (BALB/c mice) | Cysts and trophozoites | 100, 200, 400 µg/ml | 30, 60, 180 min | Chitosan and nano-chitosan at the concentrations of 100, 200, and 400 µg/ml significantly reduced the G. lamblia trophozoite ranging from 89 to 100 after 3 h exposure in vitro; they findings also showed that the oral administration of chitosan and nano-chitosan at the dose of 100 µg/kg significantly reduced the mean percentage of excrated cysts up to 10 times in infected BALB/C mice *G. lamblia*. | [14]     |
| Chitosan nanoparticles        | Ionic gelation technique            | In vivo (Syrian hamsters) | Cysts and trophozoites | 50 µg/ha | 7 d | CNPs, especially in combination with metronidazole (MTZ) significantly reduced the cysts and trophozoites counts from 63.64±9.69%. Histopathological tests demonstrated significant healing of intestinal mucosa after treatment with MTZ+CNPs. | [15]     |
| Chitosan nanoparticles        | Ionic cross-linking and spontaneous emulsification method | In vivo (Rats) | Cysts | 450 mg | 8 d | CNPs significantly reduced the cysts and trophozoites counts up to 68.2% and 79.6% in rats infected with *G. lamblia*, respectively. | [16]     |
| Gold Nanoparticles (AuNps)    | -                                   | In vitro  | Cysts | 0.05, 0.1, 0.3 µg/ml | 5, 15, 30, 60 and 180 min | In this study, AuNps were used in vitro on Giardia cysts isolated from stools. The results showed that the lethal effect of these nanoparticles with a concentration of 0.3 mg/ml in 5 min is 62% and in 180 min it reaches 96%. For this reason, it can be said that AuNps at a concentration of 0.3 mg/ml have a lethal effect similar to metronidazole. | [17]     |
| Gold nanoparticles and Citrullus colocynthis L. nanoparticles (nAu+nCc) Nano-chitosan | Green synthesis method               | In vivo (Swiss Albino Mice) | - | 20 µg | 8 d | In this study, the effect of combination therapy of nAu+nCc in the animal model was investigated. Experiments were performed on 50 Swiss Albino Mice infected with Giardia cysts using a nasogastric tube, and the results showed that combination therapy eliminated 93.2% of Giardia trophozoites. | [18]     |
| Selenium and Copper Oxide Nanoparticles (CuO NPs and Se NPs) | Purchased                            | In vitro  | Cysts | 0.15, 0.3, and 0.6 µg/ml | 10, 15, 30, 60 and 180 min | In this study, we investigated the effect of CuO NPs and metronidazole. The results showed that CuO NPs at a concentration of 0.6 mg/ml and Se NPs at a concentration of 0.3 mg/ml had a similar effect to metronidazole on cysts. | [19]     |
| Silver nanoparticles (Ag NPs) | Purchased                            | In vivo (BALB/c mice) | - | 100 µg/g | 24, 48, 72 h | In this study, the ability of Ag NPs as a combination therapy with metronidazole and alone was investigated. Experiments showed that in 72 h of combined treatment of Ag NPs and metronidazole has an effect of 83.30% and the use of nanoparticles alone has the same effect. But in 24 h the effect of Ag NPs is 66.60%, which is greater than the effect of metronidazole. | [20]     |
| Silver nanoparticles          | Ionic cross-linking and spontaneous emulsification method and green synthesis | In vivo (Rats) | Cysts | 100 ppm | 8 d | CNPs significantly reduced the *Giardia* cysts and trophozoites counts up to 72.7% and 81.1% in rats infected with *G. lamblia*. | [21]     |
| Zinc oxide nanoparticles (ZnO-NPs) | Purchased                            | In vivo (BALB/c mice) | - | 10 mg/kg | 7 d | In this study, we investigated the effect of ZnO-NPs and metronidazole on *Giardia intestinalis*-infected mice. Studies have shown that ZnO-NPs in the mentioned dose can kill 93.7% of cysts and also metronidazole in 500 mg/kg dose can kill 99.2% of cysts while combined treatment with both The drug has a 100% result. | [22]     |
Curcumin is a natural polyphenol compound derived from turmeric root with various pharmacological properties [32]. It has many therapeutic properties such as anti-inflammatory, anti-cancer, antioxidant, and antimicrobial activity. Considering the anti-parasitic activities of curcumin, reviews showed the potent efficacy of curcumin against some pathogenic species of Plasmodium, Leishmania, Trypanosoma, Schistosoma, and more commonly against other cosmopolitan parasites such as nematodes, Babesia, Giardia, and Coccidia [33]. In the study conducted by of Said et al. (2012), the results showed that curcumin nanoparticles synthesized by ionic crosslinking of curcumin solution at the dose of 450 mg for 8 d significantly reduced the number of Giardia cysts (54.6%) in the stool and trophozoites (51.7%) in intestinal sections of the rats with giardiasis [16].

Citrullus colocynthis nanoparticles

Citrullus colocynthis is an herbaceous plant from the Cucurbitaceae family that contains pectin and alkaloids such as Elytreyne A and Elytreyisin B with various pharmacological properties such as anti-diabetic, anti-cancer, anti-inflammatory, anti-oxidant, and antimicrobial properties [34, 35]. Recently, Al-Ardi et al. (2020) demonstrated that the oral administration of C. colocynthis nanoparticles at the dose of 20 μg for 8 d significantly reduced the mean number of G. lamblia trophozoites by 93.2% in Swiss Albino mice with giardiasis [18].

Inorganic nanoparticles

Gold

Gold is one of the noble elements which is broadly used in various medical fields such as biochemistry, microbiology, immunology, and cytology. Gold nanoparticles have many applications in medicine, including biosensors, chemical assays, genomics, photothermal therapy of cancer cell; they also have other effects such as analgesic, anti-angiogenesis, anti-HIV virus, and anti-parasites, including Plasmodium spp., Giardia spp., Leishmania spp., et al. [17, 18, 36, 3].

In the study conducted by Bavard et al. (2014), gold NPs were used at the dose of 0.05, 0.1, 0.3 mg/ml for 5, 15, 30, 60, and 180 min against G. lamblia cysts. Their results showed that gold NPs at the concentration of 0.3 mg/ml in 180 min were able to kill 96% of cysts [17]. In addition, the study conducted by Al-Ardi (2020) demonstrated that oral administration of gold nanoparticles at the dose of 20 μg for 8 d significantly reduced the mean number of G. lamblia trophozoites by 93.2% in Swiss Albino mice with giardiasis [18].

Silver

Silver nanoparticles are one of the unique materials that have special physical and chemical properties such as resistance to oxidation and high thermal conductivity and are used in various fields such as industry, health, and medicine. Various pharmacological properties, including anti-inflammatory, anti-cancer, antioxidant, anti-angiogenic, and antimicrobial activities, have been attributed to silver nanoparticles. Regarding the antimicrobial effects of silver nanoparticles, previous reviews have represented the antimicrobial effects of these nanoparticles on a wide range of microbial pathogens such as Escherichia coli, Candida species, and HIV virus and parasites such as Leishmania spp. and G. lamblia [21, 38].

In the study conducted by Idan and Ardalan (2020) on BALB/c mice with giardiasis, it has been proven that the use of silver nanoparticles at the dose of 100 μg/g reduced 83.30 and 66.6% of Giardia cysts after 72 and 24 h, respectively. In another study conducted by Said et al. (2012), it was proven that silver nanoparticles obtained by green synthesis at the dose of 50 μg for 8 d can reduce 72.7% of G. lamblia cysts in the mice with giardiasis [16].

Selenium

Selenium is a semi-solid metal that is classified as a trace element and was discovered as a byproduct of sulfuric acid synthesis. Many studies have studied the properties of this element, including anti-diabetic, anti-cancer, antioxidant, and anti-inflammatory [39]. In addition, this element has various antimicrobial activities such as anti-viral, antibacterial, as well as anti-parasites effects against as Entamoeba histolytica and Giardia spp. [20, 39]. In the study conducted by Malekifarid and Tavassoli (2020), the results showed that selenium nanoparticles at various concentrations, particularly at the dose of 0.6 mg/ml after 10, 15, 30, 60, and 180 min incubation, killed 100% of G. deudenalis cysts in vitro [20].

Copper oxide

Copper oxide nanoparticles are the semiconductor compound with many applications such as in industrial catalyst, gas sensors, electronic materials, biomedicines, and environmental remediation [40, 41]. In addition, it has been used as antimicrobial agents against some microbial pathogens such as Klebsiella pneumoniae, Pseudomonas aeruginosa, Entamoeba histolytica, and Cryptosporidium parvum, G. deudenalis [20, 42]. Considering the anti-parasitic effects of copper oxide nanoparticles, Malekifarid and Tavassoli (2020) found these nanoparticles at various concentrations, particularly at the dose of 0.6 mg/ml after 180 min incubation, killed 97% of G. deudenalis cysts in vitro [20].

Zinc oxide

Zinc is one of the trace elements with different compounds which have various pharmacological properties [43]. Zinc oxide (ZnO) nanoparticles are a favorable compound for use in biomedical field, particularly given their anticancer and antimicrobial activities [44]. Considering antimicrobial effects of ZnO NPs, previous studies have demonstrated these nanoparticles have potent antimicrobial properties against some of the pathogenic microbial strains such as Streptococcus pneumoniae, Bacillus subtilis, Eimeria papillata, Leishmanina spp., and Giardia spp. [45]. In the study by Reham et al. (2019), it was found that the use of ZnO nanoparticles at the dose of 10 mg/kg and for the period of 7 d alone could eliminate 93.7% of Giardia cysts in mice; if combined with metronidazole, it had 100% lethality [22].

CONCLUSION

The results of this review showed the high efficacy of a wide range of organic and non-organic NPs against giardiasis, indicating that nanoparticles could be considered as an alternative and complementary resource for treating giardiasis since they had no significant toxicity. In addition, we found no resistance formation against nanoparticles for giardiasis. However, more studies are required to elucidate this conclusion, especially in clinical systems.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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