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Review

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# A review on Most Nanoparticles Applied Against Parasitic Infections

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**ABSTRACT**

Nanoparticles (NPs) are particles with the size range approximately from 1 to 100 nanometers that are made in different shapes. Nanotechnology is an emerging technology that expected to open some new opportunities in order to destroy and control of microorganisms using of materials and systems at the scale of the atom. Parasitic diseases affect millions of people worldwide, especially in developing countries and are involved with many limitations in treatment methods. Recently, some of parasites demonstrated drug resistance, which increased the need for new effective and safer agents against parasitic infection or improvement of the drugs. There is no vaccine available for the prevention of many parasitic infections, and hence chemotherapy is the current mainstay of control. NPs have received most attention as antiparasitic drugs in few decades since current antiparasitic drugs have some side effects and their efficacy is not fully proved yet. However, little attention has been dealt to the use of nanoparticle derivatives as an antiparasitic drug. In this paper, developments in the use of NPs as anti-parasitic drugs are reviewed. Some researches indicated that gold NPs, oxidized metals, silver, chitosan and etc. have growth inhibitors or cytotoxic effect on diverse parasites, including *Giardia*, *Leishmania*, *Plasmodium*, *Toxoplasma* and helminthes including, *Echinococcus multilocularis, Trichinella spiralis* and *Fasciola hepatica*. NPs can be used separately or in combination with current drugs against parasites. Therefore, NPs are suggested as more effective and less side effects drugs for the prevention and controlling of the parasites.

**Key words: Nanoparticles, Antiparasitic, Parasitic infections.**



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## 1. INTRODUCTION

Parasites and parasitic diseases affect millions of people worldwide and are involved with many limitations in treatment and control methods (1, 2). Despite the rapid and remarkable developments in health care and health advancement in most regions of the world, intestinal parasitic infections remain as one of the most main health problems affecting the economy, especially in developing countries. According to the world health organization (WHO), around two-thirds of the world's population, which is the equivalent to 3.5 billion people, is infected with a diversity of parasites, and annually, 450 million of these people show clinical symptoms (3). Moreover, about 16 million of the whole deaths each year that happen in developing countries are associated with parasitic infections (4). Poor hygiene and environmental conditions are known to be related to the propagation of these diseases (5).

Intestinal parasites can cause malnutrition, damage, nutrient absorption and gastrointestinal disruption, such as nausea, abdominal pain, dysentery, vomiting, iron deficiency, anemia, avitaminosis, loss of immune defense, and decreased physical growth (6). In a few cases, the symptoms of intestinal infections can be very serious and cause problems such as intestinal obstruction, abdominal pain, cholecystitis, appendicitis, myocarditis, genital infection, and extra-intestinal abscess. Numerous studies have estimated that there is a 2.4% - 67.5% prevalence of intestinal parasites in people with different ages (7). Particularly, the direct and easy transmission of some intestinal parasites from infected to non-infected persons is highly prevalent in communities with high society densities (4). Few studies have been performed on NPs against parasitic infections in Iran. However, there is no study to gather this information. In this review, the recently published papers about NPs against parasitic infections

were collected and reviewed. Nanotechnology makes use of materials and systems at atomic scales (1–100 nm), where their properties differ significantly from those at a larger scale. The use of nanotechnology and nanomaterials in medical research is growing rapidly (8-10). Recently, nanotechnology progresses in microbiology have gained importance in the field of chemotherapy. Although NPs have a long history, but, they are associated with modern science (11). Nanomaterials have received more attention as antiparasitic agents (12, 13). The size of NPs is alike to that of most biological structures and molecules; therefore, nanomaterials can be helpful for both *in vivo* and *in vitro* parasitical studies and applications. The main reason is the expectation that NPs will be used in the treatment of different diseases in the future (14, 15). Parasitic diseases are of extensive worldwide significance as around 30% of the world's population experiences parasitic infections. Moreover, parasitic infections force substantial burden of mortality and morbidity round the universe and more especially in the developing countries (5, 16). Although a significant progress has been made in following the cell biology, pharmacogenomics, etiology and pathophysiology of most of parasitic infections in the last years, the scenario in the area of therapeutics is discouraging. Despite major research efforts, to date, there exists no functional vaccine against any of the major parasitic infections mostly due to the fact that most of the parasitic diseases do not obtain a strong immune response. Hence, an antiparasitic chemotherapy residue is the only weapon for fighting parasitic infections (17, 18). However, most of the currently existing anti-parasitic agents have been instituted over 50 years ago. Although these agents are effectual, but, most of them are not close to the modern concept of ‘drug’ in terms of tolerability, therapeutic regimen, the period of treatment, specificity and patient acceptance (19). The contradictory, the rate of new drug progress and new drug finding in the segment of parasitic diseases is very low compared to the other fields; it seems that this challenge is mainly due to the lack of economic reasons in this area. The fact that out of 1223 new drugs were produced to market between 1975 and 1996, only 1% of them were established for the treatment of tropical diseases such as malaria, leishmaniasis and trypanosomiasis . The carelessness towards parasitic diseases remained till 2000, as only around 0.1% of global investment in health research was related to drug discovery for anti-parasitic agents (20). Hence, the best strategy that could be appropriated to tackle the aforementioned disaster associated with parasitic diseases is to develop novel delivery systems in order to upgrade the efficacy, specificity, tolerability and therapeutic index of existing antiparasitic agents (20). Considering the side effects of antiparasitic drugs and the severity of parasitic diseases, it is necessary to investigate on new antiparasitic compounds with high activity, low toxicity that are cheaper and have more efficacies. Therefore, in this review we prepared a list of all nanomaterials, which were used against parasites.

## 2. PARASITIC INFECTIONS IN WORLD

Recently, parasitic infections have become a worldwide health problem due to appear and resistant strains of protozoa (21) such as *Plasmodium*, *Leishmania*, and *Trypanosoma*. Malaria is a hematoprotozoan parasitic infection transmitted by certain species of anopheline mosquitoes. Four species of plasmodium commonly infect humans, but one of them (*Plasmodium falciparum*), is the main cause of morbidity and mortality related to this infection. Case management has relied largely on antimalarials (mainly chloroquine, and sulfadoxinepyrimethamine [SP]), which are inexpensive and widely available, also are eliminated slowly from the body. Antipyretics and antimalarials are two most commonly used medications in tropical areas of the world. In many parts of the tropics, the majority of the population has detectable concentrations of chloroquine in the blood. The extensive deployment of these antimalarial drugs, in the past fifty years, has provided a tremendous selection pressure on human malaria parasites to evolve mechanisms of resistance. The emergence of resistance, particularly in *P. falciparum*, has been a major contributor to the global resurgence of malaria in the last three decades. Predicting the emergence and spread of resistance to current antimalarials and newly introduced compounds is necessary for planning malaria control and instituting strategies that might delay the emergence of resistance (22). Leishmaniasis is a disease complex caused by 17 different species of protozoan parasites. There are an estimated 12 million humans infected, with an incidence of 0.5 million cases of the visceral form of this disease and 1.5 to 2.0 million cases of the cutaneous form of the disease. Leishmaniasis has a worldwide distribution with important foci of infection in Central and South America, southern Europe, North and East Africa, the Middle East, and the Indian subcontinent. The current situation for the chemotherapy of leishmaniasis is more promising than it has been for several decades with both new drugs and new formulations of old drugs either recently approved or in clinical trial. These include an amphotericin B liposome, oral miltefosine, paromomycin, pentavalent antimonial and oral sitamaquine (previously WR6026). In addition, there is increasing awareness that drug treatment can be complicated by variation in the sensitivity of *Leishmania* species to drugs, variation in pharmacokinetics, and variation in drug-host immune response interaction (23). Trypanosomes are unicellular parasitic protozoa belonging to the *Trypanosoma* Genus of the Trypanosomatidae class. Human African trypanosomiasis or 'sleeping sickness' is a neglected tropical disease caused by the parasite Trypanosoma brucei. These extracellular parasites nimbly escape the humoral and cellular immune responses by periodic changes to the composition of a major surface antigen, the variant surface glycoprotein (VSG). The process of antigenic variation is both necessary for parasite

survival and is considered to sustain long-term infections. Treatment failures with melarsoprol started to appear in the 1990s and their incidence has risen sharply in many foci (24). Consequently, this has culminated into elongated treatment, higher health spending, mortality risk, and low life expectancy (25). The global disclosure of multidrug-resistant protozoa has made traditional treatment of infectious diseases difficult. Therefore, the finding of alternative new group of antiprotozoal (26) agents that can treat resistant strains is more important. Despite the attempts made in the treatment of parasitic infections especially giardiasis, toxoplasmosis, trypanosomiasis, malaria, leishmaniasis, schistosomiasis, Japanese encephalitis, and filariasis are increased particularly in tropical and developing countries continuously (27-29).

## 3. PARASITIC INFECTIONS IN IRAN

Iran, a country with an area of 1, 648, 000 $km^2$ in the Middle East, with various climates, hurts from a wide group of infectious diseases; Due to geographical location, climate, the extent of the area, cultural and biological characteristics, there is a suitable environment for the activity of various parasites in Iran (30, 31). The reasons for the high occurrence of parasites in some parts of this country are related to the results of specific climate of the regions, local traditions, and the use of human and animal fertilizers in agriculture (32). Other elements are including high population density, lack of purified water, lack of perfect disposal of waste, poor hygienic standards (social and individual), lack of well cooked food especially meat and lack of sufficient washing of vegetables that may lead to high prevalence of intestinal parasites (33, 34). The prevalence of parasitic infections in different parts of Iran is very disparate and depends on geographical location, climatic conditions, population density, disposal of garbage and human sewage and a variety of cultural, economic, social, and etc. Parasitic infection is generally considered as one of the main health issues in all the provinces of this country (35-38). Undoubtedly, health programs such as educational strategies and avoiding the use of human fertilizers in agriculture, may help to decrease the level of infection against these parasites (39). Studies in various parts of Iran show that there is an infection of intestinal parasites between studied groups. For this reason, several studies have been conducted on the prevalence of parasitic infections in different parts of the country that was 2 - 61% (40-42). According to pervious researches, the prevalence level of parasitic diseases was as follows: Kermanshah (59.13%) (43), Mazandaran (21%) (44), Kashan (46.9%) (45), and Ardabil (27.7%) (36), while it was 13.7% and 8.4% for Semnan (46) and Ghaemshahr (47) that revealed the high prevalence of these infections from the statistical viewpoint. Hamadan province has been reported as the highest (83.86%) prevalence rate of intestinal parasitic infections (IPIs) (48). Studies carried out in Hamadan province during the last couple of decades indicated that the level of sanitation and societal was low. Furthermore, people were using sewage as agriculture fertilizer, which was responsible for the transmission of parasites (cysts and eggs of parasites) through contaminated vegetables. Besides, in rural regions, animal feces were used as a fuel during the winter, which was source for the transmission of parasites. The lowest prevalence discovered in Tehran province (the capital of Iran) (12.91%). The low rate of IPIs in Tehran province seems to be because of proceeding with public health measures than in other provinces, especially in drinking water purification, as well as screening for control and treatment programs against parasitic diseases (49).

## 4. PROBLEMS ASSOCIATED WITH PARASITIC INFECTIONS TREATMENT

The problems related to parasitic infections are including drug toxicity, ineffectiveness, and developments of resistance to ordinary anti-parasitic drugs. Furthermore, treatment prices are high and there is limiting on the grant of drugs in low income countries (50). The development of new resistant strains of parasites of the current antiparasites drug has become a serious problem in public health; therefore, there is a strong incentive to develop new antiparasites agents. As a result of the restriction in antiparasitic drugs, newer approaches such as nano-biotechnology have shown remarkable improvement in the treatment of parasitic infections (26). This is based on the unique properties of NPs including AgNPs, AuNPs, chitosan, selenium oxide, and other metallic oxide NPs that have shown excellent inhibitory effects against parasitic infections including insect larvae (28-31). Moreover, poor rate of discovery in the anti-parasitic segment was seen in last few decades and has necessitated effective management of existing drugs by modulating their delivery. The NPs may not have the recognizable antimicrobial activity compared to the mass formulations of the metal oxide or solutions of metal salts. But, the stability and slow release of metal ions from NPs are the main characteristics during usage of them (51). The antimicrobial efficiency of NPs depends on the particle size (52). The smallest sized NPs showed the powerful antimicrobial effect (53). NPs are recommended for killing parasites (cytotoxic and inhibitory effects), because they act as more effective and less harmful drugs and also useful vaccines for the prevention and controlling of the parasites (27). A summary of the types of NPs susceptibility to parasites are shown in Table 1. The Table 2 described the antiprotozoa of NPs against diverse genera of protozoa and Table 3 described the antihelminth of NPs against diverse genera of helminth.

## 5. HISTORY OF NPs BIRTH

Although the production of nanosized particles had occurred in several ways in ancient times and hundreds years ago, nanomedicine as a modern science was first confirmed in the nineties of the last century only.

Nanomedicine is a clue science of the 21st century (54). NPs are synthetic and complex molecules with specified chemical structures that were synthesized firstly in the early of 1980s. These nanomaterials are nanosized polymers and are assembled from branch units. The surface of a synthetic nanomaterial has numerous chain ends, which can be tailored to complete specific chemical functions. This property could also be helpful for catalytic uses. Nanomaterials show some remarkably improved chemical and physical properties compared to traditional polymers (54). New functionalities and properties of matter are observed in a wide range of applications. Nanotechnology provides important new tools expected to have most impact on many areas in medical sciences. Polymer coated functioned metal NPs have recently appeared as an active and novel field of advanced researches. For example, silver is an important accessible metal and its NPs are superior to other nanosized metal particles for their antimicrobial effects. However, their stability is a serious problem with polar terminal groups like hydroxyl groups or amine are usually used for their stabilization (55). Three-dimensional nanomaterials may be useful for drug delivery and first have been applied in *in vitro* diagnostics for heart muscle damage, ophthalmic surgery, microbicide activity against HIV-1, cancer treatment, targeting tumor cells, gene therapy and few last decades parasitology (56).

## 6. METHODS AND SELECTION OF ARTICLES

Selected papers extracted from MEDLINE (PubMed), Scopus, Science Direct, Web of Science (ISI) and Google Scholar using the terms: NPs, antiparasitic, parasitic infections, nanomedicine, and nanodrug. To collect precise information, a comprehensive search was carried out on all published and unpublished resources, including full texts, abstracts, and parasitology congress summaries.

**Table 1. Summary of the types of NPs susceptibility to parasites**

| Type of nanoparticle | Types organisms inhibited | Type of study | Main outcome | Reference |
|---|---|---|---|---|
| Silver, chitosan, and curcumin NPs | *Giardia lamblia* | *In vivo* | The highest fighter effect was achieved by combining the three nanoforms. The parasite was found to be eradicated from stool and intestine. | (29) |
| Silver (Ag-NPs) | *Leishmania tropica* | *In vitro* | Ag-NPs demonstrated significant antileishmanial effects by inhibiting the proliferation and metabolic activity of promastigotes. | (50) |
| Copper(II) nanohybrid solids, $LCu(CH_3COO)_2$ and $LCuCl_2$ | *Plasmodium falciparum* | *In vitro* | The two compounds showed significant antimalarial activities against the parasites. | (57) |
| Gold NPs (GNPs) | *Leishmania major* | *In vitro* | The presence of GNPs during MW irradiation was more lethal for promastigotes and amastigotes in comparison to MW alone. | (58) |
| CuO (cooper oxide) and Ag (silver) | *E. histolytica*, *C. parvum* | *In vitro* | The treatment based on CuO NPs and Ag NPs showed a very important role in overcoming amoebiasis and cryptosporidiosis. | (59) |
| Chitosan–tripolyphosphate conjugated chloroquine | *Plasmodium berghei* | *In vivo* | The maximum effect of nanoconjugated chloroquine (Nch) was found at 250 mg $kg^{-1}$ bw concentration during 15 days of treatment. | (60) |
| Amphotericin B incorporated into poly(D, L -lactide-co-glycolide) | *Leishmania* | *In vitro* | Anti-leishmanial activity was observed with drug-free NPs. | (61) |
| Curcuminoids-loaded lipid | *Plasmodium berghei* | *In vivo* | The in vivo pharmacodynamic activity revealed 2-fold increase in antimalarial activity of curcuminoids entrapped in lipid NPs. | (62) |
| $TiO_2$ and $Ag_2O$ | *Leishmania* | *In vitro* | $TiO_2$ and $Ag_2O$ NPs showed significant antibacterial activity. | (63) |
| Silver NPs | *Plasmodium falciparum* | *In vitro* | The AgNPs showed antiplasmodial activity against *P. falciparum*. | (64) |
| Gold NPs | *Giardia lamblia* | *In vitro* | Gold NPs at a concentration of 0.3 mg $ml^{-1}$ can be used as an effective combination for killing Giardia cysts | (65) |
| Silver NPs | *Leishmania major* | *In vitro* | AgNPs alone did not kill *Leishmania major* Promastigotes completely. | (66) |
| Silver NPs | *Leishmania tropica* | *In vitro* | The IC50 for nanosilver solutions was high significantly (14.9 µg $mL^{-1}$). | (67) |
| Selenium and Silver | *Leishmania major* | *In vivo* | Unlike selenium NPs, AgNPs showed anti-*Leishmanial* effect *in vivo*. | (68) |
| Chitosan and silver | *Toxoplasma gondii* | *In vivo* | Results showed that used AgNPs singly or combined with chitosan have promising anti-toxoplasma potentials. | (69) |
| Silver | *Leishmania major* | *In vitro* | The combined using of both direct current electricity and AgNPs has a significant synergistic effect on promastigote mortality. | (66) |
| Nano-Nitazoxanide (NTZ) | *Cryptosporidium parvum* | *In vivo* | Nano nitazoxanide was effective on parasites at day 6. | (70) |
| Chitosan | *Leishmania infantum* | *In vitro* | Chitosan had not antileishmanial activity against *Leishmania infantum LIPA 155/10*. | (71) |
| Albendazole–chitosan microspheres | *Echinococcus multilocularis* | *In vivo* | Metacestode grown was highly suppressed during treatment with ABZ-CS-MPs. | (72) |
| Chitosan | Trichinella spiralis | *In vitro* | Although chitosan stimulated the lymphocyte response, the effect of treatment was not protective. | (73) |
| Silver NPs | *Fasciola* | *In vitro and In vivo* | The percentage of non-hatching eggs treated with the Triclabendazole drug was 69.67%, while this percentage increased to 89.67% in combination with drug and AgNPs. | (74) |

**Table 2. Antiprotozoa of NPs against diverse genera of protozoa**

| Antiprotozoal activates of NPs | |
|---|---|
| ***Giardia lamblia*** | ***Ref*** |
| Silver | (29) |
| Chitosan | (29) |
| Curcumin | (29) |
| Gold | (65) |
| ***E. histolytica*** | |
| Copper | (59) |
| Silver | (59) |
| ***Leishmania*** | |
| Gold | (58) |
| Poly(D, L -lactide-co-glycolide) | (61) |
| Titanium | (63) |
| Silver | (50, 66, 67) |
| Selenium | (66, 68) |
| Chitosan | (69) |
| ***Cryptosporidium parvum*** | |
| Nano-Nitazoxanide | (70) |
| Silver | (59) |
| ***Toxoplasma gondii*** | |
| Chitosan | (68) |
| Silver | (68) |
| ***Plasmodium*** | |
| Copper | (57) |
| Chitosan | (60) |
| Curcumin | (63) |
| Silver | (64) |

**Table 3. Antihelminth of NPs against diverse genera of helminth**

| Antihelminth activates of NPs | Ref |
|---|---|
| Echinococcus multilocularis albendazole– chitosan | (72) |
| Trichinella spiralis Chitosan | (73) |
| Fasciola -Silver | (74) |

A list of some applications of nanomaterials to biology or medicine is given below:

- Fluorescent biological labels (75-77)
- Drug and gene delivery (78, 79)
- Bio detection of pathogens (80)
- Detection of proteins (81)
- Probing of DNA structure (82)
- Tissue engineering (83, 84)
- Tumor destruction via heating (hyperthermia) (85)
- Separation and purification of biological molecules and cells (86)
- MRI contrast enhancement (87)
- Phagokinetic studies (88)

Metal NPs have gained considerable interest in various areas of science and technology. Numerous microorganisms have been exploited to synthesize metal NPs such as bacteria, fungi and yeast. Bacteria are preferred for the production of NPs over eukaryotic microorganisms due to ease of handling, easy genetic manipulation and the fact that studies on one bacterium can be easily extrapolated to others. Cell-free culture supernatants of five psychrophilic bacteria including *Pseudomonas antarctica*, *Pseudomonas proteolytica*, *Pseudomonas meridiana*, *Arthrobacter kerguelensis* and *Arthrobacter gangotriensis* and two mesophilic bacteria including *Bacillus indicus* and *Bacillus cecembensis* have been used to synthesize silver NPs (89). The NPs were biosynthesed and their efficacy were investigated against other microorganisms including, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* (90), *Staphylococcus aureus* (91), *Salmonella typhimurium* (92), *Candida albicans* (93), yeast (94), *Aspergillus flavus* (94) and etc.

## 7. CONCLUSION

Now, some of the parasites demonstrated drug resistance, which increased the need for new effective agents against parasitic infection or improvement of the present drugs and there is no vaccine available for the prevention of many parasitic infections. Therefore, nanomedicine has the potential to provide applicability for old and toxic drugs by improving their biodistribution, modify bioavailability and decreasing toxicity.

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## AUTHORS CONTRIBUTION

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## CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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