Silver Nanoparticles and Their Anti-Parasitic Significance: A Review

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ABSTRACT

The three main types of parasites found throughout the world are helminths, ectoparasites, and protozoa. Nowadays, chemotherapeutic medications and agents are used to treat these parasites; however, abuse of these medications and pesticides has led to the development of drug and pesticide resistance over time. In this case, silver nanoparticles are shown to be a significant advance in the control and treatment of parasitic illnesses. The science of Nano medicine for parasite control has advanced tremendously in the past ten years and promising outcomes have been observed while treating several kinds of parasite diseases with silver nanoparticles. They function in several ways, including as breaking down the parasite membrane, interfering with the creation of proteins, disrupting DNA (deoxyribonucleic acid), and generating free radicals. These substances also work well against intracellular parasites. One hopes that this field of study will shape the direction of contemporary medication development. The function of silver nanoparticles as possible medications for the treatment of parasitic illnesses is outlined in this review.

Keywords: Silver nanoparticles; Anti-parasitic ;parasite control

INTRODUCTION

Silver nanoparticles, or AgNPs for short, are particles made of silver atoms that are typically between one and one hundred nanometers in size (**1**). Due to its use in a range of fields, comprising biotechnology, medicine ,electronics, coatings, cosmetics and packaging, silver nanoparticles (AgNPs) are attracting a much attention (**2**). Because of their great microbial toxicity, silver ions have a variety of roles in medicine (**3**). Additionally, AgNPs have been used as antiviral, bactericidal, fungicidal, anticancer, and antiprotozoal agents, according to several research that have shown them to be pharmaceutically sound and non-toxic to people (**4**).The majority of the time, silver is involved in its nitrate form, producing a powerful antibacterial effect; however, utilizing AgNPs significantly enhances the surface area exposed to different kinds of microorganisms (**5**). Using plants to make silver nanoparticles have gained relevance in past ten years ,because it is quick, does not harm environment, doesn't employ pathogens, and only requires one step .Plant extracts contain a variety of biomolecules with high therapeutic value and benign environmental effects, such as vitamins, terpinoids, alkaloids, tannins, phenols, enzymes, and polysaccharides (**6**). It is believed that the reduction in silver ions is brought on by the polyol and water-soluble heterocyclic components, whilst the flavonone and terpenoid components from leaf broth are able to stabilize the synthesis of AgNPs. Additionally, it is well known that the activation of surface plasmon vibrations causes AgNPs made from plant extract to appear brownish in aqueous solutions (**7**). The different plant parts are utilized in order to produce AgNPs: stem, root, fruit, seed, callus, peel, leaves, bark, and flower, There are two types of extracts that can be used to produce AgNPs from the aforementioned plant parts: aqueous and alcoholic. Aqueous use plant extracts are typically preferred because they have benefits like eliminating the need for organic solvents and requiring less capital investment and energy (**8**). Also, biological methods can be employed to create AgNPs without the need of any harmful, or expensive chemicals (**9,10**). Due to its low toxic, environmental compatibility, decreased manufacturing costs, scalability, and nanoparticle stabilization when compared to chemical synthesis, the employment of microorganisms in the synthesis of nanoparticles (NPs) appears as an attractive and environmentally

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acceptable method for producing NPs (**11**). Both bacteria and fungi has the ability to naturally reduce or oxidize metal ions into metallic or oxide nanoparticles (**12**). Bacteria of both the gram-positive and gram-negative types have been employed to create AgNPs (**13**).

AgNPs' advantages in the conrol of parasites have recently been found by scientists, although the NPs are formed in irregular sizes, research indicates promising results in the treatment of parasitic illnesses. AgNPs have an anti-parasitic effect, as seen below:

AgNPs for Vector Control

Numerous parasitic diseases are spread by mosquitoes. Parasitologists have used a variety of chemical and biological techniques to control them (**14**) . However, because mosquitoes have developed resistance and there is a great deal of genetic variety, these methods are no longer viable (**15**). Parasitologists have documented great outcomes in mosquito control with bio-synthesized AgNPs over the past ten years. In one investigation, AgNPs made from the soil fungus *Beauveria bassiana* were employed to combat *Culex pipiens* larvae and pupae, The positive point of using silver nanoparticles as larvicides is that they can overcome toxicity risks to humans and other non-target creatures, environmental contamination, and insecticide resistance brought on by excessive pesticide usage (**16**).

Another study examined the effectiveness of AgNPs made from *Euphorbia hirta* leaf extract against the malarial vector *Aedes stephensi*, These NPs demonstrated outstanding larvicidal efficacy (**17**). With the aid of the entomopathogenic fungi *Isaria fumosorosea* (Ifr), the effectiveness of silver-generated larvicide against the main vector mosquitoes *Culex quinquefasciatus* and *Aedes aegypti* has been examined. As a result, Ifr-AgNPs would be widely employed as an effective mosquito larvacide (**18**). In a different study, the larvicidal activity of synthetic AgNPs using an aqueous extract from *Eclipta prostrata* was examined against fourth-instar larvae of the filariasis vector *Culex quinquefasciatus* and the malaria vector *Anopheles subpictus Grassi*, the study's findings suggest that silver nanoparticles have the potential to be a new method for controlling vectors (**19**). Together, these investigations demonstrate that these bio and green synthesized AgNPs environmentally friendly can be employed as mosquito treatment and control alternatives.

Nanoparticles of Silver for Protozoa Control

Leishmania

Leishmaniasis is a significant vector-borne metazoonosis that is brought on by the obligate intramural protozoae of the diverse and complex genus *Leishmania* (**20**). A set of infections known as leishmaniasis affect both humans and animals; some are anthroponotic, while others are zoonotic(**21**). These illnesses spread Leishmania species, which are extensively found in tropical and subtropical locations worldwide, through the bites of female phlebotomine sand flies (**22**).Silver nanoparticles have been employed as a substitute therapeutic agent to combat different types of leishmaniasis resistance. *Leishmania spp.* are relatively sensitive to ROS, which is the primary source of silver nanoparticles' antibacterial action (**23**). Similar to antimony in its mode of action, silver is inhibitor of trypanothione/trypanothione reductase (**24, 25**). Several articles have discussed how chemically and biologically synthesized silver nanoparticles can be used to treat leishmaniasis by significantly reducing the rate of promastigote proliferation and amastigote metabolic activity (**26**).Bioactive phytochemicals like flavonoids and alkaloids and other plant compounds give biogenic metal nanoparticles (Metal NPs manufactured by use different plants) their extra Antimicrobial activity **(27**), As a result, these NPs may hold promise as anti-leishmanial medications such as (**26,28 ,29, 30,31 ,32, 33**).Also there are many studies on the biosynthesis of AgNPs from other microorganisms (fungi) and their anti-leishmanial effect, the results showed a significant gradual decrease in the parasite's ability to survive outside cells in vitro and also inside infected macrophage cells with concentrations and time. such as (**34,35,36**).Additionally, (**37**) showed that visible light, IR ray, and UV increased the anti-leishmanial activity of many inorganic NPs. UV light suppressed *L. tropica* promastigotes' growth and metabolic activity, a leishmanicidal effect of silver NPS (**23**).

Plasmodium

Plasmodium is an intracellular parasite that causes malaria in afflicted people is spread by the Anopheles mosquito (**15**). Through the use of pesticides to control the vector, some progress has been made in the fight

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against malaria, but the situation has gotten worse because the parasite is developing chemical resistance (**38)**. The most dangerous human parasite, *Plasmodium falciparum*, has in particular defied all anti-Malaria medications (**39**). By directly attacking parasites, nano-biotechnology can end malaria by offering effective treatment options. In one study, The plant *Andrographis paniculata's* leaves were employed as a capping and reducing agent to successfully create silver nanoparticles from $AgNO_3$ in a green method. These nanoparticles were tested against *Plasmodium falciparum* for their antiplasmodial activity. According to this study, parasites exposed to silver nanoparticles from *A. paniculata* at a dose of 25 µg/ml showed the lowest parasitemia inhibition rate (20%), whereas parasites exposed to 100 µg/ml showed the highest inhibition (83%). (**40**). According to earlier bioactivity investigations, *A. paniculata* significantly reduced *Plasmodium berghei's* ability to multiply (Misra *et al*. 1992). Another study found that the anti-plasmodial activity of AgNPs made from plant extract of *Euphorbia hirta* and evaluated in a dose-dependent manner against *P. falciparum*, the synthesized AgNPs were significantly more effective at inhibiting plasmodial growth than *E. hirta* leaf extract in it′s aqueous solution and crude methanol (**41**).

Trypanosoma

Trypanosoma brucei gambiense or *T. brucei rhodesiense* are the culprits behind the neglected tropical disease known as African trypanosomiasis (**42**). The infectious agent is spread by the tsetse fly. American Trypanosomiasis, or Chagas disease, is caused by the protozoan *Trypanosoma cruzi*. The Americas are afflicted by this illness, which includes the USA and Canada, as well as Europe, and two drugs are being used to treat it at the moment: nifurtimox and benznidazole (BNZ). These medications possess little efficacy and considerable toxicity when the condition is persistent, which encourages to look for more effective treatment options. A bioavailable polymer made from corn cobs called xylan is one of them, In a study conducted in 2020, Silver nanoparticles were synthesized of xylan from Corn Cobs and Their cytotoxicity was evaluated against *Trypanosoma cruzi* activity in vitro , Where the results showed that NX (100 µg/mL) 95% of the parasites were made to die through necrosis (**43**).Similar to this, arginine kinase was targeted in a different study using Silver and gold nanoparticles. Since arginine kinase (phosphotransferase) is crucial for *Trypanosoma* energy metabolism and is essential for the survival of trypanosomes under stressful circumstances, its inhibition may result in a successful treatment for trypanosomiasis (**44**).

Toxoplasma gondii

intracellular protozoan parasite that causes toxoplasmosis, it is an animal source parasie of great importance in veterinary and public health (**45**). Although the infection is often asymptomatic, it can be lethal in persons with weakened immune systems (**46**). The parasite's ability to enter and reproduce inside of all nucleated cells, as well as its ability to travel to different organs within the host's body and cause infection, are characteristics that point to its capacity to cross a variety of life barriers, including the placenta (**47**). It causes the fetus to have a variety of congenital defects during pregnancy, which might result in miscarriage (**48**). There are several different regimes that able to utilized for its management and handling. However, as a result of inadequate immunization and medication resistance, the bulk of these remedies are ineffective (**49**). In one investigation, silver nanoparticles manufactured from plant extracts from *Phoenix dactylifera* and *Ziziphus spina-christi* were tested for their anti-Toxoplasma properties in experimental animals as an alternative to the use of the standard medicine sulfadiazine, According to this study, treatment with AgNPs was more effective than standard treatments. These findings point to innovative therapeutic strategies using AgNPs green synthesized, which might be used to treat the increasing liver damage brought on by toxoplasmosis (**50**). In another study, AgNPs and Chitosan were mixed, and the *Toxoplasma gondii* showed altered tachyzoite morphology, arrest of movement, and parasite burden reduction (**51**).

Echinococcus granulosus

The hydatid cyst of the parasite *Echinococcus granulosus* causes the extremely common parasitic condition known as cystic echinococcosis (CE). Additionally, it is referred to as a zoonotic illness and a neglected tropical sickness and in endemic regions including the Mediterranean countries, North and East Africa, Western and Central Asia, China, South America, and Australia, public health is still at risk (**52**).The disease is initially induced by the larval stage of the cestode, metacestodes, affecting different parts and organs of the human body such as liver and lungs leading to, sometimes, a fatal Echinococcosis (**53**). The treatment for the

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CE involves surgery which is recommended in cases with few cysts. The puncture aspiration injection respiration (PAIR) and chemotherapy are recommended in cases with multiple cysts in different body organs (**54, 55, 56**). In one study, silver nanoparticles were tested for their ability to treat infections with *E. granulosus* in balb/c mice , The results of this study showed that AgNPs that have been manufactured using extract *Zizyphus spina-christi* leaves anti-hydatic effects ,and compared to the untreated infected mice, the treated-infected animals displayed a shift in liver appearance of hydatid cysts changes from hyaline to milky hazy, as a result, these AgNPs are recommended as a therapy for echinococcal cysts ; However, more research should be done to assess its effectiveness when administered via alternative ways. Despite the encouraging outcomes, to elucidate the possible mechanism of action of AgNPs against hydatid cysts, more research is necessary (**57**).

Entamoeba histolytica

Entamoeba histolytica is a protozoan parasite that causes amoebiasis, resulting in millions of instances of liver abscess and dysentery annually , The infectious stage of *E. histolytica* is called a cyst and by ingesting food or water contaminated with cysts, the parasite enters the human body (**58**).WHO records 40–50 million amoebiasis infections and up to 100,000 fatalities worldwide each year(**59**). The current treatment for amoebiasis is metronidazole however, resistance has been documented, the medication has unpleasant side effects, and it is not very effective against asymptomatic cyst carriers in amoebiasis patients (**60**).Metronidazole is ineffective in treating cysts of the parasite, but it kills the trophozoites by altering the amoeba's protoplasmic organelles(**61,62**).Consequently, new medications will be required that have different targets and mechanisms of action than metronidazole. In a previous study, the antiparasitic activities of silver nanoparticles were evaluated on the mortality and viability of *E. histolytica* trophozoite and changes in parasite morphology were monitored microscopically, when compared to the control, the results show that the numbers of trophozoite stages decreased significantly ($P \leq 0.05$) following treatment with both AgNPs and metronidazole. Similarly, a notable variation ($P \leq 0.05$) was noted between the AgNPs cohorts and the metronidazole medication; however, there was no significant variation between the various AgNPs concentrations, According to the authors, there have been anti-parasitic effects against drug resistance *Entamoeba* when AgNPs and drugs are combined. (**63**). While Obaid, (**64**) studied how cystic stage of *Entamoeba histolytica* are affected by silver nanoparticles that produced by utilizing *Bacillus cereus* and *Chromobacterium violaceum* bacteria , It was found that silver particles significantly inhibited the cysts and the effect of nanoparticles which produced by *C. violaceum* was less than that of nanoparticles that produced by *B. cereus*, based on results of study, It was advised that use AgNPs in treatment or decontamination procedures.

Giardia

Giardia lambila, also known as *Giardia duodenalis* and *Giardia intestinalis*, is the protozoan that causes giardiasis, an infection regarded as a serious intestinal parasite disease that causes diarrhea all over the world (**65**). Typically, eating contaminated food or water with infectious cysts is how this parasites spread (**66**). The commercially available medication for treating giardiasis is metronidazole (MTZ), but due to adverse effects and development of parasite resistance, alternative therapeutic approaches must be explored (**67**). Obaid, (**64**) studied the effects of silver nanoparticles (AgNPs), which were produced using the microorganisms *Bacillus cereus* and *Chromobacterium violaceum*, on some cystic stages of intestinal protozoan parasites , It was found that all of the study parasites' cysts were considerably suppressed by the biosynthesized silver nanoparticles, particularly those of *G. lamblia*, a noteworthy impact of 23.9% , also he mentioned the impact of nanoparticles produced by *B. cereus* was more than that of nanoparticles produced by *C. violaceum*, based on the results of study, it was advised that use silver nanoparticles in treatment or decontamination procedures. While, In vivo anti-Giardial impact of AgNPs alone or in conjunction with MTZ against MTZ was evaluated in a study conducted by Idan and colleagues (**68**) , there results showed that when compared to the control group (not treated), the mice treated with AgNPs and MTZ exhibited a statistically significant decrease in the mean number of parasites in their stool. However, compared to MTZ, AgNPs and combination therapy exhibit decreased anti-Giardial activity after 24 hours, in the next hours from treatment, mice given MTZ showed no longer had parasites in their intestines, according to the results of a light microscope examination; however, mice given AgNPs showed that trophozoites were still present in their intestines, as did mice receiving both

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treatments together (AgNPs and MTZ). Also numerous histological alterations were noted in the liver and intestine, including degeneration, PMN infiltration, and cell death through necrosis and apoptosis. Similarly, (**69**) assessed the toxicity and efficacy of silver nanoparticles loaded with metronidazole in the treatment of acute giardiasis in mice, the findings indicated that a single therapy using silver nanoparticles had the greatest effect, with the highest percentages of reduced *Giardia lamblia* cysts in infected mice treated with a combination of silver nanoparticles and metronidazole. Additionally, the best way to lessen the harmful effects of this treatment on the kidney and liver in tissue homogenate was to combine Ag NPs with metronidazole. Significantly higher GSH and lower MDA levels were observed.

Cryptosporidium

A protozoan called *Cryptosporidium* causes acute gastroenteritis in a wide range of vertebrates, including humans, one of the virulence factors that helps spread and cause cryptosporidiosis is gp900 (**70**). In the immunocompromised hosts, Long-lasting infections brought on by the parasite can be lethal (**71**). The CDC and the National Institute of Health classified *Cryptosporidium* as a category B disease due to its potential to contaminate water (**72**), whose oocysts contribute significantly to the water treatment procedures' resistance (**73**). Due to a number of factors, the removing and rendering inactive *C. parvum* from water systems continues to be a very challenging issue in both industrialized and developing nations. First, the most widely used water disinfectants are not very effective against water-borne *Cryptosporidium* oocysts (**74,75,76**) such as hypochlorous acid, UV light, and chloramine (**77**), in addition to their ability to stay active for more than a year in aquatic environments. Second, its tiny infectious dosages make it extremely difficult to provide and maintain safe drinking water. (**78**). In the end, hazardous disinfection byproducts are produced by the disinfection techniques now employed in drinking water treatment, which involve chlorination to control microbiological infections (**79,80**). Thus, current studies have endeavored to discover a novel substitute for the elimination and deactivation of *Cryptosporidium oocysts*. The quantity and viability of *C. parvum* isolated from various tap water samples were examined in a study to investigate the impact of silver nanoparticles (AgNPs), the results showed that the Cysts which exposed to silver nanoparticles at different doses of 0.05, 0.1 and 1 ppm for several contact times (30 min to 4 h) showed a significant reduction in the number and viability of cysts in a dose-dependent manner but the time of contact between AgNPs and *C. parvum* was not a major influencing factor for successful application of AgNPs in the nano-water treatment (**73**). Saad *et al*. (**81**) made sliver NPs and after characterizing and verifying them, the antiparasitic activity of these particles against *Cryptosporidium parvum* was tested, where a notable decline in the viability of cysts at probability level($p \leq 0.05$) was noted and Moreover, LC50-3h of AgNPs recorded 0.34 and 0.54 mg/l respectively. Accordingly, these NPs could be suggested as a new Nano form agent for safe and effective treatment of *C. parvum* parasites.

CONCLUSION

Over the past years, parasitic diseases have been treated and controlled with various treatments and methods, but they have become ineffective, especially chemical treatments, which have led to the overuse of contraindications to their use, including side effects in some patients, in addition to the emergence of strains resistant to these drugs. Therefore, it has become necessary to find alternative treatments for these drugs. Due to the distinctive properties of nanoparticles, represented by their non-toxicity and also the lack of resistance of parasites to them, scientists and researchers have studied the possibility of using these nanoparticles, especially silver ones, in the treatment and control of parasites that are pathogenic to living organisms in general. Studies have proven, as shown in the research mentioned above, that nanoparticles prepared through various methods kill the parasite or stop its growth. There has been a tremendous development in the medical and pharmaceutical industries in recent decades regarding the use of tools and nanoparticles to treat and control parasitic diseases, and it is likely that nanoparticles will show great progress in the field of treating and combating parasites.

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