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REVIEW

Biogenically Synthesized Nanoparticles as Emerging Therapeutics for Leishmaniasis: A Review of Recent Advances and Potential Promises

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Abstract: The genus *Leishmania* consists of over 20 different species causing a spectrum of disease symptoms categorized as cutaneous, mucocutaneous, or visceral leishmaniasis. No vaccine is available in humans, and current drug regimens suffer from low efficacy, associated toxicities, and are increasingly becoming side-lined by drug resistance. Because of this, the development of new therapeutics is desperately needed. Recent years, the therapeutic use of nanotechnology has increased exponentially. The biogenic synthesis of these nanostructures creates particles similar to those chemically synthesized but are often more environmentally safe, cost-effective, and allow for increased control over size, shape, and composition. Here, we provided a review of the current publications using the biogenic synthesis of nanoparticles particularly focusing on those used in the treatment of leishmaniasis published from January 1, 2010, to April 30, 2025. The documents were analyzed by applying criteria such as nanometal type, source of green synthesis (plant or microorganism), nanoparticles size, *Leishmania* species (sp.) and stage (promastigote or amastigote), cytotoxicity, and in vivo studies. A total of 50 articles were analyzed. Among biogenic nanoparticles (NPs), silver NPs were the most extensively studied (15 studies), while *Leishmania tropica* (*L. tropica*) was the most frequently investigated sp. Plant material was the most sources starting material for green synthesis. Produced NPs' size varied between 2 and 500 nm. Regarding the effect of NPs on *Leishmania* parasites, most were done in vitro, and only 5 in vivo studies (10%) reported. Moreover, leishmanicidal effects were reported via oxidative stress, mainly through production of reactive oxygen species and nitrogen radical species. In general, green synthesis produced NPs with smaller sizes, larger surface area to volume ratios, and better internalization by the cells. Thus, green synthesis of NPs could be a promising option to resolve current treatment safety and efficacy concerns while also maintaining accessibility in low- and middle-income countries.

Keywords: *Leishmania*, biogenic nanotechnology, antimony NPs, silver NPs, plant derived NPs, Green synthetized NPs

Introduction

Leishmaniasis is a vector-borne disease that is endemic in about 98 countries throughout the world[1,2] and categorized as a neglected tropical diseases (NTDs). It is caused by the intracellular protozoan parasites of the genus *Leishmania* (L).[2,3] There are three main clinical manifestations; Cutaneous (CL), Mucocutaneus (MCL) and Visceral leishmaniasis (VL), the last of which is, respectively, more prevalent, severe, and fatal.[3,4] Approximately, 350 million people are at risk with about 1.6 million new cases annually.[5]

Leishmania parasites alternate between two morphological forms in their life cycle; an intracellular form (amastigotes) found in mammalian hosts and a motile flagellated form (promastigotes) in the sand fly midgut (Figure 1).[6] Once the promastigotes enter the mammal via the bloodmeal of an infected sand fly, they are either engulfed by neutrophils and macrophages in the skin (causing CL) or migrate to other host organs known to be rich in macrophage populations such as bone marrow, spleen, and liver (causing VL).[6]

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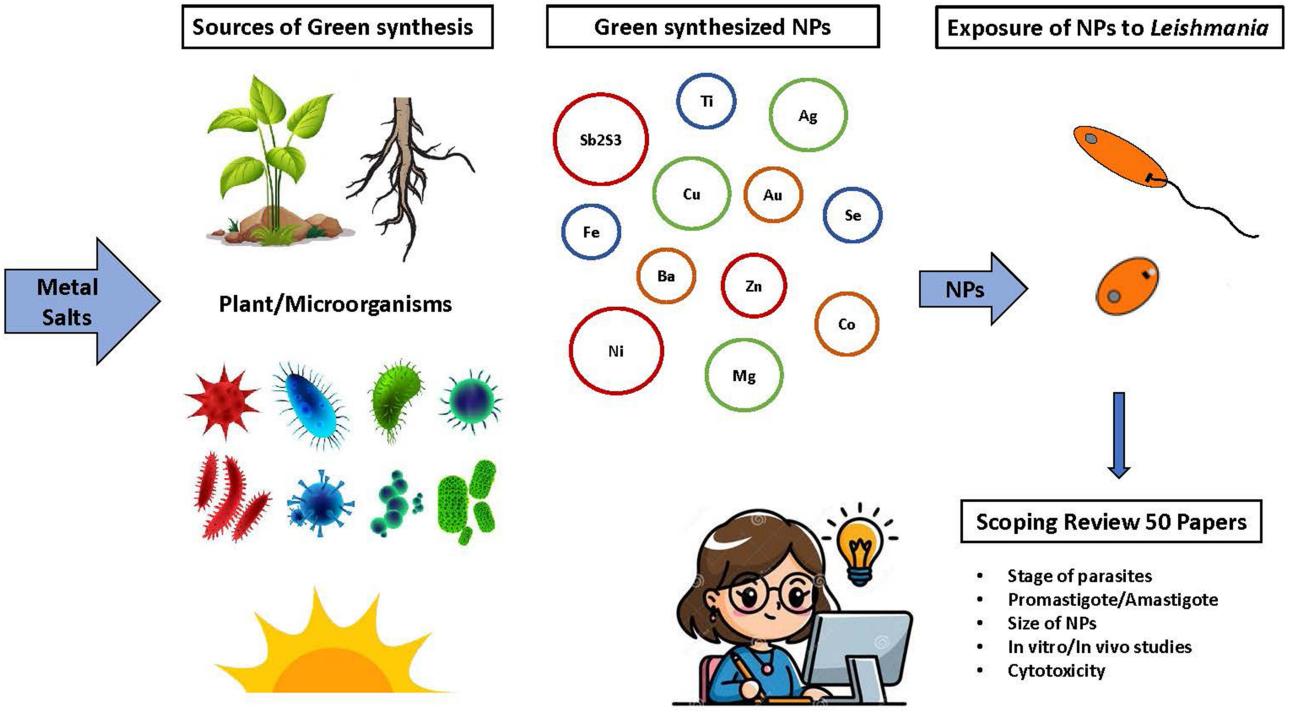
Graphical Abstract



During this migration, parasites are able to evade the host immune system by utilizing various virulence factors including entering phagocytic cells, modifying host cell signaling pathways,[7] altering immune cell activation via cytokine and chemokine profiles,[8] and regulating the lysosomal trafficking protein in sites of infection.[9,10]

To date, there is no vaccine against the human form of leishmaniasis[11] and available treatments are based on chemotherapies (Table 1) which have off target toxicities, show decreasing efficiency, are difficult to administer, and are expensive.[12] Further, drug resistant strains are increasing and immunocompromising coinfections like HIV have been reported to confound leishmaniasis.[13] Due to the limitations of current treatments and the lack of an effective vaccine against the disease, new therapeutic options are needed. Recent research emphasizes the urgent need for safer and more targeted therapies across infectious and immune-mediated diseases, especially where conventional treatments are limited by toxicity and resistance profiles.[14]

Nanotechnology and Green Synthesis of Nanoparticles in Treatment of Leishmaniasis

In the recent years, developments in nanotechnology using nanoparticles have begun to address the limitations of existing therapeutic approaches in the treatment of leishmaniasis. Nanoparticles often refer to particles with a diameter of 10–1000 nm. In leishmaniasis, macrophages engulf the nanoparticles as foreign bodies, which results in a specific delivery system against *Leishmania* parasites residing inside macrophages.[26,27] This targeted delivery allows for reduced dosing which could lower the potential toxicity of the administered drug.[28]

NPs have special features like high ratio of surface to volume, nanometers size, and deep tissue penetration which effect enhanced permeability and retention.[29] The stability of NPs depends on their ability to make metastable aqueous suspensions or aerosols in environmental liquids. This affects the movement of released NP. The colloidal stability (rate of dissolution) is controlled by size and surface capping.[30] Capping agents include surfactants, small ligands, polymers, dendrimers, cyclodextrins, and polysaccharides. They are essentially amphiphilic molecules with a polar head group and

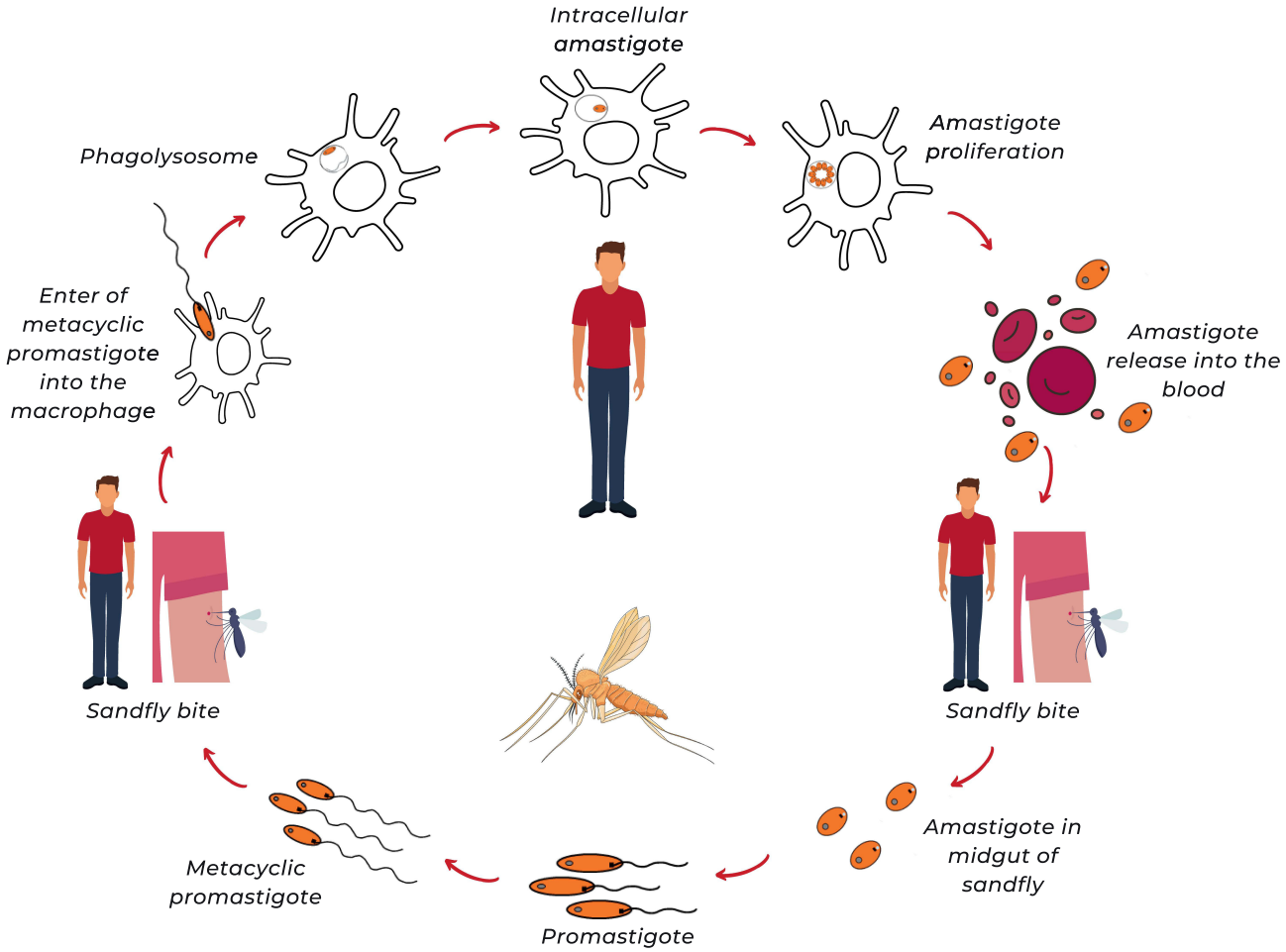


Figure 1 Life cycle of *Leishmania* parasites.

a non-polar hydrocarbon tail, with the polar head interacting with the metal of the metallic NP.[31] Surface capping also prevents further growth and agglomeration[30] while also providing electrostatic, steric, or electrosteric interactions to encourage dispersion of NP in suspensions.[32,33]

Table 1 Current Drugs Used in the Treatment of VL, CL, and MCL with Their Side Effects and Disadvantages

Drug	Type	Side Effect/Disadvantage	References
Meglumine antimoniate/sodium stibogluconate	Pentavalent antimonial	Myalgias, arthralgias, pancreatitis, leukopenia, and cardiotoxicity	[15,16]
Amphotericin B	Polyene antifungal	Highly toxic, nephrotoxicity, hemolysis, liver damage, nausea, fever	[17]
Liposomal Amphotericin B (AmBisome[a])	Liposomal formulation of Amphotericin B	Improved therapeutic but extremely expensive	[18,19]
Miltefosine	Phospholipid antimicrobial effect	Gastrointestinal distress, hemolysis, nephrotoxicity	[20,21]
Pentamidine	Antiprotozoal	Necrotic injection site lesions, nephrotoxicity, and hypoglycemia	[22,23]
Paromomycin	Aminoglycoside antibiotic	Kidney injury, hearing impairment, vestibular toxicity	[24,25]

Note: [a]Liposomal Amphotericin B.

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Metals like silver, gold, antimony, iron, zinc, selenium, and others can form metal/metal oxide nanoparticles (NP).[30] Metallic nanoparticles, especially silver and antimony-based ones, have shown promise since the early 2010s in vitro and in vivo, but have limited clinical translation to date. Several studies showed that metal oxide nanoparticles show significant promise as chemotherapeutics since the current evidence indicates that they promote the generation of intracellular reactive oxygen species (ROS) which leads to parasite DNA damage, protein and lipid oxidation, and ultimately death via apoptosis.[34,35]

Metal NP synthesis typically occurs in one of two ways: Physical/chemical or biological. Physical/chemical synthesis is known to be costly and produce toxic by-products. These processes can include radiation, precipitations, depositions, explosions, and impregnation.[36] Therefore, biological processes, ie green synthesis, are now of interest because they utilize biological starting materials, such as bacteria, fungi, algae, and plant extracts (leaves, roots, flowers, and fruits) which are more readily available components. Additionally, they are less-toxic, eco-friendly, and use a universally recognized solvent like water.[37] These benefits address the concerns of both cost and toxicity.[30,36,38]

Each biological material provides unique characteristics that affect the formation of metallic NP. Bacteria provide distinct shapes and sizes and can be easily manipulated whereas fungi possess enzymes, proteins, and reducing agents on their cell surfaces that allow production of larger amounts of metallic NP, making them a superior biological material. Yeast offers 1500 identified species that could be further utilized in green synthesis. Plants, however, are especially unique due to the phytochemicals found in their extracts.[30] These extracts can also include a broad range of additional therapeutic constituents such as triterpenoids, phenolic compounds, coumarins, alkaloids, tannins, quinines, glycosides, steroids, anthocyanins, and specific flavonoids like luteolin, all of which have been shown to possess some anti-leishmanial properties.[39]

Biogenic NPs, those synthesized by green methods, show significant potential in combating parasitic infections by directly targeting parasites, interfering with their cellular functions, and stimulating host immune defenses. Evidence of their effectiveness has been reported against other pathogens such as *Schistosoma mansoni, Toxoplasma gondii, Echinococcus granulosus, as well as Leishmania major* (*L. major*); primarily through mechanisms like membrane disruption, mitochondrial impairment, and induction of oxidative stress. Compared to conventional chemical synthesis, biogenic production methods offer reduced toxicity and environmental impact, positioning biogenic NPs as a sustainable and eco-friendly approach for developing novel antiparasitic treatments.[40–43] Although several studies have explored chemically synthesized nanoparticles for leishmaniasis, a consolidated review focusing on biogenic/green-synthesized nanoparticles remains lacking. This review addresses this gap and analyzed relevant studies from January 1, 2010, to April 30, 2025, which encompasses a broad range of metal-based biogenic nanoparticles (antimony sulfide, silver, gold, zinc, iron, copper, selenium, nickel, cobalt, magnesium, and barium), covering both plant-derived and microorganism-derived synthesis methods. The articles were analyzed by the specific search criteria such as nanometal type, source of green synthesis starting material (plant or microorganism), size of NPs produced, if any in vivo study was done, and which *Leishmania* sp. and life cycle stage was used. In vitro studies also compared cytotoxicity on *Leishmania* parasite and host cells.

Biogenic Antimony Sulfide Nanoparticles

In many countries, pentavalent antimony (Sb^V) has been the drug of choice for the treatment of all clinical forms of leishmaniasis.[44] Although the purely metallic form of antimony is not soluble or reactive under most physiological conditions, two forms (sodium stibogluconate and meglumine antimoniate) readily react in the body and have been used therapeutically.[45,46] The mode of action of pentavalent antimonial against leishmaniasis still is not well understood.[47,48] It is not even clear which form of pentavalent antimonial (Sb(V) or Sb (III)) is the activated form in humans and animals. Several studies suggest that axenic amastigotes showed Sb(V) susceptibility, whereas promastigotes did not. This suggests some life cycle stage-specific reduction of Sb(V) to Sb(III) may happen[49] (Figure 2). Regardless of the exact mechanism of action, both antimony drugs are given as injections which have several side effects, and are relatively easy for *Leishmania* to become resistant to.[44]

The use of biogenic antimony sulfide nanoparticles may offer some advantages over injectables. Aside from the benefits of any nanoparticle mentioned above, antimony sulfide nanoparticles (Sb_2S_5) can be naturally synthesized in

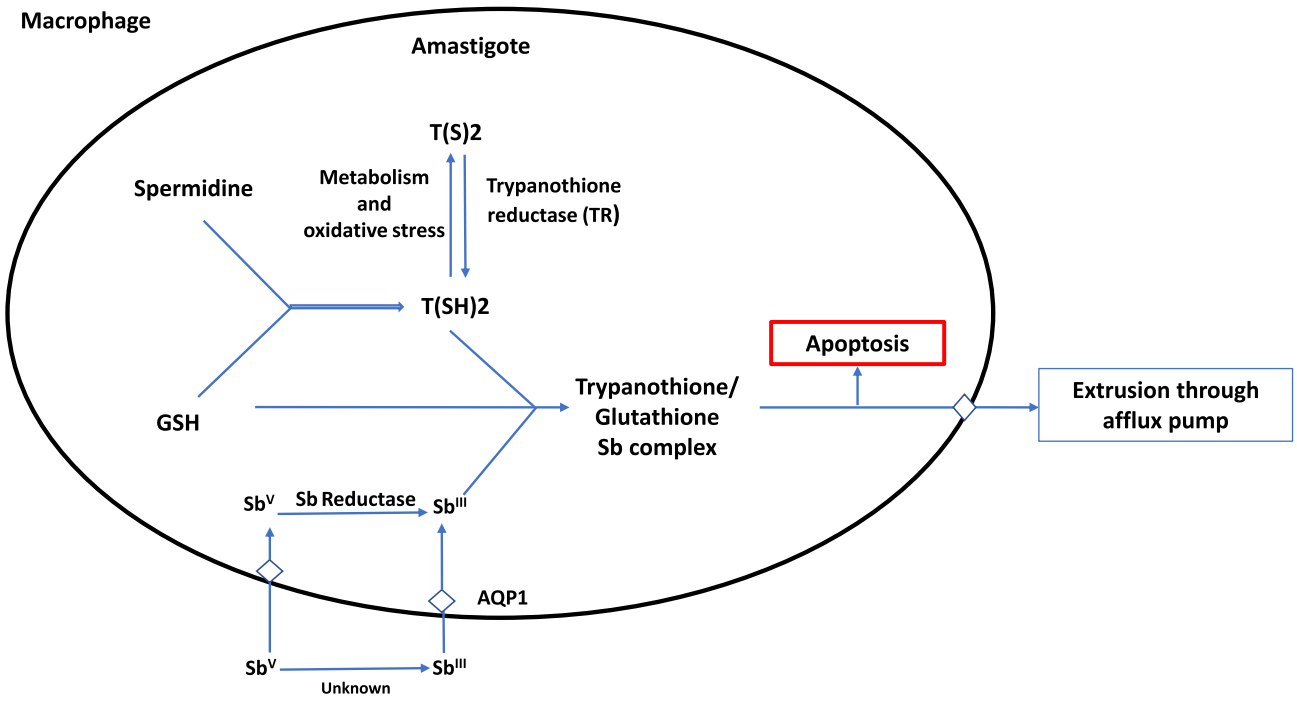

Figure 2 Proposed mechanism of antimony in *Leishmania* parasites. Sb^V is reduced to Sb^{III} in the amastigote in order to exert antileishmanial activity. SbIII uptake can be proceeded by an aquaglycoporin (AQP1). Ornithine decarboxylase (ODC) and ɣ-glutamylcysteine synthetase (ɣ-GCS) biosynthesize spermidine and glutathione (GSH), respectively in order to make trypanothione. Conjugation of Sb^{III} forms a trypanothione and glutathione stibogluconate complex, which results in apoptosis in amastigotes in the macrophages through two ways: 1- Binding to trypanothione reductase results in inhibition of the formation of trypanothione (T(SH)2) and makes cells susceptible to oxidative stress, 2- Binding to Zn finger protein results in inhibition of the expression of essential genes.[49,50]

Serratia marcescens (*S. marcescens*) bacteria that were isolated from seawater samples of the Caspian Sea and extracted using two-solvent phase partitioning systems.[51] Microorganisms can accumulate antimony as a toxic metal in their cytoplasm and other cell compartments such as the cell well.[51] The Sb_2S_5 NPs had a size of less than 35 nm and are composed of sulfur and antimony atoms with the ratio of 84/16. During incubation or extraction time, the component may be decomposed to free sulfur groups and Sb_2S_3[51] which would be more toxic for *Leishmania* parasites. One study showed that BALB/c mice inoculated with *L. major* had significantly smaller and less populated amastigote lesions over controls (IC50 = 70 µg/mL) when treated with the Sb_2S_5 NPs topically.[52] This may also be partly due to the fact that Sb(V) nanoparticles also demonstrated antibacterial activity against *S. aureus* and *E. coli*,[51] thus allowing for a faster rate of healing in the absence of some secondary opportunistic infections.[53] Also, in vitro studies showed that antimony NPs significantly reduced the number of amastigotes in the infected peritoneal macrophages after 72 h (IC50 = 62.5 µg/mL)[52] but there is no report about the cytotoxicity effect in macrophages. A second study tested the effect of these same *S. marcescens* generated biogenic antimony sulfide NPs on a different strain of *Leishmania* parasites, *Leishmania infantum* (*L. infantum*), and found that both the promastigotes and amastigotes responded to treatment by inducing apoptosis (IC50 = 50 µg/mL and 25 µg/mL, respectively).[44] Together, these studies indicate that biological antimony sulfide NPs could be considered as an alternative in treatment of leishmaniasis. However, it is still at early stages, and further studies on pharmacokinetics and pharmacodynamic of antimony sulfide NPs are needed.

Biogenic Silver and Gold Nanoparticles

Silver is the most used metal for medicinal nanoparticles. It has been shown to have anticarcinogenic, antimicrobial, and specifically antileishmanial effects.[54–56] Silver nanoparticles (Ag NPs) are relatively small in size and round. This spherical shape seems to be correlate with higher levels of phagocytosis and an ability to pass directly through parasitic cell membranes. Ag NPs undergo redox reactions creating free Ag^+ ion which can then interact with thiols or phosphates,

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inhibit enzymes, and generate ROS.[54–60] ROS can then interfere with *Leishmania* through DNA fragmentation, inhibition of trypanothione synthesis, and cell cycle arrest.[34]

Numerous green synthesis methods have looked at the bio-fabrication of silver with extracts used to reduce silver into silver NPs. Plant secondary metabolites are thought to be responsible for the reduction, chelation, and stabilization of silver. Starting with a silver salt, the metabolites form silver ions which are then chelated into the metallic core of the plant molecule. This chelation creates an NP with longer stability.[61]

Awad et al tested *Commiphora molmol* (myrrh) to create biogenic Ag NP from silver nitrate.[62] These Bio-AgNP were found to be approximately 49.06 nm and were tested against *L. major* both in vitro and in vivo. Results were compared to chemical synthesized NPs and Pentostam, a commercial drug. The biogenic Ag NPs (100, 150 µL/100 µL) showed significantly higher inhibition of parasites over both chemical synthesized Ag NP and drug controls. In the murine model, lesions were found to have healed completely by day 21 with the control groups preforming to a lesser extent.[62]

Pirestani et al used dried root powder from *Zingiber officinale (ginger)* to create AgNP. They then screened the NP against both *L. infantum* and *L. tropica* finding similar IC50 values of 4.54ppm and 4.22 ppm, respectively. They also reported a higher IC50 value closer to the 20–40ppm range[63] via MTT assays done on Raw 264.7 cells treated with the same AgNP.

Using the aerial parts of *Astragalus spinsus* as a catalyst, Majeed et al created AgNP's in the 30–40nm range. They screened these particles with or without the addition of meglumine antimoniate in *L. major* amastigotes as well as in J774-A1 cells. Both AgNP's and MA alone showed similar IC50 values (59.3 µg/mL and 51.2 µg/mL respectfully) against the amastigotes but were far less effective with the J774 cells (612.5 µg/mL and 789.8 µg/mL). A possibly synergistic affect was also tested in the amastigotes with a combination of both AgNPs+MA resulting in an IC50 of 18.6 µg/mL.[64]

The potentially beneficial generation of ROS from silver NPs has been tested by Bilal Javed et al.[61] In this study, an aqueous extract from leaves of *Mentha longofolia* was used to create Ag NPs. The Ag NPs were found to be between 10 and 100 nm in size with an IC50 of 8.73 µg/mL against *L. tropica* promastigote. Further studies showed that neither the plant aqueous extract alone nor the biogenic Ag NPs induced apoptosis in HCT116 colon cancer cells when they were exposed. Additionally, the NPs were shown to generate free radicals against *Leishmania*.[61]

Fungi have also been studied for their ability to produce biogenic Ag NPs. *Fusarium oxysporium* generated NPs with spherical shapes and a size around 57.6 nm. These were screened again both promastigotes and amastigotes of *Leishmania amazonensis* (*L. amazonensis)*. At the 24-hour treatment time, induction of a death mechanism was observed at 0.25 and 0.5 µg/mL in promastigotes and 0.5 µg/mL in amastigotes with no toxic affects noted in peritoneal macrophages.[55] In the other study, these biogenic NPs also showed 3.3-fold higher activity compared to chemically synthetized Ag NPs and a similar parasitemia inhibition in infected BALB/C mice but at a 300-fold lower concentration when compared to amphotericin B.[65]

Gold nanoparticles (Au NPs) have many properties that make them a useful tool in both genes and drug delivery systems.[66,67] From a green synthesis standpoint, they can be prepared by employing bioactive phytochemicals from aqueous plant extracts as reducing and stabilizing agents.[67] Au NPs (30–60 nm) generated from extracts of *Rhazya stricta decne* were shown to not only have activity against *L. tropica* intracellular amastigotes (IC50 = 43 mg/mL after 48 h) but also showed inhibitory effects against *E. coli* and *bacillus subtilis*.[67] It was also noted that there was no observed cytotoxicity in THP-1 cells after a 24-hour treatment.[67] Similarly, 4 mg/mL of Au NPs from *Maytenus royleanus* were screened against promastigotes of *L. tropica* with 75% inhibitory effect after 72-hour exposure.[66]

Another study reported that both Ag NPs and Au NPs nanoparticles had IC50 values of 4.37 and 5.29 µg/mL for promastigotes and amastigotes, respectively, without any notable cytotoxic effects in J774 cells under concentration of 30 µg/mL.[68]

Combination NP have also begun to be explored. Silver and gold bimetallic NP (Ag-Au NPs) have begun to show some promise.[69] Gold−silver bimetallic nanoparticles (Au−Ag BNPs) were synthesized in other study through a single-step reduction process using fenugreek, coriander, and soybean leaf extracts.[70] These Au−AgNPs demonstrated high antileishmanial effects against *Leishmania donovani* (*L. donovani*) promastigotes (IC50 = 0.03−0.035 µg/mL) which was about 300-fold lower than that of the drug miltefosine. This effect was shown to be through a ROS-mediated apoptosis-like death in the promastigotes. In addition, treatment potentiated the antileishmanial activity of macrophages, however, intracellular amastigotes numbers were reduced by only a modest 31−46%.[70]

The cytotoxicity of Ag NPs is usually from of the presence of a positive charge on silver ions that interacts with the negatively charged plasma cell membrane and disrupts the ionic balance and finally the membrane structure. The small size Bio-NPs also have abilities to interact with the nucleic acids such as DNA and RNA because of the presence of a negatively charged phosphate backbone. This interaction results in the destabilization of the DNA and RNA structures which affects cell proliferation and finally leads to cell death.[61] Monometal NPs require higher concentrations, resulting in toxicity to host cells.[70]

AuNP have also been coated with curcumin as a possible combination. S. M. Amini et al synthesized nanoparticles using DMSO, tetrachloroauric acid trihydrate, and curcumin. These curcumin coated gold nanoparticles were tested against both promastigote and amastigote forms of *L. major* as well as J774A.1 cells and infected BALB/C mice. While various concentrations were tested, IC50s of 64.79 (24 h) and 29.89 (48 h) μg/mL in promastigotes and 63.29 (24 h) and 54.04 (48 h) μg/mL in amastigotes were reported. The combination also showed significant improvement in mouse models without negative affect on J774A.1 cells.[71]

All these findings suggest that biosynthesized silver and gold nanoparticles are biocompatible nanomaterials with a broad-spectrum antimicrobial activity as they have more antileishmanial effects with less cytotoxicity and could be used as a vehicle for the delivery of bioactive natural products. Table 2 summarizes the antileishmanial activity of metal nanoparticles prepared by green methods.

Biogenic Iron Oxide Nanoparticles

The applications of iron oxide (Fe_2O_3) nanoparticles (FeO NPs) in biomedicine are growing exponentially.[93] While FeO NPs have a higher surface area and good stability, most methods of synthesis showed poor dispersion, a lack of uniformity in particle size and distribution,[105] and are often costly because of intense energy requirements during manufacturing.[106] In contrast, FeO NPs synthesized from aqueous leaf extracts showed a surface area four times bigger relative to the commercial preparations.[93,105] Furthermore, biogenic FeO NPs were found to have impressive antimicrobial properties while also being nontoxic to humans compared to their chemically produced counterparts, thus suggesting higher biocompatibility.[95,107–111]

To test its anti-leishmaniasis effects, Mehrdad Khatami et al biosynthesized FeONPs using Rosemary.[92] The results showed the fabrication of monodispersed spherical shaped FeONPs with a size 4 ± 2 nm and IC50 of 350 μg/mL against *L. major* promastigotes.[92] Similarly, *Sageretia thea* (Osbeck) generated FeO NPs with a size of 29 nm which were tested against promastigote and amastigote forms of *L. tropica* (IC50 = 17.2 and 16.75 μg/mL respectively) and showed no cytotoxicity for human red blood cells (RBCs) or macrophages.[95] The authors disclosed that these particles are also effective agents against bacterial strains and had some degree of antioxidant activities.[95,107–113] Ahsan Abbasi et al biosynthesized FeO NPs using leaves extract of *Rhamnus virgate*.[94] FeO NPs with a crystallite size of ~20 nm were seen to be effective agents in inhibiting the promastigote and amastigote forms of *L. major* after 72 h with an additional anticancer, antibacterial, and antifungal activity. Cytotoxic and potentially significant antioxidant activities were also reported.[94] Minhas et al used L-2 extracts of Cyanobacterium *Leptolyngbya sp*. to synthesize FEONP's from iron chloride hexahydrate. They were screened against both promastigotes and amastigotes from *L. tropica* (IC50 = 10.73 and 16.98 μg/mL respectively).[114]

Clear variations in the antileishmanial efficacies of the iron-based particles could be linked to the phytochemical constituents that were used to stabilize the NPs. The surface-capped biomolecules in biogenic metal-based particles also play an important role in the antimicrobial property of the prepared materials.[34]

Biogenic Zinc Oxide and Zinc Sulfide Nanoparticles

Zinc oxide nanoparticles (ZnO NPs) are novel antimicrobial and antileishmanial agents showing promise due to their high surface area to volume ratio and ability to generate ROS inside cells.[82] ZnO NPs can cause DNA, lipid and protein damages in the *Leishmania* species.[34] For synthesis of ZnO NPs, numerous physical and chemical approaches have been reported with most of these approaches showing similar drawbacks to other nanoparticles.[82,115] For green biosynthesis, leaf extracts have been used.[83] Recently, *Lilium ledebourii* tuber extract was used with both rod-shaped and spherical ZnO NPs being explored. IC50 about 0.012 mg/mL of biogenic ZnO NPs revealed a higher toxicity effect on *L. major*

Table 2 Different Nanomaterial Types are Used for Treatment of Leishmaniasis Studies

Nanoparticles	Biological Sources	Size (nm)	*Leishmania* (*L*). Species	IC50 (μg/mL) or Efficacy			In vivo	Reference
	Plant/Microorganism			Promastigote	Amastigote	Cytotoxicity/Cell Source		
Antimony sulfide (Sb_2S_3)	*Seracia marcesense*	35	*L. major*		62.5	70/ RAW 264.7[a]	Effective	[52]
			L. infantum	50	25 (axenic)			[44]
Copper (Cu)	*Capparis spinosa*	17-41	*L. major*		116.8 ± 3.05	Negative/J774[b]	Lesions shrunk 43–58 mm	[72]
Silver (Ag)	*Commiphora molmol*	49.09	*L. major*	100, 150μL/100 μL			Healed (21 D[c])	[62]
	Mentha longifolia-Leaves	10–100	*L. tropica*	8.73		Negative/ HCT116[d]		[61]
	Cuminum cyminum	125	*L. tropica*	0.5	0.75	1.56 (91%)/ J774		[73]
	Sargentodoxa cuneata-Stem	3–8	*L. tropica*	4.37				[68]
	Corn cobs (xylan)	102	*L. amazonensis*	25		Negative/3T3[e]		[69]
	Coffea arabica	20-70	*L. major*	65.4	47.70	437.2/ Hek293[f] 116.8 /MCF7[g] 72.9/ A172[h]		[74]
	Xanthium strumarium	436	*L. donovani*	8.93		18.15/ J774		[75]
	Euphorbia prostrata-Leaves	12.82	*L. donovani*	14.94	3.89	115.5/ J774		[76]
	Astragalus spinosus	30-40	*L. major*		59.3	612.5/ J774-A1[i]	Healed (28 D)	[64]
	Teucrium stocksianum-Leaf, Stem	10–15	*L. infantom*	19.42–30.71	41-28% reduced	100.02–116.81/ J774		[77]
	Olax nana	26	*L. tropica*	12.56	17.44	14.93/ HepG2[j]		[37]
	Fusarium oxysporium	57.6	*L. amazonensis*	0.25, 0.50	0.5	0.5/Peritoneal Macrophages		[55]
	Ginger rhizome	10 ± 4	*L. major*		2.35			[78]
	Cashew Nutshell Liquid-anacardic acid	424	*L. braziliensis*	86.61		6.910/J774		[79]
	Cashew Nutshell Liquid- cardol	414	*L. braziliensis*	11.54	16	195.0/J774		[79]
Amphotericin B-Silver (AmB-Ag)	*Isatis tinctoria*	10–20	*L. tropica*	2.43				[80]
Silver-Gold (Au−Ag)	Fenugreek, coriander, soybean-leaves	10–12	*L. amazonensis*	0.03−0.035	31−46% reduced	THP-1[k]		[38]

Gold (Au)	*Rhazya stricta decne*	30-60	*L. tropica*		43	Negative/THP-1		[67]
	Maytenus royleanus	30	*L. tropica*	75% reduced				[66]
	Sargentodoxa cuneata-Stem	15–30	*L. tropica*	5.29				[68]
	Olax nana	47	*L. tropica*	21.52	42.2	2.97/HepG2		[37]
Curcumin-Gold (Cur-Au)	*Dimethyl sulfoxide*		*L. major*	64.79(24H) 29.89 (48H)	63.29(24H) 54.04 (48H)	Negative/ J774A.1[L]	Reduced lesion size in BALB/C[m]	[71]
Zinc (Zn)	*Lavandula vera*	30-80	*L. major*	43.2				[81]
Zinc oxide (ZnO)	*Flax seeds- Callus and* root	61.44	*L. major*	250				[82]
	Verbena officinalis -Leaves	14–31	*L. tropica*	243.42				[83]
	Verbena tenuisecta-Leaves	65–75	*L. tropica*	414.03				[83]
	Lilium ledebourii-Tuber	350–370	*L. major*		500			[84]
	Sageretia thea	12.4	*L. tropica*	6.2	10.87	21.29		[85]
	Stevia-Leaves	10–90	*L. major*	75-100				[86]
	Rhamnella gilgitica	21	*L. tropica*	26.78	29.57	18.40/ HepG2 20.59/ HUH7[n]		[87]
	Fagonia indica (ZnO_S[o])	41	*L. tropica*	83				[88]
	Fagonia indica (ZnO_A[P])	23.4	*L. tropica*	48				[88]
	Elaeagnus angustifolia- Leaves	26	*L. tropica*	24.9	32.83	21.7/ HepG2 29.8/ HUH7		[89]
	Ziziphus Oxyphylla- Leaves	35.9	*L. tropica*	47.23±3.22				[90]
Zinc sulfide (ZnS)	Phoenix dactylifera	<70[q]	*L. major*	11.59	29.81	Negative/ Murine Macrophages		[91]

(*Continued*)

Table 2 (Continued).

Nanoparticles	Biological Sources	Size (nm)	*Leishmania* (*L*). Species	IC50 (μg/mL) or Efficacy			In vivo	Reference
	Plant/Microorganism			Promastigote	Amastigote	Cytotoxicity/Cell Source		
Iron oxide (FeO)	*Rosemary*	4 ± 2	*L. major*	350				[92]
	Leptolyngbya sp.	28.21	*L. tropica*	10.73	16.89	34.19/Shrimp		[93]
	Rhamnus virgate	20	*L. major*	8.08	20.82	32.41/ Shrimp		[94]
	Sageretia thea	29	*L. tropica*	17.2	16.75	Negative/HS[r], RBCs[s], Macrophages		[95]
	Callistemon viminalis	22-32	*L. tropica*	56.28	40	20/ HepG2		[96]
	Rhus punjabensis	41.5±5	*Leishmania*		20	11.9/ HL-60[t], 12.79/DU-145[u]		[97]
Selenium (Se)	*Bacillus* sp. MSh-1[v]	80–220	*L. major*	1.62	4.4	10.5/Peritoneal Macrophages		[98]
			L. tropica	2.7	6.4			[99]
	Polygonum bistorta Linn-Roots	69 ± 23	*L. tropica*	98.80	107.21			[100]
Cobalt oxide (CoO)	*Geranium wallichianum*- Leaves	503	*L. tropica*	3.12	9.53	31.4/HepG2, >200[w]/Human Macrophages		[101]
	Hibiscus Rosa sinensis	29.6	*L. tropica*	57% at 400	44% at 400			[102]
Magnesium oxide (MgO)	*Hibiscus Rosa sinensis*	31.6	*L. tropica*	44% at 400	54% at 400			[102]
Nickel oxide (NiO)	*Callistemon viminalis*	16.5	*L. tropica*	37.21		47/HepG2		[103]
Titanium oxide ($TiO_{2)}$	*Euphorbia prostrata- Leaves*	83.22	*L. donovani*	14.94	3.89			[76]
Barium carbonate (BaCO3)	*Black elderberry*	33.49–192.3	*L. tropica*	46.6				[104]

Notes: [a]Murine macrophage cell line; [b]Macrophage cell line derived from mouse reticulum cell sarcoma; [c]Days; [d]Human colorectal cancer cell line; [e]Fibroblast cell lines derived from mouse embryos; [f]Human cell line derived from human embryonic kidney cells; [g]Human breast cancer cell line; [h]Human brain glioblastoma cell line; [i]Murine macrophage cell line; [j]Human liver cancer cell line; [k]Human acute monocytic leukemia cell line; [l]Murine macrophage cell line; [m]Albino, laboratory-bred strain of the house mouse; [n]Human hepatoma-derived cell line; [o]Biogenic zinc oxide using zinc sulfate as a precursor salt; [p]Biogenic zinc oxide using zinc acetate as a precursor salt; [q]Less than 70 mm; [r]Human fibroblast cell line; [s]Red Blood Cells; [t]Human leukemia cell line; [u]Human prostate cancer cell line; [v]Strain of bacteria isolated from the Caspian Sea; [w]More than 200 mm.

intracellular amastigotes compared to Meglumine antimoniate (glucantime) as positive control.[84] Another study compared leaf extracts of *Verbena officinalis* (*V. officinalis*) and *Verbena tenuisecta* (*V. tenuisecta*) in the production of biogenic ZnO NPs. Both rod and flower shaped ZnO NPs were found but *V. officinalis* had a smaller size and increased phenolics, leading to more potent leishmanicidal activity (IC50 = 250 μg/mL) against *L. tropica* promastigotes.[83]

Zinc sulphide nanoparticles (ZnS NPs) were prepared using a similar green approach. ZnSNPs with a size less than 70 nm showed no cytotoxicity when tested against murine macrophages but showed leishmanicidal activity with the IC50 values of 29.81 and 11.59 μg/mL against *L. major* promastigotes and amastigotes, respectively. This result is about a 2–2.5-fold stronger effect when compared to the glucantime control.[91]

Overall, owing to their small size and electrostatic interactions, Zn NPs enter into leishmanial cells and lower the parasite's metabolic activity and proliferation values. They also induce intracellular depletion via ROS production which in turn causes cell membrane disruption, cytoplasmic leakage, and finally protozoa death.[83]

Biogenic Selenium Nanoparticles

Selenium (Se) is an essential micro-mineral element whose functions include regulating metabolism, improving immunity, enhancing reproductive performance, and preventing cancer.[116] Biogenic Selenium NPs (Se NPs) have been shown to have lower toxicity than selenium oxyanions,[117–119] and there is some evidence that Se NPs have successful antibacterial and antiparasitic effects.[42,120,121] Se NPs generated by Shakibaie et al using *Bacillus sp*. MSh-1, were spherical in shape and 80–220 nm in size.[122] They were tested against *L. major* and antileishmanial effects were shown after 72 hours with an IC50 against promastigotes (1.62 ± 0.6 μg/mL) and amastigotes (4.4 ± 0.6 μg/mL) vs peritoneal macrophages which was 10.5 ± 0.6 μg/mL. Se NPs also delayed the development of localized cutaneous lesions in a mouse model.[98]

Mahmoudvand et al examined SeNPs, separately or in combination with meglumine antimonate, against sensitive and drug resistant *L. tropica*.[123] They reported that the combination of drugs had higher efficiency against promastigotes of both sensitive and resistant strains (IC50 = 1.5 and 2.8 μg/mL, respectively) and significantly reduced proliferation of amastigotes in the macrophages at a concentration of more than 2.5 μg/mL. Pre-incubation of macrophages with SeNPs significantly reduced the infectivity of macrophages by parasites.[123] In general, Se NPs were effective against cutaneous leishmaniasis[121] and they have less toxicity against mammalian macrophages, but more studies in animal models are needed.

Other Biogenic Nanoparticles

Copper nanoparticles (Cu NPs), likely due to their high surface-to-volume ratio, are very reactive and interact with other particles.[124,125] Cu NPs synthesized by *Capparis spinosa* fruit methanolic extract had a spherical shape, and a particle size of 17 to 41 nm.[72] A combination therapy of Cu NPs and glucantime was found to significantly inhibit the growth rate of *L. major* intracellular amastigotes and triggered the production of nitric oxide (NO) in a dose-dependent manner. NO is considered to be one of the main mediators of immunity produced in macrophages, which plays a critical role in the control of *Leishmania* parasites.[126] Also, this combination reduced amastigotes in the *L. major* infected mice while having no significant cytotoxicity in J774 cells.[126] Previous studies have shown Cu NPs have potent antiparasitic effects against other protozoan parasites such *Giardia lamblia* cysts, *Entamoeba histolytica*, and *Cryptosporidum parvum*.[127,128] Antimicrobial studies suggest that Cu NPs destroy proteins in bacteria via interaction with thiol groups[129] as well as cause degradation of DNA, lipid peroxidation, and production of ROS, causing cell wall destruction and death.[130]

Nickel oxide NPs (NiO NPs) have a unique nature and interesting properties like stability, conductance, catalysis, electron transferability and wider band gap (3.7–4.0 meV). Their cytotoxicity has been previously demonstrated via ROS and Ni^{++} ions which can lead to the oxidative damage.[131–133] Biogenic NiO NPs recently synthesized by Ayesha Sani et al using floral extracts of *Callistemon viminalis* (*C. viminalis*) have spherical morphology are 16.5 nm.[103] They reported that NiO NPs had anti-leishmanial activity on *L. tropica* promastigotes (IC50 = 37.21 μg/mL) and additionally anticancer and antibacterial activity. Overall good antioxidant nature and biocompatibility were revealed.[103]

Cobalt based NPs (Co NPs) have gained the attention of the scientific community because of their ecofriendly nature, easy handling, low cost and strong electro potential.[134] Co NPs have already been shown to have a significant role as a cofactor in vitamin B12 and have been effectively used in sensing of amino acids, nitrates, glucose, arsenic and

methanol.[134] Biogenic Co NPs were created using aqueous leaf extract of *Geranium wallichianum Oliv.* and have shown a dose-dependent cytotoxicity against *Leishmania* promastigotes (IC50 = 3.12 μg/mL) and amastigotes (IC50 = 9.53 μg/mL) with additional anticancer, antibacterial, and antifungal activity being reported.[101] Cobalt oxide particles (Co_3O_4-NPs) have also been generated using aqueous extracts of *Hibiscus Rosa sinensis*.[102] These NP (29.6–31.6nm) showed activity against both forms of *L. tropica* (57.32% at 400 ug/mL for promastigotes and 48% at 400 ug/mL for amastigotes).[102]

Nanocomposites built of different metal nanoparticles have also been explored. Amini et al used ethanol extracts from the seaweed *Laurencia dendroidea* to create AgNP and CuONP but also polymeric PVP-Ag-CuO nanocomposite. These were screened against *L. amazonensis* promastigotes to show that the PVP-Ag-CuO nanocomposite was the most effective (IC50 = 17.48 μg/mL) followed closely by the AnNPs with a IC50 of 18.75 μg/mL. The CuONPs were found to be much less active with an IC50 of greater than 25 μg/mL.[135]

Pharmacokinetics (PK)

While green synthesis and nanoparticle usage are the central focus of this paper, there is the equally important question of NP safety. Other manuscripts have sought out the ADME properties of metal-based nanoparticles. These papers, while currently extremely limited, suggest that NP made of silver, gold, or zinc, tend to show that the specific route of administration has a significant effect on absorbance and distribution of the metallic particles, with toxicological effects like that which would be expected from those metals.[136] At the time of this writing, no pharmacokinetic data was available relating for NP made using selenium, cobalt, nickel, titanium, or barium. Some PK data is noted for antimony, but it is not specific to nanoparticle formulations. This limitation is one that will need to be addressed in the future.

Equally important to note in the future will be the need to understand not just how metallic ions from nanoparticles are expelled from the body, but what impacts their synthesis, even being green, would have. Many of the current methods of green NP synthesis rely on the use of weeds, grasses, moss, or other biologic material. On the small scale, much of this is starting material is readily available and often viewed as a nuisance. Should any of these materials prove to be a truly beneficial treatment, then the harvesting of these materials on a large scale could cause shifts within whatever ecosystems they exist. Work will need to be done to ensure that the effects of harvesting these biologic materials are offset by other grown.

Current Limitations and Future Directions of Green Synthesis of NPs

Green synthesis of biogenic nanoparticles is an emerging field with a lot of potential for growth, but as the field itself is fairly new, there are significant gaps in knowledge that will need to be addressed in the near future. To date, most reporting surrounding the green synthesis of NPs is limited to describing how a synthesis was done with almost no comment on the actual chemical pathways for generation. Additionally, little is currently known or speculated on regarding the transition from lab to industrial scale productions such as maintaining consistent reaction conditions (including uniform temperature, concentration, and pH), batch-to-batch variation, and economic and sourcing challenges as certain plant species used for extracts may only be available during specific flowering or harvesting periods. With how complex some of the preparations were (everything from brewing roots to long term fermentations and sun exposure), there is a distinct lack of explanation for how the researcher came to these methods. Based on the literature that there are many avenues of improvement and refinement such as scalability, reproducibility, safety, and the desired properties of the final product. As reported, different starting materials do show differences in the size, shape, and relative abundance of NP produced. Better understanding of the actual chemical processes occurring during synthesis would allow for optimization and ideal selections of starting materials based on the desired outcomes.

In its current form, green synthesis being done on a laboratory scale is relatively easy to deal with from the production side. This situation would drastically change once the production was scaled to a larger, more industrial size. The production of large bioreactors running green synthesis would require larger amounts of starting materials and biological waste that could no longer be supported by the gathering methods used in a research setting. Once better understood, the possibility of resource sharing or recycling with other production sectors could become a reality. The use of bioreactors, particularly in the case of microorganisms, could also post safety risks as they are concentrated population of what are otherwise benign organisms.

All in all, green synthesized NP hold great promise as a new synthesizing process which is not only more environmentally but potentially more customizable and targeted treatment approach. All the above-mentioned areas will still need to be explored before these systems could really move into complex biological models or preclinical trials. At that point, better regulations and globally driven benchmarking would also still need to be developed in order to more completely understandings of production chemistry, parasite biology, and ecological impacts surrounding biogenic NPs use in the treatment of *Leishmania* infections.

Conclusion

The use of nanoparticles has continuously increased due to their having a smaller size and larger surface area to volume ratio and can be more efficiently taken up by the infected macrophages than free drugs. This may make nanoparticles a promising and novel treatment option for leishmaniasis. Biogenic synthesis of nanoparticles relies on plant extracts or microorganisms rather than traditional chemicals thus reducing many of the hazardous and ecological impacts associated with nanoparticle products and waste. This method increases accessibility of the drugs and reduces the cost. Treatment of *Leishmania* is already difficult because of their genetic plasticity, ease of treatment resistance development, and a general lack of understanding of all the ways they evade host immune responses. Biological materials show promise for the treatment of leishmaniasis, especially plant extracts because they are easily accessible and generally safe. These nanoparticles can be incorporated into treatment as a monotherapy or in multifaceted therapy. Therefore, investing in green synthesis of NPs may help resolve treatment efficacy, accessibility, and cost, especially in low- and middle-income areas of the world. Different biogenic nanoparticles had been preliminary evaluated on *Leishmania* parasites such as antimony sulfide, silver, gold, zinc, iron, copper, selenium, nickel, and cobalt. Because of the previous known antimicrobial activity of silver, most studies on antileishmanial activity have been performed with silver nanoparticles. Among biogenic NPs, silver and selenium NPs demonstrated the most potent antileishmanial activity with low host cytotoxicity, while antimony sulfide NPs showed promise in early in vivo models. Although the mode of action of nanoparticles is complex, several studies suggest that they induced apoptosis in parasites by generation of intracellular ROS which leads to *Leishmania* DNA damage, protein and lipid oxidation. There was only minimal and inconsistent reporting on the process for determining EC50 values, not enough reporting on the mechanism of actions or types of cell death, and no work on understanding biodistribution of the NP. Once understood, NP could be created with additional features or to specific criteria that would allow for targeting of infected macrophages and parasites with no off-target effects that could outweigh their treatment potential. Moreover, current studies are in the early phases of testing, focused more on cutaneous strains with and animal models showing less progression toward clinical trials. In addition, more studies on visceralizing strains are needed. Furthermore, methods of green synthesis of nanoparticles need to be optimized by standardization of choice of plant parts, growth and purification requirements, and optimizing microorganisms' choice by avoiding unintended cytotoxicity and secondary infections. Moreover, potential drawbacks-such as scalability, batch variability, environmental cost of green synthesis, or safety in long-term exposure need to be studied.

Data Sharing Statement

All data generated or analyzed in the current study are included in the published article. Any other information is available from the corresponding author on reasonable request.

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