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REVIEW ARTICLE

Role of Silver Nanoparticles as an Alternative Control Strategy for the Control of Leishmaniasis Disease a Public Health Concern

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ABSTRACT

Leishmaniasis is a tropical and subtropical disease caused by protozoan parasites of the genus *Leishmania* and represents a serious public health threat in many endemic regions of the world. The main therapeutic interventions used to control leishmaniasis are based on pentavalent antimonials and amphotericin B, which are characterized by high toxicity, restrictive prices, and selection of drug-resistant strains. To avoid these drawbacks of conventional therapeutics, we are in dire need to develop new, efficient, and safe therapeutic options. Among all the alternative control and preventive strategies for leishmaniasis nanotechnology is found most promising. There are multiple types of nanoparticles, but silver nanoparticles (AgNPS) have been reported to have most potent results in controlling leishmaniasis. In this article, we review the limitations of conventional antileishmanial drugs, antileishmanial properties and mechanism of actions of AgNPs.

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INTRODUCTION

Leishmaniasis represents a complex of diseases with an important clinical and epidemiological diversity, which is caused by obligatory intracellular protozoa of the genus *Leishmania* (Tao and Jia, 2024). The parasite is transmitted by a bite on the skin of infected females of the phlebotomine sandflies (Hustedt *et al.*, 2022). In almost 100 countries of Asia, Africa, America, and the Mediterranean region, the disease is endemic and endangers about 350 million people with the disease (Bilal *et al.*, 2023). The World Health Organization (WHO) puts the estimates of new cases per year at 700,000-1 million and the resulting deaths at between 26,000-65,000 (Gonçalves *et al.*, 2023). Nevertheless, leishmaniasis is still considered a neglected tropical disease, and until recently, the disease received minimal research funding and pharmaceutical attention as compared to other infectious diseases such as malaria or tuberculosis (Sundar *et al.*, 2024). The disease has three primary clinical manifestations, depending on its clinical progression from self-healing skin lesions to lethal system organ failure (Kaur *et al.*, 2022). The most prevalent form is cutaneous leishmaniasis (CL), which produces ulcerative skin lesions, which may result in gross disfigurement, social stigmatization, and permanent scarring (Merdekios *et al.*, 2025). Mucocutaneous leishmaniasis (MCL) is also a more destructive kind and affects the mucous membranes of nose, mouth, and throat (Yadav *et al.*, 2023). The most serious type is visceral leishmaniasis (VL) or kala-azar; it is a disorder of fever, loss of weight, swollen spleen and liver (hepatosplenomegaly), and anaemia (Costa *et al.*, 2023). If left unattended, VL becomes more sever and fatal most of the times (Lopes *et al.*, 2024). The development of drugs has been facing a daunting challenge because of the biological complexity of the *Leishmania* parasite (Altamura *et al.*, 2022). The life cycle is digenetic, in which the organism is a flagellated, extracellular form known as the promastigote, which inhabits the gut of the insect host, and an intracellular, non-flagellated form called amastigote, which inhabits the mammalian host (Barrias *et al.*, 2022). When transmitted to a human host, the promastigotes are ingested by macrophages, which are immune system cells that are meant to kill pathogens (Almeida *et al.*, 2023). The parasites develop into amastigotes and multiply within the macrophage phagolysosomes (Valigurová and Kolářová, 2023). This is an intracellular site that affords the parasite protection from the humoral immune response of the host and makes most therapeutic agents hard to achieve applicate concentrations without resulting in massive collateral tissue damage to host tissues (Ezema *et al.*, 2023). There is a significant zoonotic potential of *Leishmania* spp., in which the infection is transmitted by sand flies that obtain parasites in the contact with ill animal reservoirs. Domestic dogs, rodents, and other wild mammals are major reservoir hosts, and this has sustained the lifecycle of the parasite, spilling over to humans. This animal-vector-human cycle is important toward leishmaniasis persistence and transmission in endemic areas.

Chemotherapy and control of the vectors have been the main tools used in the control of leishmaniasis, yet over the decades, there has been stagnancy in the therapeutic arena (Abbasi, 2025). As a first-line therapy, pentavalent antimonials (Sodium Stibogluconate and Meglumine Antimoniate) have been used since the 1940s (Zhang *et al.*, 2025). Although these agents were previously very useful, resistance is developing faster (Baker *et al.*, 2025). Evident drug resistance has also emerged, especially in the Indian subcontinent (e.g. Bihar state), where antimonials have failed on more than 60% (Singh *et al.*, 2023b). Moreover, antimonials are of prolonged parenteral-administration courses (which is frequently painful, intramuscular or intravenous injection), which is a serious logistical challenge in resource-deficient environments (Jing *et al.*, 2025). Major dose-dependent toxicities, such as cardiotoxicity, pancreatitis, and nephrotoxicity, are also linked to antimonials (Manavi *et al.*, 2024).

Second-line drugs including aminoglycosides, alkyl-phosphocholines, and Aromatic diamidines are the substitutes which however have their own limitations that are very severe (Zugazagoitia and Paz-Ares, 2022). Amphotericin B (AmB) is very efficacious with its standard deoxycholate formulation being infamously nephrotoxic and thereby causing acute kidney injury in most cases (Dash *et al.*, 2024). Amphotericin B (Liposomal Amphotericin B, AmBisome) is much less toxic and has a higher likelihood of reducing disease in macrophages, but this is very expensive; hence, this is not affordable to the poor groups with the highest prevalence of the disease (Kumar *et al.*, 2022). The first oral medication approved as an agent in the treatment of leishmaniasis was the drug Miltefosine which was a significant milestone in terms of administration (Palić *et al.*, 2022). However, its use is limited by severe gastrointestinal side effects and, more importantly, teratogenicity, necessitating strict contraception for women of childbearing age (Bradley *et al.*, 2023). The half-life of Miltefosine is long which favours the selection of resistant strains in case of poor adherence by the patient (Palić *et al.*, 2022). With these issues, high toxicity, poor cost, complicated administration, and increased resistance, there is an urgent need to propose innovative, affordable, and biocompatible therapy tools (Ahmad *et al.*, 2022). Among all the alternative control and preventive strategies for leishmaniasis nanotechnology is found most promising specifically the silver nanoparticles (AgNPs) (Almatroudi, 2024; Zohaib *et al.*, 2026). This review critically examines how AgNPs can help as an alternative control measure, focusing on the mechanism of action, its safety profile, and what still must be overcome before it can become clinical practice (Noga *et al.*, 2023).

Public Health Significance of Leishmaniasis: Leishmaniasis poses a significant health issue to the healthcare systems besides its clinical implications, as well as it has a huge socioeconomic and psychosocial impact on the affected communities (Merdekios *et al.*, 2025). Leishmaniasis is classified as Neglected Tropical Disease (NTD) by the World Health Organization (WHO) (Ca *et al.*, 2024). Public health significance of leishmaniasis is briefly discussed as follows:

Burden and Epidemiology: There are approximately 350 million individuals at risk of contracting the disease in 98 countries with endemic status (Zhao *et al.*, 2025). According to WHO, the estimate is 700,000 to 1 million new cases in a year and 26,000 to 65,000 mortalities (Tekle *et al.*, 2024). Yet these numbers are probably only an underestimation as there is a high level of under-reporting in isolated regions (Farooq *et al.*, 2022). In the world, the greatest number of parasitic deaths was caused by Visceral Leishmaniasis (VL) alone after malaria (Costa *et al.*, 2023). The climate change, urbanization, migration, and shifting epidemiology are increasing the habitats of the sandfly vectors into new latitudes and altitudes, which is causing a change in the epidemiology (Maia, 2024).

Socioeconomic Impact: Leishmaniasis is traditionally termed as a disease of poverty (Kumar *et al.*, 2023b). It occurs mostly in rural regions where housing is in poor condition, malnutrition and access to healthcare are very low (Adeyeye *et al.*, 2023). It has a devastating effect on the economy at the household level (Bundervoet *et al.*, 2022). Families incur substantial indirect costs even in areas with free access to antileishmanial drugs. The cost of transportation to the tertiary care centre may be high. Hospital stays usually extend to 28 days and above leading to loss of income. Besides this, the necessity of a caretaker contributes to the economic stress. All these expenses may eat up much of the amount the family earns annually (Tessema *et al.*, 2024). Research in the Indian subcontinent and Ethiopia revealed that the price of treating an episode of VL can be greater than the income per capita is in a single year of the household affected, taking the family into further debt and poverty (Siddiqui *et al.*, 2025).

Psychosocial Burden and Stigma: The effects of Cutaneous Leishmaniasis (CL) and Mucocutaneous Leishmaniasis (MCL) are not always in mortality, but in morbidity and social exclusion (Nuwangi *et al.*, 2023). The deforming scars (usually on the face and hands) cause extreme stigmatization, especially on the women and children (Mathews *et al.*, 2023). These scars may cause social death in most traditional societies, including marriage, access to education, and involvement in the community (Hasan *et al.*, 2023). Various studies have indicated that the prevalence of depression, anxiety, and lower indices of Quality of Life (QoL) is high among CL patients, which can be compared to chronic systemic diseases (Vadakkiniath, 2023).

HIV-*Leishmania* Coinfection: One of the rising health risks facing the population is the occurrence of *Leishmania*-HIV coinfection (Maksoud and El Hokayem, 2023). HIV-positive people are much more susceptible to active VL development, and the coinfection promotes the development of both conditions (Mulherkar *et al.*, 2022). Coinfection makes diagnosis (because serological tests tend to fail with a low level of antibody production) and treatment (leading to increased toxicity and relapse rates) difficult (Heidary *et al.*, 2022). This synergy has been observed in 35 countries, which presents a challenging complex to control programs that in the past have been working in silos (Lah, 2025). The morbidity of leishmaniasis is measured in Disability-Adjusted Life Years (DALYs), which is a summation of years of life lost to early death and years of life lived with disability (Reis *et al.*, 2024). Although VL is a major cause of mortality-based DALYs, CL and MCL are a major cause of disability-based DALYs as a result of disfigurement in the long-term and psychological trauma (Silva *et al.*, 2022). The net effect of the leishmaniases is that these are a great wasted human potential that would require concerted efforts in health education that would extend beyond the administration of the drug to tackle the social determinants of health (Cosma *et al.*, 2024).

Existing control measures and their limitations: The existing pharmacological repertoire for treating leishmaniasis is poor, obsolete, and also has serious disadvantages (Altamura *et al.*, 2022). Pentavalent antimonials have been the mainstay of treatment for decades (e.g., Sodium Stibogluconate and Meglumine Antimoniate) (Solomon *et al.*, 2024). Although traditionally gold standard, the action of these agents remains not entirely comprehended, presumably by inhibiting the bioenergetics of parasites (Kumar *et al.*, 2023a). Their drawbacks are severe: they need lengthy periods of parenteral administration (which in many cases are painful injections), are dose-dependent cardiotoxic and pancreatic, and cure rates have been significantly reduced in places such as Bihar, India, because of resistance of the parasites (Zeien *et al.*, 2022). The first-line rescue therapy in regions of antimonial resistance is progressively based on the use of amphotericin B (AmB) (Akinosoglou *et al.*, 2024). Although it is very effective, conventional AmB (deoxycholate) is infamously nephrotoxic (Dash *et al.*, 2024). Amphotericin B in liposomal AmBisome is much less toxic and therefore has a better effect as it targets the host cells of the parasite (macrophages) though it is very expensive, making it largely unavailable in the resource-poor areas where leishmaniasis is most common (Wasan *et al.*, 2022). The first oral drug to be registered for leishmaniasis, miltefosine, was an important development (Palić *et al.*, 2022). Nevertheless, its application is made complex by gastrointestinal side effects and especially teratogenicity, making it important that stringent contraception among women of childbearing age is taken (Bradley *et al.*, 2023). In addition, it has a long half-life, which encourages development of resistant strains in case of poor adherence (Nande and Hill, 2022). Paromomycin is used as an alternative strategy, an aminoglycoside antibiotic, which has variable management in various geographical locations and species of *Leishmania* (Alves *et al.*, 2025). Other than chemotherapy, there are other vector control measures like indoor residual spraying and insecticide treated nets, which are necessary but not enough individually (Fig. 1) (Mulebeke *et al.*, 2025). They are hampered by logistical issues, resistance to insecticides in sand flies and environmental issues (Kumari *et al.*, 2025). The resultant toxicity, cost, complexity in administration, and growing resistance towards the current strategies results in a dire need to come up with new low cost therapeutic agents such as AgNPs (Husain *et al.*, 2023).

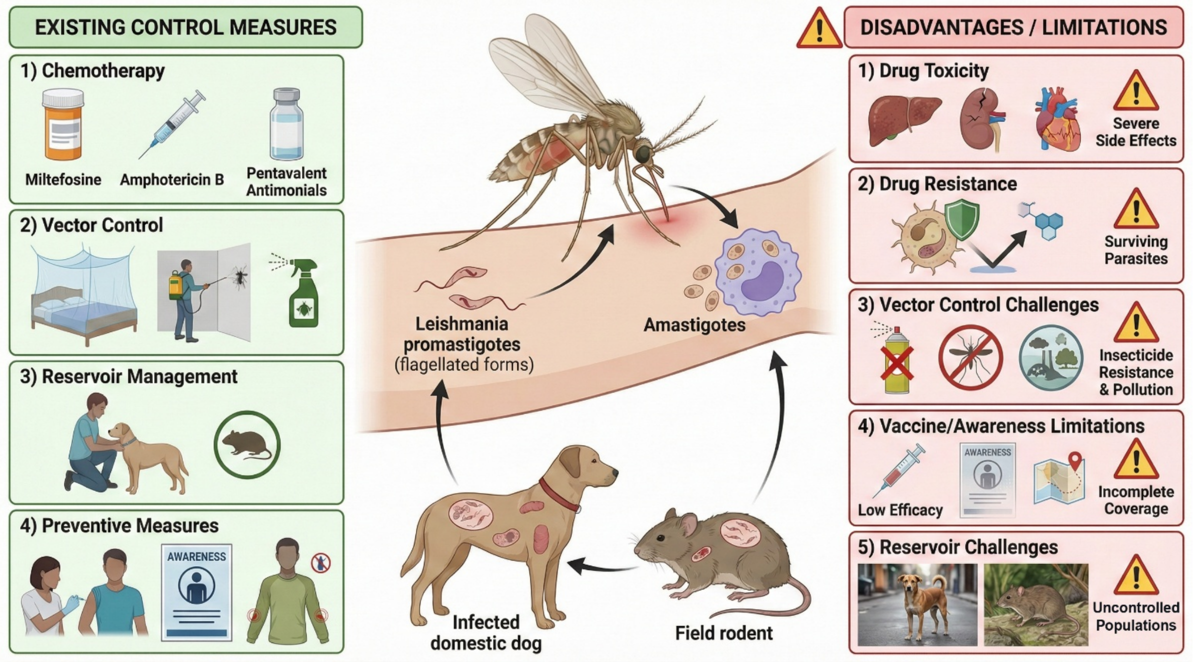

Fig. 1: Existing control measures for leishmaniasis and their disadvantages.

Nanotechnology in Parasitic Disease Control: Nanotechnology has transformed the sphere of medicine by making it possible to manipulate matter in the atomic and molecular scale, or in other words, in the range of 1 to 100 nanometres (Husain *et al.*, 2023). Nanotechnology has provided a paradigm shift of traditional "molecular" medicines, especially parasitic drugs, to "particulate" ones (Kumar *et al.*, 2022). The general strength of nanoparticles is the combination of their distinctive physicochemical characteristics, which include ultra-small size, large ratio of surface area to volume, and modifiable surface reactivity. These physicochemical properties of nanoparticles enable them to behave with the biological systems in an interactivity that large materials cannot (Desai *et al.*, 2025). The main problem in the sphere of the control of parasitic diseases has never been bioavailability: how to deliver the medication to the very place where the parasite is located without harming the host (Nemati *et al.*, 2024). As *Leishmania* parasites live in the macrophage phagolysosomes, to work, the traditional medicines have to penetrate several biological membranes and survive the acidic and hostile environment of the macrophage interior (Palomino-Cano *et al.*, 2024).

Nanoparticles provide a special solution to this delivery problem and this method is referred to as passive targeting (Umar *et al.*, 2022). Macrophages are the scavengers of the immune system; the main task which they perform is the recognition and ingestion of foreign particulate matter (Li *et al.*, 2022). Researchers can also take advantage of this natural physiological process by designing antiparasitic agents as nanoparticles (Bajwa *et al.*, 2022). Nanoparticles are readily taken up by the same cells that harbor the infection, enabling targeted action within infected cells (González-Vega *et al.*, 2022). It leads to the accumulation of the therapeutic agent in the infected macrophage in vast amounts which contributes to a large increase in drug concentration in the cell along with a decrease in systemic exposure and toxicity to other organs (Mantovani *et al.*, 2022). In the treatment of intracellular pathogens, this targeted delivery property is the answer to the promise of nanomedicine (Xu *et al.*, 2023).

Various studies have been conducted on a wide range of nanocarriers for parasitic diseases (Mengarda *et al.*, 2023). One of the earliest causes of successful translation to be clinically translated (e.g. AmBisome) was the use of liposomes, spherical vesicles made of lipid bilayers, which demonstrated the effectiveness of the targeted method (Riccardi *et al.*, 2024). Nanoparticles made of biodegradable polymers such as chitosan or PLGA which are polymeric, have demonstrated the ability to protect unstable drugs against degradation and provide time-release of drugs (Riccardi *et al.*, 2024). Nevertheless, recently metallic nanoparticles have become under scrutiny with their dual functionality (Chandrakala *et al.*, 2022). In contrast to liposomes or polymers which are mostly passive carriers of other drugs, metallic nanoparticles, including gold (AuNPs), zinc oxide (ZnO-NPs), and in particular AgNPs have an antiparasitic activity of their own (Sadiq *et al.*, 2023). They are nano-antibiotics or nano-antiparasitic in themselves (Al-Awsi *et al.*, 2023).

AgNPs are of particular interest because they possess broad antimicrobial activity (Luceri *et al.*, 2023). Silver has been used to prevent infections for thousands of years, and its effectiveness has increased greatly with nanoscale formulations (Orlando *et al.*, 2021). Besides killings directly, AgNPs have been found to alter the host immune system, which may overturn immunosuppression of the parasite (Król *et al.*, 2023). The development of what is currently known as green synthesis, which involves the use of plant extracts, fungi or bacteria to synthesize nanoparticles, has only contributed to the popularity of this technology (Jeevanandam *et al.*, 2022). This environmental-friendly method eliminates the use of toxic chemical reducing agents and may frequently end in nanoparticles capped with biological molecules which increase stability and biocompatibility (Singh *et al.*, 2023a). Therefore, nanotechnology in parasitism disease control is not only a novel method of delivery but also a system that combines targeted delivery, inherent lethality, and immunomodulation (AlGabbani, 2023).

Mechanisms of Antileishmanial Action of Silver Nanoparticles: AgNPs have diverse mechanisms of action against *Leishmania*. Antileishmanial activity of silver nanoparticles has been observed in multiple studies by different modes of action. These mechanisms of action of AgNPs include oxidative stress induction, disruption of cell membrane, and destruction of the biomolecules (Figure 2).

Oxidative Stress Induction: Oxidative stress induction through the generation of reactive oxygen species (ROS) is widely recognized as a primary mechanism by which AgNPs exert their leishmanicidal effects (Roy *et al.*, 2025). Oxidative damage is the only way in which *Leishmania* parasites are susceptible to since they have a specific and somewhat weak antioxidant defence system as compared to mammalian cells (Pawłowska *et al.*, 2023). In comparison to host cells, which use catalase and glutathione peroxidase to mitigate the effects of oxidative threats, *Leishmania* depends significantly on the trypanothione/trypanothione reductase system (de Souza *et al.*, 2025). Internalization of AgNPs by the parasite or the host macrophage involves the fast generation of excess amounts of ROS, such as superoxide anions, hydroxyl radicals, and hydrogen peroxide (Zhang *et al.*, 2023).

The increase in intracellular ROS overloads the small amount of antioxidant that the parasite possesses and results in a condition of intense oxidative stress (Pawłowska *et al.*, 2023). The effects of this are disastrous for the parasite: the excessive amount of free radicals assaults cellular lipids, which results in lipid peroxidation (Mohammed *et al.*, 2025). This eliminates the polyunsaturated fatty acids in the cell membrane of the parasite, weakening the structure and fluidity of the parasite (Rahman *et al.*, 2024). Moreover, the ROS cause direct oxidative damage to DNA and proteins (Zhao *et al.*, 2023). Research has reported that AgNP treated promastigotes experience indicators of apoptotic like cell death such as DNA fragmentation and exposing phosphatidylserine on the outer membrane leaflet (Alves *et al.*, 2023). Basically, the nanoparticles transform the intracellular environment of the parasite into a poisonous oxidation chamber, which causes a system of events resulting in collapse of the metabolic system and cell death (Król *et al.*, 2023).

Disruption of Membranes: In addition to chemical toxicity, AgNPs have a direct physical and electrostatic attack on the *Leishmania* parasite (Guerra *et al.*, 2022). *Leishmania* cells are negatively charged on the surface of the cell because it contains lipophosphoglycan (LPG) and other surface proteins (Kaushal *et al.*, 2023). The parasite is electrostatically drawn to AgNPs that release silver ions or have a positive zeta potential (Zhang *et al.*, 2023). When there is contact, the nanoparticles may attach to the cell membrane and cause serious structural changes (Pei, 2022). This mechanism has been visualized through electron microscopic studies which indicated that a number of pits or pores developed in the parasite membrane after the exposure of the parasite to AgNPs (Ferraz *et al.*, 2026).

The loss of membrane semi-permeability is critical and the result of the pitting effect (Sati *et al.*, 2024). The breach of the membrane barrier leads to the extracellular space leakage of intracellular components that are vital, including proteins, metabolic enzymes, and ions (Wang *et al.*, 2024). In addition, the communication interferes with the parasite to control its internal conditions (Bricarello *et al.*, 2023). Among the most important effects, the depolarization of the mitochondrial membrane potential should be mentioned (Zaib *et al.*, 2022). The mitochondrion is the engine of the *Leishmania* parasite (with one, large mitochondrion); with the violation of the membrane integrity, as well as the loss of the potential, the synthesis of ATP is interrupted (Benaim and Paniz-Mondolfi, 2024). Such a bioenergetic collapse, coupled with the physical loss of cytoplasm, causes striking morphological alterations, including cell shrinkage and flagellar loss in promastigotes, leading to eventual death either through necrosis or apoptosis (Chauhan *et al.*, 2024).

Disruption of Biomolecules: The third significant pillar of AgNP toxicity is the biochemical interference with vital biomolecules that are parasite-specific (Wood *et al.*, 2024). The silver ions present in the nanoparticles behave like soft acids and have a high affinity with soft bases, namely sulfur and phosphorus (Kyziol-Komosinska *et al.*, 2024). The thiol (-SH) groups of such amino acids as cysteine, which are essential elements of most enzymes, contain a lot of sulfur (Shah *et al.*, 2022). After ionic silver penetrates into the cytoplasm, the covalent binding of silver ions between the thiol groups disorganizes the three-dimensional structure of proteins and inhibits important enzymatic pathways (Esmailzadeh *et al.*, 2024).

One of the key targets is trypanothione reductase, which is a vital enzyme of the parasite to survive and resist effects of oxidative stress (González-Montero *et al.*, 2024). Silver ions block the activity of this enzyme by binding to the active site of this enzyme, rendering the parasite unable to counteract the ROS, enhancing the effect of the oxidative stress mechanism mentioned above in a synergistic manner (Zhang *et al.*, 2023). Also, the silver ions bind strongly to phosphorus moieties of the DNA backbone (Sun *et al.*, 2022). Silver can substitute itself into parasite DNA and prevent replication and transcription (Zhang *et al.*, 2023). This blockade halts the cell cycle, which is usually at G2/M phase, and the parasite will not divide and multiply (Wang, 2022). This multi-targeted assault, which destroys the membrane, enzymes, and prevents DNA replication, gives it more than an advantage over conventional medications that will typically only attack a single pathway (Doostmohammadi *et al.*, 2024).

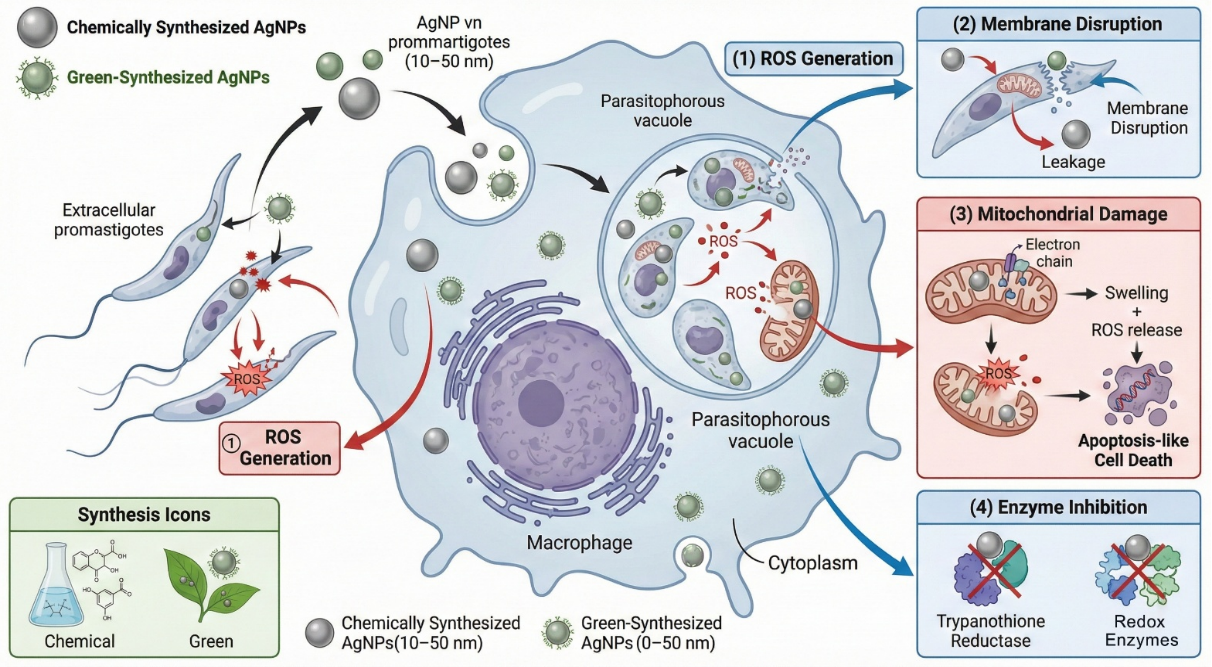

Fig. 2: Mechanism of action of silver nanoparticles against *Leishmania.*

Table 1: Experimentally validated silver nanoparticles against Various *Leishmania* Species

Sr. No.	Nanoparticle Type	Synthesis of Nanoparticles	Size of Nanoparticles	Shape of Nanoparticles	*Leishmania* Species	Target Parasitic Stage	Dose Rate	Mechanism of Action	Results	References
1.	AgNPs (ginger extract)	Green-*Zingiber officinale*	Not specified in text (nano-range confirmed by characterization)	Not specified	*L. infantum, L. tropica*	Promastigotes	0.156–80ppm	ROS increase, apoptosis induction	Dose-dependent inhibition; apoptosis reported	(Dalimi *et al.*, 2024)
2.	AgNPs (myrrh)	Green-*Commiphora molmol*	~49 nm	Not specified	*L. major*	Promastigotes and tissue amastigotes	10-150µL preparation doses	Growth inhibition, cellular damage	Promastigote inhibition and lesion healing in mice	(Awad *et al.*, 2021)
3.	Biogenic AgNPs	Biological-*Fusarium oxysporum*	Not specified	Not specified	*L. amazonensis*	Promastigotes & amastigotes	Not specified	ROS-mediated and membrane damage	Reduced parasite viability and macrophage infection	(Fanti *et al.*, 2018)
4.	AgNPs (ginger root)	Green-plant extract	Not specified	Not specified	*L. major*	Promastigotes & amastigotes	IC50 ~2–5ppm range	Programmed cell death markers	Significant parasite reduction	(Mohammadi *et al.*, 2021)
5.	AgNPs (thyme)	Green-*Thymus vulgaris*	Not specified	Not specified	*L. major*	Promastigotes & amastigotes	IC50 ~3µg/mL	Apoptosis and proliferation inhibition	Strong inhibition of both stages	(Zaki *et al.*, 2023)
6.	Ferritin-encapsulated AgNPs	Engineered protein-encapsulated	Nanoscale (<20 nm reported)	Spherical (reported in characterization)	*L. infantum*	Promastigotes & amastigotes	Lower than antimony comparator doses	Trypanothione reductase inhibition	Greater antiproliferative effect than antimony	(Baiocco *et al.*, 2011)
7.	AgNPs (*Eucalyptus camaldulensis*)	Green-plant extract	~10–31 nm	Spherical	*L. tropica*	Promastigotes & amastigotes	1.25–3.75µg/mL	ROS-linked cytotoxicity	Significant killing at low concentration	(Zein *et al.*, 2022)
8.	AgNPs + meglumine antimoniate	Green + drug combination	30–40 nm	Round	*L. major*	Promastigotes & amastigotes	Combo IC50 lower than single agents	Synergistic killing; immune activation	Greater parasite reduction than monotherapy	(Albalawi *et al.*, 2021)
9.	AgNPs (*Cuminum cyminum*)	Green-plant extract	Not specified	Spherical	*L. tropica*	Promastigotes & amastigotes	N/A	Nitric oxide–mediated macrophage activation	Reduced parasite proliferation	(Bagirova *et al.*, 2020)
10.	AgNP–PVP–antimonial composite	Biological (*Aspergillus flavus*) + polymer	<10 nm	Not specified	*L. amazonensis*	Promastigotes	~50µg/mL (drug component)	Membrane & ultrastructural damage	Lower infection index	(Harun-Ur-Rashid *et al.*, 2025)

Safety, Cytotoxicity, and Environmental Concerns: Although the therapeutic use of AgNPs is unquestioned, safety profile is a complicated and vital topic of study that needs to be addressed before the use of AgNPs in clinical practice (Dias *et al.*, 2025). The physicochemical characteristics of AgNPs such as size, concentration, and surface coating also have an inherent relationship with toxicity (Noga *et al.*, 2023). One of the biggest issues that should be considered when creating antileishmanial nanomedicine is the possibility of cytotoxicity to host mammalian cells (Zhang *et al.*, 2025). The Selectivity Index (SI) is commonly used in different studies to assess the cytotoxicity, which is a ratio of the cytotoxic concentration of host cells (usually macrophages or fibroblasts) to the effective inhibitory concentration of the parasite (Asghari *et al.*, 2022). Ideal The AgNPs are expected to have a high SI, so they can kill parasites at low concentrations without damaging host cells (Zhang *et al.*, 2023). But the pathways that cause the death of parasites, namely oxidative stress and mitochondrial destabilization, may cause damage to mammalian cells provided that the dose is not controlled (Pawłowska *et al.*, 2023). Studies have shown that over time, AgNPs may be deposited in the Reticuloendothelial System (RES), mainly liver, spleen, and lungs, causing organ specific toxicity or chronic inflammation (Noga *et al.*, 2023). Particular concern is given to smaller nanoparticles (less than 10nm) since they can enter nuclear membranes easier and cause genotoxicity in host cells (Encinas-Gimenez *et al.*, 2024).

In order to address these risks, the field has been shifting more towards a so-called green synthesis or biogenic synthesis (Fried *et al.*, 2022). AgNPs prepared with plant extracts or microbial metabolites tend to have a so-called protein corona or phytochemical coating, which stabilizes the nanoparticles and enhances non-specific toxicity of chemically synthesized nanoparticles to human cells (Mikhailova, 2024). Although with these developments, environmental safety has been a major impediment (Aiman *et al.*, 2024). AgNPs are bound to be released into the ecosystem because of the large-scale production and consumption of the product (Huang *et al.*, 2022). Silver is very toxic to aquatic life such as fish, algae, and useful bacteria even when in low quantities (Mat Lazim *et al.*, 2023). It is a legitimate concern that the release of AgNPs into wastewater may disrupt the microbial communities of the environment or become bioaccumulative in the food chain (Ramzan *et al.*, 2022). Thus, the creation of AgNP-based treatments for leishmaniasis cannot be created in a vacuum; it must be the holistic One Health approach that discusses the lifecycle of the nanomaterial (Bessa *et al.*, 2024). Disposing of waste and conducting significant research in ecotoxicology are stringent steps to guarantee that the resolution of a human health crisis does not lead to an ecological one (Pathak *et al.*, 2022).

Translational Barriers and Clinical Prospects: Although there is sufficient in vitro evidence on the effectiveness of AgNPs in combating *Leishmania*, no formulation of AgNP has been clinically approved to treat leishmaniasis yet (Badirzadeh *et al.*, 2022). These six barriers make top bench translation and bottom bedside implementation not to be closely linked. The biggest obstacle is the unstandardization (Li *et al.*, 2025). The academic literature is full of different synthesis techniques, which have produced AgNPs of completely different sizes, morphologies, surface charges, and stability characteristics (Abbas *et al.*, 2024). To win regulatory approval of a nanomedicine, as with FDA or EMA, it has to be prepared with a high level of reproducibility and characterization (Musazzi *et al.*, 2023). Recent approaches to green synthesis, although being environmentally friendly, can be more or less variable in batch-to-batch mode, which is not acceptable in drug production (Fig. 3) (Bertoni *et al.*, 2022).

Moreover, the lack of detailed in vivo data is severely lacking (Sailer *et al.*, 2023). Most of the existing studies are only limited to cell culture models (Urzì *et al.*, 2023). Although they present evidence of concept, they lack consideration of the complex pharmacokinetics (PK) and pharmacodynamics (PD) in a living organism (Alikhani *et al.*, 2025). Problems including the so-called protein corona effect, i.e. the coating of nanoparticles with blood proteins, which cause changes in their biological identity and targeting properties, can only be fully described in animals (Panico *et al.*, 2022). This sequestration of nanoparticles by the liver and the spleen, though useful in the treatment of visceral leishmaniasis, brings up the issues of chronic toxicity and organ deposition in the long-run that are not visible in short-term research (Kumar *et al.*, 2022).

Nonetheless, the clinical outlook is not as bad as it may seem (Mansur *et al.*, 2023). Topical formulations of Cutaneous Leishmaniasis (CL) result in the most immediate and viable route to the clinic (Severino *et al.*, 2022). Topical agents generally have less regulatory obstacles compared to systemic drugs because they have minimal systemic absorption and toxicity (Zhao *et al.*, 2024). There may be non-invasive alternatives to the painful intralesional injections that are currently utilized by hydrogels or ointments based on AgNPs and offered to a patient (Drosopoulou *et al.*, 2025). Moreover, nanomedicines are also becoming more regulated because an increasing number of nano-formulations (such as lipid nanoparticles of vaccines) are approved, which may soon open the door to metallic nanoparticles (Shi *et al.*, 2025).

Conclusions: Leishmaniasis has been a significant health burden in the world, which has been perpetuated by the shortcomings and ineffectiveness of the available chemotherapeutic agents. A therapeutic gap has arisen because of the development of drug resistance and extreme toxicity of pentavalent antimonials, and nanotechnology is ideally placed to occupy this gap in therapy. This review has provided the real academic evidence on the use of AgNPs as an effective alternative control method. AgNPs have shown significant leishmanicidal effects in preclinical research through oxidative stress induction and membrane disruption, and interference with metabolism. The prospects of the technique of green synthesis provide one more benefit of cost-effectiveness and less environmental impact, which is paramount to the resource-restricted environments where this disease prospers. The way between the laboratory and the patient is complicated by the necessity of strict standardization, extensive in vivo safety tests, and evident legal frameworks, however. Overcoming these obstacles should be targeted in future work especially in terms of creating standardized production approaches and finding synergistic combination therapies. AgNPs have the potential to change the leishmaniasis management process, providing a more efficient, convenient, and harmless treatment to millions of patients all over the world.

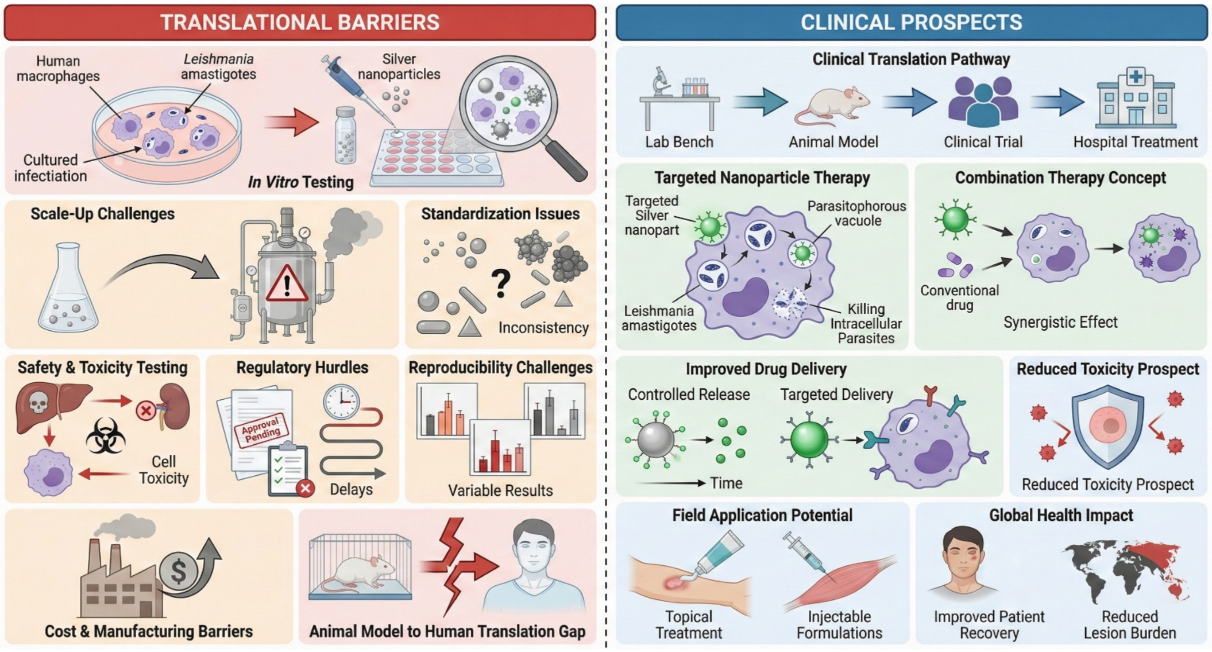

Fig. 3: Translational barriers and clinical prospects in nanoparticle-based therapies for Leishmaniasis.

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