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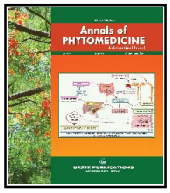

Review Article : Open Access

Exploring leishmaniasis: Contemporary modalities, potentiality of plant chemicals and green synthesized nanotherapeutics as effective leishmanicidal drugs

Neha and Sushila Devi◆

Department of Microbiology, Himachal Pradesh University, Summerhill-171005, Shimla, Himachal Pradesh, India

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Abstract

Leishmaniasis, a widely distributed contagious parasitic sickness transmitted by protozoa from the genus *Leishmania*, belonging to Trypanosomatidae family, ranking as the third most prevalent vector-borne illnesses globally, after malaria and sleeping sickness. It is well acknowledged that current pharmaceutical treatments associated with leishmaniasis treatment and other parasitic protozoan diseases lack efficiency and affordability. Additionally, current treatments are outdated and associated with several drawbacks, such as potential to damage healthy cells and the emergence of drug resistance, which might pose a serious challenge. So, there is an immediate need for innovative and effective substitutes to these chemical treatments. Natural products and herbal therapies have now emerged as potent candidates for treating leishmaniasis. Medicinal plants and green synthesized nanocarriers are thought to be a substantial source of novel compounds with therapeutic benefits; therefore, new therapeutics can be found in large numbers in the plant kingdom. This review article examines both conventional treatments and the novel approach of plant-based green synthesized nanodrugs as a promising therapeutic intervention to cure leishmaniasis, alongside discussing their futuristic improvements.

1. Introduction

Leishmaniasis is recognised as a serious public health problem affecting approximately 98 countries, most of which are developing nations. A World Health Organization data page states that, leishmaniasis causes between 20 to 30,000 deaths and over 0.7 to 1 million new cases annually. An estimated 50 to 90,000 new cases of visceral leishmaniasis (VL) and 0.6 to 1 million new cases of cutaneous leishmaniasis (CL) occurs globally every year (Nigatu *et al*., 2021). In Asia, Africa, Latin America as well as the Mediterranean region, leishmaniasis has a terrible impact on the mortality rate and morbidity rate of the population. Visceral leishmaniasis, also known as kala-azar, is the most dangerous form of the disease as it can be fatal without any therapeutic approach. Kala-azar is mainly caused by *Leishmania infantum* and *Leishmania donovani* which poses the greatest public health risk, whereas cutaneous leishmaniasis is caused by *Leishmania tropica*, *Leishmania amazonesis and Leishmania major* and is the most common form of the disease causing skin ulcers the mucocutaneous form is the most disabling form that affects the mucus membranes of the mouth, nose and throat (Boggild *et al*., 2019; Gupta *et al*., 2022). Climate change and human impacts such as deforestation and urbanisation have contributed to the emergence of leishmaniasis hotspots globally over the past decade, and some models suggest that sandflies will continue to spread due to climate change. However, only a small proportion of less than 50 of the approximately 1000 sand fly species (*Phlebotomus*) found globally are known to transmit leishmaniasis. Other, less significant transmission routes include blood transfusions, intravenous drug use in immunocompromised individuals, needle sharing post-organ transplants, congenital transmission and, mother-to-child transmission (Boggild *et al*., 2019).

The treatment of leishmaniasis is based on antimonial drug therapy, which is being used today despite of its considerable undesirable ill-effects and far from having appropriate biological properties such as the myriad of negative effects, ineffectiveness and high toxicity (Gutiérrez-Rebolledo *et al*., 2017). However, the low treatment compliance is due to the development of drug resistant strains. Therefore, it has been difficult for pharmaceutical researchers to find new antileishmanial medications with minimal toxicity and a good therapeutic index. According to World Health Organisation, plants are increasingly recognized as a suitable source for finding the alternative drugs with cost-effectiveness and a strong safety profile for a variety of health concerns (Bekhit *et al*., 2018). Therefore, the development of novel medications for the treatment of leishmaniasis is urgently needed. Based on the Ayurvedic principles, each and every substance, also involving poison, is believed to be endowed with therapeutic properties, as explained within the branch of Ayurveda dealing with medicinal plants and it depends entirely on the competence of the physician whether a drug itself poses risks or benefits (Divya *et al*., 2023). Plant extracts are considered the most abundant source molecules with a wide range of chemical structures and potential applications in food, medicine, cosmetics, agriculture and industries. Specialized research into medicinal plants typically

Corresponding author: Dr. Sushila Devi
Associate Professor, Department of Microbiology, Multifaculty building, Himachal Pradesh University, Summerhill-171005, Shimla, Himachal Pradesh, India
E-mail: negisush80@gmail.com
Tel.: +91-9418500071

begin with the biological screening of crude extracts prepared using different solvents and extraction techniques. After identifying the potentially bioactive extract, its phytoconstituents are identified using a metabolomic method, also known as biodirected fractionation to obtain a standardised extract or pure compound known as phytomedicine (Bolouri *et al*., 2022; Fitzgerald *et al*., 2020).

2. Clinical impacts of leishmaniasis

Leishmaniasis has now surpassed toxoplasmosis and cryptosporidiosis to become the third most prevalent opportunistic parasite illness, and posing significant challenges in terms of control. India is the leading country with the highest count of VL cases worldwide. Substantially, *Leishmania* species that are resistant to pentavalent antimonials are widespread, as is HIV co-infection. Throughout northwestern Ethiopia, up to 30% of VL cases have HIV co-infection. Therefore, uncompromising efforts must be made to control the disease (Shafiei *et al*., 2014; Desjeux and Alvar, 2003). Visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous or mucosal leishmaniasis (ML), are known to be the three main clinical syndromes associated with this disease. Cutaneous leishmaniasis, the most prevalent form, predominantly affects exposed body parts prone to insect bites, including ears, nose, cheeks, upper lip, thighs, forearms, hands, ankles. *etc*., leading to skin lesions, primarily ulcers, leaving permanent scars and significant functional impairment. According to Torres *et al*. (2017), the incubation period varies between one to four weeks to several years. Nearly, 95% of all cases of cutaneous leishmaniasis occur in North and South America, the Mediterranean region, Middle East and Central Asia. Syria, Afghanistan, Iran, Algeria, and Colombia contributing to over two-third of all new CL cases globally (Torres *et al*., 2017). According to a WHO manual on leishmaniasis, domestic dogs (*Canis familiaris*) serve as the principal reservoir host for the sand fly responsible for disease transmission (Romero *et al*., 2017). Multiple species of *Phlebotomus* sandflies are responsible for transmission, where *Leishmania infantum* being the only known causative factor for VL (WHO, 2012). In addition to dogs, common reservoir hosts includes jackals, foxes, wolves, and goats (Esch and Petersen, 2013). There are over 20 different *Leishmania* species associated with human infection, existing in two morphological forms, *i.e.,* amastigote and promastigote forms within mammalian and sandfly host, respectively (Wheeler *et al*., 2012). During blood-feeding, female sand fly ingests leishmanial amastigotes and further transmits infective parasitic metacyclic promastigotes into the mammalian host, after a second blood meal. Host macrophages and other phagocytic cells engulf the infective promastigote forms injected by the sandfly and transforms into amastigote form inside these cells, often resulting in cutaneous ulcers at the bite site (Serafim *et al*., 2021). Leishmanial infection in mammals can affect the spleen, bone marrow, liver, and lymph nodes resulting in symptoms such as splenomegaly and weight loss. In most infected patients, symptoms appear between three and eight months after infection, despite the parasitic incubation period may range from 10 days and upto 34 months. Anemia, organ failure or subsequent infections are the causes of death in untreated cases, which often occurs within 2 years. Male sandflies do not play any role in transmission, as only female sandflies feed on human and animal blood to fertilize their eggs. Only competent sand fly vectors or those that can carry and transmit parasites that can in turn infect humans or other host, are considered sandfly vectors (Yared *et al*., 2019).

3. Treatment strategies to combat leishmaniasis

Conventional therapies primarily include chemical therapies, with pentavalent antimonials, known to be the first-line treatment for leishmanial infection. Various other pharmaceuticals such as sodium stibogluconate, glucantime, meglumine antimoniate and pentostam are often utilized as alternatives to pentavalent antimonial preparations. The two primary categories of leishmaniasis therapies include conventional or chemical treatments and novel treatments. Pentavalent antimonials, are often administered intramuscularly or intravenously, offering high bioavailability and excellent distribution in the liver and spleen (Muñoz-García *et al*., 2019). Antimonial agents when administered orally are ineffective, and necessitating parenteral administration over a period of time makes them more effective. However, these chemical drugs have several side effects and are often very expensive. Other recent advances in leishmaniasis treatment involve approaches such as electrotherapy, cryotherapy, nanotechnology, and multidrug therapy, *etc*., as depicted in Figure 1.

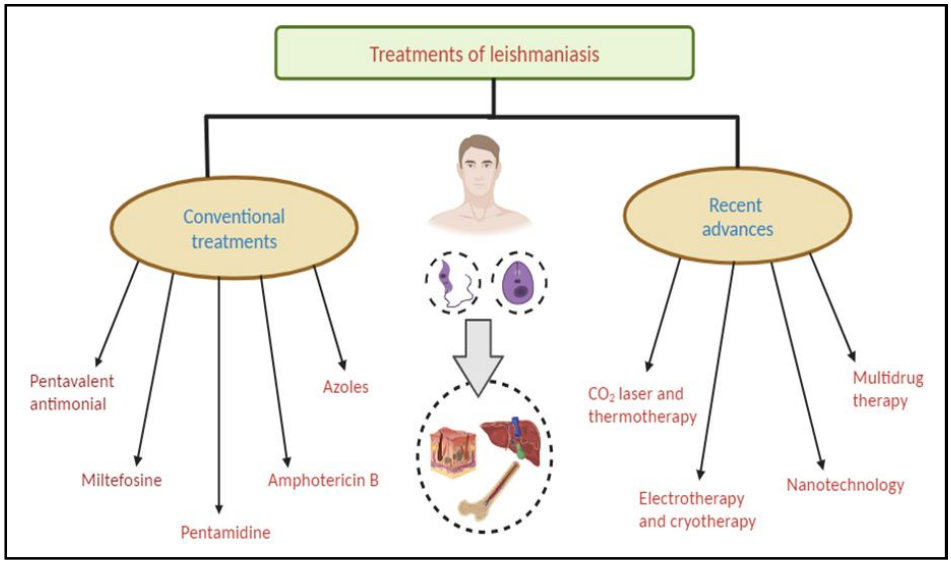

Figure 1: Treatment options for leishmaniasis.

According to Lamba and Roy (2023), antimonial drugs kill the *Leishmania* parasite by inhibiting its DNA topoisomerase I activity, preventing its glucolysis pathway, suppressing ADP phosphorylation, interfering with beta-oxidation of fatty acids and blocking non-specific SH groups of proteins of amastigote form (Lamba and Roy, 2023).

3.1 Conventional treatments

Pentavalent antimonials (Sbv) have stood as the choice of drug for approximately 7 decades. These are the preferred pharmaceutical treatments for all forms of leishmaniasis. Sodium stibogluconate (SSG) and meglumine antimoniate (MA) are the two main formulations used. The pentavalent antimonials (Sbv) act as a prodrug molecule, which gets converted into an active SbIII form inside the organism. SbIII is a borderline metal ion with a strong affinity for ligands containing sulphur and nitrogen. The antileishmanial effects of SbIII form against leishmaniasis likely result from its interaction with sulfhydryl-containing biomolecules such as proteins, enzymes, peptides and thiols. Amphotericin B, a broad-spectrum antifungal agent, is also utilized for treating *Leishmania* infection. Amphotericin B is administered to patients with leishmaniasis in two forms: liposomal amphotericin B and amphotericin B deoxycholate (Roatt *et al*., 2020). Miltefosine, another alkyl phosphocholine drug of choice (Caridha *et al*., 2019), is administered to immunocompetent individuals regulating cell surface receptor expression, phospholipase activation, protein kinase C, inositol metabolism and several other mitogenic pathways, ultimately leading to apoptosis. By altering cell membrane production and signalling pathways, this drug triggers apoptosis, effectively eliminating parasites both *in vitro* and *in vivo* (Verma and Dey, 2004).

Azoles, another class of chemotherapeutic agents are antifungal drugs primarily evaluated for cutaneous forms, have been assessed for their efficacy. Oral antifungal agents that are well tolerated include the imidazoles and triazoles. These medications exert their antileishmanial effect against certain species by inhibiting 14-demethylase, a crucial enzyme in the process of sterol production, thereby preventing the formation of parasitic cell membranes. Fluconazole, for example, is used alongside other azoles to treat *Leishmania major* (Roatt *et al*., 2020).

3.2 Recent advances in combating leishmaniasis

Parasitic treatment is associated to numerous ill-effects, such as gastrointestinal distress, nausea, headache, elevated creatinine levels, vomiting, diarrhea, *etc*., which is why new treatment methods have been introduced to overcome the drawbacks of pentavalent drugs. Recent advanced treatment comprises of CO_2 laser therapy, thermotherapy, combination therapy, nanotechnology, *etc*.

Both thermotherapy and CO_2 laser therapy are simple methods of applying external heat to damaged tissue, aiming to accelerate the healing process of skin injuries or lesions. These approaches directly target the parasite, leading to better treatment outcomes with fewer side effects compared to intralesional antimonials. According to a clinical trial, intralesional antimonials using CO_2 laser thermotherapy achieved a higher cure rate of 93.7%, compared to combination therapy (Shamsi *et al*., 2011). Stimulation with electric fields is emerging as one of the potential tool for combating microbial infections. Researchers have demonstrated that exposure to electrical currents can help heal skin lesions and stubborn ulcers (Roatt *et al*., 2020). The newly formed skin also has superior stretching properties than naturally produced skin. *In vitro*, electric fields influence the survival, motility and clumping of promastigote forms of the parasite (Dorsey *et al*., 2018). Cryotherapy, or cryosurgery, involves using liquid nitrogen at a temperature of -195°C, generating intracellular ice causing cell rupture and local ischemia necrosis, effectively eliminating parasites from lesion. When these lesions are treated with cryotherapy once or twice a week, the efficiency is over 95% (Roatt *et al*., 2020). Combination of antileishmanial drugs, have been shown to lessen the risk of possibility of harmful side effects and drug resistance. Additionally, combined therapy or multidrug therapy intends to shorten treatment length, lessen negative effects, reduce parasitic resistance, minimize expenses, as well as enhance treatment options, in particular for severe VL cases (Monge-Maillo and López-Vélez , 2013; Roatt *et al*., 2014). Although, allopurinol and intravenous pentostam are effective, relapses are noted in the first month of the therapy. Paromomycin and sodium stibogluconate are often used in combination for treating VL (Aderibigbe, 2017). Treatment with combination therapy is recommended to those patients, which have been unresponsive for monotherapy utilizing pentavalent antimonials (Sbv). In india, particularly for *Leishmania donovani* infected individuals, majority of the research studies were carried out and it was reported that combining AmB-L in 5 mg/kg/day with multiple miltefosine drug treatments resulted in greater effectiveness, *i.e*., 98 per cent vs. 91 per cent.

Nanotechnology represents advancement in pharmaceutical and medical industry, showcasing significant progress in combating various bacterial, fungal, viral, and parasitic infections (Saleem *et al*., 2019). Diverse nanocarriers are utilized with polymeric nanoparticles and liposomes for their effective uptake by macrophages, target molecules in leishmaniasis. Liposomes have the ability to encapsulate and distribute both hydrophobic and hydrophilic compounds by activating their surfaces. Being positively charged molecules, liposomes can be easily taken up by macrophages, rendering them highly suitable for leishmaniasis therapy (Saleem *et al*., 2019). In a recent *in vitro* investigation and preclinical testing comparing AmB loaded amine modified carbon-based nanoparticles (f-Comp-AmB) with AmB-D, revealed impressive antileishmanial activity (Gedda *et al*., 2020). Nanoparticle-based diagnostic methods, employing nanosensors, have been developed for detecting leishmanial infections. For example, a diagnostic kit containing four oligonucleotide probes targeting leishmanial DNA in combination with gold nanoparticles (AuNP's) have shown efficacy in identifying leishmaniasis in dogs (Sazgarnia *et al*., 2013). Nanovaccines are emerging as a fresh vaccination approach, stimulating cell-mediated and humoral immune response efficiency (Nafari *et al*., 2020). Lipidic nanoparticles (NP's) loaded with the plasmid pVAX1-NH36 served as a new leishmaniasis nanovaccine. As per the results obtained by Urena-Burquez *et al*. (2019), these advancements in nanotechnology demonstrated that the degree of stability proved more than 84% across all the samples, that might pose a potential technique for futuristic research purpose (Urena-Burquez *et al*., 2019).

3.3 Limitations associated to existing treatments

Chemical treatments are facing numerous challenges due to the growing prevalence of antimony-resistance among parasites and unavailability of true antileishmanial drugs for treating leishmaniasis. Current

pharmaceutical drugs such as pentamidine (antimicrobial), amphotericin B (antifungal), or miltefosine (antitumour) are utilized. All these chemical drugs are associated with high costs, low availability and low efficacy as of the emergence of parasitic resistance to miltefosine and amphotericin B in the clinical parasitic control. Sequentially, the variables underlying protective immunity in leishmanial pathogenesis are not understood well. A vaccine candidate, whether prophylactic or preventive, continues to be an unachieved goal. Furthermore, the emergence of insecticide-resistant sand-flies in endemic regions poses a significant challenge for existing elimination techniques. Therefore, in lieu of the limited drug treatment and the unavailability of vaccines, there is always a need for a true necessity of a true antileishmanial drug.

4. Plant-derived compounds in combating leishmaniasis

Over the course of history, plants have profoundly exerted an influence on culture, economic endeavors and intellectual pursuits. A broad spectrum of plant species, encompassing medicinal plants, weed species and aromatic plants holds substantial medicinal and economic value (Sharma *et al*., 2022). In the hunt for novel, potent and effective molecules, several traditional medical stems and practices of worldwide significance have recently been considered. The lack of an effective drug has prompted researchers to reassess historical folk treatments as potential sources for new pharmaceuticals associated with minimal toxicity and improved efficacy (Sinha and Sardana, 2018). Plants constitute natural assets that have been extensively explored for bioactive antileishmanial and immunomodulatory properties. Extracts form plants possess a wide range of biomolecules capable of naturally destroying *Leishmania* parasites and stimulating the immune system, (Bekhit *et al*., 2018) as illustrated in Figure 2.

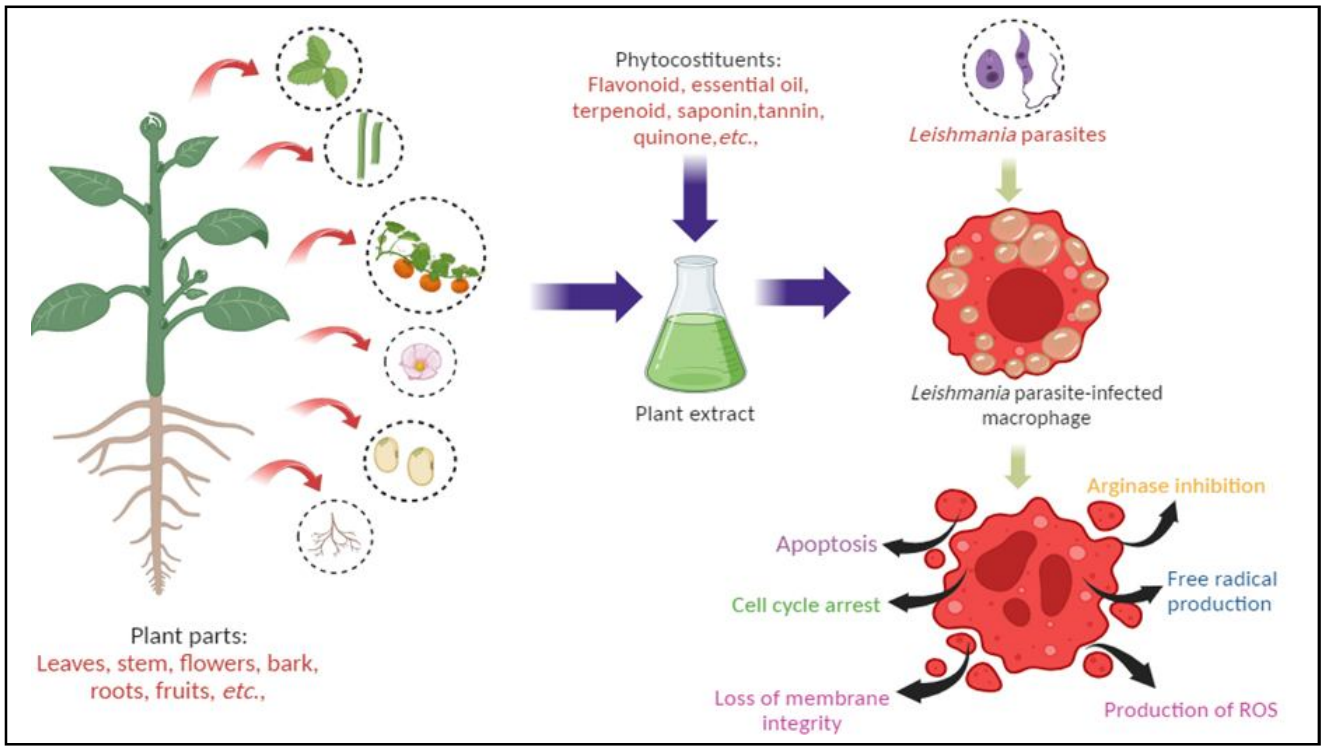

Figure 2: Role of phytoconstituents in exterminating leishmanial parasites.

Plant-based drug discovery encounters multiple challenges in the quest for innovative compounds with leishmanicidal potency (Mahmoudvand *et al*., 2014). Herbal therapy offers several significant advantages crucial for novel drug discovery including efficacy, high stability, more potency, fewer side-effects and less toxicity (Sarkar *et al*., 2013; Wink, 2012). It is estimated that approximately 25% of pharmaceuticals are either directly or indirectly derived from herbal ingredients. The main benefits of these compounds can only be demonstrated in *in vitro* studies and these herbal molecules are still in preliminary phase of preclinical testing. Due to the underdeveloped nature of this subject matter, these compounds need to be used in clinical practices (Vila-Nova *et al*., 2013; Colares *et al*., 2013). A range of herbal preparations from plant chemicals, such as flavonoids, alkaloids, tannins, saponins, indoles, sesquiterpenes, isoflavonoids, glucans and polysaccharides, are known to have immunomodulatory effects against a diverse array of diseases (Bekhit *et al*., 2017). Several plant species exhibits an inhibitory effect against certain parasites owing to the presence of these phytoconstituents.

According to Bahmani *et al*. (2015), one such plant of interest is *Artemisia annua* containing compounds such as artemisinin and artemether, displaying excellent antimalarial and antiparasitic properties (Bahmani *et al*., 2015).

Phenolics encompass a diverse group of heterogeneous compounds characterized by a benzene ring coupled with a hydroxyl group. Flavonoids, a subset of polyphenolic compounds plays a significant role as antioxidant, anticancerous and antileishmanial agents, possing a remarkable protective role against membrane damage (Manjolin *et al*., 2013). Synthetic flavonoid dimers have demonstrated the ability to enhance the intercellular accumulation of drugs, thereby preventing

drug resistance by affecting ATPase pump activity. Flavonoid compounds like catechins can form complexes with the parasitic cell wall, affecting processes that require cell linkage, thereby inhibiting parasitic growth and proliferation (Wong *et al*., 2014). In a study conducted by Manjolin *et al*. (2013), it was stated that flavonoids with low cytotoxicity, including fisetin, considered as the most potent alkaloid, 7,8-hydroxyflavone, quercetin and luteolin, inhibiting the arginase enzyme of the *Leishmania* parasites (Manjolin *et al*., 2013).

Some studies revealed that, essential oils perform an extremely significant role in controlling *Leishmania* parasite and sandflies, serving as a vector to this disease. The effectiveness of essential oils against endemic *Leishmania* species causing CL and VL has been the subject of several findings (Machado *et al*., 2014). Castor bean oil extracted from *Ricinus communis* seeds one is the best example of an essential oil, which possesses notable antileishmanial potential.

Terpenes, hydrocarbons composed of isoprene units, can readily penetrate within the lipid bilayer of cell membranes, leading to the disruption of their structural integrity, including the mitochondrial membrane (Colares *et al*., 2013).

According to numerous experimental studies various medicinal herbs and their different parts have been screened for antileishmanial characteristics along with the findings of their *in vitro* and *in vivo* studies respectively. Previous investigations have confirmed the antileishmanial efficacy of all medicinal plants and their constituents outlined in Table1.

Table 1: List of medicinal plants along with their respective parts exhibiting antileishmanial properties

S.No.	Name of the plant	Common name	Plant parts used	Active compound	Parameters studied	References
1.	*Origanum compactum*	Benth	Leaf, Stem	Carvacrol, thymol, p-cymene carvacrol, terpenine	N-hexane extract offers highest antileishmanial efficacy in comparison with glucantime (positive control)	Bouyahya *et al*., 2018
2.	*Urtica dioica*	Stinging nettle	Leaves	Gallic acid	*In vivo* analysis revealed greater reduction in lesion size with Intralesional treatment compared to amphotericin B	Badirzadeh *et al*., 2020
3.	*Ricinus communis*	Castor oil plant	Leaves, seeds, castor	Alkaloid-ricinine	*In vivo* studies with the alcoholic extract of *Ricinus comminus* leaf have shown hepatoprotective effect in rats	Ghani *et al*., 2023
4.	*Chenopodium ambrosioides*	Jesuit's tea	Leaves	Essential oil	The essential oil displayed moderate level of toxicity on macrophages of the BALB/c mouse	Monzote *et al*., 2014
5.	*Cinnamomum cassia*	Chinese cinnamon	Stick	Cinnamaldehyde and its derivatives	Reduction of parasitism in the spleen by 82.9% and the liver by 80.9%	Afrin *et al*., 2019
6.	*Handroanthusserratifolius*	Lapacho	Bark	Phenols	Reduction of splenic parasitism	Araújo *et al*., 2019
7.	*Haplophyllum myrtifolium* Boiss	Rutaceae	Leaves	Skimmianine (furoquinoline alkaloids)	Exhibits minimal impact on reducing lesion size within *L. tropica* infected laboratory mice	Dasgupta *et al*., 2023
8.	*Aniba riparia*	Louro	Fruits	Riparin E	Increased phagocytosis and lysosomal activity activating macrophages without preventing nitric oxide release	Costa *et al*., 2021
9.	*Thalictrum foliolosum*	Pitarangaa	Stem	Alkaloid	Inhibiting DNA topoisomerase I activity of *L. donovani*	Kumar *et al*., 2016
10.	*Anacyclus Pyrethrum* (L.)	Akarkara	Roots	Alkamides	Moderate activity against *L. donovani* amastigotes	Althaus *et al*., 2017
11.	*Ferula asafetida* oleo-gum-resin	Hing/ heeng	Roots	Sulfur compounds (Sesquiterpene coumarins)	All dosages suppressed parasite growth in both the stationary and logarithmic phases. The ELISA assay revealed a sharp decline in parasite viability	Monzote *et al*., 2014
12.	*Thymelaea tartonraira* (L.)	'Methnene el kharchi'	Stem	Gallic acid, chlorogenic acid, kaempferol, catechin, naringenin	Dichloromethane stem extract has promising activity against *L. donovani* axenic macrophages	Soltani *et al*., 2023

13.	*Lawsonia inermis* (L.)	Henna tree	Leaves	Flavonoids, terpenes, tannins, coumarins	Methanolic leaves/seed extracts reduced the number of promastigotes in *leishmania* parasites	Moutawali *et al*., 2023
14.	*Carissa edulis*	Natal plum	Roots, stem, bark	Carissin	The stem and bark extracts of *Carissa edulis* provide effective results against *L. major*	Njau *et al*., 2017
15.	*Pyrus armeniaca*	Dwarf apricot	Leaves	Phenols, flavanoids	Alcoholic extracts of *P. armeniaca* exhibits antileishmanial potential against *L. donovani* promastigotes	Shaheen *et al*., 2020
16.	*Artemisia aucheri*	Wormwood	Whole plant	Santonin	Stimulatory or inhibitory action through gabaergic and cholinergic stimulation mechanisms in the nervous system of worms	Bahmani *et al*., 2015
17.	*Dysphania ambrosioides* (L.)	Mexican tea	Leaves	Essential oil (70% ascaridole and limonene)	Potentiality in contemporary medicine by research on its antiparasitic and antimicrobial properties	Sundarrajan, 2023

4.1 Green-synthesized nanodrugs: Safer approach for treatment of leishmaniasis

Ethnobotany is referred as the study of efficacy of plant elements including plant leaves, flowers, roots and shoots against certain ailments (Bajwa *et al*., 2022). In addition to vaccines, ethnobotanicals are another option for the treatment and control of parasites (Swargiary *et al*., 2019), which depend on the size, shape, or material composition. Several techniques have been devised for nanoparticle synthesis (Srivastava *et al*., 2021), and all these criteria are highly dependent on the properties of the materials which vary in shape, size and material composition. Therapeutic efficacy of a drug is determined by its solubility in aqueous media and 40% of the new licensed drugs for the treatment of leishmaniasis have limited water solubility. Therefore, nanodrug delivery system serves as an innovative and promising technology for increasing the solubility characteristics of biopharmaceutical medications (de Souza *et al*., 2018). The utilization of nanotechnological approach in the field of medicine has raised the therapeutic efficiency of therapeutic molecules by refining the drug internalization procedure, decrease in drug degradation, and generation of pathways for slow release of loaded drugs. Efficiency of nanoparticle-mediated drug delivery systems is associated with several benefits, including extended lifespan, protection against enzyme degradation, bolstering of the immune system, simplifying delivery with adjuvants, accurately targeting cells via receptor-ligand interactions. All these benefits have economical, swift, and reliable relevance (Palai *et al*., 2021). Nanodrugs are synthesized using several molecular and conventional approaches which have proven to be quite effective. These conventional or *in vitro* approaches are sol-gel technique, photochemical and thermal disintegration, chemical and electrochemical reduction, bimetallic nanoparticle synthesis and green synthesis. Among all these approaches only green synthesis is the most convenient one. Green synthesis of NP's utilizing different plant extracts offers a simpler, cheaper and less hazardous set up method than other advanced techniques (Dutta *et al*., 2017) as shown in Figure 3.

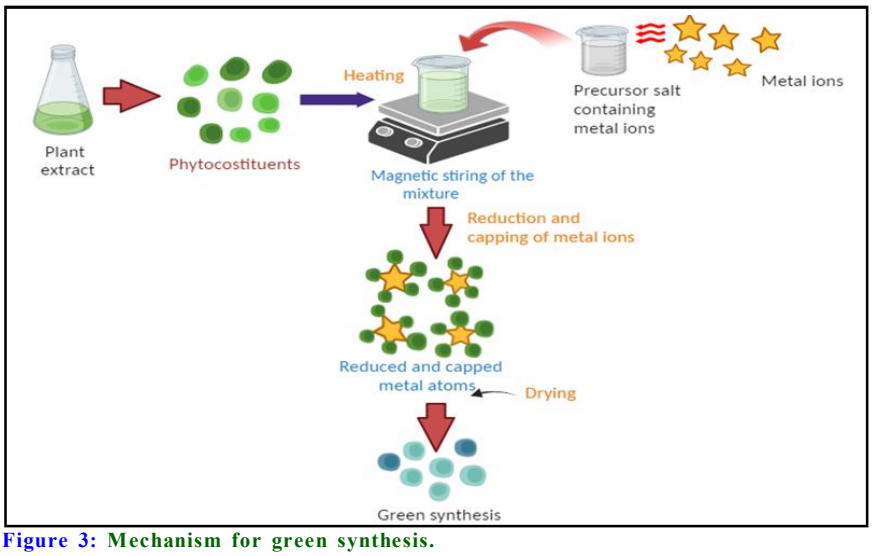

Figure 3: Mechanism for green synthesis.

Recent studies reveal that, these tiny particles limits the drug release at the intended target site and demonstrated higher effectiveness in several tests. Additionally, nanoparticle toxicity is at a lower level in comparison with other pharmaceutical drugs (Yasinzai *et al*., 2013). Furthermore, metal-based nanoparticle systems offer important benefits for the delivery of leishmaniasis drugs, such as extending the biological activity of molecule and reducing adverse effects. In addition, metal compounds with nanostructures have enhanced selectivity for parasitic protein molecules, such as cysteine protease, a putative virulence factors belonging to family of *Leishmania* enzymes. Several nanotherapeutics have received FDA approval and are being made readily accessible for clinical use (Eifler and Thaxton, 2011).

Gold (AuNP's) and silver (AgNP's) nanoparticles are among the most widely utilized nanomaterials in multiple areas of controlled drug delivery systems, sensors, *etc*., demonstrating promising outcomes in treating several parasitic diseases also. They act in several ways, including damage to parasitic membrane, DNA degradation, inhibition of protein synthesis and generation of free-radicals ultimately leading to cell death. Other nanoparticles from zinc, cobalt, nickel, platinum and iron have also exhibited promising results in treating and controlling parasite and its pathogenesis. Green synthesized copper nanoparticles have diverse applications, including antifungal and antibacterial capabilities, Genetic nanotechnology, and their use as catalyst molecules for improving chemical reactions (Sriram *et al*., 2023). The derived NP's must be stored under specified conditions; for example, nanoparticles of gold (AuNP's) need to be stored in dark conditions to avoid further oxidation. The drawback associated to this synthesis process is that the produced NP's possess irregular size (Chikkanna *et al*., 2019). Although, nanodrug synthesis is under developmental phase and has found to work very efficiently, as it is a promising method in developing modern drugs. Presently, this type of approach is preferred, due to its environmental safety. Other significant benefits include the fact that it is very easy, cost effective, more eco-friendly method and requires less material, lesser chemicals and consumes less energy (Castillo-Henríquez *et al*., 2020). Moreover, it has certain disadvantages such as uncontrolled product size, less purity and lack of botanical expertise (Devatha and Thalla, 2018).

The green synthesis of cobalt oxide nanoparticles utilizing *Geranium wallichianum* leaves extracts, silver oxide nanoparticles using *Ficus benghalensis* root extract and nickel oxide nanoparticles from *Rhamnus virgate* leaves extract exerts promising results in treating leishmanial infection (Iqbal *et al*., 2019). Ahmad *et al*. (2019), established an environmental friendly approach for generating biogenic silver nanoparticles (AgNP's) and biogenic amphotericin B-bounded silver nanoparticles (AmB-AgNP's) using extracts from *Isatis tinctoria* plant and the findings of the study indicated improved outcomes (Ahmad *et al*., 2019). Another research demonstrated that the green synthesis of silver and titanium dioxide nanoparticles employing *Euphorbia prostrata* extracts resulted in a shift from apoptosis to G0/G1 arrest and followed by necrotic cell death in *Leishmania* parasite (Zahir *et al*., 2015). Biogenic nanoparticles from gold and silver have been generated utilizing aqueous extract of Olax nana plant, exhibiting promising outcomes in the innovative therapy and fighting with leishmanial parasites (Ovais *et al*., 2018). This compound served as an effective stabilizer molecule.

AuNP's embedded in natural rubber membranes have been used to target promastigotes of *Leishmania brasiliensis* (Sazgarnia *et al*., 2013) and the results revealed that the physiological behavior of promastigote forms changed and there is decrease in the growth rate and lifespan of promastigote forms. Additionally, these particles promoted angiogenesis in the affected regions of the skin. Treatments using AuNP's, paired with microwave irradiation at an intensity of 2450 MHz have shown greater efficacy rates (Nafari *et al*., 2020).

5. Conclusion

As we know, leishmaniasis infections are among the most serious health problems worldwide due to their high endemicity in developing countries. The prevalence of leishmaniasis has risen due to the inefficacy of conventional drugs, unpleasant side effects, lack of vaccine, higher cost of current medications associated with multiple side effects. It is recommended that plant based medications would be another promising source for safer and more efficient treatment compared to conventional drugs So, efforts to investigate other medicinal plant species in search of active molecules is very important which can be employed as prototype molecules for developing new medications with a distinctive mechanism of action from those currently used. Therefore, the need for novel medications is very high as, parasites develop certain mechanisms in order to evade the host's immune system. For this reason, parasitologists in cooperation with other pharmacologists, biochemist, and many other specialists have been studying the efficacy of nanomaterials to combat parasites as these NP's have the potential to bring significant breakthrough in the field of parasitic control and treatment.

The distinctive characteristics of NP's offer a competitive edge over other treatment options, including the lack of toxicity and parasitic resistance. NP's synthesized using different conventional and molecular techniques have demonstrated its potential in killing or arresting the parasite growth and may be employed to diagnose parasitic diseases. However, further researches are still required in order to better understand the mechanism of action of NP's and to develop safe diagnostic and treatment options. In the present review, we have discussed various medicinal plants that have an inhibitory effect on the *Leishmania* parasite. Different plant groups exhibits antileishmanial effects, providing promising prospects for the development of novel antileishmanial drug. From this review, it is also concluded that natural plants and herbs are safer alternative in comparison to synthetic drugs as studies have suggested that herbal could be safer and more efficient compared to conventional antileishmanial drugs.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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