Exploring Herbal Remedies for Anti-Leishmanial Activity: A Comprehensive Review

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Abstract: - Leishmaniasis remains a serious neglected illness worldwide, posing significant challenges in its treatment due to the side effects of existing medications and the rising cases of parasite resistance resulting from indiscriminate treatment. To address this issue, exploring complementary remedies using natural products presents a promising option by combining the empirical knowledge of local populations with scientific research on the medicinal properties of plants. Several studies have investigated herbal treatments for leishmaniasis; however, more research is needed to identify safe and non-toxic remedies. To consolidate the latest findings, researchers from around the globe have compiled a comprehensive article on herbal and organic medicines used to treat leishmaniasis. While many medicinal plants have not been extensively studied, promising candidates have undergone prospective clinical trials. Recent articles have explored the active constituents of these medicinal plants, such as quinones, phenolic compounds, lignans, tannins, terpenes, and oxylipins, shedding light on their potential therapeutic benefits. Pharmacognosy views medicinal plants as valuable sources for developing novel medications and supporting traditional therapies, offering a practical approach to managing various illnesses. In summary, harnessing the power of natural goods and integrating traditional knowledge with scientific research provides a viable and desirable strategy to combat leishmaniasis, promoting safer and more effective treatment options in the future.

1 Introduction

Leishmaniasis, caused by Leishmania protozoa, poses a significant global public health challenge, giving rise to a variety of illnesses. Approximately 100 countries with endemic areas report an estimated 0.7 to 1 million new cases each year[1]. In the last decade, improved accessibility to diagnosis, treatment, and intensive vector management has led to a notable decline in reported visceral leishmaniasis cases in Asia. However, it is important to consider that seasonal variations in transmission intensity could also contribute to these changes. As efforts continue to drive towards eradicating the disease, understanding and addressing the impact of seasonal fluctuations on transmission will be crucial to sustain and further enhance the progress made in combating visceral leishmaniasis[2]. Visceral leishmaniasis (VL) is a more severe and potentially fatal form of the disease, unlike cutaneous leishmaniasis (CL), which is characterized by skin lesions that can heal and recede naturally if not treated[3]. The *Leishmania donovani* complex parasites responsible for causing visceral leishmaniasis (VL) exhibit distinct geographical distributions. *L. infantum* is prevalent in North America, the Middle East, Central Asia, China, and the Mediterranean Basin. On the other hand, *L. donovani* is primarily found in India and Central Africa. These parasites pose a significant zoonotic disease threat to humans in their respective regions[4].

The World Health Organization (WHO) lists three primary leishmaniasis forms.:

Visceral leishmaniasis (VL) Kala-azar, also known as visceral leishmaniasis, has an alarming fatality rate of over 95% if left untreated. The disease is characterized by intermittent fever attacks, weight loss, and enlargement of the liver and spleen, along with anemia. The majority of cases are concentrated in India, East Africa, and Brazil. According to estimates, the World Health Organization (WHO) receives reports of 25% to 45% of the presumed 50,000 to 90,000 new cases of visceral leishmaniasis annually. This parasitic disease remains one of the most dangerous and potentially fatal illnesses. In 2020, more than 90% of all new cases reported to the WHO originated from ten countries: Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen. These regions are particularly affected by the disease, necessitating urgent attention and intervention to curb its impact on public health[5].

Cutaneous leishmaniasis (CL) Cutaneous leishmaniasis (CL) is the most prevalent form of leishmaniasis, characterized by the development of skin lesions, primarily ulcers, on exposed areas of the body. These lesions often

result in permanent scars, leading to significant impairment and social discomfort. The majority of CL cases, approximately 95%, are concentrated in regions such as the Americas, the Mediterranean, the Middle East, and Central Asia. Among the countries with the highest incidence rates in 2020 were Afghanistan, Algeria, Brazil, Colombia, Iraq, Libya, Pakistan, Peru, the Syrian Arab Republic, and Tunisia, accounting for more than 85% of all reported new CL cases. Globally, there are between 600,000 to 1 million new cases of CL reported each year, highlighting the ongoing concern surrounding this neglected disease. The prevalence of CL and its potential for serious consequences emphasize the need for effective and accessible treatment options and underscore the importance of continued research and efforts to combat the disease [5].

Mucocutaneous leishmaniasis (ML) Mucocutaneous leishmaniasis is a debilitating condition characterized by the complete or partial disintegration of the mucous membranes in the mouth, throat, and nose. The countries with the highest prevalence of this disease are Brazil, Ethiopia, Peru, and Bolivia, collectively accounting for over 90% of reported cases[5].

Phlebotomine sandflies, which feed on blood to produce eggs, transmit leishmaniasis through bites from females who are infected with the parasite that causes the disease. The local ecological characteristics of the transmission sites, the parasite and sandfly species, the historical and current exposure of the human population to the infection, and human behaviour all have an impact on leishmaniasis epidemiology. It has been determined that Leishmania parasites naturally live in about 70 animal species, including human[5].

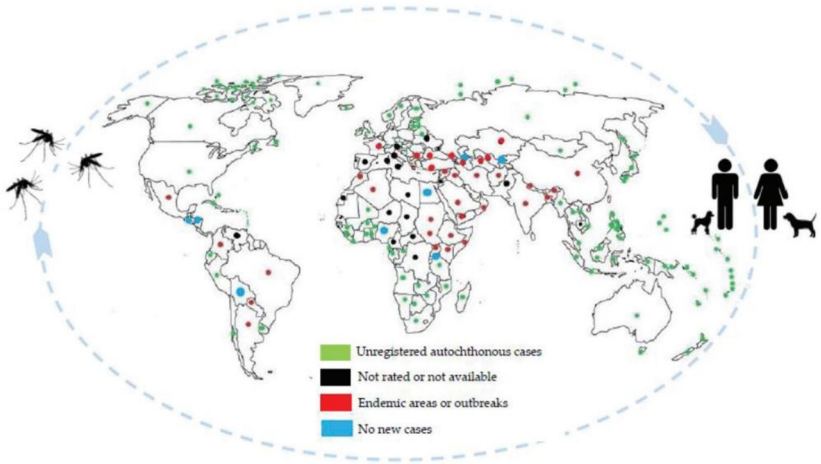

Fig.1 Status of endemicity of visceral leishmaniasis worldwide, 2015. Source: Adapted from WHO (2019)[5]

2 Therapeutic modalities for leishmaniasis

2.1 Chemotherapy

Visceral leishmaniasis (VL) plays a crucial role in both human and animal health; however, treatment options remain limited. The primary medication therapy for leishmaniasis is pentavalent antimony, specifically sodium stibogluconate and meglumine antimoniate. These antimonials form the foundation of therapeutic protocols for human patients. Unfortunately, due to the requirement for hospitalization and the severe side effects associated with their administration, many patients discontinue treatment prematurely. This issue contributes to the development of parasite resistance, which can lead to disease relapse[1].

Amphotericin B, miltefosine, paromomycin, and petamidine are examples of medications that have been repurposed to treat leishmaniasis. Leishmaniasis has also been researched using azole antifungals, and itraconazole was found to be more effective than fluconazole and ketoconazole at preventing the development of most Leishmania strains[6].

Meltefosine emerged as a significant advancement in the treatment of visceral leishmaniasis (VL), offering the convenience of oral administration for patients. Originally developed for breast cancer and solid tumors, its use was limited due to gastrointestinal side effects. As alternatives to meltefosine, medications like paromomycin, pentamidine, and sitamaquine are commonly employed in therapeutic regimens for VL. Despite their utility, these substitutes exhibit lower efficacy compared to the reference drugs, either due to increased side effects or reduced cure rates[7].

2.2 Phytotherapy

Medicinal plants encompass a wide range of botanical species that, when administered to humans or animals through various methods, offer medicinal benefits. Throughout the course of human history, numerous new molecules with therapeutic properties have been derived from plants. Even in modern times, many products used in everyday medicine continue to be sourced from plant-based origins. These natural compounds play a crucial role in healthcare and have been integral to the development of various pharmaceutical and medicinal preparations. In developing nations, the utilization of medicinal plants as a complementary or alternative approach to allopathic medicine has gained prominence, especially in areas with limited access to public health resources, both in urban and rural communities. This age-old tradition, passed down through generations, has evolved into a burgeoning field of modern science[8].

3 Mechanism of leishmaniasis

Mitogen-activated protein kinases (MAPKs), well-known eukaryotic signal transduction mediators, regulate vital processes like as proliferation, differentiation, stress response, and apoptosis. In Leishmania, MAPK1 has a variety of functions that control vital cellular processes such parasite survival, contagiousness, and treatment resistance. We have previously demonstrated that LdMAPK1 regulates heat shock protein post-translational modification and possibly antimony susceptibility via inhibiting the P-glycoprotein (P-gp) efflux pump. Comparative phosphoproteomics investigation of wild type (Dd8+/+), LdMAPK1 over-expressing (Dd8++/++), and LdMAPK1 single deletion (Dd8+/-) mutant parasites was carried out with the aim of discovering LdMAPK1 controlled phosphoproteins. After biological triplicates were run on the orbitrap fusion, the protein search was performed using Proteome Discoverer 2.2 software against the L. donovani database supplied from Uniprot. Comparatively, iTRAQ labelling and quantitative analysis of biological triplicates of wild-type (Dd8+/+), LdMAPK1 over-expressing (Dd8++/++), and single deletion (Dd8+/-) mutant parasites, respectively, showed 420, 512, 320 phosphopeptides for 210, 255, and 142 phosphoproteins. Only eight of these phosphoproteins, including acetyl-coenzyme A synthetase, heat shock protein 83-1, serine/threonine-protein phosphatase, elongation factor 1-alpha, nucleolar protein, and three unknown proteins, displayed a 1.5-fold upregulation in LdMAPK1 overexpressing parasites, compared to seven others. whereas seven proteins (including eukaryotic release factor-3 and eukaryotic translation initiation factor 5a. With the exception of one, none of the up- or down-regulated proteins in overexpressing parasites had differential expression in parasites with single deletion mutations (eukaryotic translation initiation factor 5a). The study found that over-expressed LdMAPK1 changes the expression of phosphoproteins implicated in a number of pathways, notably those involved in metabolism, signal transduction, translation, and molecular chaperone[9].

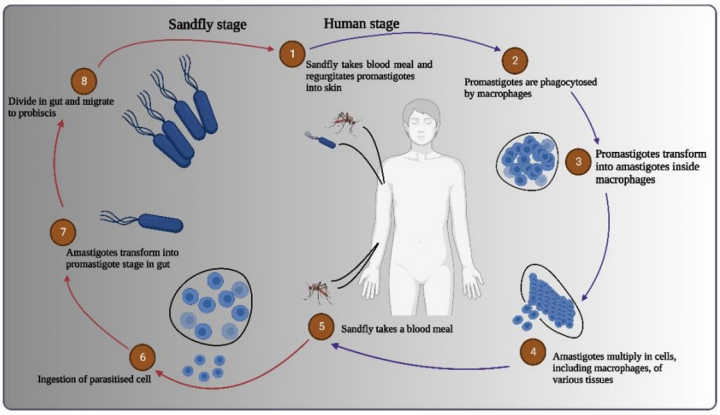

Fig. 2 Mechanism of leishmaniasis

4 Global prevalence

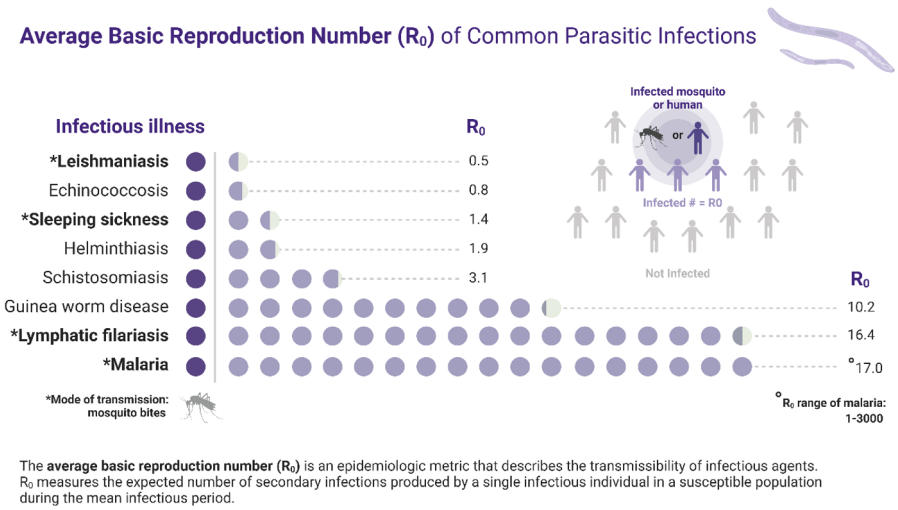

Fig. 3 Average basic Reproduction Number

These illnesses predominate in the tropics, although their preference for hot climates stems mostly from the fact that poverty is concentrated in distant rural areas, urban slums, and displaced populations near the equator.We should regard NTDs to be essentially illnesses of the "bottom billion" the world's poorest one-sixth of the population[10].

NTDs should not be thought of as tropical diseases, but rather as diseases affecting the "bottom billion," or the poorest one-sixth of the global population. At least five NTDs are present in all low-income countries at any given time, and many residents of these nations are simultaneously afflicted by several pathogens.

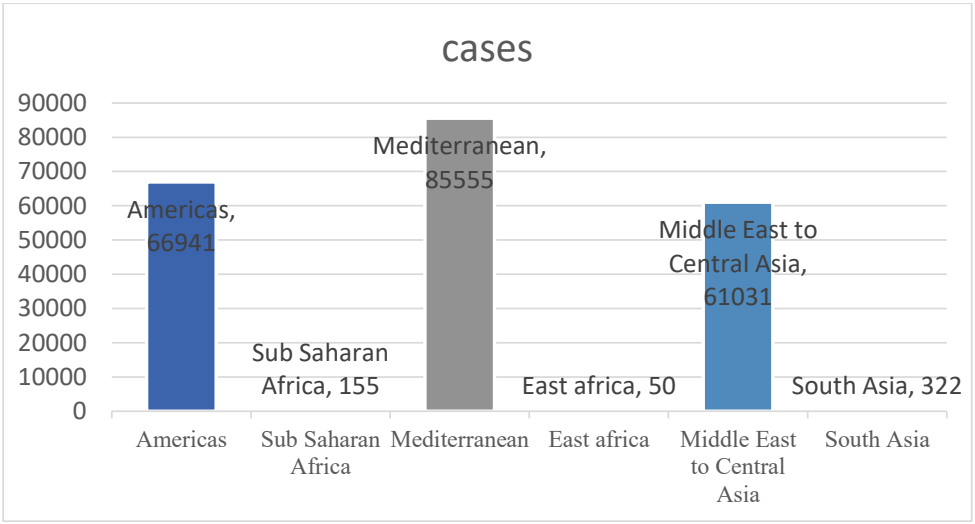

Fig.4 Cases of Cutaneous Leishmaniasis

5 Herbal remedies

The World Health Organization (WHO) and the Indian government reached an agreement to open the WHO Global Centre for Traditional Medicine. With a $250 million investment from the Government of India, this worldwide knowledge centre for traditional medicine intends to harness the power of traditional medicine from across the world using cutting-edge science and technology to benefit both human and environmental health[11].

According to estimates, traditional medicine is used by about 80 percent of the world's people. 170 of the 194 WHO Member States have so far acknowledged using traditional medicine, and their governments have requested WHO's assistance in compiling solid evidence and statistics on these procedures and goods[12].

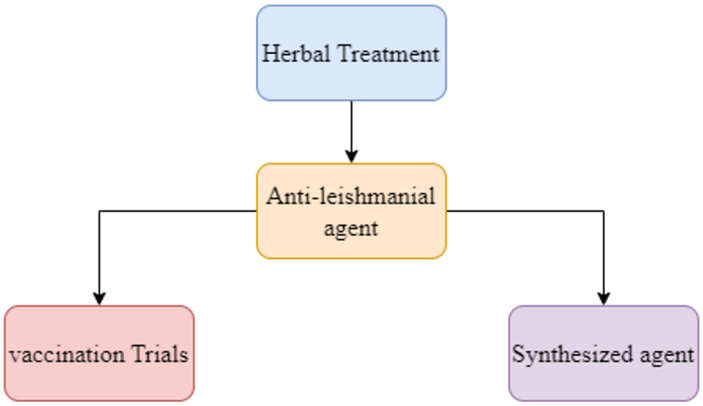

Fig. 5 Classification of Herbal Treatment

5.1 Flavonoids and chalcones

Natural compounds like luteolin and quercetin, derived from plants like *Vitex negundo* and *Fagopyrum esculentum*, were successfully employed to isolate flavonoids. Administering luteolin and quercetin (3.5 mg/kg) substantially reduced splenic parasites in rats by 90% during in vivo trials. Notably, quercetin at this dose exhibited no harm to human T cells and displayed potential in inhibiting topoisomerase I. Another promising compound, licochalcone A, sourced from *Glycyrrhiza spp.*, demonstrated potent action against *L. donovani* amastigotes and L. major promastigotes in vitro, with IC50 values of 0.9 g/mL and 7.2 g/mL, respectively. Administering licochalcone A (20 mg/kg body weight) to infected hamsters led to over 90% reduction in liver and spleen parasite counts[13].

Licochalcone A's potential mechanism of action involves disrupting the ultrastructure of parasite mitochondria, as proposed by a theoretical framework. Notably, in vitro investigations indicate no adverse impact on human lymphocytes, leucocytes, or monocytes due to this compound. Another chalcone derivative, 2',6'-Dihydroxy-4'-methoxychalcone (DMC), sourced from *piperaduncum*, has shown efficacy against *L. amazonensis*. Enhancing the effectiveness and delivery of DMC has been a subject of exploration for various research teams.

Torres-Santos and co-researchers conducted multiple experiments exploring the nitrosylation process of DMC, along with its incorporation into nanoparticle formulations. Notably, these efforts demonstrated favorable outcomes against Leishmania both in in vivo and in vitro settings. The reported results were comparable to the efficacy of established therapeutic medications like *Glucantimepentostam*[14].

Table. 1 Plants having Chalcones and Flavoniods

Plant compound	**Name of the preparation or drug**	**Part used**	**Concentration/dose**	**Leishmania spp.**	**Ref.**
Chalcones					
Glycyrrhiza glabra/Glycyrrhiza inflata (Fabaceae)	Licochalcone A	Roots	Logarithmic promastigotes (ID50 = 4 µg/ml); stationary promastigotes (ID50 = 2.5 µg/ml); amastigotes (ID50 = 0.5 µg/ml)	*L.major/L. donovani*	[15]
	Licochalcone A	Roots	Promastigotes (ID50 = 7.2 mg/ml (21 µM)	*L. major*	[16], [17]
			Amastigotes (ID50 = 0.9 mg/ml (2.7 µM)	*L. donovani*	
Piper rusbyi(Piperaceae)	Flavokavain B and kavapyrone	Leaves	Promastigotes (ID50 = 11.2 µg/ml); promastigotes (ID50 = 81.9 µg/ml)	*L. donovani, L. braziliensis, and L. amazonensis*	[18]

Piper dennisii Trelease (Piperaceae)	3′,7′-Dimethy-l-2′,6′- -octadienyl)-4-methoxybenzoic acid	Leaves	Axenic amastigote (ID50 = 20.8 µg/ml); intracellular macrophage-infected model (ID50 = 4.2 µg/ml)	*L.amazonensis*	[19]
Piper aduncum (Piperaceae)	2,6-Dihydroxy-4-- methoxy chalcones (DMC) + several naturally occurring chalcones	Inflorescences	Promastigotes (ID50 = 0.5 µg/ml (1.9 mM)); intracellular amastigotes (ID50 = 24 µg/ml (89 mM))	*L. amazonensis and L. donovani*	[20]
Psorothamnuspolydenius (Fabaceae)	2,4-Dihydroxy-6-- methoxy-3,5-- dimethylchalcone (methanolic extract)	Plant	Axenic amastigotes (IC50 = 5.0–7.5 µg/ml)	*L. donovani/L. Mexicana*	[21]
	Dalrubone and eriodictyol	Plant	Axenic amastigotes (IC50 = 7.5 µg/ml)	*L. donovani/L. Mexicana*	
Flavonoids					
Psorothamnusarborescens (Fabaceae)	Isoflavone	Roots	Axenic amastigotes (IC50 = 13 µg/ml)	*L. donovani*	[22]
	Chalcone	Roots	Axenic amastigotes (IC50 = 20.7 µg/ml)	*L. donovani*	
Kalanchoe pinnata (Crassulaceae)	Kaempherol	Leaves	In vivo (IC50 = 320 mg/kg for 30 days (BALB/c mice); in vivo (IC50 = 8 mg/kg for 18 days (BALB/c mice)	*L. amazonenesis*	[23]
	α-L-rhamnopyranoside		In vivo (IC50 = 400 mg/kg for 30 days (BALB/c mice)	*L. chagasi*	
	Quercetin	Leaves	Amastigotes (IC50 = 4.3 µM)	*L. amazonensis*	
Fagopyrum esculentum (Polygonaceae)	Isoquercitin	Leaves	Amastigotes (IC50 = 3.8 µM)	*L. donovani*	[24], [25]
	Quercetin	Leaves	Amastigotes (IC50 = 45.5 µM)		
Vitex negundo Linn (Lamiaceae)	Luteolin	Leaves	Amastigotes (IC50 = 9–12.5 µM)	*L. donovani*	[26]

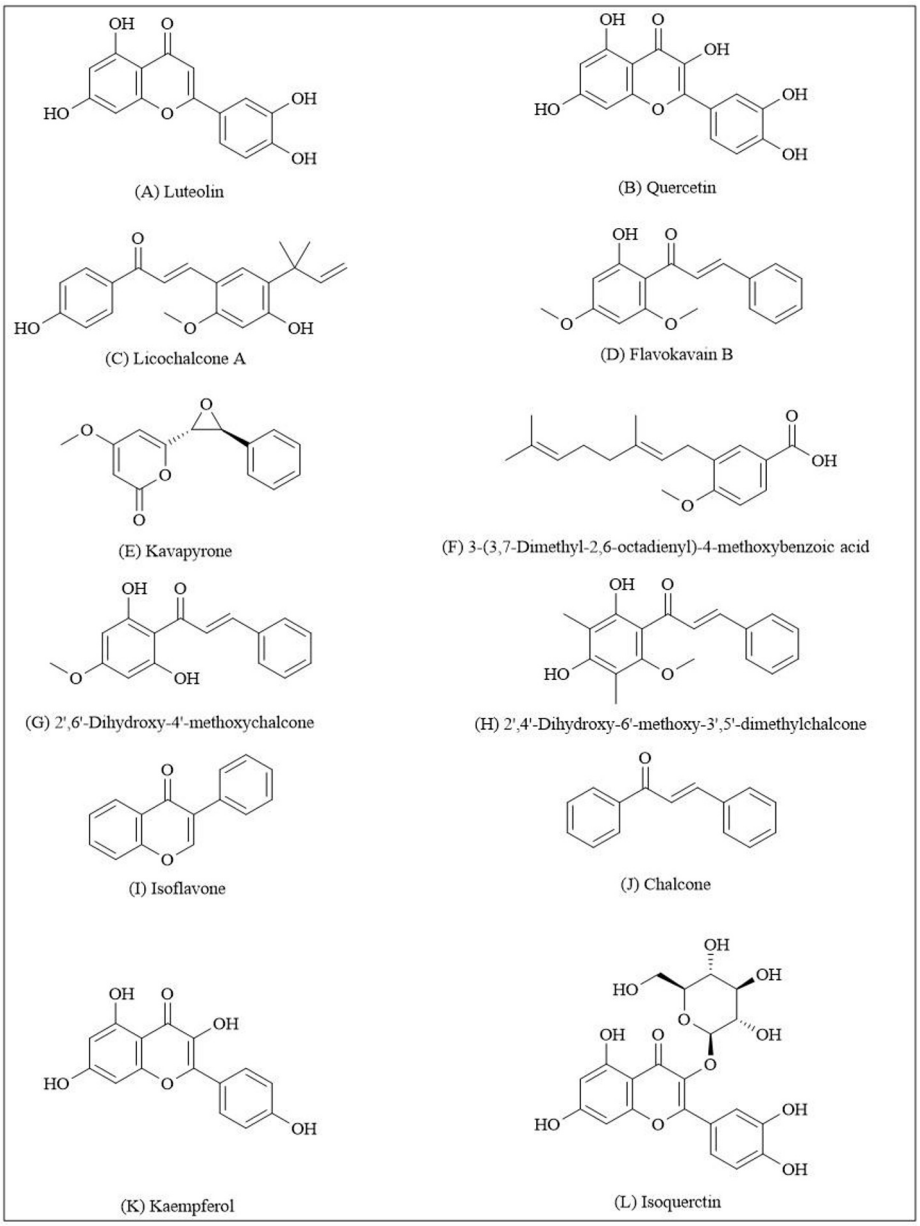

Fig. 6 Phytoconstituent having Chalcones and Flavoniods as anti- leishmanial activity[27]

5.2 Naphthoquinones and iridoids

Historically, naphthaloquinones such as 3,3'-biplumbagin and 8,8'-biplumbagin derived from the Bolivian plant *Perabenensis* have been utilized to address leishmaniasis caused by *L. braziliensis*. In an in vivo investigation by Fournet and colleagues, the over-the-counter drug Glucantime administered at 400 mg/kg/day exhibited comparable efficacy to the compound 8,8'-biplumbagin at 50 mg/kg/day against *L. amazonensis* and *L. venezuelensis*. Notably, plant-derived naphthoquinones have been shown to eliminate parasites and disrupt DNA via topoisomerase II activity[28].

Iridoids, a class of plant metabolites, exhibit notable antileishmanial properties. These compounds manifest their antileishmanial effects by impeding topoisomerase I, hindering DNA from forming complexes with the enzyme. Amarogentin, extracted from *Swertia chirata*, has been studied using hamster models, revealing its ability to inhibit *L. donovani's* topoisomerase I activity by preventing enzyme-DNA binding. The prescribed dose for this approach is 2.5

mg/kg/day for a six-day regimen. Amarogentin's antileishmanial potential has been explored in both liposomal and niosomal formulations. Researchers have advocated for amarogentin's clinical usage in leishmaniasis treatment, attributing greater efficacy to its niosomal form compared to liposomal and unbound variants[29].

In the realm of research, the isolated compounds plumericin and isoplumericin were harnessed to assess Plumeria bicolor's potential in combatting leishmaniasis, employing a chloroform extract. The recorded IC50 values stood at 3.17 µM and 1.41 µM, respectively, underscoring plumericin's robust inhibition of *L. donovani* promastigotes and amastigotes. Conversely, isomer isoplumericin exhibited relatively higher IC50 values (7.2 µM for promastigotes and 4.1 µM for amastigotes of *L. donovani*), indicative of its comparatively subdued potency[30].

5.3 Saponins and quinoline

Maesa balansae synthesizes saponin compounds referred to as maesabalides III and IV, both showcasing potent antileishmanial effects. In vitro investigations conducted by Germonprez et al. unveiled IC50 values of 7 ng/mL for Maesabalide III and 14 ng/mL for Maesabalide IV.
In MRC-5 human fibroblast cell lines, doses of up to 32 µg/mL exhibited no cytotoxicity. Nevertheless, the experimental outcomes are intricate, with diverging perspectives on the saponin compounds' impact on human cell varieties. In an in vivo trial, administering purified maesabalides at 0.4 mg/kg/day to mice livers led to a remarkable 95% reduction in parasites after one day. Contrastingly, human cell types like macrophages and MRC-5 faced cytotoxicity from maesabalide saponins even at concentrations as low as 1 µg/mL[31].

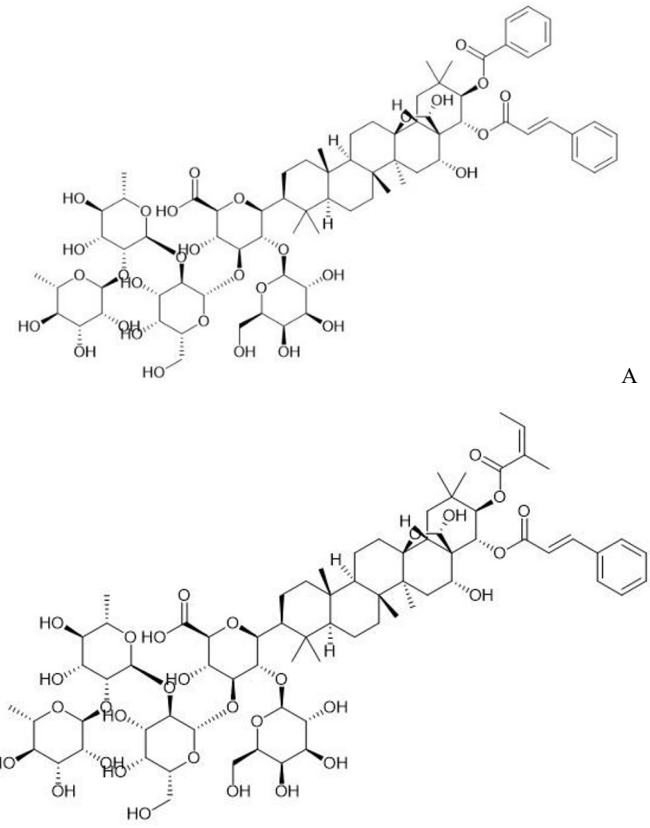

Fig. 7(A)Maesabalides III (B)Maesabalides IV

Racemoside A, a further plant-derived saponin with antileishmanial qualities, was found in *Asparagus racemosus*. Racemoside A was shown to be active against *L. donovani* promastigotes with an IC50 value of 1.31 g/mL. It was discovered that the saponin compounds alpha-, beta-, and hederacolchiside A1 had antileishmanial effects and were safe for human macrophages up to 10 g/mL[32].

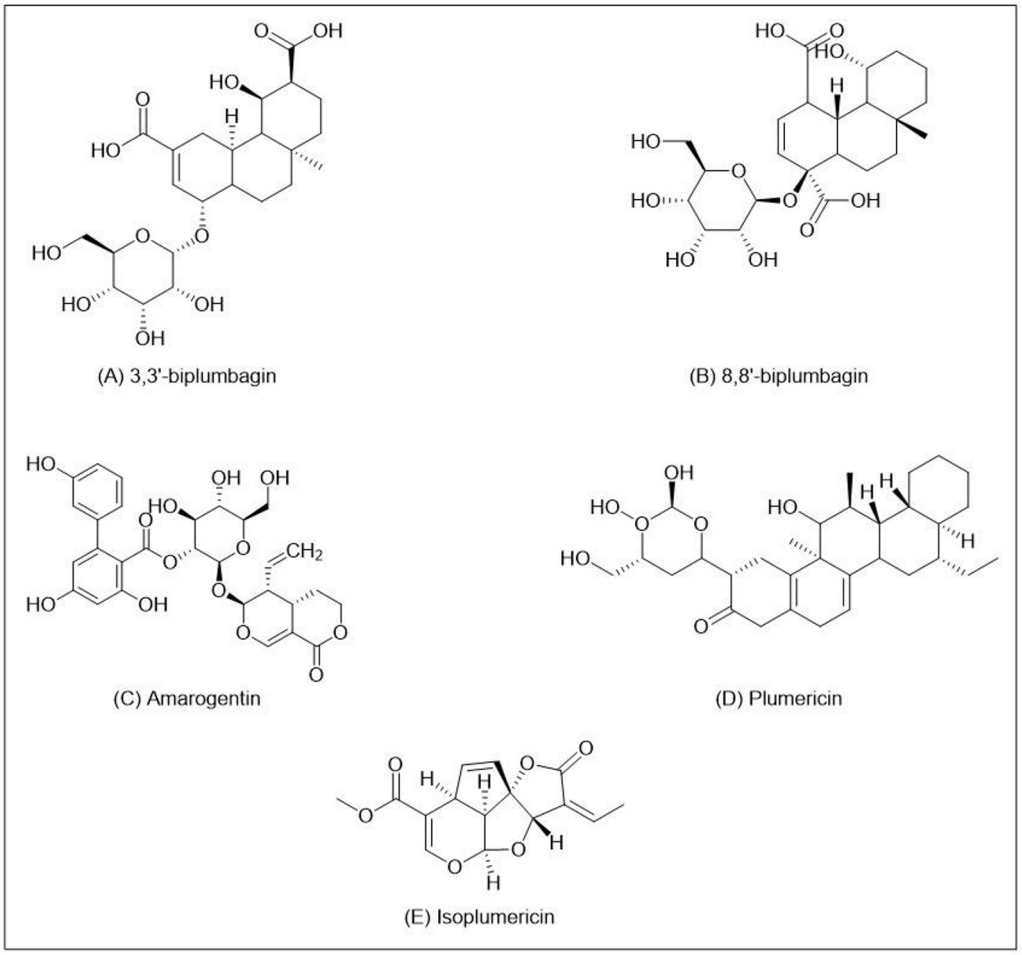

Fig.8 Phytoconstituent having Naphthoquinones and iridoids as anti-leishmanial activity

The researchers meticulously evaluated potential toxicity on mammalian cells in vitro. Among the examined compounds, HederacolchisideA1 demonstrated the highest efficacy. All compounds exhibited inhibitory effects on *L. infantum* parasites, achieved by perturbing the parasite membrane integrity (18). However, the studied saponins hindered DNA synthesis in human monocytes. Despite this, the observed cytotoxicity was deemed moderate, leading to the proposition of utilizing saponins for developing potential antileishmanial drugs. It is advisable to proceed with assessing precise cytotoxic dosages, along with potential impacts on other human cell lines and animal models, before advancing the use of these saponin compounds[33].

Several quinolones with activity against extracellular forms of Leishmania spp. were extracted from *Galipealongiflora*. According to studies, chimanine B and D demonstrated antileishmanial activity that was equivalent to that of over-the-counter drugs. The researchers found that when chimanine B was injected twice daily for 15 days at intervals of 4 days, the parasite load was decreased by 95%. There is further research that back up the efficacy of chimanine D and 2-n-propylquinoline[34].

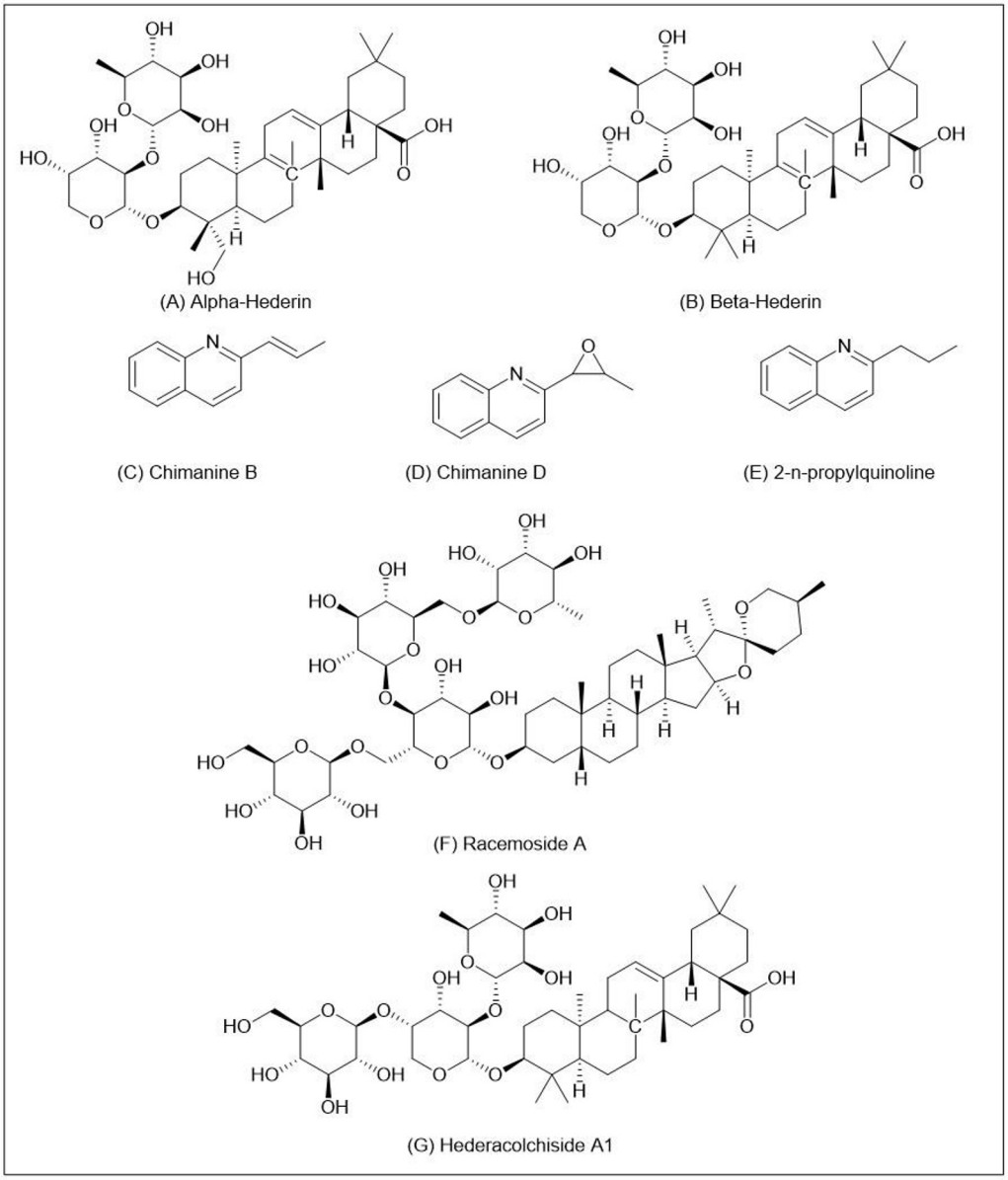

Fig.9 Phytoconstituent having Saponinsandquinoline as anti-leishmanial activity

5.4 Taxane-type diterpenoids and lignans

Isolated metabolites from *Taxus baccata* exhibited remarkable therapeutic potential against *L. donovani* amastigotes, boasting an IC50 value of 70 nM. The chemical compound 10-Deacetylbaccatin III displayed efficacy against *L. donovani* within the range of 200 nM to 1 µM, while remaining non-toxic to human macrophages at higher concentrations (5 µM). Extracted from *Virola pavonis*, Neolignans demonstrated effectiveness against *L. donovani* at a concentration of 100 µM. In vivo, at a dosage of 100 mg/kg, this substance demonstrated promise by reducing liver amastigotes by 42%[35]

Extensive research has focused on various *Artemisia species* as potential herbal remedies for protozoal diseases. These species hold promise as candidates for treating conditions like leishmaniasis and malaria. Ethanol extracts from certain Artemisia species have demonstrated robust in vitro leishmanicidal effects. Notably, the essential oil of *Artemisia annua*, containing camphor, exhibited resistance against leishmaniasis in both promastigotes and intracellular

amastigotes. Furthermore, the application of ointments containing artemether notably reduced *L. major*-induced lesions when employed as a treatment[2].

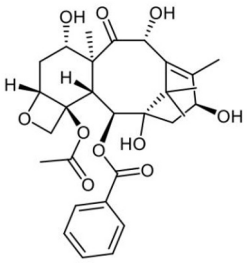

Fig.10 10-Deacetylbaccatin III

Moreover, essential oils derived from *Artemisia dracunculus* (tarragon) exhibited the ability to reduce lesion width or completely eliminate small lesions. Similarly, significant antileishmanial activity was observed in essential oils from *Satureja punctata* and *Artemisia abyssinica* species. Extensive research into artemisinin and its analogues has shown considerable potential. Following WHO guidelines, artemisinin was found effective against Plasmodium and amastigotes, either as a standalone treatment or in combination therapy[36].

For its antileishmanial action, synthetic artemisinin derivatives have been researched. For instance, many trifluoromethyl artemisinin compounds are tested for their in vitro antileishmanial activity. The alteration was carried out to increase the compounds lipophilicity and in vivo stability. The p-methoxy aniline derivative, which had an IC50 of 1.5 M, was the most potent derivative tested against the promastigote of *L. donovani*. Avery et al. also altered the original artemisinin's structure by adding various aliphatic and aryl groups at carbon 9, then investigated the drugs' dual-action antimalarial and antileishmanial properties. The activity was found to be enhanced by removing the carbonyl group from C-10 to generate the 10-deoxy nucleus[37].

In terms of performance, the replacement derivatives at C-9 outperformed the counterparts. explains how a modification like that might be made precisely. The 10-deoxy 9- [3,5-bis(trifluoromethyl)phenyl] derivative was found to be 46 times more effective than its C-10 carbonyl derivative among the 70 artemisinin derivatives studied, with an increased oral action and an IC50 of 0.3 M. In contrast, the 10-hydroxy counterpart showed little action when compared to the common medications pentamidine and amphotericin B[38].

The discovery of herbal semisynthetic analogues has intensified the trend of developing novel antileishmanial medications with less adverse effects. Different inuloxins produced from *Inula viscosa* were examined for their in vitro leishmanicidal activity by Avolio et al. They also looked at the structure-activity connection of their semi-synthetic derivatives.[58] The furanone ring and the C-11 exocyclic methylene group were shown to be crucial structural determinants by observing the action of inuloxins against *L. donovani*.[59] The antileishmanial activity is eliminated when this group is saturated with inuloxin. Inuloxin's terminal C-4 hydroxyl group was a key component of its antileishmanial action.[60,61] In comparison to the original inuloxin, the activity was decreased by the acetylation of the hydroxyl group in the molecule[39].

Table.2 Different plants having anti-leishmanial activity

Plant	**Phytoconstituent**	**Plant part used**	**Concentration/dose**	**Leishmania spp.**	**Ref.**
Quinones					
Diospyros montanaroxb (Ebenaceae)	Diospyrin(D1)	Bark	Promastigotes/MIC of 1ug/ml	*L. donovani*	[27]
	Diospyrin(D17)	Bark	Amastigotes (IC_{50}, 0.18uM) invivo,2 mg/kg (i.p.)(BALB/c mice)	*L.donovani*	[40]
Perabenensis(*Peraceae*)	Plumbagin	Stembarks	Amastigotes (IC_{50}=0.42–1.1µg/ml)	*L.donovanian d L. amazonensis*	[41]
	Plumbagin	Stembarks	Promastigotes(IC_{50}=0.21µ M)	*L.donovani*	[42]

	Plumbagin	Stembarks	Invivo,2.5mg/kg/day Invivo,5mg/kg/day	*L.amazonensis L.venezuelensis*	[43]
	Plumbaginand 8,8′-Biplumbagin	Stem barks	Promastigotes (IC_{90}=5µg/ml)	*L.braziliensis,*	[44]
Cephaelis camponutans (*Rubiaceae*)	Acetyl benzoisochroman-quinone	Stemandroots	Promastigotes (IC50 = 2.32 µg/ml); Amastigotes (IC50 = 1.98 µg/ml)	*L.donovani*	[45]
Tabebuia impetiginosa (*Handroanthusimpetiginosa)*	Isolapachol, dihydrolapachol, and lapachol (naphthoquinone)	Seedsandheartwood	Anti-amastigoteactivity (76–89%)atconc.of 0.0125to0.05mg/mland notoxicitytomacrophagesatconc. <0.1mg/ml	*L.amazonensis and L.braziliensis*	[46]
Alkaloids					
Ancistrocladusealaensis(*Ancistrocladaceae*)	AncistroealainesAandB	Root	Amastigotes (IC_{50}=4–10µg/ml(3 compounds)	*L.donovani*	[47]
Ancistrocladuslikoko (*Ancistrocladaceae*)	Ancistroealaines AandD	Root	IC_{50}=5.9µg/ml	*L.donovani*	[48]
Ancistrocladusgriffithii (*Ancistrocladaceae*)	AncistrogriffinesAandC	Root	IC_{50}=18.8–30µg/ml (5 compounds)	*L.donovani*	[46]
Ancistrocladuscongolensis(*Ancistrocladaceae*)	Ancistrocongolines B and C	Root	IC_{50}=4.4–30µg/ml (8 compounds)	*L.donovani*	[49]
Ancistrocladustanzaniensis(*Ancistrocladaceae*)	AncistrotanzaninesAandB,ancistrotectorilineA, andancistrotazanineA	Root	IC_{50}=1.8–10µg/ml(3 compounds)	*L.donovani*	[50]
Enantiachlorantha (*Annonaceae*)	Palmatine,columbamine,and jatrorrhizine(protoberberinealkaloid)	Stembark	Amastigotes(IC_{50}=0.79µM)	*L.infantum*	[51]
Berberis aristate L. (berberidaceae)	Berberine chloride	Roots	Amastigote (IC50 = 1–2.5 µg/ml); in vivo (50 and 100 mg/kg/day in two 5-day cycles	*L. donovani*	[52]
Berberis vulgaris L. (Berberidaceae)	Berberine	Roots	Amastigote (IC50 = 3.9 ± 0.1 µg/ml); promastigotes (IC50 = 2.7 ± 0.05 µg/ml)	*L. infantum*	[53]
	Berberine	Roots	Amastigote (IC50 = 4.7± 0.1 µg/ml); promastigotes (IC50 = 2.9 ± 0.05 µg/ml)	*L. tropica*	
Psychotriaklugii(Rubiaceae)	Klugine	Stem bark	promastigotes (IC50 = 0.40 µg/ml)	*L. donovani*	[54]
	Cephaelin	Stem bark	promastigotes (IC50 = 0.03 µg/ml)		
	Isocephaeline	Stem bark	promastigotes (IC50 = 0.45 µg/ml)		

Psychotriaprunifolia (Rubiaceae)	Oxoprunifoleine	Leaves	IC50 = 16.0 µg/ml	*L. amazonensis*	[55]
	Strictosamide	Leaves	IC50 = 40.7 µg/ml		
Tabernaemontanacatharinensis(Apocynaceae)	Indole alkaloid enriched fraction (AF3)	Branches and leaves	Promastigotes (IC50 = 38 ± 5 µg/ml)	*L. amazonensis*	[56, 57]
Heliettaapiculata(Rutaceae)	Furoquinoline and coumarins	Stem bark	Promastigote (IC50 = 17–> 50 µg/ml)	*L. amazonensis*	[37]
Galipealongiflora(Rutaceae)	Alkaloid extract of Evanta	Bark	Promastigotes (IC50 = 10 µg/ml); immunization in vivo, 6.25–12.5 mg for 15 days (C57BL/6 mice)	*L. braziliensis*	[38]
	Chimanine B-D and 2-n- -propylquinoline	Stem bark and leaves	Treatment in vivo, 50 mg/kg for 15 days (BALB/c mice)	*L. amazonensis, L. venezuelensis, and L. donovani*	[39]
Stephania dinklagei(Menispermaceae)	N-Methyllirioden-dronine	Air-dried aerial parts	Amastigotes (IC50 = 36.1 µM)	*L. donovani*	[27]
	Liriodenine	Air-dried aerial parts	Amastigotes (IC50 = 26.16 µM)	*L. donovani*	
Nuphar lutea (Nymphaeaceae)	MeOH extract	plant	Amastigotes (ID50 = 0.65 µg/ml); promastigotes (ID50 = 2 µg/ml)	*L. major*	[40]
Aspidospermaramiflorum(Apocynaceae)	Ramiflorines A	Plant	Promastigotes (LD50 = 16.3 µg/ml)	*L. amazonensis*	[41]
	Ramiflorines B	plant	Promastigotes (LD50 = 4.9 µg/ml)		
Thamnosmarhodesica(Rutaceae)	Rhodesiacridone, gravacridonediol, and hydroxy-10-methylacridone	Roots	Slight toxicity at 10 µM concentration against the promastigotes but not against amastigotes	*L. major*	[42]
Peschiera australis (Apocynaceae)	Coronaridine	Stem	Amastigote (IC50 = 12 µg/ml)	*L. amazonensis*	[43]
Kopsiagriffithii(Apocynaceae)	Harmane	Leaves	Promastigotes (IC50 = 6.25 µg/ml)	*L. donovani*	[44]
	Pleiocarpin	Leaves	Promastigotes (IC50 = 25 µg/ml)		
	Buchtienin	Leaves	Promastigotes (IC50 = 1.56 µg/ml)		

6 Conclusion

In the twenty-first century, humans are still at risk from parasite infections. The absence of efficient Chagas disease chemotherapy, the growth of Leishmania/HIV co-infection, and the frightening decline in our ability to access effective antiparasitic drugs as a result of the emergence of drug resistance underline the need for novel prophylactic and therapeutic medicines. Remember that patients with these diseases must have access to any new medications. It would be advantageous to follow the successful path used to develop natural product-based antimalarial drugs because many of the same requirements must be met for antineoplastic therapies. Both the antimalarial drugs quinine and artemisinin have been used successfully, and both have served as models for the development of other antimalarials. The quinoline core of quinine, which acted as a readily accessible building component, allowed for the development of other quinoline-containing antimalarials including chloroquine and mefloquine. Due to its inexpensive manufacture, chloroquine was the best antimalarial drug up to the establishment of resistance.Although the adoption of such artemisinin-class combination treatments is usually made more difficult by cost, artemisinin and its semi-synthetic

derivatives artemether and artesunate are used in combination therapy to treat malaria. However, because of how well these drugs worked to treat malaria, researchers began looking for less expensive artemisinin analogues with excellent pharmacokinetic qualities and robust antimalarial action.The objective of this study was to provide scholars with the most recent knowledge and a compilation of the most noteworthy publications in this field. In order to help with the development of fresh, potent leishmaniasis treatments, this review has highlighted a number of plant extracts. It is important to note that some experiments and those with promising results were carried out in vitro rather than in vivo and that the exposure time for some herbal extracts was inadequate. Additionally, rather than using human participants, the majority of the results were based on animal models.

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