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TREATMENT AND PROPHYLAXIS - REVIEW

Recent researches in effective antileishmanial herbal compounds: narrative review

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Abstract

Leishmaniasis are neglected diseases and a public health problem; they are caused by protozoan species belonging to the genus *Leishmania* and mostly influences the poor populations in many developing countries. The lack of effective medications, and an approved vaccine, high toxicity and life-threatening side effects and many cases of drug resistance reported in different countries have resulted in the necessity to discover new, efficient, inexpensive, and safe antileishmanial compounds with less or no toxicity. This increase in consumer demand of natural herbal-derived plant extracts as alternative medicines continues despite the low scientific information to establish their efficacy and safety profiles. Various studies have been conducted so far concerning the application of herbal medicines for the treatment of leishmaniasis, but research on relatively effective and low toxic substances is still needed. In this review, we have summarized recent developments and reported studies concerning about herbal and naturally derived therapeutics in the treatment of leishmaniasis, conducted by several researchers worldwide. Some of these medical herbs with promising results have undergone prospective clinical researches, but many others have either not yet been explored. Recent articles described these medical herbs and their active and important molecules, including quinones, phenolic derivatives, lignans, tannins, terpenes, and oxylipins. We searched ISI Web of Science, PubMed, SID, Scholar, Scopus, and Science Direct, and articles published up to 2019 were included. The keywords of leishmaniasis and some words associated with herbal medicines and natural products were used in our search. This review can serve as a quick reference database for researchers.

Keywords Leishmaniasis · Plant extracts · Herbal medicine · Natural products

Introduction

The leishmaniasis are a group of neglected tropical diseases which are very important and have a complex ecology (Alvar et al. 2012; WHO 2020). These diseases are vector-borne infections caused by the intramacrophage protozoa from more than 20 *Leishmania* species, transmitted via the bites of phlebotomine sand flies (Alvar et al. 2012; Behravan et al. 2017). There are four main forms of the diseases, namely, cutaneous leishmaniasis (Mbwambo et al. 2004), mucocutaneous leishmaniasis (Ghosh et al. 1985), visceral leishmaniasis (VL, often known as kala-azar), and post-kala-azar dermal leishmaniasis (PKDL) (Cobo 2014; Nagle et al. 2014).

The major clinical presentations of these diseases depend on the complex interaction between the causative parasite and the immune response of the host (Antinarelli et al. 2015). These range from simple ulcerative skin lesions through disfiguring cutaneous leishmaniasis and finally visceral leishmaniasis, which can be fatal if left untreated (Dutta et al. 2007). Leishmaniasis are endemic in 98 countries and are closely associated with poverty. Leishmaniasis has afflicted 12–15 million people, and approximately 350 million people are at risk of this infection worldwide (Nagle et al. 2014; World Health Organization Regional Office for Africa n.d.).

The current clinically used drugs for the treatment of leishmaniasis are based on pentavalent antimonials. Amphotericin

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B and pentamidine are also commonly used, but these drugs are very toxic and have many severe side effects (Croft and Olliaro 2011; Singh and Sundar 2012). Due to drug resistance and the absence of an effective vaccine for leishmaniasis, there is an urgent need for the emergence of effective drugs to replace those in current use (Sundar and Chatterjee 2006). After being neglected for a long time, plant-derived and other natural antileishmansis drugs have been vastly studied in original and review articles (Akendengue et al. 1999; Chan-Bacab and Pena-Rodriguez 2001; Dupouy-Camet 2004; Ghotloo et al. 2015; Handman 2001; Heidari-Kharaji et al. 2016; Hoseini et al. 2016; Kayser et al. 2003c; Sen and Chatterjee 2011).

Herbal extracts and plant-derived products, due to being low cost, having less side effects, and being available for almost all patients, are regarded as safe and valuable sources that are commonly applied to alleviate symptoms and treat a wide range of diseases including leishmaniasis (Balana-Fouce et al. 1998). There are approximately 250,000–500,000 plant species around the world, but only about 6% of them have undergone pharmacological research (Kayser et al. 2003c; Rates 2001; Salem and Werbovetz 2006; Soosaraei et al. 2017). Some of these medical herbs with promising results have undergone prospective clinical researches, but many others have either not yet been explored. It is remarkable that 65% of 15 antiparasitic drugs that have been approved by special health authorities during 1981–2006 are natural compounds and derivatives (Newman and Cragg 2012; Soosaraei et al. 2017). This suggests that the study of plant extracts for the treatment and reduction of complications of the diseases such as leishmaniasis is still ongoing. Scientists believe that for an effective drug design, investigations must be performed into *Leishmania* biology to find new parasite targets (Le Pape 2008).

The aim of this study was to outline the various classes of natural compounds, isolated from medical plants, which were found effective against different species of *Leishmania*.

Materials and methods

This study is going to review and summarize information about effect of herbal-derived therapeutics against leishmaniasis. In this study, the keywords searched included natural drugs, medicinal plants, herbal medicines, and leishmaniasis. We searched English-reported and English-published articles in local and international journals over the period 1990–2019 using various databases including ISI Web of Science, PubMed, SID, Scholar, Scopus, and Science Direct. Then, the related articles were reviewed.

During this time, many articles have been published, but we tried to select and review articles that introduced effective medicinal plants and their compounds against leishmaniasis and did not mention articles that described the very specific fractions of these plants. It should be noted that the articles referring to highly poisonous plants have been removed from this study. Presenting this review and similar articles may be helpful in planning future researches.

Herbal products with antileishmanial effects against *Leishmania* spp.

In different cultures and countries, indigenous medicinal plants are used to treat diseases, especially leishmaniasis. Table 1 shows a list of various medical herbs and natural products, whose effects are scientifically proven on leishmaniasis.

Many plant-derived products including chalcones, terpenoids, naphthoquinones, neolignans, lignans, alkaloids, quinones, oxylipin, flavonoids, saponins, and terpenes have shown promising antileishmanial activity (Balana-Fouce et al. 1998; Croft and Hogg 1988; Meneguetti et al. 2016).

Quinones

Naphthoquinones

Diospyrin, which is a natural product reported to have antileishmanial effects, is a bis-naphthoquinone derivative isolated from the bark of *Diospyros montana Roxb* (*Ebenaceae*) (Hazra et al. 2013). Diospyrin interacts with parasite topoisomerase I and stabilizes the enzyme-DNA cleavable complex. Structural modification of diospyrin was reported to be active against *L. major* and *L. donovani* promastigotes (Hazra et al. 2013). Plumbagin, which is a medicinal plant-derived naphthoquinone isolated from roots of *Plumbago zeylanica* L (Chitrak), has antileishmanial effects against *L. donovani*. Plumbagin mechanism of action is totally different from that of diospyrin. Plumbagin induces topoisomerase II-mediated mammalian DNA cleavage in vitro and delays the expansion of *L. venezuelensis* and *L. amazonensis* infection in experimental mice (Torres-Santos et al. 2004). Furthermore, lapachol, which is an abundant naphthoquinone naturally found in South American *Handroanthus* species (*Tabebuia*, Bignoniaceae), has exhibited leishmanicidal activity against metacyclic promastigotes of *L. amazonensis* and *L. braziliensis* and amastigotes of *L. donovani* in peritoneal macrophages (Araujo et al. 2019; Chan-Bacab and Pena-Rodriguez 2001; Lima et al. 2004).

Anthraquinones and anthropoids

Aloe-emodin, the anthraquinone obtained from the aerial parts of African shrub *Stephania dinklagei* (Menispermaceae), has shown antileishmanial activity against *L. donovani* promastigotes and amastigotes (Salem and Werbovetz

Table 1 List of various antileishmanial herbs and natural products

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
Quinones *Diospyros montana Roxb* (*Ebenaceae*)	Diospyrin (D1)	Bark	Western Ghats of India, Sri Lanka, and IndoChina	Promastigotes/MIC of 1 μg ml^{-1}	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
	Diospyrin (D17)	Bark	Western Ghats of India, Sri Lanka, and IndoChina	Amastigotes (IC_{50}, 0.18 μM); in vivo, 2 mg kg^{-1} (i.p.) (BALB/c mice)	*L. donovani*	Hazra et al. (2013)
Pera benensis (*Peraceae*)	Plumbagin	Stem barks	Colombia, Peru, and Bolivia	Amastigotes (IC_{50} = 0.42–1.1 μg ml^{-1})	*L. donovani* and *L. amazonensis*	Fournet et al. (1992); Chan-Bacab and Pena-Rodriguez (2001), and Awasthi et al. (2016)
	Plumbagin	Stem barks	Colombia, Peru, and Bolivia	Promastigotes (IC_{50} = 0.21 μM)	*L. donovani*	Torres-Santos et al. (1999); Polonio and Efferth (2008), and Gutierrez-Rebolledo et al. (2017)
	Plumbagin	Stem barks	Colombia, Peru, and Bolivia	In vivo, 2.5 mg kg^{-1} day^{-1} In vivo, 5 mg kg^{-1} day^{-1}	*L. amazonensis* *L. venezuelensis*	Fournet et al. (1992) and Chan-Bacab and Pena-Rodriguez (2001)
	Plumbagin and 8,8′-biplumbagin	Stem barks	Colombia, Peru, and Bolivia	Promastigotes (IC_{90} = 5 μg ml^{-1})	*L. braziliensis*, *L. amazonensis*, and *L. donovani*	Fournet et al. (1992), Chan-Bacab and Pena-Rodriguez (2001), and Awasthi et al. (2016)
Cephaelis camponutans (*Rubiaceae*)	Acetyl benzoisochroman-quinone	Stem and roots	Panama	Promastigotes (IC_{50} = 2.32 μg ml^{-1}); amastigotes (IC_{50} = 1.98 μg ml^{-1})	*L. donovani*	del Rayo Camacho et al. (2004)
Tabebuia impetiginosa (*Handroanthus impetiginosa)* (*Bignoniaceae*)	Lapachol, isolapachol, and dihydrolapachol (naphthoquinone)	Seeds and heartwood	Northern Mexico to northern Argentina	Anti-amastigote activity (76–89%) at concentrations of 0.0125 to 0.05 mg ml^{-1} and no toxicity to macrophages at concentrations < 0.1 mg ml^{-1}	*L. amazonensis* and *L. braziliensis*	Teixeira et al. (2001) and Lima et al. (2004)
Alkaloids *Ancistrocladus ealaensis* (*Ancistrocladaceae*)	Ancistroealaines A and B	Root	Tropical Africa, Indian subcontinent, and Southeast Asia	Amastigotes (IC_{50} = 4–10 μg ml^{-1} (3 compounds)	*L. donovani*	Bringmann et al. (2000)
Ancistrocladus likoko (*Ancistrocladaceae*)	Ancistroealaines A and D	Root	Tropical Africa, Indian subcontinent and Southeast Asia	IC_{50} = 5.9 μg ml^{-1}	*L. donovani*	Bringmann et al. (2003)
Ancistrocladus griffithii	Ancistrogriffines A and C	Root	Tropical Africa, Indian	IC_{50} = 18.8–30 μg ml^{-1} (5 compounds)	*L. donovani*	Bringmann et al. (2002)

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
(*Ancistrocladaceae*)			subcontinent, and Southeast Asia			
	Ancistrogriffithine A	Root	Asian ancistrocladus species	$IC_{50} = 18.3\ \mu g\ ml^{-1}$	*L. donovani*	Bringmann et al. (2002)
Ancistrocladus congolensis (*Ancistrocladaceae*)	Ancistrocongolines B and C	Root	Tropical Africa, Indian subcontinent, and Southeast Asia	$IC_{50} = 4.4–30\ \mu g\ ml^{-1}$ (8 compounds)	*L. donovani*	Bringmann et al. (2002), Bringmann et al. (2002), and Bringmann et al. (2008)
Ancistrocladus tanzaniensis (*Ancistrocladaceae*)	Ancistrotanzanines A and B, ancistrotectoriline A, and ancistrotazanine A	Root	East and tropical Africa	$IC_{50} = 1.8–10\ \mu g\ ml^{-1}$ (3 compounds)	*L. donovani*	Bringmann et al. (2003)
Enantia chlorantha (*Annonaceae*)	Palmatine, columbamine, and jatrorrhizine (protoberberine alkaloid)	Stem bark	Southwestern region of Nigeria	Amastigotes ($IC_{50} = 0.79\ \mu M$)	*L. infantum*	Nkwengoua et al. (2009)
	Methyltetrahydroberberinium iodide	Stem bark	Southwestern region of Nigeria	In vivo (best activity at 416 mg kg^{-1})	*L. donovani* and *L. braziliensis*	Vennerstrom et al. (1990)
Berberis aristata Linnaeus (*Berberidaceae*)	Berberine chloride	Roots	Sub-tropical regions of Asia (e.g., Iran), Europe, and America	Amastigote ($IC_{50} = 1–2.5\ \mu g\ ml^{-1}$); in vivo (50 and 100 mg kg^{-1} day^{-1} in two 5-day cycles)	*L. donovani*	Ghosh et al. (1985)
Berberis vulgaris Linnaeu (*Berberidaceae*)	Berberine	Roots	Sub-tropical regions of Asia (e.g., Iran) and Europe	Amastigote ($IC_{50} = 3.9 \pm 0.1\ \mu g\ ml^{-1}$); promastigotes ($IC_{50} = 2.7 \pm 0.05\ \mu g\ ml^{-1}$)	*L. infantum*	Mahmoudvand et al. (2014)
	Berberine	Roots	Sub-tropical regions of Asia (e.g., Iran) and Europe	Amastigote ($IC_{50} = 4.7 \pm 0.1\ \mu g\ ml^{-1}$); promastigotes ($IC_{50} = 2.9 \pm 0.05\ \mu g\ ml^{-1}$)	*L. tropica*	
Psychotria klugii (*Rubiaceae*)	Klugine	Stem bark	South American	Promastigotes ($IC_{50} = 0.40\ \mu g\ ml^{-1}$)	*L. donovani*	Muhammad et al. (2003) and Calixto et al. (2016)
	Cephaelin	Stem bark	South American	Promastigotes ($IC_{50} = 0.03\ \mu g\ ml^{-1}$)		
	Isocephaeline	Stem bark	South American	Promastigotes ($IC_{50} = 0.45\ \mu g\ ml^{-1}$)		
Psychotria prunifolia (*Rubiaceae*)	Oxoprunifoleine	Leaves	South American	$IC_{50} = 16.0\ \mu g\ ml^{-1}$	*L. amazonensis*	Faria et al. (2010) and Calixto et al. (2016)
	Strictosamide	Leaves	South American	$IC_{50} = 40.7\ \mu g\ ml^{-1}$		

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
Tabernaemontana catharinensis (*Apocynaceae*)	Indole alkaloid enriched fraction (AF3)	Branches and leaves	South American	Promastigotes ($IC_{50} = 38 \pm 5$ μg ml^{-1})	*L. amazonensis*	Soares et al. (2010)
Helietta apiculata (*Rutaceae*)	Furoquinoline and coumarins	Stem bark	Argentina and Paraguay	Promastigote ($IC_{50} = 17 -> 50$ μg ml^{-1})	*L. amazonensis*	Ferreira et al. (2010)
Galipea longiflora (*Rutaceae*)	Alkaloid extract of Evanta	Bark	Bolivia	Promastigotes ($IC_{50} = 10$ μg ml^{-1}); immunization in vivo, 6.25–12.5 mg for 15 days (C57BL/6 mice)	*L. braziliensis*	Calla-Magarinos et al. (2013)
	Chimanine B-D and 2-*n*--propylquinoline	Stem bark and leaves	Bolivia	Treatment in vivo, 50 mg kg— for 15 days (BALB/c mice)	*L. amazonensis*, *L. venezuelensis*, and *L. donovani*	Fournet et al. (1996)
Stephania dinklagei (*Menispermaceae*)	*N*-Methyllirioden-dronine	Air-dried aerial parts	East and Central Africa	Amastigotes ($IC_{50} = 36.1$ μM)	*L. donovani*	Camacho et al. (2000)
	Liriodenine	Air-dried aerial parts	East and Central Africa	Amastigotes ($IC_{50} = 26.16$ μM)	*L. donovani*	Camacho et al. (2000)
Nuphar lutea (*Nymphaeaceae*)	MeOH extract	Plant	Temperate regions of Europe, northwest Africa, and western Asia	Amastigotes ($ID_{50} = 0.65$ μg ml^{-1}); promastigotes ($ID_{50} = 2$ μg ml^{-1})	*L. major*	El-On et al. (2009 and Ozer et al. 2010)
Aspidosperma ramiflorum (*Apocynaceae*)	Ramiflorines A		Brazil and Bolivia	Promastigotes ($LD_{50} = 16.3$ μg ml^{-1})	*L. amazonensis*	Ahua et al. (2004)
	Ramiflorines B		Brazil and Bolivia	Promastigotes ($LD_{50} = 4.9$ μg ml^{-1})		
Thamnosma rhodesica (*Rutaceae*)	Rhodesiacridone, gravacridonediol, and hydroxy-10--methylacridone	Roots	Africa	Slight toxicity at 10 μM concentration against the promastigotes but not against amastigotes	*L. major*	Ahua et al. (2004)
Peschiera australis (*Apocynaceae*)	Coronaridine	Stem	Brazil	Amastigote ($IC_{50} = 12$ μg ml^{-1})	*L. amazonensis*	Delorenzi et al. (2001)
Kopsia griffithii (*Apocynaceae*)	Harmane	Leaves	Southeast Asia	Promastigotes ($IC_{50} = 6.25$ μg ml^{-1})	*L. donovani*	Gutierrez-Rebolledo et al. (2017)
	Pleiocarpin	Leaves	Southeast Asia	Promastigotes ($IC_{50} = 25$ μg ml^{-1})		
	Buchtienin	Leaves	Southeast Asia	Promastigotes ($IC_{50} = 1.56$ μg ml^{-1})		
Chalcones *Glycyrrhiza*	Licochalcone A	Roots	Southern Europe and parts of Asia	Logarithmic promastigotes ($ID_{50} = 4$ μg ml^{-1}); stationary promastigotes ($ID_{50} = 2.5$ μg ml^{-1});	*L. major/L. donovani*	Chen et al. (1993, 1994) and Zhai et al. (1999)

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
glabra/*Glycyrrhiza inflata* (*Fabaceae*)				amastigotes (ID_{50} = 0.5 μg ml^{-1})		
	Licochalcone A	Roots	Southern Europe and parts of Asia	Promastigotes (ID_{50} = 7.2 mg ml^{-1} (21 μM) Amastigotes (ID_{50} = 0.9 mg ml^{-1} (2.7 μM)	*L. major* *L. donovani*	Torres-Santos et al. (1999a, b), Polonio and Efferth (2008), and Gutierrez-Rebolledo et al. (2017)
Piper rusbyi (*Piperaceae*)	Flavokavain B and kavapyrone	Leaves	Tropical regions, such as (Bolivia)	Promastigotes (ID_{50} = 11.2 μg ml^{-1}); promastigotes (ID50 = 81.9 μg ml^{-1})	*L. amazonensis*, *L. donovani*, and *L. braziliensis*	Flores
Piper dennisii Trelease (*Piperaceae*)	3′,7′-Dimethy-l-2′,6′--octadienyl)-4--methoxybenzoic acid	Leaves	Tropical regions (South and central Americas, Asia)	Axenic amastigote (ID_{50} = 20.8 μg ml^{-1}); intracellular macrophage-infected model (ID_{50} = 4.2 μg ml^{-1})	*L.amazonensis*	Cabanillas et al. (2012)
Piper aduncum (*Piperaceae*)	2,6-Dihydroxy-4--methoxy chalcones (DMC) + several naturally occurring chalcones	Inflorescences	Southern Mexico/tropical South America/tropical Asia	Promastigotes (ID_{50} = 0.5 μg ml^{-1} (1.9 mM)); intracellular amastigotes (ID_{50} = 24 μg ml^{-1} (89 mM))	*L. amazonensis* and *L. donovani*	Torres-Santos et al. (1999) and Kayser and Kiderlen (2001)
Psorothamnus polydenius (*Fabaceae*)	2,4-Dihydroxy-6--methoxy-3,5--dimethylchalcone (methanolic extract)	Plant	Southwestern USA	Axenic amastigotes IC_{50} = 5.0–7.5 μg ml^{-1}	*L. donovani*/*L. mexicana*	Salem and Werbovetz (2005) and Salem and Werbovetz (2006)
	Dalrubone and eriodictyol	Plant	Southwestern USA	Axenic amastigotes (IC_{50} = 7.5 μg ml^{-1})	*L. donovani*/*L. mexicana*	Salem and Werbovetz (2005) and Salem and Werbovetz (2006)
Flavonoids	Isoflavone	Roots	Southwestern North America	Axenic amastigotes (IC_{50} = 13 μg ml^{-1})	*L. donovani*	Salem and Werbovetz (2006)
Psorothamnus arborescens (*Fabaceae*)	Chalcone	Roots	Southwestern North America	Axenic amastigotes (IC_{50} = 20.7 μg ml^{-1})	*L. donovani*	Salem and Werbovetz (2006)
Kalanchoe pinnata (Crassulaceae)	Kp	Leaves	Temperate regions of Asia and Hawaii	In vivo (IC_{50} = 320 mg kg^{-1} for 30 days (BALB/c mice); in vivo (IC_{50} = 8 mg kg^{-1} for 18 days (BALB/c mice) In vivo (IC_{50} = 400 mg kg^{-1} for 30 days (BALB/c mice)	*L. amazonenesis* *L. chagasi*	Da Silva et al. (1995), Torres-Santos et al. (2003); Muzitano et al. (2009); Garcia et al. (2010); and Gomes et al. (2010)
	Quercetin	Leaves	Southeast Asia	Amastigotes (IC_{50} = 4.3 μM)	*L. amazonensis*	

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
Fagopyrum esculentum (*Polygonaceae*)	Isoquercitrin	Leaves	Southeast Asia	Amastigotes (IC_{50} = 3.8 μM)		Mittra et al. (2000); Polonio and Efferth (2008); Manjolin et al. (2013), Gutierrez-Rebolledo et al. (2017)
	Quercetin	Leaves	Southeast Asia	Amastigotes (IC_{50} = 45.5 μM)	*L. donovani*	
Vitex negundo Linn (Lamiaceae)	Luteolin	Leaves	Tropical Eastern and Southern Africa and Asia	Amastigotes (IC_{50} = 9–12.5 μM)	*L. donovani*	Mittra et al. (2000); Polonio and Efferth (2008); Manjolin et al. (2013); Gutierrez-Rebolledo et al. (2017)
Cotinus coggygria (*Anacardiaceae*)	Fisetin	Leaves	Southern Europe, central Asia, and northern China	Amastigotes (IC_{50} = 1.4 μg ml^{-1})	*L. donovani* and *L. amazonensis*	Manjolin et al. (2013)
Piper betle (*Paan*) Linn (*Piperaceae*)	Piper betle-Bangla Mahoba (PB-BMM)	Leaves	South and Southeast Asia	Promastigotes (IC_{50} = 11.2 ± 1.23 μg ml^{-1}); intracellular amastigotes (IC_{50} = 9.31 ± 0.53 μg ml^{-1})	*L. donovani*	Misra et al. (2009)
	Ethanolic extract	Leaves	South and Southeast Asia	Promastigotes (IC_{50} = 9.8 μg ml^{-1}); amastigotes (IC_{50} = 5.45 μg ml^{-1})	*L. donovani*	Sarkar et al. (2008)
Punica granatum Linn (*Punicaceae*)	Hydroalcoholic extracts	Leaves	North and tropical Africa/South and Central Asia	Intracellular amastigotes (IC_{50} = 69.6 μg ml^{-1})	*L. amazonensis*	Maes et al. (2004); Garcia et al. (2010), and Georgiadou et al. (2015)
Bidens pilosa Linn (*Asteraceae*)	Hydroalcoholic extracts	Leaves	North and tropical Africa/South and central Asia	Intracellular amastigotes (IC_{50} = 42.6 μg ml^{-1})	*L. amazonensis*	Maes et al. (2004); Garcia et al. (2010), and Georgiadou et al. (2015)
Maesa lanceolata (*Primulaceae*)	Methanolic extract	Leaves	Afrotropics (Madagascar)	Single subcutaneous = 0.4 mg kg^{-1} at 1 day after infection or 1.6 mg kg^{-1} of body weight at 14 days after infection	*L. donovani*	Maes et al. (2004)
				Amastigotes (IC_{50} = 0.04 μg ml^{-1}); CC_{50} = 1 μg ml^{-1} (BALB/c mice)	*L. infantum*	
Camellia sinensis (*Theaceae*)	Epigallocatechin-3-gallate (EGCG) (type of catechin)	Leaves (green tea)	East Asia, Indian subcontinent, and Southeast Asia	Promastigotes (IC_{50} = 26.3 ± 0.6 μg ml^{-1})	*L. infantum*	Imperatori et al. (2019)
	Crude ethanolic extract	Leaves (green tea)	East Asia, Indian subcontinent, and Southeast Asia	Promastigotes (IC_{50} = 12 mg ml^{-1})	*L. major*	Feily et al. (2012)

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
Terpenes *Maesa balansae* (*Myrsinaceae*)	Maesabalides III and IV (saponins)	Flowers	Vietnam	In vivo (IC_{50} = 20 ng ml^{-1}) IC_{50} = 0.4 μg ml^{-1}; CC_{50} = 12 μg ml^{-1}	*L. donovani* *L. infantum*	Majester-Savornin et al. (1991); Delmas et al. (2000), and Germonprez et al. (2005)
Ivy Hedera helix/*Hedera colchica* (*Araliaceae*)	Hederasaponin/hederagenin (saponins)	Leaves	Ireland to Scandinavia/Ukraine/Iran/Turkey	–	*L. infantum* and *L. tropica*	Majester-Savornin et al. (1991)
	α-Hederin, β-hederin/hederacolchiside A1 (saponins)	Leaves	Ireland to Scandinavia/Ukraine/Iran/Turkey	Promastigotes (IC_{50} = 1.5 ± 0.2 μM)	*L. mexicana*	Ridoux et al. (2001)
Pseudelephantopus spiralis (*Asteraceae*)	Aqueous extracts (sesquiterpenoid)	Aerial parts	Caribbean and Latin America	Axenic amastigotes (IC_{50} = 13.4 μg ml^{-1})	*L. infantum*	Girardi et al. (2015)
	Hirsutinolides	Crude extract	Caribbean and Latin America	Axenic amastigotes (IC_{50} = O.2–0.37 μM)	*L. amazonensis*	Odonne et al. (2011)
	Ursolic acid (sesquiterpene lactones)	Crude extract	Caribbean and Latin America	Axenic amastigotes (IC_{50} = 0.99 μM)	*L. amazonensis*	Odonne et al. (2011)
Acanthospermum hispidum (*Asteraceae*)	Sesquiterpenic lactones	Aerial parts	Central and South America	Promastigotes (IC_{50} = 0.94 ± 0.05 μM); promastigotes (IC_{50} = 2.54 ± 0.19 μM)	*L. mexicana mexicana*	Ganfon et al. (2012)
Betula sp. (*Betulaceae*)	Disuccinyl betulin (DiSB)	Cork layer	Europe and Asia continent	Amastigotes (IC_{50} = 11.8 μM)	*L. donovani*	Chowdhury et al. (2011)
	Diglutaryl dihydrobetulin (DiGDHB)	Cork layer	Europe and Asia continent	Amastigotes (IC_{50} = 15.3 μM)		
	Disuccinyl dihydrobetulin (DiSDHB)	Cork layer	Europe and Asia continent	Amastigotes (IC_{50} = 24.2 μM)		
Tinospora sinensis (*Menispermaceae*)	EtOH extract *n*-butanol fraction	Stems	South and Southeast Asia	Promastigotes (IC_{50} = 37.6 ± 6.2 μg ml^{-1}); intracellular amastigotes (IC_{50} = 29.8 ± 3.4 μg ml^{-1}); in vivo (76.2 ± 9.2% inhibition at 500 mg kg^{-1} day^{-1} × 5 oral dose level	*L. donovani*	Singh et al. (2008) and Maurya et al. (2009)
Tanacetum parthenium (*Asteraceae*)	Parthenolide	Aerial part	Europe, North America, and Iran	Promastigote (IC_{50} = of 29 μg ml^{-1}); amastigotes (IC_{50} = of 5 μg ml^{-1})	*L. amazonensis*	Tiuman et al. (2005)
Artemisia dracunculus (*Asteraceae*)	Ethanolic extract	Plant	Eurasia and North America	Promastigote (IC_{50} = of 10–25 μg ml^{-1})	*L. major*	Rezaei et al. (2017)

Table 1 (continued)

Plant compounds	Preparation or drugs name	Part used	Native	Concentration/dose	*Leishmania* spp.	References
Artemisia Indica (*Asteraceae*)	Ethanolic extract	Leaves	E. Asia, China, Japan, and India	Promastigotes (IC_{50} = 430 μg ml^{-1})	*L. major*	Ganguly et al. (2006)
				Promastigotes (IC_{50} = 290 μg ml^{-1})	*L. amazonensis*	
				Promastigotes (IC_{50} = 210 μg ml^{-1})	*L. donovani*	
				Promastigotes (IC_{50} = 340 μg ml^{-1})	*L. mexicana*	
				Promastigotes (IC_{50} = 390 μg ml^{-1})	*L. infantum*	
				Promastigotes (IC_{50} = 330 μg ml^{-1})	*L. tropica*	
	Artemisinin	Leaves	E. Asia, China, Japan, and India	Promastigotes (IC_{50} = 100–120 μM); in vivo, 10 and 25 mg kg^{-1} body weight (BALB/c model of VL)	*Leishmania* species	Sen et al. (2010)
Artemisia annua (*Asteraceae*)	Artemisinin (artemether)	Leaves	Temperate Asia and scattered parts of North America	Promastigotes (IC_{50} = 25 μg ml^{-1})	*L. major*	Ebrahimisadr et al. (2013) and Mesa et al. (2017)
Satureja khuzestanica (*Lamiaceae*)	Ethanolic and methanolic extracts	Leaves	North Africa, Southeastern Europe, the Middle East, and Central Asia	Promastigotes (IC_{50} = 300–600 μg ml^{-1})	*L. major*	Sadeghi-Nejad et al. (2011)
	Hydroethanolic extracts	Leaves	North Africa, Southeastern Europe, the Middle East, and Central Asia	Promastigotes (IC_{50} = 4.3 μg ml^{-1})	*L. major*	Khademvatan et al. (2019)
				Promastigotes (IC_{50} = 5.5 μg ml^{-1})	*L. infantum*	
	S. khuzestanica essential oil (SKEO)	Leaves	North Africa, Southeastern Europe, the Middle East, and Central Asia	Amastigotes (IC_{50} = 10.19 ± 0.16 μg m-L_{-1}); promastigotes (IC_{50} = 11.31 ± 0.22 μg ml^{-1})	*L. major*	Delfan et al. (2016)

2006). Vismione D, bianthrone A1, and emodin obtained from the ethanolic extract of stem bark of Tanzanian plant *Vismia orientalis* (Clusiaceae or Guttiferae) display a wide range of antiprotozoal activities against *Plasmodium falciparum* strain K1, *Trypanosoma cruzi*, *Trypanosoma rhodesiense*, and *L. donovani* (Camacho et al. 2000; Mbwambo et al. 2004). Also, 4-hydroxy-1-tetralone isolated from the bark of *Ampelocera edentula* (Ulmaceae) is an active natural product against promastigotes of *L. donovani*, *L. braziliensis*, *L. venezuelensis*, and *L. amazonensis* (Salem and Werbovetz 2006). The use of this metabolite is limited because of its cytotoxic, mutagenic, and carcinogenic effects in experimental animals (Fournet et al. 1994).

Phenolic derivatives

Chalcones

Chalcone is a common and privileged structure found in many natural compounds and has been widely used for drug discovery (Matos et al. 2015; Zhuang et al. 2017). Chalcones have displayed a wide spectrum of biological and pharmacological activities with clinical potentials against several diseases (Matos et al. 2015; Zhuang et al. 2017). Chalcones have been studied in several *Leishmania* species (Andrighetti-Frohner et al. 2009; de Mello et al. 2016; Quintin et al. 2009). Licochalcone A is an oxygenated chalcone, a type of natural phenol. It can be isolated from the root of chinese liquorice plant *Glycyrrhiza glabraor* (Fu et al. 2004) and *Glycyrrhiza inflata* and may cause the inhibition of mitochondrial dehydrogenases (Zhai et al. 1999) in addition to the inhibition of parasite respiratory chain. This extract prevents growth of *L. major* and *L. donovani* promastigotes (Chen et al. 2001). Finally, 2′,6′-dihydroxy-4′-methoxychalcone (DMC) has been isolated from inflorescences of *Piper aduncum*. This extract has displayed significant effects against promastigotes and amastigotes of *L. amazonensis* (Torres-Santos et al. 1999a, b).

Flavonoids

Flavonoids are a large group of polyphenolic compounds that are widely distributed in the plant kingdom and search for their antiparasitic activity has yielded compounds like luteolin (Mittra et al. 2000), flavone A(Croft and Coombs 2003), quercetin (Mittra et al. 2000; Weina et al. 2004), fisetin, (Manjolin et al. 2013), and isoorientin (Handman 2001). Luteolin (3′,4′,5,7-tetrahydroxyflavone) isolated from *Vitex negundo*, Quercetin (3,3′,4′,5,7-pentahydroxyflavanone) derived from *Fagopyrum esculentum* and fisetin (3,7, 3′,4′-tetrahydroxyflavone) isolated from *Cotinus coggygria* (smoke tree), fruits, and vegetables are the main members of the flavonoid family and are abundantly present in fruits, vegetables, tea, olive oil, and the propolis of apiary (Mittra et al. 2000). Quercetin and luteolin inhibit parasite DNA synthesis and promote apoptosis mediated by topoisomerase-II-mediated linearization of kDNA minicircles synthesis in *L. donovani* (Mittra et al. 2000). Quercetin inhibits arginase (ARG-L) and ribonucleotide reductase (RNR) (da Silva et al. 2012; Sen and Majumder 2008) and induces cell death and mitochondrial dysfunction in *L. amazonensis* (Fonseca-Silva et al. 2011; Manjolin et al. 2013). Also, isoquercitrin (quercetin-3-O-b-glucoside) and quercitrin (quercetin-3-O-rhamnoside) inhibit ARG-L of *L. amazonensis* by a noncompetitive mechanism (da Silva et al. 2012).

The ethanolic and methanolic extracts of *Piper betle* display leishmanicidal activity against promastigotes and intracellular amastigote of *L. donovani* via accelerating apoptosis by the production of ROS, targeting the mitochondria without any cytotoxicity toward macrophages (Sarkar et al. 2008).

Epigallocatechin 3-O-gallate (EGCG) that is the most abundant flavonoid constituent of green tea has demonstrated in vivo and in vitro functions against *L. infantum*. EGCG has been reported as a novel agent for the treatment of visceral leishmaniasis (Inacio et al. 2019).

Alkaloids

Alkaloids are the most important natural compounds with the highest antileishmanial activity.

Quinoline and isoquinoline analogs

Berberine, a quaternary isoquinolinic alkaloid found in plants such as *Berberis* (e.g., *Berberis vulgaris*, *Berberis aristata*, *Mahonia aquifolium*, *Hydrastis canadensis*, and *Tinospora cordifolia*) is one of the alkaloids with the highest antileishmanial activity (Chan-Bacab and Pena-Rodriguez 2001). Berberine chloride isolated from *Berberis aristata* inhibits amastigote respiration by targeting mitochondrial enzymes and triggers a free radical-mediated, caspase-independent, apoptotic-like death (Ghosh et al. 1985). Other isoquinolinic alkaloids, including isoguattouregidine, anonaine, and liriodenine, have been reported to show activity against *L. donovani*, *L. amazonensis*, and *L. braziliensis* (Chan-Bacab and Pena-Rodriguez 2001).

Steroidal alkaloids

Sarachine (3-P-amino-22,26-epiminocholest-5-ene), an aminosteroid isolated from leaves of the bolivian plants *Saracha punctata* (Solanaceae), completely inhibits the growth of the promastigote forms of different strains of *Leishmania*. Eight steroidal alkaloids including holacurtine, holamine, *N*-demethylholacurtine, and 15-α-hydroxyholamine, obtained from the ethanolic extract of

Holarrhena curtisii (Apocynaceae) leaves have shown leishmanicidal activities against promastigotes of *L. donovani* (Chan-Bacab and Pena-Rodriguez 2001; Kam et al. 1998). N-demethylconodurine (gabunine) and bis-indole alkaloid obtained from the stem bark of *Peschiera van heurkii* (Apocynaceae) demonstrate in vitro activity against *L. braziliensis* and *L. amazonensis* promastigotes (Munoz et al. 1994).

Indole analogs

Harmaline is a fluorescent psychoactive indole alkaloid from the group of harmala alkaloids and beta-carbolines. Harmaline is the main constituent of a number of herbs utilized in traditional medicine to cure leishmaniasis, including *Passiflora incarnata* and *Peganum harmala* (Syrian rue) (Chan-Bacab and Pena-Rodriguez 2001). Their mechanism of action on the promastigote form of the parasite involves interactions with intercalate DNA or interfering with the metabolism of aromatic amino acids in the parasite (Chan-Bacab and Pena-Rodriguez 2001; Di Giorgio et al. 2004).

Harmaline, due to its activity as a reversible inhibitor of monoamine oxidase A, induces severe psychopathic effects that prevent its application as a curative agent (Chan-Bacab and Pena-Rodriguez 2001; Di Giorgio et al. 2004).

Lignans

Diphyllin, isolated from *Haplophyllum bucharicum* (Rutaceae), an endemic plant of Uzbekistan, displayed antiproliferative activity in *L. infantum* promastigotes by interacting with macromolecules, resulting in cell cycle arrest in the S phase and causing a drop in intracellular protein content. Its activity in amastigotes was related to its capability to prevent parasite attachment to macrophages and their subsequent entry (Di Giorgio et al. 2004; Salem and Werbovetz 2006). Liriodendrin, a lignan glycoside of *Phlomis brunneogaleata* (Lamiaceae), has shown antileishmanial effect against *L. donovani* amastigotes (Kayser et al. 2003b; Kirmizibekmez et al. 2004).

Tannins

Tannins represent a unique group of phenolic metabolites in numerous woody and some herbaceous higher plant species (Vannier-Santos et al. 1988). A series of tannins and structural analogs have shown antileishmanial activity, as they increased the release of NO, enhanced the expression of pro-inflammatory TNFα and IFNγ cytokines in host cells, and upregulated mRNA expression of TNFα and IFNγ, IL-12 IL-18, iNOS, and IL-1 in *Leishmania*-infected macrophages (Kolodziej and Kiderlen 2005).

Terpenes

Monoterpenes

Monoterpenes, the linalool-rich essential oil (3,7-dimethylocta-1,6-dien-3-ol) isolated from leaves of *Croton cajucara* (Euphorbiaceae), effectively increased the production of NO in *L. amazonensis*-infected macrophages. They directly target the parasite through mitochondrial swelling and alterations in the organization of nuclear and kinetoplast chromatin (do Socorro et al. 2003). Another member of monoterpenes, espintanol, isolated from the bark of *Oxandra espintana* (Annonaceae), is reported to have high toxicity toward macrophages and display remarkable effects against promastigotes of different *Leishmania* species (Chan-Bacab and Pena-Rodriguez 2001). Piperogalin and grifolin derivatives from *Peperomia galoides* cause total lysis of the promastigote forms of different *Leishmania* species (Chan-Bacab and Pena-Rodriguez 2001).

Iridoids

Iridoids are cyclopentan[*c*]pyran monoterpenoid glycosides known as biosynthetic precursors of indole alkaloids. Amarogentin is a secoiridoid glycoside isolated from the Indian plant *Swertia chirata* (Gentianaceae) (Chan-Bacab and Pena-Rodriguez 2001; da Silva Filho et al. 2004) and potently inhibits the DNA relaxation activity of topoisomerase I of *Leishmania donovani*. Picroliv, a fraction of iridoid glycosides picroside I and kutkoside and isolated from the roots and rhizomes of *Picrorhiza kurroa*, is reported to induce a high degree of protection against promastigotes of *L. donovani* (Chan-Bacab and Pena-Rodriguez 2001; Staerk et al. 2000). Amarogentin, a secoiridoid glycoside isolated from *Swertia chirata* (Gentiaceae), can inhibit the catalytic activity of topoisomerase I of *L. donovani*.

Sesquiterpenes

Artemisinin (also called qinghaosu) is a sesquiterpene lactone obtained from the ethanolic extract of *Artemisia indica* leaves. This compound increases mRNA expression of iNOS to levels present in uninfected macrophages and enhances the release of IFNγ, suggesting that artemisinin has direct parasiticidal activity and indirect immunomodulatory activity (Sen et al. 2010). Artemisinin has demonstrated antileishmanial activity against several *Leishmania* species including strains responsible for CL, MCL, and VL (Sen et al. 2010). Dehydrozaluzanin C, a sesquiterpene lactone obtained from the leaves of *Munnozia maronii* (Asteraceae) inhibits the growth of 11 species of *Leishmania* promastigotes like *L. mexicana* and *L. amazonensis* (Chan-Bacab and Pena-Rodriguez 2001). Several sesquiterpenes isolated from the

roots of *Maytenus macrocarpa* and the aerial parts of *Crossopetalum tonduzii* were investigated for reversal of daunomycin-resistance in a multidrug-resistant *Leishmania tropica* (Salem and Werbovetz 2006). Parthenolide (Deshpande et al. 1998) isolated from *Tanacetum parthenium* and Helenalin (Araujo et al. 1999) found in *Arnica chamissonis foliosa* and *Arnica montana* are sesquiterpene lactones and have demonstrated antileishmanial activity against *Leishmania amazonensis* promastigotes (Salem and Werbovetz 2006). Sesquiterpenes isolated from *Jasonia glutinosa* and *Vernonia brachycalyx* species belonging to the Asteraceae family have shown leishmanicidal activity against the promastigote forms of *L. major* and *L. donovani* (Bermejo et al. 2002; Chan-Bacab and Pena-Rodriguez 2001; Puri et al. 1994).

Diterpenes

Diterpenoid phorbol esters of Euphorbiaceae family, well known as tumor promoters, are highly cytotoxic. TPA (12-O-tetradecanoyl phorbol-13-acetate) is one of these phorbol esters that is able to cause several structural changes in *L. amazonens*. *Jatrophone* and *jatrogrossidione* isolated from Euphorbiaceae species have toxic effects against the promastigote forms of *L. amazonensis*, *L. braziliensis*, and *L. chagasi* (Mittal et al. 1998; Ray et al. 1996). Tanshinones are a group of diterpene compounds isolated from *Perovskia abrotanoides* (native to central Asia and southwestern). Tanshinones isolated from *Salvia miltiorrhiza* (native to Japan and China) are utilized to cure cutaneous leishmaniasis (Salem and Werbovetz 2006).

Triterpenes

Dihydrobetulinic acid, a triterpene, displays antileishmanial effects through targeting both DNA topoisomerases and preventing DNA cleavage, hence, inducing apoptosis in *L. donovani* (Alakurtti et al. 2010; Chowdhury et al. 2003). Also, 18 beta-glycyrrhetinic acid (GRA), a pentacyclic triterpene obtained from the root of *Glycyrrhiza glabra*, has shown antileishmanial effects through triggering Th1 cytokine response concomitant with the elevated production of iNOS in experimental visceral leishmaniasis (Ukil et al. 2005). The prevalent triterpenes, ursolic acid, obtained from the bark of *Jacaranda copaia*, and betulinaldehyde, isolated from the stem of *Doliocarpus dentatus* (Dilleniaceae), inhibited promastigotes and intracellular amastigotes of *L. amazonensis* by influencing the phagocytic activity of macrophages (Oketch-Rabah et al. 1998; Salem and Werbovetz 2006; Torres-Santos et al. 2004). Carboxylic acid, a triterpene obtained from *Celaenodendron mexicanum*, has shown activity against promastigotes and amastigotes of *L. donovani* (Tiuman et al. 2005). Epi-oleanolic acid, obtained from the leaves of *Celaenododendron mexicanum* (Euphorbiaceae), has shown anti-*Leishmania* activity against *L. donovani* promastigotes (Vannier-Santos et al. 1988).

Saponins

Hederagenin, α-hederin and β-hederin obtained from the leaves of ivy *Hedera helix* and Hederacolchiside A1 isolated from *Hedera colchica* have demonstrated toxic activity against promastigotes and amastigotes of *L. tropica*, *L. infantum*, and *L. mexicana* (Chan-Bacab and Pena-Rodriguez 2001; Loukaci et al. 2000; Majester-Savornin et al. 1991). Their powerful antiproliferative activity is due to their ability to disturb the parasite membrane integrity (Chan-Bacab and Pena-Rodriguez 2001; Loukaci et al. 2000; Majester-Savornin et al. 1991). Oleane-type triterpene saponins isolated from the methanolic extract of *Maesa balansae* leaves (Myrsinaceae) have potent prophylactic and therapeutic effects against visceral *Leishmania* species (Maes et al. 2004).

Muzanzagenin, isolated from the roots of *Asparagus africanus* (Liliaceae), and mimengoside A, obtained from the leaves of *Buddleja madagascariensis* (Loganiaceae), show activity against promastigotes of *L. major* and *L. infantum*, respectively (Delmas et al. 2000; Emam et al. 1996; Majester-Savornin et al. 1991). A steroidal saponin obtained from *Yucca filamentosa* (agavaceae) has display inhibitory effects against *L. mexicana* amazonensis promastigotes (Sairafianpour et al. 2001).

Oxylipin

In vitro, oxylipin (3S)-16,17-didehydrofalcarinol isolated from the methanolic extract of *Tridax procambens* (Asteraceae) has shown direct leishmanicidal activity against promastigotes and amastigotes of *L. mexicana*, independent of NO production in recombinant IFNγ-stimulated macrophages (Martin-Quintal et al. 2010). The ethanolic extract and butanol fraction isolated from *Tinospora sinensis* have displayed leishmanicidal effects against experimental visceral leishmaniasis caused by *L. donovani* in hamsters (Sen and Chatterjee 2011; Singh et al. 2008). This ethanolic extract increases the production of ROS and NO and kills the parasite (Singh et al. 2008). Aqueous extract of *Momordica charantia*, Indian green fruits, has shown in vitro and in vivo antileishmanial effects against *L. donovani* through inhibiting parasite superoxide dismutase (SOD), without affecting host SOD (Gupta et al. 2010; Sen and Chatterjee 2011; Sen et al. 2010). *Himatanthus sucuuba* Latex (Apocynaceae) or HsL displays antileishmanial effects against amastigotes of *L. amazonensis* through increased NO and TNFα and decreased TGFβ production in macrophages (Sen and Chatterjee 2011; Soares et al. 2010).

Other metabolites

Acetogenins such as squamocine, senegalene, sylvaticin, asimicine, rolliniastatin-1, molvizarine, annonacin A, and goniothalamicin are isolated from pantropical plant family, Annonaceae, such as *Annona senegalensis*, *Annona glauca,Rollinia emarginata*, and *Podolepsis hieracioides*. They inhibit the growth of *L. braziliensis*, *L. amazonensis*, *L. donovani*, *L. major*, *L. infantum*, and *L. enriettii* promastigotes (Da Silva et al. 1995; Kayser et al. 2003a; Rasmussen et al. 2000; Waechter et al. 1997; Zerehsaz et al. 1999). Argentilactone isolated from the hexanic extract of roots of *Annona haemantantha* (Annonaceae) has parasiticidal effects against promastigotes of *L. amazonensis*, *L. donovani*, and *L. major* and other strains of *Leishmania* spp. (Chan-Bacab and Pena-Rodriguez 2001; Waechter et al. 1997).

Bixa orellana (Bixaceae) crude seed extract and its hydroalcoholic extract (BO-A and BO-B) have shown good leishmanicidal effects against *L. amazonensis* promastigotes (García et al. 2011). The aqueous leaf extract of plant *Kalanchoe pinnata* (Crassulaceae), a medicinal plant used for the treatment of cutaneous lesions, has displayed antileishmanial activity against *L. amazonensis* in vivo. This natural remedy reduces intracellular amastigote growth through NO production although it has no direct repressive effects on extracellular promastigotes (Da-Silva et al. 1999). The G3 fraction of the methanolic extract of *Allium sativum* Linn (garlic) and the A6 fraction (Withaferin A, a steroidal lactone) from *Withania somnifera* Dunal (ashwagandha) displayed remarkable antileishmanial activity against *L. donovani* (Sen et al. 2007; Sharma et al. 2009). The antileishmanial activity of Withaferin A induced apoptosis via the inhibition of protein kinase C (PKC), while the extract of garlic exerted its parasiticidal effect through disruption of the plasma membrane integrity and enhancing proinflammatory Th1 cytokines (Sen et al. 2007; Sen and Chatterjee 2011; Sharma et al. 2009). Ajoene, a major bioactive component obtained from *Allium sativum* Linn, showed potent leishmanicidal activity in vitro against *L. m. venezuelensis, L.donovani chagasi*, *L. mexicana*, and *L. amazonensis* (Ledezma et al. 2002; Urbina et al. 1993).

Coccinia grandis leaf extract (Cg-Ex) can markedly reduce the intracellular load of *L. donovani* parasite. Serine protease inhibitor(s)-rich Cg-Ex demonstrates antileishmanial function in vitro. This occurs as a result of the modulation of proinflammatory cytokines (Pramanik et al. 2017).

A chloroquinoline derivative named 2-((7-chloroquinolin-4-y)loxy)-3-(3-methylbut-2-en-1-yl) naphthalene-1,4-diona or GF1059 is reported to be highly effective against *L. amazonensis* and *L. infantum*. GF1059 is also useful in the treatment of infected macrophages. This compound inhibits the infection of these cells at the time the parasites are pre-incubated with it. Moreover, it can induce some changes in the parasites' cell integrity and mitochondrial membrane potential and may increase the production of reactive oxygen species in *L. amazonensis* (Soyer et al. 2019).

Mechanisms of action of plant derived compounds

One of the most important mechanisms of action of plant-derived compounds is inhibitory effects against topoisomerases of kinetoplastid parasites, enzymes necessary for DNA replication (Capranico et al. 2004). These inhibitors are divided into two classes, namely, (a) compounds that stimulate the formation of topoisomerase I poisons and (b) products that interfere with enzymatic functions of the topoisomerase II (Capranico et al. 2004). Another process includes compounds targeting enzymes such as those involved in trypanothione-dependent antioxidant system. These rate-limiting enzymes can function as potential drug targets (Schmidt and Krauth-Siegel 2002; Sen and Chatterjee 2011). Other enzymes that can be considered as relevant targets are sphingolipids, fumarate reductase, microtubule-associated protein (MAP2), squalene synthase, cysteine proteases, methionine aminopeptidase 2 (MetAP-2), and protein kinases. Another mechanism of these compounds is their effect on the parasite mitochondria. Disturbing the mitochondrial membrane via plant-derived compounds can lead to cell death through an apoptotic process (Sen and Majumder 2008; Sen and Chatterjee 2011). Leishmaniasis are associated with immunological dysfunction of T cells and natural killer cells (NK cells) and inability of macrophages, leading to the establishment of the parasite. Therefore, antileishmanial compounds which are capable of recovering the Th1 response via activation of macrophages can be employed as potential drugs (Sen and Chatterjee 2011).

Conclusion and future trends

Leishmaniasis are one of the oldest known parasitic infectious diseases affecting millions of patients around the world. Researchers worldwide should devote more time and attention to leishmaniasis, as neglected protozoan diseases with a high importance in public health. Current drugs for the treatment of leishmaniasis are limited because of high price, serious side effects, long treatment duration, availability, and drug resistance. The lack of access to appropriate treatment and a significant drug resistance worldwide has made it imperative to research for new effective, inexpensive, and safe antileishmanial drugs.

The main criteria of searching for novel and innovative antileishmanial agents are its efficacy along with relatively lower side effects as compared with current drugs. Due to various reasons, access to antileishmanial drugs remains

limited, often leading patient in endemic areas suffering from leishmaniasis to depend upon traditional and folk medicines to reduce the symptoms (Sen and Chatterjee 2011). Medicinal herbs have the potential for the generation of novel drugs to be used as alternative or complementary with conventional remedies. Recently, scientific evaluation of medical herbs used in the preparation of traditional compounds should be conducted to discover useful and safe herbal-derived therapeutics and modern effective medicine. These compounds may decrease the price and improve the quality of treatment.

The purpose of this study was to gather the best work in this field and provide up-to-date knowledge to researchers. This review has highlighted a wide range of plant extracts to improve the development of new effective agents against leishmaniasis. It is important to note that some of the investigations and promising results were carried out in vitro and were not performed in vivo, and the period of exposure of some herbal extracts was not enough. Also, most results were obtained from animal model and were not tested on volunteer patients.

Although screening and purification of biocompounds from plant extracts with multiple molecules require a great deal of curiosity, time, and strong capital, there is a hope for further progress in this area to aid patients.

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