CHAPTER 04

Anti-Leishmanial Effects of Medicinal Plants

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SUMMARY

Leishmaniasis is a parasitic infection caused by *Leishmania* species of protozoan parasites, which affects millions of people all around the world. It is transmitted by the bite of infected sandflies and can cause a range of symptoms such as skin lesions, fever, splenomegaly, and hepatomegaly. Currently, there is no vaccine developed to control this disease and the available treatment options are limited and usually come with side effects. However, medicinal plants have been investigated for their potential anti-leishmanial effects, and some have shown promising results. One such plant is *Artemisia annua*, also known as sweet wormwood. It contains artemisinin. Studies have demonstrated the efficacy of artemisinin against several species of *Leishmania* parasites. Another plant such plant is *Lantana camara*, commonly known as red sage in the English language. It has shown leishmanicidal effects both in *in vitro* and *in vivo* studies. The organic extracts of *L. camara* have shown potential activity against *Leishmania* species, especially *Leishmania major*. Other medicinal plants that have been investigated for their potential anti-leishmanial effects include *Berberis vulgaris*, *Ferula macrecolea*, and *Calendula officinalis*. Extracts of these plants have shown activity against *Leishmania* parasites in various studies. The major active constituent of *Berberis vulgaris*, berberine, hinders the growth of different parasitic forms of the *Leishmania* parasite. The roots of *B.vulgaris* are highly efficacious against certain species of *Leishmania* including *L. tropica*, *L.donovani*, and *L. infantum*. The essential oil *Ferula macrecolea* works against *L. tropica* whereas the methanolic extracts of *Calendula officinalis* are found effective against *L.major*. Overall, medicinal plants offer a promising approach for the development of new anti-leishmanial treatments.

INTRODUCTION

Leishmaniasis is a zoonotic infection caused by cell-invading parasites belonging to the genus *Leishmania* from the Trypanosomatidea family (Croft et al., 2006) that affects millions of people worldwide. These parasites can be from any species of the genus such as *Leishmania* (*L.*) *infantum*, *L. mexicana*, *L. tropica*, *L. major*, *L. donovani*, and *L. amazonensis* (Nicolas et al., 2002). It is more prevalent in South America, the Mediterranean areas, Africa and Asia (Torres-Guerrero et al., 2017). Although it has a high mortality and morbidity rate still it is a neglected tropic disease. The vector responsible for the transmission of leishmaniasis is a female sand fly belonging to the genera *Lutzomyia* and *Phlebotomus* (Dietmar, 2017). When the phlebotomine sand flies bite the infected mammal, they also become diseased with the parasite that causes leishmaniasis as shown in Figure 1. This protozoal parasite replicates inside the body of the sand fly and is

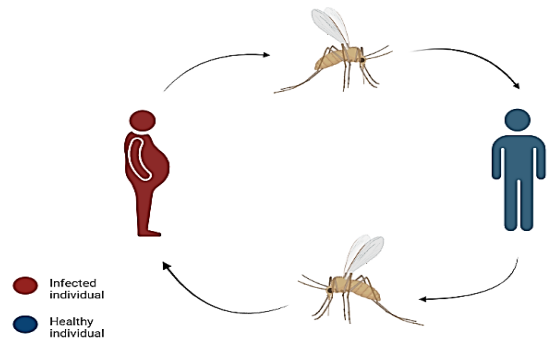

Fig 1. Transmission of *Leishmania* from an infected person to a healthy individual through the sand fly.

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transferred to the healthy person who gets bitten by the sand fly (Moriconi et al., 2017).

The life cycle of *Leishmania* generally consists of two phases; amastigotes and promastigotes (Wheeler et al., 2011) as shown in Fig 2. Amastigote is an intra-cellular, non-motile form that is observed in the hosts whereas promastigote is an extra-cellular, motile form that can be found in the gut of the parasite *(Wheeler* et al., 2011). The Leishmania parasite has a life cycle that involves two distinct stages: the sand fly stage and the mammalian host stage (Gossage et al., 2003). In the sandfly stage, the parasite resides in the gut of the sandfly as a flagellated, spindle-shaped form known as a promastigote. During a blood meal, an infected sandfly transmits the promastigotes into the skin of a mammal, along with its saliva. Once inside the mammalian host, the promastigotes are engulfed by macrophages and transform into amastigotes (Serafim et al., 2021). These amastigotes replicate within the macrophages, causing cellular damage and leading to the characteristic symptoms of leishmaniasis, which can include fever, weight loss, anemia, and skin ulcers. The parasite can be transmitted back to another sandfly when it feeds on an infected mammal. The sandfly ingests the amastigotes along with the macrophages (Serafim et al., 2021). Within the sandfly's gut, the amastigotes transform back into promastigotes and multiply, eventually migrating to the proboscis of the sandfly. The life cycle is completed when the infected sandfly bites another mammal and injects promastigotes into the skin, starting the cycle anew (Serafim *et al.*, 2021).

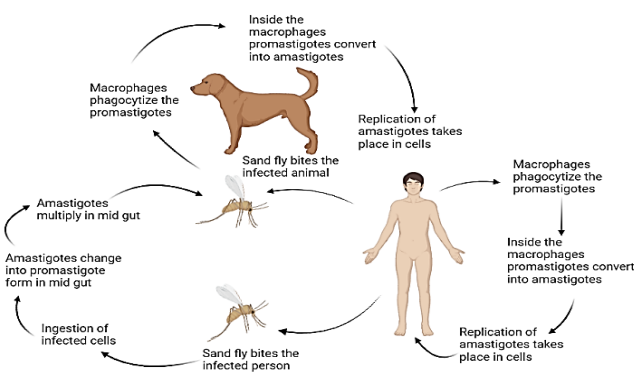

Fig 2. The life cycle of *Leishmania*

Leishmaniasis can be categorized into three groups; visceral leishmaniasis, cutaneous leishmaniasis, and mucocutaneous leishmaniasis. Visceral leishmaniasis, also referred to as kalaazar, is the most severe form of the disease. It affects the internal organs, particularly the liver and spleen, and can be fatal if left untreated. Symptoms of visceral leishmaniasis include malaise, chronic fever, nocturnal hyperhidrosis, anemia, weight loss, and enlargement of the liver and spleen (Kumar & Nylén 2012; Griensven & Diro 2012). Moreover, infected children may show the features of diarrhea and stunted growth. Cutaneous leishmaniasis involves the superficial and inner layer of the skin presenting painless lesions (Hepburn, 2003; Reithinger et al., 2007). It is the most common form of the disease. It is characterized by the development of skin lesions, which may appear as ulcers or nodules on exposed parts of the body, such as the face, arms, and legs. Cutaneous leishmaniasis usually heals on its own, but it can leave permanent scars or disfigurement. Whereas, the mucocutaneous type of leishmaniasis involves the mucosal layer of the mouth, nose, and throat as well as the skin (Boakye et al., 2005). It is a rare and severe form of the disease. It is caused by certain species of *Leishmania* and can lead to extensive tissue destruction and disfigurement if left untreated. The degree of severity of leishmaniasis may vary based on multiple factors such as the species of *Leishmania* involved, the immune status of the host, and other related factors. Several antimicrobial, anti-parasitic, and antibiotic drugs are being used in order to cure leishmaniasis but due to the increasing risk of drug resistance, these drugs are not as efficacious as they used to be (Rezaei et al., 2017). These synthetic drugs also cause financial damage to families as there is repetitive administration of large doses via injection and have adverse effects on various body organs such as the heart and liver (Rezaei et al., 2017). So, there is a dire need to discover and explore alternative methods to overcome this crisis and control the spread of leishmaniasis. In search of alternative methods, some medicinal plants like *Artemisia annua*, *Berberis vulgaris*, *Abutilon indicum*, *Allium sativum*, *Lantana camara*, *Ferula macrecolea*, etc. are found effective against this disease due to the presence of chemical constituents having anti-parasitic effect (Tagboto and Townson, 2001; Khare et al., 2014; Mans et al., 2016).

MEDICINAL PLANTS EFFECTIVE AGAINST LEISHMANIASIS

Several plants and botanical extracts have presented such curative properties that these medicinal plants can be used to treat and control this neglected disease, leishmaniasis. A few medicinal plants that show encouraging effects against leishmaniasis are discussed below:

Lantana camara L.

The common name of *Lantana camara* in English is yellow sage and red sage (Ghisalberti, 2000), which is an annual shrub that remains green throughout the year. It is small and has broad leaves. It belongs to the Verbenacae family having woody stems. Its height and width are about one to six and three to five feet respectively (Saraf et al., 2011). *Lantana*s show a remarkable ability to thrive in environments with high salt content, nutrient-deficient soil, and limited water availability (Priyanka et al., 2013). It is usually found in subtropical and

tropical areas of America. A few species are also found in Asia and Africa (Ghisalberti, 2000).

Lantana is commonly used against various human and animal conditions. Its leaves and stems are extensively used for therapeutic purposes (Mahdi-Pour et al., 2012; Delgado-Altamiranoet al., 2017). It works as an antioxidant and also inhibits DNA damage. It is also used in amoebic infections, stomach tooth, and earache, also has anti-cancer properties, used against skin diseases (Patel, 2011; Saxena et al., 2012). It shows anti-parasitic actions that's why it is used against leishmaniasis. The organic extracts that are prepared from *L. camara* show leishmanicidal activity. *L. camara* is used for the development of phytomedicines and as a source of natural products, which may represent lead compounds for the design of new drugs against leishmaniasis. The leishmanicidal activity involves a rise in reactive oxygen species, it down-regulates the expression of the enzyme *L. donovani* glutamate–cysteine ligase (LdGCLC) and upregulates the mGCLC of mammals, and the polarization of the Th1 immune response is shown by it, which augments the gene expression levels of IL-12β, IL-10, TGF-β1, IFN-γ, Tbx21, and GATA3 (Delgado-Altamiranoet al., 2017; Delgado-Altamirano et al., 2019). This indicates the high potential of natural products and their immunological regulating ability to fight leishmaniasis (Delgado-Altamiranoet al., 2017). The chloroform extract taken out from the leaves of *L. camara* contains triterpenes that have anti leishmanial effect against *Leishmania major* promastigotes (Begum et al., 2014).

Berberis vulgaris

The common name of *Berberis vulgaris* in English is barberry. It belongs to the family of Berberidaceae. It is a shrub that grows up to 4 meters having oval leaves that are small in size. Barberry is commonly found in Asia, southern Europe, Africa, North America, and Canada (Rahimi-Madisehet al., 2017). In traditional medicines, different parts of this plant like fruits, bark, leaves, and roots are used in various ways to treat several diseases. Certain alkaloids are present in its all organs or parts like berberine, oxycanthine, and columbamine (Mokhber-Dezfuli et al., 2014). Berberine is the most important alkaloid (Imenshahidi & Hosseinzadeh 2016) and is effective in heart diseases, strengthens our body tissues, has strong anti-oxidants, purifies blood, and is anti-parasitic and anti-leishmanial (Mokhber-Dezfuli et al., 2014; Rahimi-Madiseh et al., 2017).

The chemical composition of *B. vulgaris* showed that the most important constituents of this plant are isoquinoline alkaloids such as berbamine, palmatine, and particularly berberine. The last one, berberine suppressed the growth rate of promastigotes based on a dose-dependent response. Unlikely the crude extract of *B. vulgaris*, berberine indicated much higher activity against promastigote forms. Similarly, methanolic extract was more effective in inhibiting promastigotes growth than aqueous and chloroform extracts of *B. vulgaris*. Other than mentioned extracts the Aqueous extract revealed the lowest antileishmanial activity against these parasitic forms. Berberine exhibited more cytotoxicity against murine macrophages as compared with B. vulgaris. Results of some lab investigations and research showed that when parasites were pre-incubated with *B. vulgaris* their ability to infect murine macrophages was significantly decreased the alcoholic and aqueous extracts of *B. vulgaris* roots are highly efficacious against the species of *Leishmania* which are *L. tropica*, *L. donovani*, and *L. infantum*. Berberineretards the growth rate of promastigotes and reduces the number of amastigotes (Mahmoudvand et al., 2014).

Ferula macrecolea

Ferula macrecolea belongs to the genus *Ferula*. The English names of *Ferula macrecolea* are safoetida, gum foetida, gum, and Ferula. In Urdu, it is known as hing, hiltit, heng, vaghayani, hinghi, and ushi, and in Arabic its name is hiltit. It belongs to the Umbelliferae or Apiaceae family. This genus comprises more than 150 species (Sadeghi et al., 2023). It is generally found in central Asia, the Mediterranean area, and North Africa (Salehi et al., 2019). Ferula extracts involve various therapeutic effects on the human and animal body such as anti-microbial, anti-inflammatory, anti-parasitic, and antioxidant (Sadeghi et al., 2023).

The essential oil of *Ferula* extract contains terpinolene which acts as the main anti-leishmenic agent. It also contains glucantime that works usually against *L. tropica* amastigotes and promastigotes (Mahmoudvand et al.,2022). Both chemicals have minimum toxic effects on macrophages. Increasing the concentration of essential oil causes a significant decrease in the number of amastigotes and promastigotes (Mahmoudvand et al., 2022).

Artemisia annua

The English names of *Artemsia annua*are sweet wormwood, annual wormwood, and annual mugwort (Das, 2012). It is found in the northern areas of Pakistan, the temperate region of Asia, and several other countries like Bulgaria, Italy, America, Hungary, Argentina, Spain, France, and Romania (Das, 2012). The family of *Artemisia* is Asteraceae (Mannan et al., 2010) and it grows yearly having straight brownish stems. It is usually 100 cm (about 3.28 ft) tall (Das, 2012). *Artemisia* which is found in Pakistan has a long history of being used as a medicinal plant. There are many therapeutic features of this plant evaluated (Mannan et al., 2010). Extract of *Artemisia* is typically used which is taken from its leaves and stems. It has anti-inflammatory, pain relieving, brain boosting, anti-parasitic, and anti-oxidant properties (Das, 2012). *Artemisia* is remarkably

effective against promastigotes of *L. major* (Emami et al., 2012). Extract of *Artemisia* species has leishminicidal properties against *L. tropica* and *L. major* (Emami et al., 2012). Its extract works by breaking the DNA of the parasite into fragments (Rupashree et al., 2010; Bahmani et al., 2015). The active constituent of *Artemisia annua* is called *qinghaosu*, which was extracted from the plant in the 1970s; this compound is now known as artemisinin. Artemisinin, which is widely used as an anti-malarial drug, has shown anti-promastigote activity and the 50% inhibitory concentration (IC_{50}) ranged from 100 µM to 120 µM irrespective of *Leishmania* species studied. *Leishmania donovani*-infected macrophages do disastrous changes to the host bodies, they demonstrate decreased production of nitrite as well as mRNA expression of inducible nitric oxide synthase, It was normalized by artemisinin, hence indicating that it exerted both a direct parasiticidal activity as well as inducing a host protective response (Sen, 2010).

Calendula officinalis

Calendula officinalis belongs to the Asteraceae family (Dhingra et al., 2022). It is commonly known as pot marigold in English (Kemper, 1999; Leach, 2008). It is an aromatic plant having soft leaves and beautiful yellow, orange, or red flowers (Kemper, 1999). It grows annually or biennially (Pirzad & Shokrani 2012). It is native to Europe, England, Asia, and America (Kemper, 1999). It has a wide range of medicinal uses such as antispasmodic, emmenagogue, and stimulant, in the treatment of measles, ulcers, frostbites, constipation, and jaundice (Dhingraet al., 2022). Its ointments are used for treating wounds. It also possesses anti-leishmanial properties. For leishmaniasis, methanolic extracts of *Calendula officinalis* are used (Bahmani et al., 2015). It inhibits the growth of promastigotes and amastigotes of *L. major*. It reduces the number of amastigotes (Nikmehr et al., 2014).

Tab 1., depicts some medicinal plants other than the above-mentioned plants which are found to be effective against leishmaniasis and show encouraging medicinal properties against leishmaniasis. This table presents a summary of some of the other medicinal plants that have demonstrated leishmanicidal activity, highlighting their potential as alternative therapies for leishmaniasis.

CONCLUSION

Leishmaniasis, being a neglected tropical disease influences the organisms adversely and has a high mortality rate. While the treatment of leishmaniasis depends on anti-leishmanial drugs, their efficacy is limited by drug resistance, toxicity, and high

Tab 1. Some other medicinal plants showing leishmanicidal activity.

Scientific Names (Common name)	Family Names	Active Constituents	Mechanism of action	References
Allium sativum (Garlic)	Amaryllidaceae	Allicin, Alliin	It has inhibitory effect against the promastigotes.	Ghazonfari et al., 2000; Gharavi et al., 2011; Shang et al., 2019
Artemisia absinthium (Wormwood)	Asteraceae	Endo-peroxide	It has inhibitory effect against promastigotesandaxenicamastigotes	Tariku et al., 2011; Azizi et al., 2016
Artemisia aucheri (Artemis)	Asteraceae	Camphene, β-Myrcene	It is effective against promastigotes.	Sharif et al., 2006
Capsicum annuum (Kapsa)	Solanaceae	Flavonoids (apigenin&luteolin)	It inhibits the growth of promastigotes.	Yakhchali & Ranjbariki-Jandabeh, 2013
Cassia fistula (Amaltas)	Fabaceae	Sterol and clerosterol	It destroys the promastigote form of the parasite.	Sartorelli et al., 2007; Barati et al., 2010
Cinnamomum cassia (Cassia)	Lauraceae	α-Pinene & β-Pinene	It hinders the proliferation of amastigotes.	Afrin et al., 2019
Eucalyptus globules (Blue gum)	Myrtaceae	Eucalyptol, α-pinene, p-cymene, β-cymene	It minimizes the lesions formed in cutaneous leishmaniasis.	Khou et al., 2007
Ferula asafetida (Asafoetida)	Apiaceae	Resin Volatile oil, Eucalyptol	It hinders the growth of the parasite.	Bafghi et al., 2014
Glycyrrhiza glabra (Liquorice)	Fabaceae	Glycyrrhizic acid	It suppresses the growth of promastigotes and amastigotes	Dinesh et al., 2017; Sheikhi et al., 2022
Haplophyllumbucharicum (Sadaap)	Rutaceae	Diphyllin	It has inhibitory effect against the intracellular amastigotes.	Giorgio et al., 2005
Mimosa tenuiflora (Juremapreta)	Fabaceae	Tannins and flavonoids	It hinders the growth of the parasite.	Shamsedini et al., 2006
Nigella sativa (Blach seed)	Ranunculaceae	Tymoquinone	It inhibits the growth of the parasite.	Pirali-Kheirabadi et al., 2013; Mahmoudvand et al., 2015
Peganumharmala (Harmal)	Nitrariaceae	Harmane, Harmine, Harmaline	It hinders the growth of promastigotes and amastigotes	Giorgio et al., 2004; Yousefi et al., 2009
Stachyslavandulifolia (Wood betony)	Lamiaceae	β-phellandrene α-pinene Germacrene-D	It is effective against promastigotes.	İşcan et al., 2012; Naserifard et al., 2013
Zajuriamultifl or a Boiss (Thyme)	Lamiaceae	Thymol	It hinders the parasitic growth.	Hejazi et al., 2009; Kowalczyk et al., 2020

cost. It is the need of time to look for a way of treatment that should be safe and economical. As there are no vaccines in the present day for this fatal illness and the risk of drug resistance is increasing day by day, it is necessary to switch to the natural and alternative compounds. Medicinal plants have been found to possess significant anti-leishmanial activity and have the potential to offer a promising alternative therapy for the cure of leishmaniasis. The active compounds present in these plants have shown efficacy against the parasite and have fewer side effects as compared to the conventional drugs. Substituting the synthetic medicines and compounds with naturopathic products can minimize the risk of drug resistance and contribute in management and control of leishmaniasis. The potential of medicinal plants as an alternative or complementary therapy for leishmaniasis treatment holds significant potential for future advancements. Further research is required to evaluate the effectiveness, safety, and economic viability of plant-based treatments, as well as to recognize the bioactive components and their mechanisms of action. Also, the development of standardized formulations and quality control checks are a prerequisite to maintaining the consistency and reproducibility of plant-based therapies. Moreover, the use of plant-based remedies along with conventional anti-leishmanial drugs could bring about improved therapeutic outcomes and decreased drug resistance.

REFERENCES

Afrin F, G Chouhan, M Islamuddin, MY Want, HA Ozbak & H Hemeg, 2019. *Cinnamomum cassia* exhibits antileishmanial activity against *Leishmania donovani* infection in vitro and in vivo. PLOS Neglected Tropical Diseases13(5):e0007227.

Azizi K, F Shahidi-Hakak, Q Asgari, GR Hatam, MR Fakoorziba, R Miri & MD Moemenbellah-Fard, 2016. In vitro efficacy of ethanolic extract of*Artemisia absinthium* (Asteraceae) against *Leishmania major L*. Using cell sensitivity and flow cytometry assays. Journal of Parasitic Diseases 40(3):735-740.

Khou LB, M Mohebali, N Lahiji & A Mehrabitavana, 2007. The therapeutic effects of *Eucalyptus*, *Myrtus*, *Ferula*, *Aretmisia*, *Allium* and *Urtica* extracts against cutaneous leishmaniasis caused by *Leishmanaia major* in small white mice (out-bred). Hakim Research Journal 10(2):21-27.

Bafghi AF, SM Bagheri & S Hejazian, 2014. Antileishmanial activity of *Ferula assa-foetida* oleo gum resin against *Leishmania major*: An in vitro study. Journal of Ayurveda and Integrative Medicine 5(4):223.

Bahmani M, K Saki, B Ezatpour, S Shahsavari, Z Eftekhari, M Jelodari, M Rafieian-Kopaei & R Sepahvand, 2015. Leishmaniosis phytotherapy: Review of plants used in Iranian traditional medicine on leishmaniasis. Asian Pacific Journal of Tropical Biomedicine 5(9):695-701.

Barati M, I Sharifi & F Sharififar, 2010. Antileishmanial activity of *Artemisia aucheri*, *Ferula asa-foetid* and *Gossypium hirsutum* extracts on *Leishmania major* promastigotes in vitro. Annals of Military and Health Sciences Research 8(3):166-172.

Begum S, A Ayub, S Qamar Zehra, B Shaheen Siddiqui & M Iqbal Choudhary, 2014. Leishmanicidal triterpenes from *Lantana camara*. Chemistry & Biodiversity 11(5):709-718.

Boakye D, M Wilson & M Kweku, 2005. A review of leishmaniasis in West Africa. Ghana Medical Journal 39(3):94.

Croft SL, S Sundar & AH Fairlamb, 2006. Drug resistance in leishmaniasis. Clinical Microbiology Reviews 19(1):111-126.

Das S, 2012. *Artemisia annua* (Qinghao): A pharmacological review. International Journal of Pharmaceutical Sciences and Research 3(12):4573-4577.

Delgado-Altamirano R, RI López-Palma, L Monzote, J Delgado-Domínguez, I Becker, JF Rivero-Cruz, N Esturau-Escofet, PA Vázquez-Landaverde & A Rojas-Molina, 2019. Chemical constituents with leishmanicidal activity from a pink-yellow cultivar of *Lantana camara* var. *aculeata* (L.) collected in Central Mexico. International Journal of Molecular Sciences 20(4):872.

Delgado-Altamirano R, L Monzote, A Piñón-Tápanes, H Vibrans, JF Rivero-Cruz, C Ibarra-Alvarado & A Rojas-Molina, 2017. In vitro antileishmanial activity of Mexican medicinal plants. Heliyon 3(9):e00394.

Dhingra G, P Dhakad & S Tanwar, 2022. Review on phytochemical constituents and pharmacological activities of plant *Calendula officinalis linn*. Biological Sciences 2(2):216-228.

Di Giorgio C, F Delmas, V Akhmedjanova, E Ollivier, I Bessonova, E Riad & P Timon-David, 2005. In vitro antileishmanial activity of diphyllin isolated from *Haplophyllum bucharicum*. Planta Medica 71(04):366-369.

Di Giorgio C, F Delmas, E Ollivier, R Elias, G Balansard & P Timon-David, 2004. In vitro activity of the β-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species *Leishmania infantum*. Experimental Parasitology 106(3-4):67-74.

Dietmar S, 2017. The history of leishmaniasis. Parasites & Vectors 10(1):82.

Dinesh N, S Neelagiri, V Kumar & S Singh, 2017. Glycyrrhizic acid attenuates growth of *Leishmania donovani* by depleting ergosterol levels. Experimental Parasitology 176:21-29.

Emami SA, SZT Rabe, A Ahi & M Mahmoudi, 2012. Inhibitory activity of eleven *Artemisia* species from Iran against *Leishmania major* parasites. Iranian Journal of Basic Medical Sciences 15(2):807.

Gharavi M, M Nobakht, S Khademvatan, F Fani, M Bakhshayesh & M Roozbehani, 2011. The effect of aqueous garlic extract on Interleukin-12 and 10 levels in *Leishmania major* (MRHO/IR/75/ER) infected macrophages. Iranian Journal of Public Health 40(4):105.

Ghazanfari T, ZM Hassan, M Ebtekar, M Ahmadiani, G Naderi & A Azar, 2000. Garlic induces a shift in a *Leishmania major*–infected BALB/c mice. Scandinavian Journal of Immunology 52:491-495.

Ghisalberti EL, 2000. *Lantana camara L.*(Verbenaceae). Fitoterapia 71(5):467-486.

Gossage SM, ME Rogers & PA Bates, 2003. Two separate growth phases during the development of leishmania in sand flies: Implications for understanding the life cycle. International Journal for Parasitology 33(10):1027-1034.

Hejazi SH, L Shirani-Bidabadi, A Zolfaghari–Baghbaderani, S Saberi, MA Nilforoushzadeh, S Moradi, M Mahmoudi, S Khosravi & A Ataei, 2009. Comparision effectivness of extracts of thyme, yarrow, henna and garlic on cutaneous leishmaniasis caused by *L. major* in animal model (BALB/c). Journal of Medicinal Plants 8(30):129-136.

Hepburn N, 2003. Cutaneous leishmaniasis: An overview. Journal of Postgraduate Medicine 49(1):50.

Imenshahidi M & H Hosseinzadeh, 2016. *Berberis vulgaris* and berberine: An update review. Phytotherapy Research 30(11):1745-1764.

İşcan G, B Demirci, F Demirci, F Göger, N Kırımer, YB Köse & K Başer, 2012. Antimicrobial and antioxidant activities of *Stachys lavandulifolia subsp.lavandulifolia* essential oil and its infusion. Natural Product Communications 7(9):1241-1244.

Kemper KJ, 1999. Calendula (*Calendula officinalis*). Longwood Herbal Task Force.

Khare P, P Rastogi, S Gupta, R Mauyra & A Dube, 2014. In vitro and in vivo efficacy of a new herbaceous Indian plant- *Abutilon indicum* against *Leishmania donovani* infection. American Journal of Phytomedicine and Clinical Therapeutics 2(1):134-139.

Kowalczyk A, M Przychodna, S Sopata, A Bodalska & I Fecka, 2020. Thymol and thyme essential oil—New insights into selected therapeutic applications 25(18):4125.

Kumar R & S Nylén, 2012. Immunobiology of visceral leishmaniasis. Frontiers in Immunology 3:251.

Leach MJ, 2008. *Calendula officinalis* and wound healing: A systematic review. Wounds 20(8):236-243.

Mahdi-Pour B, SL Jothy, LY Latha, Y Chen & S Sasidharan, 2012. Antioxidant activity of methanol extracts of different parts of *Lantana camara*. Asian Pacific Journal of Tropical Biomedicine 2(12):960-965.

Mahmoudvand H, SA Ayatollahi Mousavi, A Sepahvand, F Sharififar, B Ezatpour, F Gorohi, E Saedi Dezaki & S Jahanbakhsh, 2014. Antifungal, antileishmanial, and cytotoxicity activities of various extracts of *Berberis vulgaris* (Berberidaceae) and its active principle berberine. ISRN Pharmacology 2014.

Mahmoudvand H, R Tavakoli, F Sharififar, K Minaie, B Ezatpour, S Jahanbakhsh & I Sharifi, 2015. Leishmanicidal and cytotoxic activities of *Nigella sativa* and its active principle, thymoquinone. Pharmaceutical Biology 53(7):1052-1057.

Mahmoudvand H, JG Yadegari, AK Khalaf, MJ Hashemi, S Dastyarhaghighi & I Salimikia, 2022. Chemical composition, antileishmanial, and cytotoxic effects *Ferula macrecolea* essential oil against *Leishmania tropica*. Parasite Epidemiology and Control 19:e00270.

Mannan A, I Ahmed, W Arshad, MF Asim, RA Qureshi, I Hussain & B Mirza, 2010. Survey of artemisinin production by diverse *Artemisia* species in northern Pakistan. Malaria Journal 9:1-9.

Mans D, T Beerens, I Magali, R Soekhoe, G Schoone, K Oedairadjsingh, J Hasrat, E Van Den Bogaart & H Schallig, 2016. In vitro evaluation of traditionally used Surinamese medicinal plants for their potential anti-leishmanial efficacy. Journal of Ethnopharmacology 180:70-77.

Mokhber-Dezfuli N, S Saeidnia, AR Gohari & M Kurepaz-Mahmoodabadi, 2014. Phytochemistry and pharmacology of *Berberis* species. Pharmacognosy Reviews 8(15):8.

Moriconi M, G Rugna, M Calzolari, R Bellini, A Albieri, P Angelini, R Cagarelli, MP Landini, RN Charrel & S Varani, 2017. Phlebotomine sand fly–borne pathogens in the Mediterranean Basin: Human leishmaniasis and phlebovirus infections. PLOS Neglected Tropical Diseases 11(8):e0005660.

Naserifard R, A Dalimi Asl & N Ahmadi, 2013. Influence of aqueous extract *Scophularia straiata* on growth of *Leishmania major* in mice peritoneal macrophages (BALB/c). Pejouhesh 36(5):12-18.

Nicolas L, E Prina, T Lang & G Milon, 2002. Real-time PCR for detection and quantitation of leishmania in mouse tissues. Journal of Clinical Microbiology 40(5):1666-1669.

Nikmehr B, H Ghaznavi, A Rahbar, S Sadr & S Mehrzadi, 2014. In vitro anti-leishmanial activity of methanolic extracts of *Calendula officinalis* flowers, *Datura stramonium* seeds, and *Salvia officinalis* leaves. Chinese Journal of Natural Medicines 12(6):423-427.

Patel S, 2011. A weed with multiple utility: *Lantana camara*. Reviews in Environmental Science and Bio/Technology 10:341-351.

Pirali-Kheirabadi K, A Dehghani-Samani, M Adel & F Hoseinpour, 2013. The effect of essential oil of *Nigella sativa* and *Satureia hortensis* on promastigot stage of *Leishmania major*. Armaghane-danesh, Yasuj University of Original Article Medical Sciences Journal 18(9):687-698.

Pirzad A & F Shokrani, 2012. Effects of iron application on growth characters and flower yield of *Calendula officinalis L.*under water stress. World Applied Sciences Journal 18(9):1203-1208.

Priyanka N & P Joshi, 2013. A review of *Lantana camara* studies in India. International Journal of Scientific and Research Publications 3(10):1-11.

Rahimi-Madiseh M, Z Lorigoini, H Zamani-Gharaghoshi & M Rafieian-Kopaei, 2017. *Berberis vulgaris*: Specifications and traditional uses. Iranian Journal of Basic Medical Sciences 20(5):569.

Reithinger R, JC Dujardin, H Louzir, C Pirmez, B Alexander & S Brooker, 2007. Cutaneous leishmaniasis. The Lancet Infectious Diseases 7(9):581-596.

Rezaei R, KH Tappeh, S Seyyedi & P Mikaili, 2017. The anti-leishmanial efficacy of *Artemisia dracunculus* ethanolic extract in vitro and its effects on IFN-γ and IL-4 response. Iranian Journal of Parasitology 12(3):398.

Rupashree S, S Ganguly, P Saha & M Chatterjee, 2010. Efficacy of artemisinin in experimental visceral leishmaniasis. International Journal of Antimicrobial Agents 36(1):43-49.

Sadeghi N, H Sadeghi, DN Mohan, A Sepahvand, A Alizadeh & S Garavand, 2023. Chemical composition, anti-fungal and cytotoxic effects of *Ferula macrecolea* essential oil against *Candida albicans* resistant and sensitive strains. Journal of Herbmed Pharmacology 12(2):228-232.

Salehi M, MR Naghavi & M Bahmankar, 2019. A review of *Ferula* species: Biochemical characteristics, pharmaceutical and industrial applications, and suggestions for biotechnologists. Industrial Crops and Products 139:111511.

Saraf A, S Quereshi, K Sharma & NA Khan, 2011. Antimicrobial activity of *Lantana camara L.* Journal of Experimental Sciences 2(10):50-54.

Sartorelli P, SP Andrade, MS Melhem, FO Prado & AG Tempone 2007. Isolation of antileishmanial sterol from the fruits of *Cassia fistula* using bioguided fractionation. Phytotherapy Research 21(7):644-647.

Saxena M, J Saxena & S Khare, 2012. A brief review on: Therapeutical values of *Lantana camara* plant. International Journal of Pharmacy and Life Science 3(3).

Serafim TD, IV Coutinho-Abreu, R Dey, R Kissinger, JG Valenzuela, F Oliveira & S Kamhawi, 2021. Leishmaniasis: The act of transmission. Trends in Parasitology 37(11):976-987.

Shamsedini S, S Rajab Alian, M Mirzaei & M Brofei, 2006. Efficacy of *Mimosa tenuiflora* extract on growth of Leishmania protozoa in vitro. Iranian Journal of Dermatology 9(2):173-178.

Shang A, SY Cao, XY Xu, RY Gan, GY Tang, H Corke, V Mavumengwana & HB Li, 2019. Bioactive compounds and biological functions of garlic (*Allium sativum L.*). Foods 8(7):246.

Sharif M, H Ziaei, M Azadbakht, A Daryani, A Ebadattalab & M Rostami, 2006. Effect of methanolic extracts of *Artemisia aucheri* and *Camellia sinensis* on *Leishmania major* (in vitro). Turkish Journal of Medical Sciences 36(6):365-369.

Sheikhi S, A Khamesipour, T Radjabian, T Ghazanfari & A Miramin Mohammadi, 2022. Immunotherapeutic effects of *Glycyrrhiza glabra* and glycyrrhizic acid on *Leishmania major*-infection BALB/c mice. Parasite Immunology 44(1-2):e12879.

Tagboto S & S Townson, 2001. Antiparasitic properties of medicinal plants and other naturally occurring products. Advances in Parasitology 50:199-295.

Tariku Y, A Hymete, A Hailu & J Rohloff, 2011. In vitro evaluation of antileishmanial activity and toxicity of essential oils of *Artemisia absinthium* and *Echinops kebericho*. Chemistry & Biodiversity 8(4):614-623.

Torres-Guerrero E, MR Quintanilla-Cedillo, J Ruiz-Esmenjaud & R Arenas, 2017. Leishmaniasis. F1000Research 6:750.

van Griensven J & E Diro, 2012. Visceral leishmaniasis. Infectious Disease Clinics of North America 26(2):309-322.

Wheeler RJ, E Gluenz & K Gull, 2011. The cell cycle of leishmania: Morphogenetic events and their implications for parasite biology. Molecular Microbiology 79(3):647-662.

Yakhchali M & M Ranjbariki-Jandabeh, 2013. Effects of *Nerium oleander* leaf, *Ricinus communis* oil, *Capsicum* spp. seeds, and almond compound on cutaneous leishmaniasis caused by *Leishmania* species under laboratory condition and its effect on cutaneous lesion progression in mice. Scientific journal of Kurdistan University of Medical Sciences 18(3):13-19.

Yousefi R, F Ghaffarifar & AD Asl, 2009. The effect of *Alkanna tincturia* and *Peganum harmala* extracts on *Leishmania major* (MRHO/IR/75/ER) in vitro. Iranian Journal of Parasitology 4(1):40-47.