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Revisión / Review

Therapeutic potential of medicinal plants against Leishmaniasis: a public health concern

[Potencial terapéutico de plantas medicinales contra la Leishmaniasis: Un problema de salud pública]

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Abstract: Leishmaniasis is an important disease affecting global public health which is spread by sand fly having different species. Various chemical drugs are used to treat and control Leishmaniasis including pentavalent antimonials, antimicrobial and antibiotics. Due to emergence of drug resistance, these therapeutic options are losing effectiveness in attaining success. Furthermore, these drugs are expensive and have toxic effects on liver and kidneys. There has been an emerging interest and excellent response by using plant based drugs and extracts to control Leishmaniasis. Different medicinal plants including Glycyrrhiza glabra, Allium sativum, Peganum harmala and Nigella sativa have shown excellent anti-leishmanial activity. Therefore, medicinal plants can help in effective drug development against Leishmaniasis diseases in both animals and humans which will be safer and health protective.

Keywords: Medicinal Plants; Leishmaniasis; Health; Treatment; Resistance.

Resumen: La Leishmaniasis es una enfermedad importante que afecta la salud pública mundial y que es transmitida por las moscas de la arena, que tienen diferentes especies. Se utilizan varios medicamentos químicos para tratar y controlar la Leishmaniasis, incluidos los antimoniales pentavalentes, antimicrobianos y antibióticos. Debido a la aparición de resistencia a los medicamentos, estas opciones terapéuticas están perdiendo eficacia para lograr el éxito. Además, estos medicamentos son costosos y tienen efectos tóxicos en hígado y riñones. Ha habido un interés emergente y una excelente respuesta mediante el uso de extractos y medicamentos a base de plantas para controlar la Leishmaniasis. Diferentes plantas medicinales como *Glycyrrhiza glabra*, *Allium sativum*, *Peganum harmala* y *Nigella sativa* han mostrado una excelente actividad anti-leishmanial. Por lo tanto, las plantas medicinales pueden ayudar en el desarrollo de fármacos eficaces contra las enfermedades de la leishmaniasis tanto en animales como en seres humanos, lo que será más seguro y proteja la salud.

Palabras clave: Plantas medicinales; Leishmaniasis; Salud; Tratamiento; Resistencia.

INTRODUCTION

Parasitism is a global problem effecting health of human and animal population all over the world (Li *et al.,* 2020; Salman *et al.,* 2020). Parasites have complex lifecycles and have variation in transmission routes. Parasites also act as vector of many important diseases which appose serious threat to public health like *Leishmaniasis* (Oryan *et al.,* 2015). *Leishmaniasis* is an important widespread disease affecting both humans and animals which is caused by *Leishmania* parasites having different species (*L. donovani*, *L. major*, *L. mexicana*, *L. amazonensis*) and is transmitted by vector sand fly of genus *Phlebotomus* and *Lutzomyia*. The parasite lives in mononuclear phagocytic cells of vertebrates (Dujardin *et al*., 2008; Li *et al.,* 2020). According to World Health Organization, *Leishmaniasis* is endemic in 88 countries of the world including Middle East, South America, Europe and Asia, and is one of the seven most important tropical diseases with a potentially fatal outcome (Andrade-Narváez *et al.,* 2003). Overall in the world about 12 and 15 million people are infected with *Leishmania* species. About 350 million people are at risk and each year 1-2 million new cases are reported while 70,000 deaths are attributed to this disease (Bravo & Sanchez, 2003; Khezzani & Bouchemal, 2017).

Leishmaniasis mostly occurs in visceral form, known as kala-azar, and cutaneous form which causes serious threats to human health including young children and adult population all over the world. In cutaneous *Leishmaniasis* form, major clinical signs include severe cutaneous lesions which start in the nasal and oral mucosa and spread to pharynx, larynx, forearms and esophagus (Khezzani & Bouchemal, 2017). In extreme cases, death may also occur due to pain and atrophy of respiratory mucosa. In visceral *Leishmaniasis*, black fever lesions may appear in reticuloendothelial system and may include lymphadenopathy, hepatomegaly, splenomegaly, cutaneous pigmentation, weight loss and ultimately death (Desjeux, 2004).

Various drugs are used to treat *Leishmaniasis* including pentavalent antimonials, antimicrobial and antibiotics (Rezaei *et al.,* 2017). Pentavalent antimonials are used as first line of treatment against cutaneous and visceral *Leishmaniasis.* The second choice therapeutic agents are amphotericin-B and pentamidine which are used to treat the visceral form (Amato *et al.,* 2008). Unfortunately, commercially available anti-leishmanial drugs are losing their effectiveness mainly because of emergence of resistant strains of Leishmania, furthermore, toxic effects of on human health are additional drawbacks of these drugs (WHO, 2010).

So, exploration of diverse and alternative compounds and therapeutic agents against diseases of public health and livestock is appealing approach (Abbas *et al*., 2017; Abbas *et al*.,2019; Afsheen *et al*., 2019; Ali *et al*., 2020; Zhang *et al*., 2020). Among natural agents botanicals and their compounds have shown encouraging therapeutic properties against various parasitic diseases including *Leishmaniasis* (Townson, 2001; Khare *et al.,* 2014; Mans *et al.,* 2016; Rahman & Mohsin, 2019).

A considerable work has been reported on the successful development of anti-lesihmanial drugs from medicinal plants. Some previous and recent work is summarized in Table No. 1.

Anti-leishmanial effects of some important medicinal plants

Glycyrrhiza glabra

Glycyrrhiza glabra belongs to the Fabaceae family and contains glycyrrhizic acid (GA) which has shown anti-leishmanial activity and its mode of action has also been discovered. GA showed dose dependent anti-leishmanial efficacy by inhibiting the promastigotes and intracellular amastigotes stages of the parasites (Dinesh *et al*., 2017). The results of this study showed that GA inhibits the parasites growth by affecting sterol biosynthetic pathway, especially by inhibiting the enzymatic activity.

Ferula szowitsiana

More than 133 species belonging to the Apiaceae family are distributed throughout the Mediterranean area and central Asia such as Iran and Afghanistan and most found genus is Ferula (Bafghi *et al*., 2014). The part used is an oleo gum resin, obtained by incision from the stem and root, and called asafetida, which is used for its anticonvulsant, antispasmodic, carminative, digestive, expectorant, sedative, antihysteric, laxative, aphrodisiac, antiseptic and analgesic activities (Iranshahi *et al*., 2007). Many Asian countries use this plant against intestinal parasites (Emami *et al*., 2010). Sesquiterpene coumarins which were isolated from Ferula szowitsiana showed anti-leishmanial effects against the promastigote forms (Iranshahi *et al*., 2007).

Table No. 1
Plants reported for their anti-leishmanial activity

Plants	Common Name/English Name	Family Name	Main Component	Reference
Allium sativum	Garlic	Amaryllidaceae	Allicin, Alliin	Ghazonfari *et al.*, 2000 Shang *et al.*, 2019
Allium sativum	Garlic	Amaryllidaceae	Allicin, Alliin	Ghazonfari *et al.*, 2000 Shang *et al.*, 2019
Artemisia absinthium	Wormwood	Asteraceae	Endoperoxide	Azizi *et al*., 2016
Artemisia absinthium	Wormwood	Asteraceae	Endoperoxide	Azizi *et al*., 2016
Artemisia aucheri	Artemis	Asteraceae	Camphene β-Myrcene	Sharif *et al*., 2006
Artemisia aucheri	Artemis	Asteraceae	Camphene β-Myrcene	Sharif *et al*., 2006
Artemisia dracunculus	Estragon	Asteraceae	α-Pinene, Myrecene, Limonene	Rezaei *et al*., 2017
Artemisia dracunculus	Estragon	Asteraceae	α-Pinene, Myrecene, Limonene	Rezaei *et al*., 2017
Cassia fistula	Amaltas	Fabaceae	Sterol, clerosterol	Barati *et al*., 2010 Sartorelli *et al*., 2007
Cassia fistula	Amaltas	Fabaceae	Sterol, clerosterol	Barati *et al*., 2010 Sartorelli *et al*., 2007
Cinnamomum cassia	Cassia	Lauraceae	α-Pinene, β-Pinene	Afrin *et al*., 2019
Echinacea purpurea	Purple coneflower	Asteraceae	Cichoric acid	Sadati *et al*., 2011
Echinacea purpurea	Purple coneflower	Asteraceae	Cichoric acid	Sadati *et al*., 2011
Ferula asafetida	Asafoetida	Apiaceae	Resin, volatile oil, Eucalyptol	Alborzi *et al.*, 2003 Bafghi *et al.*, 2014
Ferula asafetida	Asafoetida	Apiaceae	Resin, volatile oil, Eucalyptol	Alborzi *et al.*, 2003 Bafghi *et al.*, 2014
Ferula szowitsiana	Asafoetida	Apiaceae	Coumarins, Phenylpropanoid	Iranshahi *et al.*, 2007
Glycyrrhiza glabra	Liquorice	Fabaceae	Glycyrrhizic acid	Chen *et al.*, 1993 Dinesh *et al.*, 2017
Glycyrrhiza glabra	Liquorice	Fabaceae	Glycyrrhizic acid	Chen *et al.*, 1993 Dinesh *et al.*, 2017
Haplophyllum bucharicum	Sadaap	Rutaceae	Diphyllin	Giorgio *et al.*, 2005
Tasmanian bluegum	Eucalyptus	Myrtaceae	Galic acid	Tahir *et al*., 1998
Tasmanian bluegum	Eucalyptus	Myrtaceae	Galic acid	Tahir *et al*., 1998

Table No. 2
Effects of medicinal plants on *Leishmania* parasite

Plant Name	Common Name	Family Name	Effects	Refernce
Allium sativum	Garlic	Amaryllidaceae	Destroyed Promastigote form	Gharavi *et al.,* 2011
Aloe latex	Aloe	Asphodelaceae	Effect on growth	Delavari *et al.,* 2013
Artemisia annua	wormwood/Gandwash	Asteraceae	Effective against the promastigote form	Emami *et al.,* 2012
Capsicum annuum	Kapsa	Solanaceae	Effective against the promastigote form	Yakhchali *et al.,* 2013
Cassia fistula	Amaltas	Fabaceae	Destroyed the Promastigote form	Barati *et al.,* 2010
Eucalyptus globulus	Blue gum	Myrtaceae	Reduced cutantaneous lesions	Babaee *et al.,* 2007
Haplophyllum bucharicum	Sadaap	Rutaceae	Inhibited growth of amastigote form	Giorgio *et al.,* 2005
Mimosa tenuiflora	Jurema	Fabaceae	Reduced parasitic growth	Shamsuddini *et al.,* 2006
Nigella sativa	Blach seed	Ranunculaceae	Reduce the parasitic growth	Pirali-Kheirabadi *et al.,* 2013
Peganum harmala	Harmal	Nitrariaceae	Inhibitory effect on promastigote and amastigote forms	Yousefi *et al.,* 2009
Stachys lavandulifolia	Wood betony	Lamiaceae	Inhibitory effect on promastigotes	Naserifard *et al.,* 2013
Zajuria multiflora Boiss	Thyme	Lamiaceae	Reduce the parasitic growth	Hejazi *et al.,* 2009

Artemisia annua

Plants of the *Asteraceae* family are popular for their various medicinal properties. Artemisinin is a well know antimalarial compound derived from *Artemisia annua* or sweet wormwood. Artemisinin has also been reported for its activity against *Leishmania donovani* which infects the macrophages and normalizes the nitrite production and mRNA expression, this study showed the parasiticidal and host protective response. In another study, artemisinin has also shown depolarization of the mitochondrial membrane along with a substantial depletion of adenosine triphosphatase (ATP) in *Leishmania* promastigotes (Heidari *et al.,* 2012; De Sarkar *et al.,* 2019). Furthermore, artemisinin when administered at doses of 10 mg/kg and 25 mg/kg of body weight lowered the parasitic burden (Sen *et al.,* 2010).

Cassia fistula

Cassia fistula belongs to the *Fabaceae* family. Hexane extract from fruits of *Cassia fistula* has been reported for its antileishmanial activity against the promastigote forms of *Leishmania L. chagasi*. IC_{50} value of 10.03 µg/mL showed inhibitory effect against the promastigote stages of the parasites (Sartorelli *et al.,* 2007). Another study showed that the combination of meglumine antimoniate and *Cassia fistula* fruit gel was very effective in curing cutaneous *Leishmaniasis* and proved to be the best choice against cutaneous *Leishmaniasis* (Jaffary *et al.,* 2010).

Haplophyllum bucharicum

Haplophyllum bucharicum belongs to *Rutaceae* family and have shown antiproliferative activity towards human monocytes and *Leishmania*

promastigotes by inhibiting the protein synthesis (Giorgio *et al.,* 2005). In an *in vitro* study, diphyllin isolated from *H. bucharicum* exerted a strong specific inhibitory activity against *Leishmania* by interference with surface molecules of the promastigote membrane. Diphyllin exerted a strong specific inhibitory activity resulting from the inhibition of parasite internalization within macrophages (Giorgio *et al.,* 2005).

Nauclea diderrichii

Nauclea diderrichii belongs to *Rubiaceae* family. Quinovic acid glycosides and the alkaloid cadambine acid have been identified in this plant. Four quinovic acid glycosides and cadambine acid revealed a strong antileishmanial activity (IC_{50} = 1 µM) highly specific for the intracellular amastigote form of the parasite. Four quinovic acid glycosides and cadambine acid revealed a strong anti-leishmanial activity (IC_{50} = 1 µM) highly specific for the intracellular amastigote form of *L. infantum*. Quinovic acid glycosides were shown to inhibit parasite internalisation by interfering with promastigotes while cadambine acid exerted immunomodulatory activity by inducing NO production in human macrophages (Lamidi *et al.,* 1995, Giorgio *et al.,* 2006). Another study reveals that quinovic acid glycosides having immunomodulatory activity by inducing NO production in human macrophages and inhibit promastigotes internalization (Ogunkolade *et al.,* 1990). The combination of amphotericin B and cadambine acid used as conventional therapy against *Leishmania* species (Giorgio *et al.,* 2006).

Portulaca werdermannii

Plants of *Portulacaceae* family are distributed all over the world having pharmacological properties such as analgesic, antibacterial, skeletal muscle-relaxant, wound-healing, anti- infammatory and a radical scavenger (Askari *et al.,* 2016). In one study, the extracts of *Portulaca werdermannii* and *Portulaca hirsutissima* showed *in vitro* anti-leishmanial and immunomodulatory effects against *L amazonensis* and *T. cruzi* parasite cultures (Costa *et al.,* 2007).

Piper rusbyi

Piper rusbyi belongs to the *Piperaceae* family has various bioactive compounds like kavapyrone (7 R,8S)-epoxy-5,6-didehydrokavain (Nwaka & Hudson, 2006) and the chalconeflavokavain B have anti-leishmanial effects (Pérez *et al.,* 2002). All bioactive compounds showed *in vitro* anti-leishmanial activity. Likewise, *in vivo* efficacy of kavapyrone was also shown against cutaneous *leishmaniasis*.

Artemisia absinthium

Artemisia absinthium belongs to family *Asteraceae*, commonly known as wormwood enriched with essential oils (Chamazulene, nuciferol butanoate, nuciferol propionate, caryophyllene oxide, phellandrene, pinene, azulene -thujone) and phenolic compounds like syringic, chlorogenic, caffeic acid, ferulic acid which have diverse biological properties (Cefalu *et al.,* 2008). They are known to have diverse antiparasitic, antibacterial, antifungal, antidepressant and cytotoxic. Anti-parasitic apoptotic effect was seen at high concentrations of *A. absinthium* against promastogote *L. major* (Azizi *et al.,* 2016). In another study, essential oil of *A. Absinthium* showed *in vitro* inhibitory effect on promastigote form of *L. major*. The essential oil of *A. Absinthium* also reduced the progression of lesions (Khanjani *et al.,* 2015).

Artemisia dracunculus

Artemisia dracunculus (Tarragon) from the *Asteraceae* family contains artemisinin compounds, have antiparasitic effects due to endoperoxide groups (Mueller *et al.,* 2004). In a recent study, the *in vitro* anti-leishmanial effect of the extract of *Artemisia dracunculus* was evaluated and compared to control treatment with pentavalent antimony (meglumine). Results of study revealed that all concentrations significantly reduced the number of promoastigotes of *L. major* with an efficacy of more than 50% at 10 µg/mL (Rezaei *et al.,* 2017).

Urtica dioica

Urtica dioica commonly known as stinging nettle belongs to family *Urticaceae* is enriched with many active compounds including tannins and glucoside compounds. *Urtica dioica* has been used as anticancerous, anti-inflammatory, antirheumatic and antioxidant agent (Bourgeois *et al.,* 2016). In a recent study, aqueous extract of *Urtica dioica* killed the *L. major* amastigotes. In addition, the lesion size and parasite load were decreased in the treated infected mice (Badirzadeh *et al.,* 2020).

Mechanism of action of medicinal plants

Natural compounds obtained from different parts of plants (leaves, roots, fruits or seeds) are commonly used in medicine to treat *Leishmaniasis* (Colares *et*

al., 2013). These compounds act against *Leishmania* by different mechanisms. Some medicinal plants are enriched with esssential oils which are composed of different hydrophobic molecules (sesquiterpenes and terpenes, monoterpenes) which can diffuse easily across cell membranes and consequently gain access to intracellular targets (Colares *et al.*, 2013; Machado *et al.*, 2014). Terpenes can easily penetrate the lipid bilayer of cell membrane and produce changes in the integrity of cell structures and mitochondrial membrane of *Leishmania* parasite (Colares *et al.*, 2013). Furthermore, the active ingredients in some plant extracts such as diphyllin isolated from *Haplophyllum bucharicum* are involved in interaction with macromolecules and lead to cell cycle arrest and inhibition of protein synthesis of parasite (Giorgio *et al.*, 2005). Plants enriched with antioxidant compounds such as flavonoids (catechins) are able to form complexes with the parasite cell wall and hence inhibit the parasitic growth. Artemisinin present in *Artemesia annua* plant causes depolarization of the mitochondrial membrane along with a substantial depletion of adenosine triphosphatase (ATP) (Ogeto *et al*., 2013; De Sarkar *et al.*, 2019).

Concluding Remarks

Leishmaniasis is a neglected disease affecting a large human population with fatal outcome. Given the fact that anti-leishmanial vaccines may not become available in the near future, the search for better drugs should be continued. Due to drug resistance and toxic effects of synthetic drugs on health, this method is not much appealing. Natural products may offer an unlimited source of chemical diversity to identify new drugs against *Leishmaniasis*. Different medicinal plants as reported in this review have shown therapeutic effects and have potential in effective drug development against *Leishmaniasis* disease. Exploration of different medicinal plants can provide a better solution to control this severe disease and can play an important role in addressing public health issue.

REFERENCES

Abbas A, Abbas RZ, Khan MK, Raza MA, Mahmood MS, Saleemi MK, Hussain T, Khan JA, Sindhu ZD. 2019. Anticoccidial effects of *Trachyspermum ammi* (Ajwain) in broiler chickens. **Pak Vet J** 39: 301 - 304. **https://doi.org/10.29261/pakvetj/2019.056**

Abbas A, Iqbal Z, Abbas RZ, Khan MK, Khan JA, Sindhu ZuD, Mahmood MS and Saleemi MK. 2017. *In vivo* anticoccidial effects of *Beta vulgaris* (sugar beet) in broiler chickens. **Microb Path** 111: 139 - 144. **https://doi.org/10.1016/j.micpath.2017.07.052**

Afrin F, Chouhan G, Islamuddin M, Want MY, Ozbak HA, Hemeg HA. 2019. *Cinnamomum cassia* exhibits antileishmanial activity against *Leishmania donovani* infection *in vitro* and *in vivo*. **PLOS Negl Trop Dis** 1 - 28. **https://doi.org/10.1371/journal.pntd.0007227**

Afsheen N, Rehman KU, Jahan N, Khan KM, Zia MA. 2019. Optimization of cardioprotective potential of various concentrations of medicinal plants by using response surface methodology. **Pak Vet J** 39: 13 - 18. **https://doi.org/10.29261/pakvetj/2018.111**

Alborzi A, Namjoian F, Azadbakht M, Obodi B, Panjehshahin M, Rasoli M. 2003. Effects of *Ferula assa-foetida* and its effective fractions on *Leishmania* (*in vitro*). **Infect Tropic Dis Iran** 8: 36 - 40.

Ali S, Ijaz M, Ahmed A, Aziz MU, Naveed M, Javed MU, Nawab Y, Ghumman NZ, Ghaffar A. 2020. Prevalence and associated risk factors of bovine babesiosis in Lahore, Pakistan. **Agrobiol Records** 2: 17 - 23. **https://doi.org/10.47278/journal.abr/2020.009**

Amato VS, Tuon FF, Bacha HA, Neto VA, Nicodemo AC. 2008. Mucosal *leishmaniasis* current scenario and prospects for treatment. **Acta Trop** 1: 105 - 109. **https://doi.org/10.1016/j.actatropica.2007.08.003**

Andrade-Narváez FJ, Vargas-González A, Canto-Lara SB, Damián-Centeno AG. 2003. Clinical picture of cutaneous leishmaniases due to *Leishmania (Leishmania)* in the Yucatan peninsula. **Mem Inst Oswaldo Cruz** 96: 163 - 1677. **https://doi.org/10.1590/s0074-02762001000200005**

Askari VR, Rezaee SA, Abnous K, Iranshahi M, Boskabady MH. 2016. The influence of hydro- ethanolic extract of Portulacaoleracea L. on T1/T2 balance in isolated human lymphocytes. **J Ethnopharmacol** 194: 1112 - 1121. **https://doi.org/10.1016/j.jep.2016.10.082**

Azizi K, Shahidi-Hakak, F, Asgari Q, Hatam GR, Fakoorziba MR, Miri R. Moemenbellah-Fard MD. 2016. *In vitro* efficacy of ethanolic extract of *Artemisia absinthium* (Asteraceae) against *Leishmania major* L. using cell sensitivity and flow cytometry assays. **J Parasitic Dis** 40: 735 - 740. **https://doi.org/10.1007/s12639-014-0569-5**

Babaee KL, Mohebali M, NiakanLahiji MR, MehrabiTavana A. 2007. The therapeutic effect of Eucalyptus,

Myrtus, Ferula, Aretmisia, Allium and Urtica extracts against cutaneous Leishmaniasis caused by *Leishmanaia major* in small white mice (outbred). **Hakim Res J** 10: 21 - 27.

Badirzadeh A, Heidari-Kharaji M, FallahOmrani V, Dabiri H, Araghi A, Salimi CA. 2020. Antileishmanial activity of *Urtica dioica* extract against zoonotic cutaneous leishmaniasis. **PLoS Negl Trop Dis** 14: e0007843. **https://doi.org/10.1371/journal.pntd.0007843**

Bafghi AF, Bagheri SM, Hejazian SH. 2014. Antileishmanial activity of *Ferula assa-foetida* oleo gum resin against *Leishmania major*: An *in vitro* study. **J Ayurveda Integr Med** 5: 223 - 226. **https://doi.org/10.4103/0975-9476.146567**

Barati M, Sharifi I, Sharififar F. 2010. Antileishmanial activity of *Artemisia aucheri*, *Ferula assafoetida* and *Gossypium hirsutum* extracts on *Leishmania major* promastigotes *in vitro*. **Ann Mil Health Sci Res** 8: 166 - 172. **https://doi.org/10.2174/22113525113119990005**

Bourgeois C, Leclerc EA, Corbin C, Doussot J, Serrano V, Vanier JR. 2016. Nettle (*Urtica dioica* L.) as a source of antioxidant and anti-aging phytochemicals for cosmetic applications. **Comptes Rendus Chimie** 19: 1090 - 1100. **https://doi.org/10.1016/j.crci.2016.03.019**

Bravo F, Sanchez MR. 2003. New and re-emerging cutaneous infectious diseases in Latin America and other geographic areas. **Dermatol Clin** 21: 655 - 668. **https://doi.org/10.1016/s0733-8635(03)00090-1**

Cefalu WT, Ye J, Zuberi A, Ribnicky DM, Raskin I, Liu Z, Wang ZQ, Brantley PJ, Howard L, Lefevre M. 2008. Botanicals and the metabolic syndrome. **Am J Clin Nutr** 87: 481s - 487s. **https://doi.org/10.1093/ajcn/87.2.481s**

Chen M, Christensen SB, Blom J, Lemmich E, Nadelmann L, Fich K, Lichochalcone A. 1993. A novel antiparasitic agent with potent activity against human pathogenic protozoan species of leishmania. **Antimicrob Agents Chemother** 37: 2550 - 2556. **https://doi.org/10.1128/aac.37.12.2550**

Colares AV, Almeida-Souza F, Taniwaki NN, Souza SC, da Costa JG, Calabrese KS, Abreu-Silva AL. 2013. *In vitro* antileishmanial activity of essential oil of *Vanillosmopsis arborea* (Asteraceae) baker. **Evid Based Complement Alternat Med** 2013: 727042. **https://doi.org/10.1155/2013/727042**

Costa JFO, Kiperstok AC, David JPL, David JM, Giulietti AM, Queiroz LP. 2007. Anti-leishmanial and immunomodulatory activities of extracts from *Portulaca hirsutissima* and *Portulaca werdermannii*. **Fitoterapia** 78: 510 - 514. **https://doi.org/10.1016/j.fitote.2007.05.005**

Delavari M, Dalimi Asl A, Ghaffarifar F, Sadraei J. 2013. Effect of aloeemodin on growth and induction of apoptosis in *Leishmania major* promastigotes *in vitro*. **J Kashan Univ Med Sci** 17: 422 - 428.

Desjeux P. 2004. Leishmaniasis: current situation and new perspectives. **Comp Immunol Microbiol Infect Dis** 27: 305 - 318.

De Sarkar S, Sarkar D, Sarkar A, Dighal A , Chakrabarti S, Staniek K, Gille L, Chatterjee M. 2019. The leishmanicidal activity of artemisinin is mediated by cleavage of the endoperoxide bridge and mitochondrial dysfunction. **Parasitology** 146: 511 - 520. **https://doi.org/10.1017/s003118201800183x**

Dinesh N, Neelagiri S, Kumar V, Singh S. 2017. Glycyrrhizic acid attenuates growth of *Leishmania donovani* by depleting ergosterol levels. **Parasitology** 176: 21 - 29. **https://doi.org/10.1016/j.exppara.2017.02.015**

Dujardin J, Campino L, Boelaert M. 2008. Spread of vector-borne diseases and neglect Leishmaniasis, Europe. **Emerg Infect Dis** 14: 1013 - 1018. **https://doi.org/10.3201/eid1407.071589**

Emami SA, Rabe SZT, Iranshahi M, Ahi A, Mahmoudi M. 2010. Sesquiterpene lactone fraction from *Artemisia khorassanica* inhibits inducible nitric oxide synthase and cyclooxygenase-2 expression through the inactivation of NF-kappaB. **Immunopharmacol Immunotoxicol** 32: 688 - 695. **https://doi.org/10.3109/08923971003677808**

Emami SA, TaghizadehRabe SZ, Ahi A, Mahmoudi M. 2012. Inhibitory activity of eleven Artemisia species from Iran against *Leishmania major* parasites. **Iran J Basic Med Sci** 15: 807 - 811.

Gharavi M, Nobakht M, Khademvatan S, Fani F, Bakhshayesh M, Roozbehani M. 2011. The effect of aqueous garlic extract on interleukin-12 and 10 levels in *Leishmania major* (MRHO/IR/75/ER) infected macrophages. **Iran J Public Health** 40: 105 - 111.

Ghazonfari T, HassaniZ, Ebtekar M, Ahmadiani M, Naderi AG, Azar A. 2000. Garlic induces a shift in a *Leishmania major* - infected balby mice. **Scand J Immunol** 52: 491 - 495. **https://doi.org/10.1046/j.1365-3083.2000.00803.x**

Giorgio CD, Delmas F, Akhmedjanova V, Ollivier E, Bessonova I, Riad E, Pierre David PT. 2005. *In vitro* antileishmanial activity of diphyllin isolated from *Haplophyllum bucharicum*. **Planta Med** 71: 366 - 369.

https://doi.org/10.1055/s-2005-864106

Giorgio CD, Lamidi M, Delmas F, Guy Balansard G, Ollivier E. 2006. Antileishmanial activity of quinovic acid glycosides and cadambine acid isolated from *Nauclea diderrichii*. **Planta Med** 72: 1396 - 1402. **https://doi.org/10.1055/s-2006-951726**

Heidari FI, Ghaffarifar F, Dalimi A, Dehkordi NM, Nikoo SG. 2012. *In vitro* study of the effect of artimisinin on promastigotes and amastigotes of *Leishmania major*. **Modares J Med Sci Pathobiol** 15: 33-43.

Hejazi SH, Shirani-Bidabadi L, Zolfaghari-Baghbaderani A, Saberi S, Nilforoushzadeh MA, Moradi SH. 2009. Comparison effectiveness of extracts of Thyme, yarrow, henna and garlic on cutaneous leishmaniasis caused by *L. major* in animal model (Balb/c). **J Med Plants** 8: 129 - 136.

Iranshahi M, Arfa P, Ramezani M, Jaafari MR, Sadeghian H, Bassarello C. 2007. Sesquiterpene coumarins from *Ferula szowitsiana* and *in vitro* antileishmanial activity of 7-prenyloxycoumarins against promastigotes. **Phytochemistry** 68: 554 - 561. **https://doi.org/10.1016/j.phytochem.2006.11.002**

Jaffary F, Nilforoushzadeh MA, Ansari N, Rahimi M. 2010. Treatment of cutaneous leishmaniasis: *Cassia fistula* fruit gel-intralesional glucantime Vs. placebo gel-intralesional glucantime combination. **Tehran Univ Med J** 67: 705 - 711.

Khare P, Rastogi P, Gupta S, Maurya R, Dube A. 2014. *In vitro* and *in vivo* efficacy of a new herbaceous indian plant *Abutilon indicum Leishmania* against *Leishmania donovani* infection. **Am J Phytomed ClinTher** 2: 134 - 139.

Khanjani JS, Farazmand A, Amin MDA, Shirzadi MR, Razavi MR. 2015. Methanolic extract's activity of Artemisia absinthium, Vitexagnus-castus and Phytolaca americana against *Leishmania major*; *in vitro* and *in vivo*. **Int Arch Health Sci** 2: 69 - 74.

Khezzani B, Bouchemal S. 2017. Demographic and spatio-temporal distribution of cutaneous leishmaniasis in the Soufoasis (Eastern South of Algeria): Results of 13 years. **ActaTropica** 166: 74 - 80. **https://doi.org/10.1016/j.actatropica.2016.11.012**

Lamidi M, Ollivier E, Faure R, Debrauwer L, Nze-Ekekang L, Balansard G. 1995. Quinovic acid glycosides from *Naucleadi derrichii*. **Planta Med** 61: 280 - 281. **https://doi.org/10.1055/s-2006-958075**

Li K, Zhang L, Luo H, Mehmood K, Shahzad M, Naseer MU. 2019. Besnoitiosis: an emerging parasitic disease in yaks (bos grunniens) and tibetan sheep (ovies aries) on the qinghai tibetan plateau, China. Pak Vet J 39: 447 - 450. **https://doi.org/10.29261/pakvetj/2019.086**

Li K, Luo H, Mehmood K, Shahzad M, Li J, 2020. Exploring the potential parasitic pathogens causing diarrheal death to yak calves with bloody excrement through high-throughput sequencing. **Agrobiol Records** 1: 1 - 5. **https://doi.org/10.47278/journal.abr/2020.002**

Machado M, Dinis AM, Santos-Rosa M, Alves V, Salgueiro L, Cavaleiro C, Sousa MC. 2014. Activity of *Thymus capitellatus* volatile extract, 1,8-cineole and borneol against Leishmania species. **Vet Parasitol** 200: 39 - 49. **https://doi.org/10.1016/j.vetpar.2013.11.016**

Mans DRA, Beerens T, Magali I, Soekhoe RC, Schoone GJ, Oedairadjsingh K, Hasrat JA, van den Bogaart E, Schallig HDFH. 2016. *In vitro* evaluation of traditionally used Surinamese medicinal plants for their potential anti-leishmanial efficacy. **J Ethnopharmacol** 180: 70 - 77. **https://doi.org/10.1016/j.jep.2016.01.012**

Mueller MS, Runyambo N, Wagner I, Borrmann S, Dietz K, Heide L. 2004. Randomized controlled trial of a traditional preparation of *Artemisia annua* L. (annual wormwood) in the treatment of malaria. **Trans R Soc Trop Med Hyg** 98: 318 - 321. **https://doi.org/10.1016/j.trstmh.2003.09.001**

Naserifard R, Asl AD, Ahmadi N. 2013. Influence of aqueous extract *Scrophularia striata* on growth of *Leishmania major* in mice peritoneal macrophages (BALB/c). **Res Med** 36: 12 - 18.

Nwaka S, Hudson A. 2006. Innovative lead discovery strategies for tropical diseases. **Nature Rev Drug Discov** 5: 941 - 955. **https://doi.org/10.1038/nrd2144**

Ogeto TK, Odhiambo RA, Shivairo RS, Muleke CI, Osero BO, Anjili C, Ingonga JM, Osuga IM. 2013. Antileishmanial activity of *Aloe secundiflora* plant extracts against *Leishmania major*. **Adv Life Sci Tech** 13: 9 - 18.

Ogunkolade BW, Colomb-Valet I, Monjour L, Rhodes-Feuillette A, Abita JP, Frommel D. 1990. Interactions between the human monocytic leukaemia THP1 cell line and old and new world species of *Leishmania*. **Acta Trop** 47: 171 - 176. **https://doi.org/10.1016/0001-706x(90)90023-s**

Oryan A, 2015. Plant-derived compounds in treatment of leishmaniasis**. Iranian J Vet Res** 16: 1 - 19.

Pérez-Victoria JM, Di Prieto A, Barron D, Ravelo AG, Castanys S, Gamarro F. 2002. Multidrug resistance phenotype mediated by the P-glycoprotein-like transporter in *Leishmania*: a search for reversal agents. **Curr Drug Targets** 3: 311 - 333. **https://doi.org/10.2174/1389450023347588**

Pirali-Kheirabadi KH, Dehghani-Samani A, Adel M, Hoseinpour F. 2013. The effect of essential oil of *Nigella sativa* and *Satureia hortensis* on promastigot stage of *Lishmania major*. **Armaghan Danesh J** 18: 687 - 698.

Rahman SU, Mohsin M. 2019. The under reported issue of antibiotic-resistance in foodproducing animals in Pakistan. **Pak Vet J** 39: 323 - 328.

Rezaei R, Hazrati K, Seyyedi S, Mikaili P. 2017. The anti-leishmanial efficacy of Artemisia dracunculus ethanolic extract *in vitro* and its effects on IFN-gamma and IL-4 response. **Iran J Parasitol** 12: 398 - 407.

Sadati MS, Sarkari B, Asgari Q, Hatami S, Tavakl E. 2011. The effect of *Echinacea purpurea* on cutaneous leishmaniasis in mice infected with *Leishmania* major. **Armaghane Danesh** 16: 31 - 40.

Salman S, Zahid RZ, Israr M, Abbas A, Mehmood KM, Khan MK, Sindhu ZD, Hussain R, Saleemi MK, Shah S. 2020. Repellent and acaricidal activity of essential oils and their components against *Rhipicephalus* ticks in cattle. **Vet Parasitol** 283: 109178. **https://doi.org/10.1016/j.vetpar.2020.109178**

Şandru CD, Niculae M, Popescu S, Paştiu AI, Pall E, Spınu M. 2016. *Urtica dioica* alcoholic extract increases the cell-mediated innate immune potential in chickens. **Ind Crop Prod** 88: 48 - 50. **https://doi.org/10.1016/j.indcrop.2016.02.032**

Sartorelli P, Andrade SP, Melhem MSC, Prado FO, Tempone AG. 2007. Isolation of antileishmanial sterol from the fruits of *Cassia fistula* using bioguided fractionation. **Phytother Res** 21: 644 - 647. **https://doi.org/10.1002/ptr.2131**

Sen R, Ganguly S, Saha P, Chatterjee M. 2010. Efficacy of artemisinin in experimental visceral Leishmaniasis. **Int J Antimicrob Agents** 36: 43 - 49. **https://doi.org/10.1016/j.ijantimicag.2010.03.008**

Shamsuddini S, Rajab Alian S, Mirzayi M, Boroufiei M. 2006. Efficacy of *Mimosa tenuiflora* extract on growth of Leishmania protozoa *in vitro*. **Iran J Dermatol** 9: 175 - 180.

Shang A, Cao SY, Xu XY, Gan RY, Tang GY, Corke H, Mavumengwana V, Li HB. 2019. Bioactive compounds and biological functions of garlic (*Allium sativum* L.). **Foods** 5: 246. **https://doi.org/10.3390/foods8070246**

Sharif M, Ziaei H, Azadbakht M, Daryani A, Ebadattalb A, Rostami M. 2006. Effect of methanolic extract of *Artemisia auchori* and *Camellia sinensis* on *Leishmania major* (*in vitro*). **Turk Sci** 36: 365 - 369.

Tahir AE, Ibrahim AM, Satti GMH, Theander TG, Kharazmi A, Khslid AS. 1998. The potential antileishmanial activity of some Sudanse medicinal plants. **Phytother Res** 12: 576 - 579. **https://doi.org/10.1002/(sici)1099-1573(199812)12:8<576::aid-ptr354>3.0.co;2-#**

Townson S. 2001. Antiparasitic properties of medicinal plants and other naturally occurring products. **Adv Parasitol** 50: 199 - 295. **https://doi.org/10.1016/s0065-308x(01)50032-9**

WHO, 2010. **Control of *Leishmaniases***. WHO Technical Report series, Geneva, Switzerland.

Yakhchali M, Ranjbari-Kijandabeh M. 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. **Sci J Kurdistan Univ Med Sci** 18: 13 - 19.

Yousefi R, Ghaffarifar F, Dalimi Asl A. 2009. The effect of *Alkanna tincturia* and *Peganum harmala* extracts on *Leishmania major* (MRHO/IR/75/ER) *in vitro*. **Iran J Parasitol** 4: 40 - 47.

Zhang K., Li X, Na C., Abbas A, Abbas RZ, Zaman MA. 2020. Anticoccidial effects of *Camellia sinensis* (green tea) extract and its effect on blood and serum chemistry of broiler chickens. **Pak Vet J** 40: 77 - 80. **https://doi.org/10.29261/pakvetj/2019.119**