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(REVIEW ARTICLE)

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Potential anti-leishmanial remedies from natural sources

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Abstract

Leishmaniasis is caused by a protozoa parasite from over 20 *Leishmania* species. Over 90 sandfly species are known to transmit *Leishmania* parasites. There are 3 main forms of the disease, visceral (the most serious form because it is almost always fatal without treatment), cutaneous (the most common, usually causing skin ulcers), and mucocutaneous (affecting mouth, nose and throat). The disease affects some of the world's poorest people and is associated with malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources. An estimated 700 000 to 1 million new cases occur annually. Chemotherapy based on the use of pentavalent antimonials, amphotericin B, paromomycin, miltefosine and liposomal amphotericin B, is currently the only effective treatment. However, adverse effects, long-term treatment and the emergence of parasite resistance have led to the search for alternative treatments. In this review, PubMed, Google Scholar, Web of Science, EBSCO, Science Direct, and Scopus were searched for medicinal plants with anti lieshmanial activity to encourage identification of the active ingredients, determination of clinical efficacy, investigation of the mode of action and safety.

Keywords: Medicinal plants; Pharmacology; Antiparasitic; Anti lieshmanial

1. Introduction

Parasitic diseases are one of the major public health problem[1]. Roughly 70 protozoa species have already were infecting humans [2]. Leishmaniasis comprises six widespread tropical diseases that are endemic in 98 countries, affecting 12 million people globally. These diseases are caused by more than 20 protozoan species of the genus *Leishmania*[3]. Three types of clinical manifestations have been reported: cutaneous, mucocutaneous and visceral leishmaniasis. The last is the most severe form; it is also known as *kala-azar* and occurs when the parasite migrates to visceral organs (especially the spleen and liver), leading to death. Chemotherapy is the most effective treatment for leishmaniasis. However, the drugs currently in use require long-term treatment, have high toxicity and are expensive and not well tolerated by patients. However, adverse effects, long-term treatment and the emergence of parasite resistance have led to the search for alternative treatments[4-11]. This review discuss the plants with anti lieshmanial activity to encourage further investigation of plants or plant derivatives as potential origins for novel therapies for Lieshmania infections.

2. Medicinal plants with anti-leishmanial effects

2.1. Achillea santolina

Achillea santolina essential oil was investigated for *in vitro* antileishmanial activity against *Leishmania infantum* promastigote. The treatment with glucantime and *Achillea santolina* essential oil had similar efficiency with

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the concentration of 1000 ml/mg after 72 h. The results showed that viability was significantly lower in the oil treated group [12-13].

2.2. Allium species

Allium cepa also exerted anti-parasitic activity for many helminthes and protozoa such as, *Trichinella spiralis*, and *leishmania*[14-15].

Sulfur compounds of the plant, such as Allicin, diallyl trisulphide (DAT) and ajoene can reduce developing different protozoan parasites such as *Giardia lamblia*, *Leishmania major* and *Leptomonas colosoma* [16-21]. 30 µg/mL was very efficiently inhibited the growth of other protozoan parasites such as *Giardia lamblia, Leishmania major, Leptomonas colosoma,* and *Crithidia fasciculate*[22].

The methanolic extract of *A. sativum* bulbs was screened for *in vitro* and *in vivo* antileishmanial activity against *Leishmania major* strain (NLB 145) and *L. donovani* strain (NLB 065). BALB/c mice and golden hamsters (*Mesocricetus auratus*) were used in *in vivo* studies of *L. major* and *L. donovani*. The extract showed IC_{50} values of 34.22 µg/ml and 37.41 µg/ml against *L. major* and *L. donovani* promastigotes respectively, compared to 1.74 µg/ml against *L. major* and 1.18 µg/ml against *L. donovani* for Amphotericin B. The multiplication indices for *L. major* and *L. donovani* amastigotes in macrophages treated with 100 µg/ml of the extract were significantly decreased [23]. Cytotoxic potential of *A. sativum* on *L. major* (MRHO/IR/75/ER) promastigotes was determined using the MTT assay in order to find 50% inhibitory concentration (IC_{50}) of this herbal extract. *A. sativum* showed a dose-dependent cytotoxic effect in *L. major* with almost 100% death at a concentration of 93 µg/ml [24].

2.3. Betula alba

Disuccinylbetulin, diglutaryldihydrobetulin, and disuccinyldihydro betulin of *Betula alba* inhibit the growth of *Leishmania donovani*, they reduced the intracellular parasite burden in macrophages infected with wild-type *L. donovani.* They targeting enzyme type IB topoisomerase of the parasite[25-26].

2.4. Bryophyllum calycinum

The antileishmanial effect of the plant extracts and its flavonoids components was evaluated *in vivo* in murine model of cutaneous leishmaniasis. Quercetin 3- O-α-L-arabinopyranosyl, α-L-rhamnopyranoside, quercetin 3-O-α-L- rhamno pyranoside and free quercetin were able to control the lesion growth caused by *Leishmania amazonensis* and significantly reduce the parasite load. These flavonoids were as effective as the crude aqueous extract which indicated that the antileishmanial effect could be attributed to flavonoids[27-28].

2.5. Citrullus colocynthis

Albino mice were intraperitionally infected with 100 X 10^6 promastigotes of *Leishmania donovani* (MHOM/ IQ/ 982/BRCI) strain. The inoculation of albino mice caused elevation of liver and spleen weight after 7-15 days. The mice treated with 20-100 mg/kg from *Citrullus colocynthis* showed decreased average liver and spleen weight in comparison to the positive control. The most important histopathologcal results in the positive control included scattered necrosis, lymphatic infiltration, proliferation of macrophages and a variable number of leishman bodies were observed. 80-100 mg/kg of *Citrullus colocynthis* return liver section to normal histology[29-30].

2.6. Cordia myxa

The anti-leishmanial activity of the mucilage extract of *Cordia myxa* was examined against promastigotes of *L. infantum* (MCAN/IR/96/LON49) and *L. major* (MRHO/IR/75/ER) (1×10^6 cells/ ml). They were seeded in a 96-well microtiter plate, in the presence of the serial concentrations (0, 0.61, 1.22, 2.44, 4.88, 9.75, 19.5, 39, 78, and 156 mg/ ml w/v) of the extract and then incubated at 24°C, for 72 hours. Antileishmanial activity was assayed by light microscopy and (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide) MTT method. The concentration inhibiting parasite growth by 50% (IC_{50} value) was calculated with a sigmoid dose-response curve. Mucilage extract of *Cordia myxa* was active against promastigotes form of *L. major* and *L. infantum*, with an IC_{50} of 26 ± 2.2 mg/ml and an IC_{50} of 35 ± 2.2 mg/ml, respectively. The survival percentage of *L. major* and *L. infantum* promastigotes after 72 hours treatment appeared concentration dependent. Percentage of survival *Leishmania major* after 72 hours reached 17.68% in a concentration of 156 mg/ml, while the percentage of survival of *L. infantum* promastigotes after 72 hours reached 16.68% in a concentration of 156 mg/ml[31-32].

2.7. Crocus sativus

The effectiveness of *Crocus sativus* and its apoptotic activity against *Leishmania major* (MRHO/IR/ 75/ER) promastigotes was studied using MTT assay to find viability of *L. major* promastigotes and the results were explicated as IC_{50} (50% inhibitory concentration). ED_{50} (50% effective doses) for *L. major* amastigotes were also analyzed. Annexin-V FLUOS staining was performed to study the cell death properties of saffron by using FACS analysis. Qualitative analysis of the DNA fragmentations was accomplished by agarose gel electrophoresis, and light microscopy was used to observe morphological changes of promastigotes. The results revealed that *L. major* promastigotes and amastigotes are sensitive to saffron at different concentrations and time dependent manner, with apoptotic features including DNA laddering, cytoplasmic shrinkage, and externalization of phosphatidylserine. IC_{50} and ED_{50} of this extract after 48 h of incubation was 0.7 and 0.5 mg/ml respectively[33-34].

2.8. *Cupressus sempervirens*

The ethanol extract of the powdered cones of *Cupressus sempervirens* , collected from Oxford, Mississippi, exhibited potent antiparasitic activities. Bioassay-guided fractionation using a centrifugal preparative thin-layer chromatography led to isolation of many diterpenes, 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one), taxodione, ferruginol and sugiol. 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one) and taxodione, displayed potent antileishmanial activity with half-maximal inhibitory concentration (IC_{50}) values of 0.077 µg/ml and 0.025 µg/ml, respectively, against *Leishmania donovani* promastigotes, compared to those of the standard antileishmanial drugs, pentamidine (IC_{50} 1.62 µg/ml) and amphotericin B (IC_{50} 0.11 µg/ml)[35-36].

2.9. Equisetum arvense

E. arvense water extract showed anti-leishmanial effects. The number of *L. tropica* decreased gradually by using 0.5 to 2.5 µg/ml concentrations of *E. Arvense* extract, Moreover, the extracts effect on number and time of generation, an inverse relationship could be established between concentration of the extract and growth mean of the parasite. Inhibitory concentration of 50% of promastigotes (IC_{50}) was 1.5 µg/ml, whereas at logarithmic phase (96 hrs of cultivation). The *Equisetum arvense* dissolve in cold and hot water found to cause reduction in protein, carbohydrates and total nucleic acid contents in *Leishmania tropica* promastigotes that were treated with IC_{50} of the tested extracts[257-258].

2.10. Eryngium creticum

Antileishmanial activity of *Eryngium creticum* extract was tested *in vitro* on a culture of *Leishmania donovani* promastigotes. IC_{50} of dichloromethane extract of the aerial parts of *Eryngium creticum* against *L. donovani* was 38µg/ml, while IC_{50} of methanolic extract of the aerial parts of *Eryngium creticum* was 35µg/ml[37-38].

2.11. Eucalyptus species

The effect of methanolic and aqueous extracts of *Eucalyptus camaldulensis* was studied on the promastigotes of *Leishmania major*. The stationary phase promastigotes of *L. major* was incubated in the methanolic and aqueous extractions *in vitro*. Tartar emetic was used as the positive control drug. After 72 h of incubation the activity of the extracts was measured, using MTT method. The IC_{50} values were 586.2 ± 47.6 and 1,108.6 ± 51.9 µg/ml for methanolic and aqueous extracts, respectively, whereas it was 32.5 ± 6.8 µg/ml for tartar emetic[264].

2.12. Fumaria parviflora

N-octacosan 7β ol was isolated from the methanolic extract of whole plant of *Fumaria parviflora*. The *in vitro* antileishmanial evaluation of isolated compound against *Leishmania donovani* promastigotes was investigated by growth kinetics assay, reversibility assay, analysis of cellular morphology, adverse toxicity and determination of 50% growth inhibitory concentration [GI_{50}]. N-octacosan-7β-ol [OC], possessed significant anti-*Leishmania donovani* promastigotes activity with GI_{50} = 5.35[43-44].

2.13. Gossypium species

The anti-leishmanial activity of methanolic extracts of *Gossypium hirsutum* was studied on *Leishmania major* promastigotes by colorimetric assay in comparison to a trivalent antimony compound (tartar emetic). The plant extracts and tartar emetic inhibited the growth of promastigote stage of *L.major* after 72 hours of incubation. Tartar emetic as positive control gave a 50% inhibitory concentration (IC_{50}) of 4.7µg/ml, while the IC_{50} values of G. hirsutum was 3.6 µg/ml[45-46].

2.14. Hedera helix

Saponins of ivy, *Hedera helix* possessed antileishmanial activity *in vitro* on promastigote and amastigote forms of *Leishmania infantum* and *Leishmania tropica*. Monodesmosides were found to be as effective on promastigote forms as the reference compound (pentamidine). Against amastigote forms only hederagenin exhibited a significant activity which was equivalent to that of the reference compound (N-methylglucamine antimonate)[47].

The *in vivo* activity of an alcoholic extract of *Hedera helix* (20% and 70% alcoholic extract) was studied in experimental ulcer of zoonotic Cutaneous leishmaniasis (CL) in Balb/c mice. The results revealed that the main lesion size did not decrease significantly, and the small lesions did not completely disappear after treatment by H. helix alcoholic extract. Amastigotes counts (mean ± SD) of the skin lesions decreased in placebo control and 20% concentration groups, but in negative control and 70% concentration groups the number of parasites did not reduce[48-49].

2.15. Juglans regia

The antileishmanial activity of *Juglans regia* hydroalcoholic extract was tested on the growth of the promastigotes of *Leishmania major*. The results showed that both *J. regia* extracts reduced the promastigotes number significantly ($P<0.01$)[50].

The effects of topical application of the ointment-based extract (2 and 4% of 50% ethanol extract) of *Juglans regia* was studied on *Leishmania major* (MRHO/ IR/75/ ER) induced infection in mice. The results showed significant post-treatment decrease in the lesion size and parasite count in infected animals, compared to control groups[51-52].

2.16. Lawsonia inermis

The synergistic anti-leishmanial effect of *Peganum harmala* and *Lawsonia inermis* was studied using MTT assay. A significant ($p< 0.01$) inhibition of promastigotes of *L. tropica* was possessed by both extracts at low and moderate concentrations, the combined extracts revealed a synergistic inhibitory effect in comparison with each one[53].

Constituents of *Lawsonia inermis* showed antileishmanial (*Leishmania tropica*) effects. Luteolin was the most potent anti-antileishmanial compound with an IC_{50} value of 4.15 µg/ml[54].

The antileishmanial effect of *Lowsonia inermis* methanolic extracts (0.07, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10 mg/ml) was studied on *Leishmania major* promastigotes using the MTT assay. *Lowsonia inermis* methanolic extract inhibited the growth of promastigote forms of *L. major in vitro* after 72 h of incubation, and showed IC_{50} of 1.25 mg/ml[55].

The *in vitro* antileishmanial activity of the hydroalcoholic extract of *Lawsonia inermis* was tested on the growth of the promastigotes of *Leishmania major*. The results showed that *Lawsonia inermis* extracts reduced the promastigotes number significantly ($p< 0.01$)[56-57].

2.17. Lithospermum officinale

Shikonin from *Lithospermum officinale* showed antiparasitic activity against *Culex pipiens* and *Aedes aegypti* and exhibited high toxicity for intracellular persisting *Leishmania major*[58-60].

2.18. *Matricaria recutita*

The activity of *Matricaria chamomilla* essential oil was evaluated *in vitro* against axenic amastigotes of *Leishmania braziliensis* at concentrations lower than or equal to 250µg/ml. The essential oil of *Matricaria chamomilla* also showed activity against intracellular amastigotes of *L. panamensis* and *L. braziliensis* (EC_{50} of 2.87 and 10.30µg/ml, respectively [61-62].

2.19. Musa paradisiaca

The leishmanicidal activity of *Musa paradisiaca* was studied using promastigotes and amastigotes of *L. chagasi*. Two fractions of the aqueous ethanolic extract of Musa paradisiaca showed IC_{50} value of 1.70 and 1.83 µg/ml against promastigotes and 14.18 and 16.54 µg/ml against amastigotes[63].

The leishmanicidal activity of triterpenes and sterols isolated from *Musa paradisiaca* fruit peel was studied against L. infantum chagasi promastigotes and amastigotes. Five isolated compounds (three triterpenes: cycloeucalenone, 31-norcyclolaudenone; and 24-methylene-cicloartanol and a mixture of two sterols: beta-sitosterol and stigmasterol)

showed statistically similar activity against promastigote compared to pentamidine with the exception of cycloeucalenone, furthermore, all compounds acting against amastigotes, excluding 31-norcyclolaudenone[64-65].

2.20. *Myrtus communis*

Antileishmanial effects of essential oil and methanolic extract of *Myrtus communis* were studied on promastigote and amastigote forms of *Leishmania tropica*. Furthermore, their cytotoxic activities were investigated against J774 cells were Myrtus communis, particularly the essential oil, significantly ($P<0.05$) and dose-dependently inhibited the growth rate of promastigote and amastigote forms of *L. tropica* based on a dose-dependent response. The IC_{50} values for essential oil and methanolic extract was 8.4 and 28.9 µg/ml against promastigotes, and 11.6 and 40.8 µg/ml against amastigote forms, respectively. The essential oil and methanolic extract possessed no significant cytotoxicity in J774 cells. However, essential oil indicated a more cytotoxic effect as compared with the methanolic extract of Myrtus communis [66-67].

2.21. Ocimum basilicum

The antileishmanial activity of *Ocimum basilicum* leaves extract against *Leishmania tropica* was investigated. *Ocimum basilicum* showed good antileishmanial activity with LC_{50} value of 21.67 µg/ml[68-69].

3. Conclusion

Natural products still play an important role in therapy, between 1981 and 2006, 1,184 new drugs were registered of which 28% were natural products or their derivatives. Several of the parasites have become resistant to chemotherapy. The chemical drugs also have many side effects, so medicinal plants can be considered as an alternative to synthetic drugs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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