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Herbal Drugs with Promising Anti-*Leishmanial* Activity: New Hope for Leishmaniasis Treatment

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Abstract

Context: Leishmaniasis is one of the most common parasitic diseases. Many medicinal plants have been utilized for the treatment of leishmaniasis.
Evidence Acquisition: Recent clinical trials have proven the efficacy of a number of herbal drugs. Synthetic agents and current drugs on the market have some disadvantages, such as side effects, high cost, and painful injections. Given the efficiency of herbal drugs, they can be a source of natural and harmless compounds for *Leishmania* treatment.
Results: Several researches have shown a wide range of plant extract exhibiting remarkable anti-leishmanial activity in vitro and in vivo.
Conclusions: Attempts for discovery of an effective strategy for leishmaniasis treatment with nominal side effects are being continued and herbal drugs are receiving much interest. More clinical studies should be done to investigate the efficacy and safety of herbal drugs for the production of effective and safe drugs for leishmaniasis treatment. This may also provide new hope for leishmaniasis treatment.

Keywords: Anti-Leishmanial Activity, Leishmaniasis, Medical Drugs, Plants, In vitro, In vivo

1. Context

Leishmaniasis is an important disease in tropical and subtropical areas. The disease is caused by various species of Leishmania parasites. Leishmaniasis is transmitted by biting of infected female sand flies (1, 2). Leishmania has 2 forms, amastigotes and promastigotes. Amastigotes are intracellular, without flagellum, spherical, and non-motile forms, which proliferate within the phagolysosomes of phagocytic cells like macrophages of the vertebrate host. The other form, promastigotes, are inside the sandflies, extracellular, spindle-shape, motile, and flagellated. Three clinical forms of leishmaniasis exist, including Cutaneous Leishmaniasis (CL), visceral leishmaniasis, and mucocutaneous leishmaniasis. The most common form of leishmaniasis is cutaneous leishmaniasis that involves the skin. Leishmaniasis is endemic in 98 countries and 350 million people are at the risk of infection. Leishmanicidals have to be controlled at low doses because frequently used drugs have severe side effects, and therefore drug resistance could appear rapidly (1-4). About 90% of the CL occur in 8 countries, including Iran, Saudi Arabia, Iraq, Afghanistan, Algeria, Syria, Brazil, and Peru (2, 5, 6). From 1959, pentavalent antimony is utilized for leishmaniasis yet it has some disadvantages like toxicity, side effects, and prolonged injections (3). Accordingly, the efficacy of pentavalents has been reduced and development of resistant parasites restrict their usage (7, 8). The first line drugs for leishmaniasis treatment, such as meglumine antimoniate (Glucantime), sodium stibogluconate (Pentostam), and pentamidine (Pentacarinat) are not effective orally and prolonged injections are needed. The second line drugs like amphotericin B and pentamidine are very toxic (4, 7). Furthermore, vaccination methods have failed to enter clinical trials and still chemotherapy is temporarily the exclusive treatment strategy. Therefore, an urgent need for producing novel and more effective drugs with improved features exists, to change or supplement those in current use. Effective drugs from plant derivatives or plant ex-

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tracts are expected to become a valuable source of new medicinal agents. Natural products and many compounds derived from natural sources show anti-leishmanial activities (9). It has been estimated that there are approximately 250,000 pharmaceutical plant species around the world (10). However, the biological effect of only around 6% of them have been assessed. Besides, only about less than 1% of therapeutic plant compounds have been evaluated in clinical trials (8, 11). This review attempted to provide an overview on some current medical plant with anti-leishmanial activity.

2. Evidence Acquisition

Natural agents may be a good source of chemical diversity to produce new drug modules. Synthetic agents and current drugs on the market have some disadvantages, such as side effects, high costs, and painful injections. New agents should be more efficient and non-toxic. Plant extracts, essential oils, and other useful compounds could be an effective source for producing new anti-leishmanial drugs. Recent clinical trials have proven the efficacy of some herbal drugs. Given the efficiency of herbal drugs, they can be a source of natural and harmless compounds for *Leishmania* treatment. This present review described some medicinal plants used against leishmaniasis.

3. Results

3.1. In Vitro Study of Herbal Drugs

Mothana and colleagues evaluated in vitro anti-leishmanial activity of medicinal plants against 3 forms of *leishmania* (L.) *tropica*, *L. major* and *L. infantum* promastigotes. They reported that some species form the *Lamiaceae* family have anti-leishmanial effects (12). In mahmoudvand's study, in vitro anti-leishmanial activity of different extracts of B. vulgaris against promastigote and amastigote of *L. tropica* and *L. infantum* was assessed in a murine macrophage model. Furthermore, they showed that *B. vulgaris* displayed effective in vitro leishmanicidal properties against L. tropica and *L. infantum* by the MTT assay (13). In vitro studies on activity of Tridax procumbens extracts against promastigotes of *Leishmania* Mexicana showed potent activity with no effect on mammalian cells (14). In vitro anti-leishmanial activity of *Urechites andrieuxii* (*Apocynaceae*) was evaluated and a significant effect was reported (15). The extracts from *Salvia verbenaca* (L.) *Briq*. ssp *verbenaca Maire* (S. *clandestina Batt*. non L) that have been reported in other in vitro studies, have anti-leishmanial activities; the effect of extract on parasite and cell viability was determined by the MTT assay (16). It has been reported in the work carried out by Ezatpour et al. 2015, that *Pistacia khinjuk* from *Anacardiaceae* have in vitro anti-leishmanial effects against *Leishmania tropica* and *Leishmania major*; anti-amastigotes activity of the extracts was evaluated by counting the number of amastigotes in each macrophage by examining 100 macrophages in comparison to the positive control. The findings of this study revealed that the *P. khinjuk* triggered production of nitric oxide compared to untreated macrophages (17). Also, another research revealed that *Rhazya stricta* Decne leaves extracts were effective against *Leishmania* parasites (18). *Citrullus colocynthis* fruit extract and its fractions showed anti-leishmanial properties (19). Biological activity of different essential oils (EOs) from various plants on *Leishmania* (L.) *amazonensis promastigotes* forms was investigated and the results showed that EOs were effective against L. *amazonensis promastigotes* with low cytotoxic activity against L6 cells (20). Anti-leishmanial property of *Artemisia sieberi* essential oil against *Leishmania infantum* was assessed with MTT measurements (21). However, many in vitro studies have demonstrated that a number of plants have effective anti-leishmanial activities.

3.2. In Vivo Herbal Therapy

Maleki et al.'s in vivo experiments showed that some plant extracts are effective against *Leishmania major*; the plant extracts in this research were able to increase the level of NO that suppressed the parasite (22). In vivo anti-leishmanial effects of *Pistacia khinjuk* (*Anacardiaceae*) alcoholic extract on *Leishmania tropica* and *Leishmania major* was shown by Ezatpour et al. The extract increased NO production (17). In another study in vivo potential effectiveness of *Artemisia annua* against *Leishmania* was reported (23). The methanolic extract from the leaves of the Vietnamese medicinal plant Maesa balansae displayed effective in vivo activity against *Leishmania infantum* with 90% reduction of liver amastigote burden (24). The experiments done by Maes et al. showed that Triterpenoid Saponin Extract (PX-6518) from the Plant Maesa balansae had promising in vivo anti-leishmanial potential against Species of visceral *Leishmania* in BALB/c mouse model, and 80% reduction of liver amastigote burden was reported (25). The results of another research indicated that plant extract based-ointments were effective in decreasing ulcer size in inbred mice infected with *Leishmaniamajor* and could increase production of NO that is needed for stoping parasite propagation (22). Nilforoushzadeh et al. reported that Thymus vulgaris, *Achillea millefolium*, and propolis extracts had effective property in treatment of mice that were infected with Cutaneous leishmaniasis and the extracts were significantly effective in decreasing ulcer size (26). It has been reported that cutaneous leishmaniasis in BALB/c

mice was improved by alcoholic extract of *Berberis vulgaris* and could decrease the surface area of CL lesions (27). Other experimental research revealed that Artemisia essence was effective on BALB/c mice infected with *Leishmania major* promastigote and ulcers' diameter was reduced (28). It has been proven that *Tephrosia vogelii* extracts have anti-leishmanial activity on *L. major* infection in BALB/c mice with significantly larger reduction in lesion size and inhibition of parasite burden. Also, this study showed that the level of Nitric oxide produced was increased in the extract-treated groups (29). Metwally works demonstrated that Allicin has anti-leishmanial effects in BALB/c mice infected with *L. major* (30).

4. Conclusions

Leishmaniasis is a worldwide parasitic disease. Until now, no effective vaccine or drug for the treatment of Leishmaniasis has been reported. Currently, efforts are persistent to discover an effective strategy for leishmaniasis treatment with nominal side effects. Glucantime as a standard drug has many side effects. There are still much trouble associated with leishmaniasis treatment. This review showed that herbal medicines and medicinal plants have in vivo and in vitro effectiveness against Leishmaniasis. Some species of *Fabaceae*, *Asteraceae*, *Berberidaceae*, *Apiaceae*, and *Lauraceaes* families' extracts have anti-leishmanial activity and have been highly recommended by many researches. Based on the findings of these studies, medicinal plants exhibited anti-leishmanial activity with inhibitory effect in both promastigotes and amastigotes forms of *Leishmania*. Different groups of plants that have proved anti-leishmanial activity bring about hope to produce novel anti-leishmanial drugs.

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