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REVIEW: A Review of the Effects of Herbal Medicines on Leishmaniasis

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ABSTRACT

Leishmaniasis is a tropical mistreated sandfly-borne contagion caused by hemoflagellate protozoa of the *Leishmania* species and it is endemic in many countries such as Iran, Afghanistan, Syria, Saudi Arabia, Brazil, and Peru. After malaria, leishmania spp. causes the highest rates of mortality and morbidity. Several major risk factors are involved in the spread of leishmaniasis such as drug resistance, environmental changes, HIV epidemic, inadequate vector control and migration of non-immune individuals to endemic areas. Leishmaniasis is a disease with diverse clinical manifestations that depends on both infecting species of *Leishmania* and the immune response of the host. Different forms of the disease include cutaneous, mucocutaneous and visceral forms. The most dangerous form is Visceral Leishmaniasis (VL) which can be fatal among untreated patients. The availability of the inadequate number of antileishmanial chemotherapeutic compounds, high-cost treatment, rising drug resistance as well as severe toxicities of the drugs obscures the treatment of VL. Many investigations showed antileishmanial activity of herbal extracts or chemical derivatives from natural sources *in vitro* against promastigote and amastigote forms or *in vivo* against *Leishmania*-infected animals. A review of related studies revealed that herbal extracts demonstrating antileishmanial activities in vivo or in vitro alone or combined with suggested drugs seem to confirm their use in folk medicine. Additionally, the antileishmanial activity of more than a hundred plants have been recognized in this regard. It is worth noting that plants are notable sources of medicine production, because of their long association with parasites.

Introduction

Leishmaniasis is a common disease among humans and animals and it is caused by a protozoan parasite of the genus Leishmania (1). Leishmania is a protozoan of the trypanosomatid family of the genus Sarcomastigophora which has two distinct stages in its life cycle. The promastigote form is flagellated and motile and reproduces in the intestine of the sandfly. The amastigote form is immobile and settles inside the mammalian host's macrophages (2). Leishmaniasis is endemic in many tropical countries and in Iran it is known as Oriental ulcer, too (1).

Leishmaniasis is transmitted through infected female sandflies including Phlebotomus and Lutzomyia. The disease is endemic in more than 98 countries and an estimated 350 million people are at risk of infection. The overall prevalence is 12 million and the annual incidence is nearly 2 - 2.5 million. In most countries, the number of cases is likely

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to be underestimated because cases are not detected and reporting is not obligatory. Depending on the infected species, infection with Leishmania parasites can lead to three main clinical manifestations. The first form is named localized Cutaneous Leishmaniasis (3) with single or multiple skin lesions, satellite lesions, or nodular lymphangitis (4). It is the most common form and causes skin wounds, lasting lesions with a serious disability. The second form is Mucocutaneous Leishmaniasis (MCL), which causes total or partial damage of nose, mouth and throat mucous. The third one is systemic Visceral Leishmaniasis (VL) which involves internal organs such as liver, spleen and bone marrow. It can be fatal among untreated individuals (4, 5).

Different classifications are considered for leishmaniasis. According to geographical classification, it is divided into New World and Old World disease. Old World forms of leishmaniasis are endemic in Africa, Asia, the Middle East, and the Mediterranean. These are transmitted through the blood meal of Phlebotomus sandflies. While the New World form is transmitted mainly by Lutzomyia flies. In this regard, Texas through South America is a leishmaniasis-endemic region (6).

In the New World, CL is caused by many species of the subgenera Leishmania and Viannia parasites, primarily L. amazonensis, L. braziliensis, L. guyanensis, L. mexicana and L. panamensis, whereas in the Old World, CL is just caused by five species of Leishmania including L. aethiopica, L. donovani, L. infantum, L. major and L. tropica (7). CL has been clinically observed in Iran in two forms: rural (wet wound) and urban (dry wound). Rural CL is a common disease of humans and animals and is called Zoonotic Cutaneous Leishmaniasis (ZCL). Urban CL is known as Anthroponotic Cutaneous Lishmaniasis (ACL). The causative agent of urban CL is L. tropica (8).

Based on the World Health Organization (WHO) report, in 2020 over 85% of new CL cases were observed in 10 countries: Afghanistan, Algeria, Brazil, Colombia, Iraq, Libya, Pakistan, Peru, the Syrian Arab Republic and Tunisia. While, over 90% of MCL cases were reported in Bolivia, Brazil, Ethiopia and Peru. Concerning VL, more than 90% of new cases were detected in 10 countries: Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan and Yemen (5).

Currently, the most important drug used to treat various clinical forms of leishmaniasis is the 5-valent antimony compounds, which include glucantime and pentostam. Following the administration of these drugs, there have been reports of significant side effects. It is pointing that topical treatments, heat therapy and cold therapy are used to treat CL. Today, due to the resistance of genus Leishmania to common antibiotics, replacing them with newer antibiotics is desirable. Likewise, the tendency to use herbal medicinal compounds is so widespread these days. In this regard, 25% of the currently used drugs are derived from plant sources (9).

The point is that effective treatment of CL with glucantime usually requires injection at the site of the lesion, and since the lesions are mainly seen on hands or face, the injection of the drug is painful. Concerning its effect on the parasite, glucantime can destroy the person's normal cells and it is one of the most important side effects of glucantime treatment. In most cases wounds do not cause a serious problem for the patient and recover spontaneously, but for a variety of reasons such as the length of the wound recovery, the deformity of the scar, and the possibility of secondary infections at the site of the lesion, providing tolerable treatment without side effect seems reasonable. Thus, the use of herbal products and native plants of endemic areas that provide a rich source of anti-leishmaniasis compounds is one of the important goals of the WHO and other health institutions in the world and Iran. In fact, medicinal plants have fewer side effects in comparison with chemical drugs (10).

Methods

In this non-systematic review, the data were

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gathered via searching keywords and phrases such as herbal medicines, therapeutic plants, Leishmania protozoa and Leishmaniasis and a combination of those in PubMed, Science Direct, ELSEVIER, Google Scholar, Embase and SID (Scientific Information Database) from 2000 to 2020. The results of the related studies were used in this investigation.

Literature review

Review of related studies revealed that nutritional value and medicinal plants have been considered for the control and treatment of diseases due to their various compounds, including antioxidants. The most important benefits of herbal medicines are their low cost, low incidences of serious side effects and their respectable effectiveness. Unfortunately, the effectiveness of the herbal compounds has only been shown in laboratory studies and they are still in the early stages of clinical trials and studying their results in clinical practice is a neglected issue. It is estimated that plant products are directly or indirectly involved in the production of about 25% of drugs (11).

Several studies have shown that different plant species have inhibitory activity against certain types of parasites such as L. major. Some plants' oil has regulatory effects on the immune system, which makes them useful in the treatment of leishmaniasis. In this regard, several novel compounds have proved leishmanicidal activity. Besides, a vast number of herbal extracts, such as alkaloids, chalcones, phenolics and terpenes are presented for treatment (12). The antileishmanial activity of some herbal extracts has been attributed to flavonoids. Flavonoids are a group of polyphenolic compounds found naturally in fruits and vegetables and are known as antioxidants and anti-cancer drugs with significant protective effects against membrane damage. Flavonoids are able to complex with the parasite's cell wall to affect the processes of cell attachment and inhibit parasitic growth (13).

Even though the use of therapeutic plants in leishmaniasis treatment has been interrupted by unknown mechanisms, researchers are looking for isolating pure compounds from herbal for immunomodulatory properties, antileishmanial activity or to decrease drug toxicity (14-16). Thus, the current pattern of drug discovery has failed to meet the treatment needs for high-priority diseases in developing countries. In fact, leishmaniasis is a good example that almost no new effective drugs have been produced in the last 70 years (17). Concerning health issues, several studies have investigated the effect of some herbal extracts on leishmaniasis (18-21).

In this realm, García et al, investigated the antileishmanial action of 21 species of plants. They collected plants and screened their hydroalcoholic extracts against promastigotes and amastigotes of L. amazonensis. Their toxicity was also assayed against peritoneal macrophages from BALB/c mice. Five extracts showed significant growth inhibitory activity against promastigote form. Only the extracts from Bidens pilosa L. (Asteraceae) and Punica granatum L. (Punicaceae) inhibited the growth of intracellular amastigotes, with IC50 values of 42.6 and 69.6µg/mL, respectively. In addition, low toxicity on macrophages from BALB/c mice was observed too (22). In the same vein Zahir et al, evaluated the antileishmanial activity of acetone and methanol leaf extracts of Anisomeles malabarica, Ocimum basilicum, the flower of Gloriosa superba, leaf and seed of Ricinus communis against L. donovani. Results demonstrated that leaf methanol extracts of A. malabarica, and R. communis showed good antileishmanial activity and could play an important role in herbal formulations for the treatment of VL. In ***Table 1*** and ***Table 2***, main outcomes of some related studies have been highlighted (23).

Conclusion

Leishmaniasis includes a group of diseases caused by numerous species of Leishmania and shows a variety of clinical symptoms. Besides, contagions due to protozoa of the genus Leishmania are a main worldwide health problem, with high endemicity in dev-

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Table 1. Related studies in world

Authors	Year	Medicine source	Main Findings
Le Pape, et.al (24)	2000	*Pachymatisma johnstonii,*	High activity of isolated sponge glycoprotein against *L. donovani, L. braziliensis* and *L. mexicana* and aphidicolin *in vitro* was reported.
		nigrospora sphaerica	The growth of promastigotes and amastigotes of *L. donovani* was inhibited by a fungal metabolite.
Plock, et.al (25)	2001	*Yucca filamentosa*	Ethanolic extract of *Yucca filamentosa* had potent activity against *L. amazonensis* at a concentration of 5 mg/mL.
Lamidi, et al. (26)	2005	*Polyalthia suaveolens*	*L. infantum* showed the highest effect to methanolic extracts from the leaves of *Polyalthia suaveolens, Dioscorea preussii, Augouardia letestui* and stem bark of *Cola lizae* plants (IC50< 5 µg/mL).
		Dioscorea preussii	
		Augouardia letestui	
Braga, et al. (27)	2007	*Vernonia polyanthes*	Ethanolic extracts of medicinal plants *Vernonia polyanthes* and *Ocimum gratissimum* were most active against *L. amazonensis* at IC50 (4 µg/mL) and *L. chagasi* at IC50 (71 µg/mL).
		Ocimum gratissimum	
Dutta, A. et al. (28)	2007	*Asparagus racemosus*	A water-soluble compound, obtained from the fruits of *Asparagus racemosus* was effective against antimonial-sensitive as well as antimonial-resistant L. donovani promastigotes by inducing apoptosis.
Fokialakis, et al. (29)	2007	*Eryngium amorginum*	IC50 < 10 µg/mL with no cytotoxicity was observed by *treating with* dichloromethane extracts of *Eryngium ternatum, Origanum Dictamnus, Origanum microphyllum* and the methanolic extracts of *Eryngium amorginum*.
		Eryngium ternatum	
		Origanum Dictamnus	
		Origanum microphyllum	
Mori, et al. (30)	2008	*Cordia fragrantissima*	The crude extract isolated from *Cordia fragrantissima* wood had minimal inhibitory concentration of 12.5 µg/mL against *L. major* promastigotes.
Misra, et al. (31)	2009	*Piper betle*	Methanolic extract of *Piper betle landrace Bangla Mahoba* had selective inhibitory effect on promastigote and amastigote forms of Leishmania parasite by persuading apoptosis without toxicity effect on uninfected macrophages.
Mohammad BA. (32)	2011	*Aloe vera*	The combination of traditional drugs *Aloe vera, Euphorbia milli* with turmeric and animal fat showed noticeably good antileishmanial activity. It has represented more efficient remedy resulted in wound healing and tissue softening in comparison with glucantime treatment in mice.
		Euphorbia milli	
		animal fat	
Rodrigues, et. al (33)	2011	*Syagrus coronata*	Outcomes revealed *in vitro* leishmanicidal activity of aqueous extract of *Syagrus coronata* on *L. amazonensis with* minimal inhibitory concentration of 8.3 µg/mL had no cytotoxic effects on mammalian cells.
Rondon, et al. (3)	2011	*Aloe vera*	The extract of these plants presented potent activity against promastigote and amastigote forms of Leishmania parasite.
		Coriandrum sativum	
		Ricinus communis	
Iqbal, et. al. (34)	2012	*Aloe vera leaf*	*Tamarix aphylla* bark and *Aloe vera* leaf had considerable effect on motility rate of *L. tropica*.
		Tamarix aphylla bark	
Jain, et al. (35)	2013	*Agave americana*	*Agave americana* and *Azadirachta indica* showed the significant toxicity while *Eclipta alba* and *Piper longum* showed the least or negligible toxicity.
		Azadirachta indica	
		Eclipta alba	
		Piper longum	

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Kyriazis, et al. (16)	2013	*Olea europaea var koroneiki*	The oleuropein compound extracted from olive tree decreased the load of parasite in L. donovani infected mice.
Mishra, et al. (36)	2013	*Plumbago zeylanica*	A naphthoquinone compound, prenyloxy-nanphtoquinone extracted from roots of *Plumbago zeylanica* presented considerable activity against promastigote and amastigote forms of L. donovani.
Lezama-Dávila, et al. (37)	2014	*Pentalinon andrieuxii*	This investigation represented both immunomodulatory and antileishmanial in vitro activities of hexane extract of *Pentalinon* andrieuxii (PARE) roots.

Table 2. Related studies in Iran

Authors	Year	Medicine source	Main Findings
Nilforoushzadeh, et.al **(38)**	2008	*Achillea millefolium (yarrow)* *Thymus vulgaris (thyme)*	The highest efficacy of herbal extracts in reduction of ulcer size was reported for propolis, followed by *Achillea millefolium* and then *Thymus vulgaris*.
Bonyadian, et al. **(39)**	2015	*Lavender*	Findings revealed that the proliferation rate of promastigotes reduced meaningfully after adding plant essential oil. Besides, it indicated the inhibitory effect of growth and lethality of lavender essential oil in vitro on the shape of Leishmania major promastigote.
Eskandari et al. **(8)**	2016	*Medicago lupulina*	Alcoholic extract and essential oil of the tested plant had significant anti-leishmaniasis effects in vitro and they can be considered as anti-leishmaniasis medicinal plants.
Nasiri et al. **(40)**	2016	*Black tea*	The outcome showed that black tea decoction has a beneficial effect on the elimination of L. major promastigotes in extrinsic conditions.
Bagherian et al. **(41)**	2017	*Thyme*	The results of light absorption and IC 50 showed that thyme is effective for the treatment of CL.
Ghaderi et al. **(10)**	2018	*Alpha-pinene compound*	Findings revealed the antileishmanial effect of alpha-pinene on L. major promastigotes, in vitro. Moreover, topical ointment of the extract could decrease size of the wounds caused by the parasite, in vivo.
Poursafavi et al. **(42)**	2018	*Olive*	The results showed that the aqueous extract at a concentration of 2.5 mg / ml and the hydroalcoholic extract of olive leaf at a concentration of 25 µg / ml on the third day killed all glucantime-sensitive Leishmania tropica amastigotes within macrophages.
Mardani et al. **(43)**	2020	*Cornus mas*	The results showed the effect of Cornus mas extract on inhibiting parasite growth influenced by the dose and time of treatment. Besides, all concentrations of the extract were able to reduce wound diameter and parasitic load.

eloping countries. In the present investigation, useful and identified natural products for three forms of leishmaniasis treatment were reviewed. It seems crucial that the antileishmanial activity of herbal extracts to be investigated in all phases of leishmania parasite regardless of the species. The dominant issue is the identification of potent chemical leishmanicidal compounds isolated from natural sources as a step forward in the exploration of antileishmanial drugs. Future perspective in the treatment of leishmaniasis depends on vaccine development, vector control, screening the effectiveness of treatment and high diagnosis sensitivity. The severity and diversity of leishmaniasis, the inadequacy of antileishmanial medicines and variable reactions in different locations made researchers discover novel antileishmanial compounds including arylimidamide, buparvaquone and nitroquinolines. This can lead to the design of many platforms for the upcoming products of second-generation compounds for the leishmaniasis treatment.

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Supplementary improvement in disease control can be achieved by genomic identification of parasites. In addition, information on medicines used for other contagions and new natural extracts might be useful in finding novel advantageous strategies to alleviate this infection.

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Conflicts of Interest

None has been announced.

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