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Alternative treatment studies for Leishmaniasis

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ABSTRACT

Leishmaniasis is a vector-borne zoonotic disease that is common in the world. Because of the difficulties in the treatment and control of the disease, the disease has gained popularity among researchers. Today, however, no vaccine has been developed for human protection. Considering the fact that the vector can survive in a wide ecosystem and the disease can be detected in many mammals such as humans, dogs, rodents, prevention from leishmaniasis and treatment of the disease require a combined intervention. The toxic effects of the drugs used in the treatment of leishmaniasis, the expensive treatment and the resistance of the parasite to the drug have led to the research of alternative treatment methods. This review is intended to provide an overview of leishmaniasis alternative treatment practices and to guide new researchs.

Keywords: *Leishmania, Phytotherapy, Apitherapy, Maggot therapy*

INTRODUCTION

Leishmania species are intracellular living blood and tissue protozoa seen in many vertebrate hosts. The parasite is transferred to other vertebrate hosts by the vector female sand fly (*Phlebotomus, Lutzomyia*). (İça, 2004; Harman, 2015). The disease caused by these parasites especially in human, dogs, other mammals, rodents and reptiles is called Leishmaniasis. (İça, 2004; Aytekin, 2009). Dogs are one of the most important mammals suffering from the disease. In addition, dogs are an important reservoir of disease transmission to humans (Gönül et al., 2010).

The parasite is found in amastigote form in the blood and tissues of the vertebrate hosts and in the promastigot form in the vector sand fly which are invertebrate hosts. Amastigotes are oval or round shaped, 2-4 µm in size and immobile in macrophage cells of vertebrate hosts. When the parasite is multiplied in the cell and destroy the cell, it can be seen individually or in clusters outside the cell (Yazar et al., 2016). Promastigot form can be detected in the digestive systems of vector. They are single whip shaped or shuttle shaped with a length of 10-20 µm, a width of 1.5-2.5 µm. Promastigotes proliferate in axenic cultures and in the digestive tract of the invertebrate vector (Ateş et al., 2011).

Leishmaniasis, which is the third after malaria and trypanosomiasis in vector-borne parasitic diseases, is of great importance in the world due to the treatment and control difficulties (Yaman, 2008). According to World Health Organization (WHO) data, approximately 20 million people in 98 countries around the world are infected and 350 million people are at risk (Limoncu et al., 2013; Harman, 2015). Leishmaniasis is one of the reportable diseases and is usually seen in tropical and subtropical regions (Kuhlencord et al., 1992; Memişoğlu, 1997; Barroso et al., 2015).

The disease has four clinical forms; cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), mucocutaneous leishmaniasis (MCL) and post kala-azar dermal leishmaniasis (PKDL) (Yazar et al., 2016). In the course of the disease, CL and MCL can cause deformities in the skin and mucosa while internal organ involvement leading to death may be seen in VL (Gönül et al., 2010) .

Leishmaniasis extends from Africa to Central and South America, from Eastern and Southern Europe to Asia. Visceral leishmaniasis is endemic in more than 80 countries and deaths up to 100% can be seen if untreated. More than 90% of cases occur in India, Bangladesh, Nepal, Sudan and Brazil (Murray et al., 2005).

Cutaneous leishmaniasis has emerged as a serious public health problem in certain regions of our country, especially in Southeastern Anatolia and Çukurova region. It is endemic in Çukurova region of Mediterranean region and Southeastern Anatolia region. According to the Ministry of Health data, approximately half of the 50381 cases identified across the country between 1988 and 2010 were reported from Şanlıurfa (Harman, 2015). The disease is common in Şanlıurfa, Osmaniye, Adana, Hatay, Diyarbakır, Kahramanmaraş and Mersin. Cutaneous leishmaniasis detected in Hatay and nearby places mostly reported from İskenderun, Altınözü and Kırıkhan (Culha and Akçali, 2006). The cases reported in recent years from the western and northern regions of our country consist primarily of refugees from neighboring countries, including Syria (Harman, 2015).

Visceral Leishaniasis cases in our country are mostly reported from Mediterranean and Aegean regions and *L. infantum* has been proven as a causative agent of the disease (Balcı et al., 2011). While the disease is endemic in Aegean and Mediterranean regions, it is sporadic in Central Anatolia, Marmara and Black Sea regions. The number of deaths related to the disease was reported as two persons in 1997 and one in each 1998 and 2000 (Altıntaş, 2008).

Four Leishmania species and the diseases they cause are more common in Turkey; *Leishmania donovani, Leishmania infantum, Leishmania tropica, Leishmania major*. The first two of these species usually cause VL (kala-azar, internal organ leishmaniasis) in the human and the other two produce CL in the skin. (Yazar et al., 2016).

Medical Treatment

Cutaneous leishmaniasis cases are healed spontaneously within a year, leaving a scar if not treated. Treatment provides uncomplicated recovery. The first stage in CL is to keep the lesion site clean and intralesional therapy. If necessary, treatment can be supported with systemic therapy (Ateş et al., 2011; Harman, 2015). The drugs used in the treatment of cutaneous leishmaniasis, physical methods and routes of administration can be listed as follows; i) Topical and intralesional therapies: intralesional five-valued antimony injection, paromomycin ointment, imiquimod, topical amphotericin B, cryotherapy, localized controlled heat (thermotherapy), carbon dioxide laser and photodynamic therapy ii) Oral treatments: azoles, azithromycin, miltefosine and oral zinc sulphate, iii) Intravenous or intramuscular treatments: systemic antimonals, antimonals and other drug combinations, pentamidine and amphotericin B (Aytekin, 2009).

Systemic treatment is required in visceral leishmaniasis. The development of drug resistance and the high toxicity of this group highlighted different treatment groups. Although drugs such as pentamidine, amphotericin B and liposomal Amphotericin B are highly cost-effective, they are recommended for resistant strains. Control of fever, regression of lymphadenopathy and hepatosplenomegaly, and elevation of hemoglobin levels are the signs of improvement in visceral leishmaniasis cases. Patients should be given bedside support, vitamin and protein-rich high-calorie diet. (Kuhlencord et al., 1992; Güneş et al., 2004; Limoncu et al., 2013; Harman, 2015).

Pentavalent antimony (SbV) compounds are most preferred drugs in the treatment of leishmaniasis. The best known of these pentavalent antimony compounds, which form the basis of leishmaniasis therapy since the 1940s; are meglumine antimonate (Glucantime®) and sodium stibogluconated (Pentostam®) (Harman, 2015). Although drugs such as meglumine antimonate (Glucantime®) and sodium stibogluconate (Pentostam®) are considered as the gold standard in the treatment of leishmaniasis, they are highly toxic to humans. There are also many side effects such as cardiotoxicity, hepatotoxicity, pancreatitis, anemia, leukopenia, thrombocytopenia, abdominal pain, nausea and vomiting. If there are any problems in the treatment of pentavalent antimony, alternative drugs such as amphotericin B, liposomal amphotericin B, miltefosine, paromomycin and pentamidine should be used. (Akbari et al., 2017).

Alternative Treatment Methods

Most of the antileishmanial drugs are highly toxic, there is resistance to the drug, the treatment is expensive and hospitalization is required for systemic treatment. (Ateş et al., 2011; Harman, 2015). Reasons like this have led to research on alternative treatment methods. Traditional treatment practices are increasing day by day and there are hundreds of literatures in the treatment of various diseases (Ahmad et al., 2017).

Alternative treatment modalities were studied in vitro and in vivo to treat the disease and the effects of the substances used on the parasite were investigated. When the studies on *Leishmania* species are examined, alternative treatment methods can be grouped under five headings.

Thermotherapy

Thermotherapy is an alternative therapy option for new world CL (Valencia et al., 2013). Laboratory studies have shown that *Leishmania* species cannot proliferate in macrophages at temperatures above 39 ° C. In particular, *L. braziliensis* and *L. mexicana* were observed to have a high thermosensitivity. Such observations support the use of hot bath, infrared light, direct electrical stimulation, laser and photodynamic therapy and thermotherapy for the treatment of CL lesions. In a study, thermotherapy provided an 85.7% improvement in CL lesions. However, side effects such as itching (16.7%), burning sensation (5.6%), pain (33.3%) and blisters were observed (Goncalves and Costa, 2018). In another study, single session thermotheraphy was performed after the lesions were cleaned with aseptic solution and 2% local anesthetic was applied. The thermal application was carried out at 50 ° C for 30 seconds. For 10 days after the thermotherapy session, an antibiotic ointment (fusidic

acid) was applied on the lesions and covered with sterile gauze to prevent secondary infections. Meglumine antimoniate (Glucantim) was administered intramuscularly at 20 mg Sb^5 / kg / day for 20 days. Although the efficiency rate of meglumine antimoniate for the treatment of CL was higher than thermotherapy, it was found that there was no statistically significant difference between the two treatment methods. However, the side effects of meglumine antimoniate were myalgia, arthralgia, headache and fever, whereas the only side effect in thermotherapy was pain in the lesion region. It has been reported that thermotherapy should be the first choice for the treatment of CL because the side effects and cost of meglumine antimoniate ($ 200 per patient) are higher than thermotherapy (Lopez et al., 2012). In addition, a heat pack named HECT-CL was adapted to provide low-cost, safe, reliable and renewable conduction heat to be widely used in endemic areas. The cumulative definitive treatment rate with this thermotherapy method was 68.4%, and the rate of treatment was 75% in patients who had recurrent CL after antimonial treatment (Valencia et al., 2013). In another study, the rates of glucantime cost and therapeutic efficacy were compared with thermotherapy. According to this study, cost per patient was $ 298.4 for Glucantime and $105.1 for thermotherapy. Therapeutic efficacy rates were 64.2% for thermotherapy and 85.1% for Glucantime (Cardona-Arias et al., 2017).

Cryotherapy

Cryotherapy is considered as an alternative treatment to pentavalent antimony for the local treatment of CL. Liquid cryotherapy (N_2) at -196 ° C is used in CL cryotherapy. Recently, it has been reported that carbon dioxide (CO_2) at -78.5 ° C is also used in CL cryotherapy. The efficacy of cryotherapy (N_2 and CO_2) on BALB / c mice infected with *L. major* was investigated. It has been reported that liquid N_2 cryotherapy can be superior and effective than CO_2 cryotherapy. It has been reported to be successful in more than 95% of cutaneous lesions with liquid nitrogen (N_2) (Shaddel et al., 2018). Liquid N_2 cryotherapy is easy to perform, relatively inexpensive, does not have any systemic side effects, does not require local anesthesia. Hence cryotherapy can be an effective treatment option in CL patients infested with *L. donavani.* In this study, success rate of treatment was found to be 91.7% (Ranawaka et al., 2011). The improvement was reported to be 92% in cases who received 2-7 cryo-sessions at 1-3 week intervals. Mild and transient side effects such as pain and hypopigmentation were observed in the study (Dobrev et al., 2015). Although cryotherapy shows a similar efficacy with pentavalent treatment, it is presented as an advantageous method because it shows better compliance and better treatment. (Lopez-Carvajal et al., 2016).

Table 1. In vitro antileishmanial effects of some plants.

Plants	Leishmania species	Conclusion	References
Allium sativum (garlic) bulb *Acacia nilotica* (acacia) fruits *Azadirachta indica* (neem tree) leaves	*L. major*	The plants, *A. indica, A. sativum*, and *A. nilotica,* had a considerable in-vitro anti-leishmanial effect on *L. major* promastigotes.	(Fatima et al., 2005)
Arbutus unedo (strawberry tree) leaves	*L. tropica*	The extract of *Arbutus unedo* leaves can be a promising antileishmanial agent.	(Kıvçak et al., 2009)
Ferula galbaniflua (galbanum) resin essential oil	*L. amazonensis*	Essential oil is effective against *L. amazonensis* promastigotes forms and has low cytotoxic activity.	(Andrade et al., 2016)
Portulaca oleracea (purslane) stems and leaves	*L. major*	The ingredients of the herb leaves and stem essence had significant antileishmanial effect on *L. major* promastigotes.	(Eskandari et al., 2016)
Artemisia dracunculus (tarragon) *Satureja hortensis* (savory) *Plantago psyllium* (fleawort)	*L. major*	Plant extracts exhibited promising leishmanicidal activity against promastigotes. Tarragon and savory extracts may make it possible to use them in the treatment of cutaneous leishmaniasis as a complementary or alternative therapy.	(Mirzaei et al., 2016)
Guatteria latifolia branches, leaves and fruits	*L. amazonensis*	Plant extract exhibited promising leishmanicidal activity against promastigotes.	(Ferreira et al., 2017)
Virola surinamensis (baboon wood) leaves	*L. chagasi* *L. amazonensis*	*V. surinamensis* presented high activity against promastigote	(Veiga et al., 2017)

Phytotherapy

The history of phytotherapy, which is used for herbal treatment, is as old as human history. The origin of phytotherapy used today is based on China and India (Durusoy and Ulusal, 2007). Herbs are traditionally used in the treatment of many diseases. Although the active substance of some drugs is of plant origin, there is an abundance of medicinal and veterinary practitioners against herbal treatment. The way to avoid this is to do more studies to increase the efficiency and reliability of such studies (Yipel et al., 2016). About 25% of prescribed drugs are obtained from plants. Most high-build plants are a potential source of antimicrobial agents. In the

parasites such as *Entamoeba, Plasmodium, Trypanosoma* and *Leishmania*, positive results were obtained by studying these plants (Ataş et al., 2003).

Most of the leishmaniasis-related phytotherapy methods have been studied in vitro. Some plants investigated for in vitro effects on *Leishmania* species are given in Table 1 (Fatima et al., 2005; Kıvçak et al., 2009; Andrade et al., 2016; Eskandari et al., 2016; Mirzaei et al., 2016; Ferreira et al., 2017; Veiga et al., 2017). Nearly 30 herbs were studied to investigate the in vitro effects on CL in Turkey. It was found that 16 of 30 plants were more effective compared to glucantime. The plant species with favorable results have been reported as *Allium* (lilyaceae), *Tanacetum* (chamomile), *Pimpinella* (parsley) and Origanum respectively (Ataş et al., 2003).

In 2017, Sarkari et al. performed one of the most recent in vivo studies. The researchers formed six groups by infecting BALB / c mice with *Leishmania major*. In this study, the antimony compounds used in the classical treatment of leishmaniasis and *Echinacea purpurea* (echinacea) plant extracts were administered orally and they measured the lesion sizes at different concentrations. However, they have reported that the plant is not very effective when compared with antimony compounds (Sarkari et al., 2017). In another study, the in vivo and in vitro antileishmanial effect of essential oil of *Pistacia vera* was investigated. The effect of the plant was compared with meglumine antimonate. It inhibited the growth rate of amastigotes in *L. major* and *L. tropica*-infected BALB / c mice and reduced the mean diameter of the lesions by 0.56 cm. Such studies provide evidence that plants can be used in conventional medicine, especially during prevention and treatment of CL. (Mahmoudvand et al., 2016).

Apitherapy

Apitherapy is the art and science of preserving health by using products of bees such as honey, pollen, propolis, royal jelly and bee venom (Fratellone et al., 2016). In the studies, especially the treatment properties of honey and propolis apitherapy products are emphasized. Studies conducted in vivo and in vitro suggest that honey and propolis can be used as an alternative to the healing of infected wounds, inhibition of bacterial growth, corneal wound healing, antioxidant effects, effects on glucose metabolism and treatment of dermatophytosis. (Cam et al., 2009; Can et al., 2015; Atayoğlu et al., 2016; Fratellone et al., 2016; Medeiros Vde et al., 2016; Saral et al., 2016; Yusof et al., 2016). The effects of propolis on *Leishmania* species were also investigated and anti-protozoonal effect against *L. tropica* was reported (Duran et al., 2008; Özbilge et al., 2010). In an in vitro study, propolis was compared with antimony compounds and was shown to have inhibitory and anti-proliferation properties on *L. tropica* promastigotes. It has also been reported that propolis inhibited parasite production at 64 µg/ml when sodium stibogluconate inhibited at 500 µg/ml (Özbilge et al., 2010). In another study, it was found that propolis extracts had a leishmanisidal effect against amastigote and promastigot forms of *L. braziliensis*. Low cell toxicity and effective microbisidal effect of alcoholic or glycolic propolis extracts indicate that propolis may be an alternative treatment for cutaneous leishmaniasis (Reboucas-Silva et al., 2017).

Maggot therapy

Maggot therapy is the use of sterile myiasis fly larvae in skin and soft tissue wound treatments. Larvae dissolve and disinfect dead tissue on the wound with enzymes. This method is also called Larval Debridement Therapy (LDT) (Arrivillaga et al., 2008; Polat and Kutlubay, 2014; Sanei-Dehkordi et al., 2016).

In an in vivo study in Spain, golden hamsters with CL infested with *L. amazonensis*, were treated with *Lucilia sericata* larvae. After 12 hours, reduction of 80% - 100% in lesion size and regression in disease were observed starting (Arrivillaga et al., 2008). In another study the antileishmanial effects of *L. sericata* and *Calliphora vicina* larvae were examined on BALB / c mice infected with *L. major*. Although the larvae of both fly species had reduced lesion size, *L. sericata* larvae treated the *L. major* source lesions statistically significantly (Sanei-Dehkordi et al., 2016). For the treatment of CL on *Mesocricetus aureatus* (golden hamsters) infected with *L. panamensis*, *L. sericata* and *Sarconesiopsis magellanica* (butterfly) larvae were investigated. *Lucilia sericata* larvae have been reported to be therapeutic in this study. (Cruz-Saavedra et al., 2016).

Polat et al. reported that secretions of sterile larvae of *L. sericata* had an anti-parasitic effect on *L. tropica*-infected BALB / c mice (Polat et al., 2012). Polat and Kutlubay successfully treated the CL caused by glucantine resistant *L. major* in human. They applied the 1st stage *L. sericata* larvae directly on the lesion and secretions of the larvae that transforming to 3rd stage from 2nd stage into the lesion (Polat and Kutlubay, 2014).

CONCLUSION

The disease caused by *Leishmania* species is very important because it has a wide range of hosts. People and animals who have the disease and who act as potential reservoirs must be treated to be protected from zoonotic and anthroponotic character. When alternative treatment approaches for leishmaniasis are examined, cryotherapy and thermotherapy are medically accepted methods. However, apitherapy applications have not gone beyond a few studies. Further studies are needed in vivo and / or in vitro. In phytotherapy applications, mostly in vitro studies were performed. In most of these studies, the effects of phytotherapy on promastigotes, which is the form of parasite produced in the vector and produced in culture, were evaluated. Further studies need to be done to determine the effects of plant extracts and oils on the amastigote form of vertebrate hosts. Maggot therapy as an alternative treatment option has proven its success in both in vitro and in vivo studies. Since maggot therapy is a natural option and low in cost, it can be used as an alternative treatment method in

patients with resistance to medical treatment especially in patients with CL.

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