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Review Article:

Medicinal Plants With Antileishmanial Properties: A Review Study

Elham Gharirvand Eskandari[1], Mahbubeh Setorki[2], Monir Doudi[1*]

1. Department of Microbiology, Falavarjan Branch, Islamic Azad University, Isfahan, Iran.
2. Department of Biology, Izeh Branch, Islamic Azad University, Izeh, Iran.

*** Corresponding Author:**
Monir Doudi, PhD.
Address: Department of Microbiology, Falavarjan Branch, Islamic Azad University, Isfahan, Iran.
Phone: +98 (31) 37420134-5
E-mail: monirdoudi@yahoo.com; doudi@iaufala.ac.ir

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ABSTRACT

Background: Leishmaniasis is an infectious disease caused by various species of the *Leishmania* parasites. An effective vaccine or drug to prevent the infestation or a suitable medication to cure the disease without side effects has not been provided yet.

Objectives: The use of medicinal herbs in the treatment of many diseases, especially parasitic ones, dates back to prehistoric times. This article is a review study on these herbs used for the treatment of leishmaniasis.

Methods: In this regard, we searched PubMed, Science Direct, and Google Scholar databases. We prepared this review on the treatment of cutaneous leishmaniasis with medicinal plants because of the prevalence of this disease, chemical drugs' failure to fully control it, increase in the number of reports on drug resistance, and contradictory research on the side effects of synthetic drugs.

Results: In general, the use of medicinal herbs for the treatment of various diseases has a long history. Because of Iran's diverse climate and flora, we have the potential to identify the active herbal ingredients in different indigenous plants of the country and extract them to produce them on an industrial scale.

Conclusion: In this article, several herbs used to treat cutaneous leishmaniasis from the past to today in Iran and other countries are studied and evaluated.

Introduction

Cutaneous leishmaniasis is a parasitic, zoonotic disease caused by various species of *Leishmania* parasites. The disease has several names in different parts of the world [1, 2].

The disease could be traced in ancient times. Potteries from the prehistoric period of Indians in Ecuador and Peru indicate images of skin lesions and malformations in the human face, which are a relatively accurate indication of cutaneous and cutaneous-mucosal lesions of leishmaniasis (Chiclero's ulcer or Aleppo boil).

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Other reports suggest the familiarity of Greek and Muslim Iranian physicians with the disease [3]. Cunningham in 1885 and Frith in 1891 were the first ones who observed Leishmania tropica. In 1898, Beruschi, a Russian military surgeon, discovered the protozoan nature of the disease with the study of cutaneous ulcers in Turkmenistan. In 1900, William Leishman isolated small elliptical bodies in the spleen of a patient, which was later called Leishman [4].

World Health Organization (WHO) reports suggest that about 350 million people in 88 countries around the world are currently at risk of developing this disease. The number of people infected with the disease is now estimated to be 12 million, and about 1-2 million new cases occur annually. About 90% of cases of cutaneous leishmaniasis have been reported in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria [5]. The rate of contamination in Iran is about 16.000, but its actual rate is more than three times the reported statistics [6].

In 1902, Shalgin stated that the mosquito would transmit the disease. Wright from Boston was the first to describe the parasite in 1903 when he saw it in an American soldier and named it *Helcosoma tropica*. In 1904, Rojers managed to culture the parasite for the first time and observed its flagellate form in a medium containing rabbit blood, which is used nowadays in most research laboratories. In 1906, Lühe described *Leishmania tropica* as the organism responsible for causing oriental sore. The culture medium containing rabbit blood developed by Rojers was introduced and named by Navi, Nicole, and McNeil as the N.N.N culture medium, and it is used now in most research laboratories. In 1911, another scientist, Vianna, from South America called this parasite *Leishmania braziliensis*. In the same year, Vianna showed that the vector of the disease is *Phlebotomus papatasi*, and later on, *Phlebotomus seregenti*. The others also confirmed that result. In 1915, Gashe, a medical professor at Dar al-Fonoun, tested 21 stray dogs in Tehran. Of those, 15 dogs had leishmaniasis [6-8].

Cutaneous leishmaniasis has long been known in Iran, and nowadays, our country is considered as one of the most important endemic areas of the disease in the world [9]. In Iran, the anthroponotic type or the urban type of cutaneous leishmaniasis has been commonly found in cities of Tehran, Shiraz, Kerman, and Bam, as well as Khorasan Province, while the rural type has been observed in provinces of Isfahan, Golestan, Khuzestan, and Ilam as well as cities of Bushehr, Semnan, and Dehloran [10].

Cutaneous leishmaniasis in Iran has been clinically observed in rural (wet wounds) and urban (dry wounds) forms. Rural cutaneous leishmaniasis is a zoonosis disease and called ZCL (Zoonotic Cutaneous Leishmaniasis). The urban cutaneous leishmaniasis is known as anthroponotic and called Anthroponotic Cutaneous Leishmaniasis (ACL). *Leishmania major* is the causative agent of rural cutaneous leishmaniasis, and *Leishmania tropica* is the cause of urban cutaneous leishmaniasis. It should be noted that the ZCL type is dominant in most parts of Iran. The recorded statistics of the patients with cutaneous form in Iran are about 20000 each year, and some believe that the actual figures are about 4 to 5 times that number, and it is one of the most important parasitic diseases in Iran after malaria [11]. In the Middle East, 14 of the 22 countries are involved with leishmaniasis. Rural focal areas of cutaneous leishmaniasis are mostly found in Afghanistan, Egypt, Iran, Iraq, Jordan, Libya, Morocco, Tunisia, Palestine, Pakistan, Saudi Arabia, Syria, and Yemen, while the urban type is more seen in Afghanistan, Iran, Iraq, Morocco, Pakistan, Saudi Arabia, Syria, and Yemen. *Leishmania* parasite that causes visceral leishmaniasis in Iran is either *Leishmania infantum* or *Leishmania donovani*. Visceral leishmaniasis has been one of the most important endemic diseases in the northwestern part of Iran in the last 10 years [12, 13].

In areas where endemic leishmaniasis exists, chemical and physical treatment methods, including copper sulfate, acid, water, or hot metals, have also been used. Although these methods have been invasive and the scarring from them can be worse than the sore itself, amastigotes have been proven to be sensitive to heat. Therefore, if localized heat up to 40˚C or ultrasound waves is applied to the wound, the wound healing will be expedited. It has been even mentioned in some cases that the thermal treatment has a curable effect like glucantime [8, 14].

No proper vaccine or drug to prevent the parasite and no suitable chemical or physical method to fight with its carrier have been developed so far. The appropriate treatment for leishmaniasis depends on the infecting *Leishmania* species and its clinical syndrome. Pentavalent antimonials, sodium stibogluconate (pentostam) and meglumine antimoniate (glucantime) have been the main treatments in recent decades- but with increasing reports on their treatment failure. Amphotericin B deoxycholate is an effective but relatively toxic drug and has not been identified as a thoroughly satisfactory treatment so far.

The use of medicinal herbs in the treatment of parasitic diseases dates back to ancient times when *Cinchona*

succirubra (Rubiaceae) was used as an antimalarial drug [15]. The treatment of cutaneous leishmaniasis has been documented in traditional medicine in various forms, such as oral remedies, ointment, and poultice. In this medicine, herbs have also been used for their topical and systemic effects [1]. In general, the use of medicinal plants for the treatment of diseases has a long history [16]. Recent research on natural plant compounds has revealed antileishmanial effects of quinoline, alkaloids (such as cupsarin and skimmianine), isoquinoline alkaloids (such as lymacine and isotetradine), flavonoids (such as luteolin and fistin), saponins (such as alpha-hederin), naphthoquinones (such as lapachol and plumbagin), terpenes and tetralenes on some species of *Leishmania* [1]. This article reviews several herbs that are used to treat cutaneous leishmaniasis in Iran and some countries around the world. We hope that herbal medicines become a proper approach to prevent drug resistance and the toxic effects of antileishmanial chemical drugs.

Materials and Methods

This research is a review study. It is based on valid articles published from 1983 to 2018 in this field. The databases used for this article were PubMed, Science Direct, and Google Scholar. The qualified papers contained the history of identifying *Leishmania* parasites, treatment of the disease using medicinal herbs as well as physical, chemical, biological therapeutic methods with topical and systematic approaches.

Results

The treatment of cutaneous leishmaniasis has been discussed since 1911. It consists of topical or systemic approaches in four physical, chemical, biological, and immunological modes [17]. The topical treatment of cutaneous leishmaniasis is a suitable method since it is easier to apply, absorbed at the site, and without the complications of systemic drugs. Mapacrine, emetine, and berberine acid sulfate can be used for injection into the lesion, which are all chemical treatments. Among the above methods, the use of emetine is highly recommended by the WHO in endemic areas [18]. According to the findings, the protocol for the treatment of cutaneous leishmaniasis is often recommended with the following drugs: glucantime, pentamidine isethionate, amphotericin B, fluconazole, itraconazole, ketoconazole, and allopurinol [19, 20].

One of the essential issues in the treatment of this disease is the side effects of chemical drugs. For example, the side effects of sodium stibogluconate include joint pain, muscular pain, increased liver enzymes, anemia, leukopenia, thrombocytopenia, and electrocardiogram changes in inverse T and QT forms, prolonged ST, and changes in clinical function tests [20, 21]. Before 1990, amphotericin B has been rarely used due to its side effects, including renal disorders, anorexia, lethargy, fever, chills, bone pain, changes in electrolytes, and occasionally heart attacks. The drug affects the metabolism of leishmaniasis and fungi sterols. This drug attaches to the ergosterol in the *Leishmania* membrane, causes cell permeability, and kills the parasite. Based on the WHO recommendation, amphotericin B is used in cases where patients are resistant to antimony compounds. This drug is taken through intravenous injection. The above complications have been observed in 25% of users [22].

The chemical pentamidine medicine has fewer clinical complications than sodium gluconate, but in 30%-50% of the subjects, it leads to complications such as tachycardia, headache, vomiting, muscular pains, hypoglycemia, severe low blood pressure, sudden death, thrombocytopenia, anemia, neutropenia, and increased levels of liver enzymes [23, 24]. Many studies have shown that some natural plant compounds have antileishmanial effects against some species of *Leishmania* [25-32]. This review article examined and discussed a number of herbs used to treat cutaneous leishmaniasis since ancient times.

Herbal treatments of cutaneous leishmaniasis in ancient Iranian medicine

Several reports of this disease in ancient texts of traditional medicine have revealed that in the time of Zakariya al-Razi, the following procedure has been used to treat the disease ulcers in the hands and feet (Table 1):

They grinded the caraway (*Cuminum cyminum L.*) (Mosaddegh, 2010) and separated its shell. Then, they washed the powder thoroughly with warm water and rubbed over the wound overnight. On the next morning, they put the hand or foot in hot water and washed it with water. This process was repeated several times until full recovery [3].

In Khorasan Province, the natural extract of barberry (*Berberis vulgaris*) (Hashemi, 2012; Maspi, 2010) plant has been used in traditional treatment. Studies on the antileishmanial effect of barberry alcoholic extract have reported a significant leishmanicidal effect. The results show a significant decrease in the size of the ulcers in mice exposed to the extract compared to the control group after two weeks of starting the treatment. The sores of the con-

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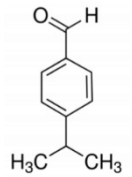
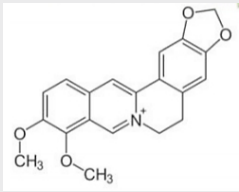
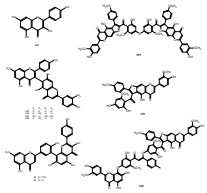
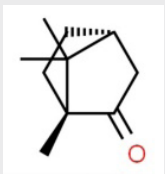
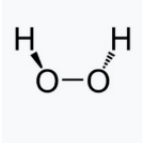
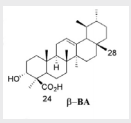
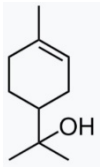
Table 1. Study of chemical composition and effects of medicinal plants on cutaneous leishmaniasis in ancient Iranian medicine

Caraway	*Cuminum cyminum L.*	Treatment of wounds, including cutaneous leishmaniasis	Cuminaldehyde ($C_{10}H1_{20}$) *p*-Cymene ($C_{10}H_{14}$) α-Terpinene β-Pinene ($C_{10}H_{16}$) γ-Terpinene ($C_8H_{14}O_4$) [35]	Cuminaldehyde  [36]
Barberry	*Berberis vulgaris*	Hypolipidemic, antidiabetic, treatment of cutaneous leishmaniasis, Berberine in Leishmania plant destroys murine peritoneal macrophages [7, 15].	Isoquinoline alkaloids: Berberine ($C_{20}H_{18}NO_4$+) Bargustanine ($C_{29}H_{34}N_2O_7$) Berbamine ($C_{37}H_{40}N_2O_6$) Berlambine Palmatine ($C_{21}H_{24}NO_4$+) Secondary metabolites: Caffeic acid ($C_6H_8O_6$) Pectin Tannin [37]	Berberine  [37]
Birthwort	*Aristolochia mauro-rum L.*	Worm killer, the antidote to animal and vegetable poisons, scorpion poison killer, and lice insect. It is used with honey for wound healing. It is used with iris and honey for wound healing [19].	Aristolochic acid Aristolactams Aporphines Protoberberines Isoquinoline Benzylisoquinolines Amides Flavonoids Lignans Biphenyl ethers Coumarins Tetralones Terpenoids Steroids Ethers [38]	Flavonoids found in Zaravand:  [38]
Camphor	*Cinnamomum camphora*	The antidote to scorpion and snake venoms. Healing late wounds like a seeker. Its 1%-3% solution is itchy. It is anti-inflammatory at concentrations less than 100 µg/mL [2, 4]. Anti-virus software [39], fumigant toxicity [40].	Linalool ($C_{10}H_{18}O$) D-camphor ($C_{10}H_{16}O$)	D-Camphor  [39]
Honey	-	Wound healing, burns, scratches, reducing edema, inflammation, and pain [1]. It is used in combination with glucantime for the treatment of cutaneous leishmaniasis [16]. Treatment of infectious wounds [6]. Anti-bacterial [41].	Hydrogen peroxide (H_2O_2)	(H_2O_2)  [41]
Boswellia	*Boswellia carterii*	Antifungal, antibacterial, anti-parasitic. Healing of deep wounds, especially fresh injuries and blood clots. Decreased inflammatory response and accelerated recovery at the site of inflammation [5, 34].	Acid triterpenoids, especially beta-acid and its derivatives [17, 41] β-Boswellic aldehyde [42]	B-Boswellic aldehyde  [42]

Lemon	*Citrus limon*	Treatment of small and red pimples. Burns the skin and eliminates pus [1, 4]. Antifungal, antibacterial immune regulator, anti-larvae, cytotoxic against prostate, stomach, and breast cancer cells [13].	A-Terpineol Linalool Geraniol Linalyl acetate ($C_{12}H_{20}O_2$) [43]	A-Terpineol  [43]

trol group that had been only in contact with ethanol were reported still growing and worsening. Various alkaloids are found in the barberry plant, including berberine, jatorrhizine, columbamine, palmatein, oxyacanthine, berbamine, bervulcine, isotetradine, volrysin, and magnoflorine. Berberine effectively eliminates the *Leishmania major* in macrophages in the peritoneal cavity of the mice, while its topical use has induced anti-leishmaniasis effects [10, 15].

Birthwort (*Aristolochia maurorum L.*) has been introduced in ancient Iranian traditional medicine as a plant with a warm and dry nature. This herb has been used as an antidote for plant and animal toxins and a lethal agent for the gastric worm. The poultice of this plant has been used to neutralize the lethality of scorpion venom and insects' bites and other wounds and used with honey to treat fresh and chronic ulcers. It was also used with *Lilium* and honey to fill and heal the wounds. If rubbed with oil on the body, it will kill and repel the lice. With wound disinfecting properties, this herb has been used to heal wounds of cutaneous leishmaniasis [19].

Camphor (*Cinnamomum camphora*) (Lamidi, 2005; Dutta, 2007) with its cool and dry nature has been the antidote for venoms of scorpions and snakes, and the healing agent for obstinate wounds. Its 1%-3% solution was used as an antipruritic remedy. In non-toxic concentrations (less than 100 µg/mL), camphor has anti-inflammatory effects. According to the research results, the anti-inflammatory effects of camphor are related to its regulating effects on cytokines, nitric oxide, prostaglandin E2 production, and oxidative stress. This material was also used to heal cutaneous leishmaniasis ulcers [2, 4].

In the past, honey (Ramezani, 2012) has been used as a therapeutic agent in the treatment of infectious ulcers [9], including oriental sores. Honey has been placed as a coating on wounds, burns, and scratches to reduce edema, inflammation, and pain. By encoding the enzymes producing hydrogen peroxide and other substances, and bees give antibacterial properties to honey [1]. In a study, honey with glucantime has been used inside the lesion to treat cutaneous leishmaniasis. Then, it was put on the wound sufficiently to exacerbate its effect. It was shown in this study that the therapeutic effect of honey when used with glucantime decreases compared with using the glucantime alone. This study revealed that honey does not have anti-inflammatory properties but provides a nutritional source for damaged cells [33].

Boswellia (*Boswellia carterii*) (Verma, 2004; Torres, 1999) with a warm and dry nature has been used in traditional medicine to heal and repair deep wounds, especially fresh injuries, and stop their bleeding as well as to prevent the spread of obstinate wounds. It was also used to heal cutaneous leishmaniasis ulcers. The anti-inflammatory effects of boswellia have been demonstrated both in vitro and in vivo conditions. Having triterpenoids, especially beta-boswellic acid and its derivatives, boswellia is a specific inhibitor of 5-lipoxygenase 1 enzyme and inhibits and reduces leukotrienes. By reducing the number of white blood cells in the inflammation site, it will reduce inflammatory responses and accelerate the healing process. Antibacterial, antifungal, and anti-parasitic properties of boswellia have also been proven in this study [5, 34].

Lemon (*Citrus limon*) (Mohseni, 2012; Dutta, 2007) with a cold and dry nature has been used in ancient Iranian medicine to treat tiny, red, and burning papules of the skin and to eliminate the pus. This plant has been applied to heal cutaneous leishmaniasis as well [1, 4]. It has anti-fungal, antibacterial, immune system regulating, and anti-larval effects, and its cytotoxic effects on cancer cells of prostate, stomach, lung, and chest have been proven [13].

Herbal remedies for cutaneous leishmaniasis in modern medicine

During an experiment, Torres Santos et al. found out that 2',6'-dihydroxy-4'-methoxychalcone extracted from *Piper aduncum* has a significant effect against the promastigotes and amastigotes of the *Leishmania amazonensis* so that the IC_{50} of this substance against pro-

Table 2. Study of chemical composition and effects of medicinal plants on cutaneous leishmaniasis in modern medicine

Plant	Main Components	Impact Assessment
Piper aduncum	2',6'-dihydroxy-4'-methoxychalcone (Torres-Santos, 1999) [34]	IC_{50} Against promastigotes=0.5 mg/mL Against amastigote=24 mg/mL (Torres-Santos, 1999) [34]
Aloe vera	Glucomannan, prostaglandin, lignin, saponins, anthocyanin, flavonoid (Soudi, 2006) [25]	IC_{50}= 100-180 mg/mL (Soudi, 2006) [25]
Echinacea purpurea	Alkaloid, caffeic acid, glycoprotein (Manayi, 2015) [68]	IC_{50}= 50 mg/mL (Taran, 2010)
Pistacia atlantica	α-Pinene, camphor, β-myrcene, limonene, 2,2'-diphenyl-1-picrylhydrazyl (Grecco, 2012) [45]	No concentration. The gum was applied directly to the wound (Grecco, 2012) [45]
Bacchari sretusa	Sucrantin Naringenin (Rodrigues, 2013) [48]	Sucrantin is not anti-leishmania. Naringenin: IC_{50}=43-52 mg/mL (Rodrigues, 2013) [48]
Lantana ukambensis	6,7,3',4',5'-Pentamethoxyflavone (Sawadogo, 2012) [19]	IC_{50}=9.6 mg/mL (Sawadogo, 2012) [19]
Camellia sinensis	Epigallocatechin gallate, which is an antioxidant polyphenol (Abbas, 2009) [69]	At a concentration of 12 mg/mL, it affected equivalent to glucantime at a concentration of 85 mg/mL (Ogeto, 2013).
Aloe secundiflora	Aloenin, aloenin B, barbaloin, Chromones, phenylpyrones, phenyl-ethyl-amine alkaloid ($C_8H_{11}N$) , N-methyltyramine (Rodrigues, 2013) [48]	Aqueous extract IC_{50}=279.488 µg/mL Ethanol extract IC_{50}=42.824 µg/mL (Rodrigues, 2013) [48]
Croton cajucara	Hydroxy-calamene (Saleheen, 2004) [27]	Against Leishmania chagasi The minimum lethal concentration of essential oil=250 µg/ mL The minimum lethal concentration of 7-hydroxy calamene=15.6 µg/mL (Saleheen, 2004) [27]
Allium cepa	S-alkyl-L-cysteine sulfoxide (Shariatifar, 2011) [49]	Against Leishmania major, donovani, tropica, mexico IC_{50}=0.376 mg/mL (Shariatifar, 2011) [49]
Cassia fistula	Tannin, flavonoid, glycoside, anthraquinone (Ajay, 2017) [70]	Lethal concentrations 0.1-0.9 1-9 0.003-0.009 mg/mL (Amanzadeh, 2006) [50]
Allium stipitatum	Antioxidant enzyme, phenol, superoxide dismutase (Sharif, 2006) [28]	Third day 0.01-0.1 First day 0.2 mg/mL lethal (Sharif, 2006) [28]
Artemisia aucheri Boiss.	Anti-inflammatory, antioxidant, flavonoid compounds (Asadi, 2012) [54]	IC_{50}=5.9 µg/mL (Asadi, 2012) [54]
Ferula assa-foetida L.	Coumarinic esters, camolenol, tetrasulfide, terpenoid (Sadoughi, 2015) [71]	IC50=7.5 µg/mL (Asadi, 2012) [54]
Gossypium hirsutum	Gossypol ($C_{30}H_{30}O_8$) (Asadi, 2012) [54]	IC_{50}=3.6 µg/mL (Asadi, 2012) [54]
Calendula officinalis	Flavonoid, carotene, saponins, sterol (Verma, 2018) [72]	Alcoholic extract IC_{50}=170 µg/mL Aqueous extract IC_{50}=215 µg/mL (Khademvatan, 2011) [55]

Plant	Main Components	Impact Assessment
Hypericum perforatum	Tannin, hypersoid, hyperin (Khademvatan, 2011) [55]	Within range 50-100 µg/mL The lethal and the higher the concentration, the greater the lethality (Khademvatan, 2011) [55]
Mespilus germanica	Phenolic component Tannin, flavonoid Amanzadeh, (2006) [50]; Khademvatan, (2011) [55]	Within range 50-100 µg/mL The lethal and the higher the concentration, the greater the lethality (Khademvatan, 2011) [55]. At a concentration of 60%, it reduced the diameter of the wound by 20% and killed almost 66% of the parasites (Amanzadeh, 2006) [50].
Allium sativum L.	Alicines, allicin, polysulfide, mercaptans, thiosulfinates (Sadoughi, 2015) [71] Sulfur compounds, alicine, alicatin	At a concentration of 93 µg/mL, hundreds of parasites were killed (Sadoughi, 2015) [71]. At a concentration of 47 µg/mL, it killed promastigotes in macrophages.
Crataegus aronia	Phenolic component	After 24 hours 0.5-60 µg/mL After 48 hours 20.94-20.11 µg/mL After 72 hours 55.14-35.19 µg/mL (Lethal Range)
Curcuma longa	Curcumin, curcominindium, gallium curcuma, diacetyl curcumin	Curcumin IC_{50}=38 µg/mL Gallium curcuma IC_{50}=32 µg/mL Diacetyl curcumin IC_{50}=26 µg/mL
Arnebia euchroma	Naphthoquinones (Borazjani, 2018) [73]	5% gel was effective on the wound (Borazjani, 2018) [73]
Achillea millefolium	Apigenin, rutin, luteolin, kaemferol (BeigiBoroujeni, 2014) [59]	IC_{50}=25 µg/mL (Kuo, 2012) [38]
Artemisia absinthium	Caryophyllene oxide, p-cymene, 1,8-cineole, (Z)-laceol acetate (Ozkan, 2005) [74]	IC_{50}=25 µg/mL (Kuo, 2012) [38]
Juglans regia L.	Linolenic acid, linoleic acid, oleic acid (Amiri, 2011) [75]	IC_{50}=25 µg/mL (Kuo, 2012) [38]
Scophularia straiata	L-linalool, 6,10,14-trimethylpentadecane-2-ol, dibutyl phthalate, β-damascone (Srivastava, 2010) [76]	With concentration of 25 µg/mL killed 100% of the parasites inside the macrophage, and the culture medium on the third day (Naserifard, et al, 2013) [16]
Artemisia annua	Artemisinin (Yousefi, 2014) [60, 61]	Against Leishmania donovani amastigotes IC_{50}=6.0±1.4 µg/mL (Yousefi, 2014) [60, 61]
Crocus sativus	Terpene, esters (Afsharypour, 2006) [77]	IC_{50}=0.7 mg/mL Bonyadian, 2015[31]; Samarghandian (2014) [61]
Lavendula officinalis	Linalool, 1,8-cineol, camphor, terpinene-4-ol, α-terpineol (Nehdai, 2018) [78]	It has a lethal effect at concentrations above 10%. After 72 hours, it killed 100% of the parasites (Gharirvand, 2016) [62].
Medicago lupulina	Medicagenic acid, 7,4'-dihydroxyflavone, diethyl fumarate, coumarin, tricin (Gharirvand, 2016) [62]	Alcoholic extract on parasite isolated from a patient IC_{50}=130 µg/mL Disease on parasite isolated from a patient IC_{50}=340 µg/mL Alcoholic extract on the standard strain parasite IC_{50}=98 µg/mL (Gharirvand, 2016) [62]
Propolis	Phenol, esters, flavanone, dihydroflavonol, flavoon, chalcone	Directly wound healing
Portulaca oleracea	Phytol, palmitic acid, squalene, apigenin, bergapten (Gharirvand, 2016) [62]	Hydroalcoholic extract IC_{50}=360 µg/mL Essential oil IC_{50}=680 µg/mL (Gharirvand, 2016) [62]

Plant	Main Components	Impact Assessment
Crataegus microphylla	Artesin, apigenin-7-O-glucisid diethyl ester (Shirazi, 2017) [65]	IC_{50}=1094 µg/mL (Shirazi, 2017) [65]
Phoenix dactylifera	Oleic acid, lauric acid, linoleic acid, α-tocotrienol, γ-tocotrienol, α-tocopherol, γ- tocopherol (Basta, 2007) [79]	Kernel IC_{50}=23 µg/mL Fruit IC_{50}=500 µg/mL (Albakhit, 2016)
Cichorium intybus	Flavonoids, alkaloids (Shirazi, 2017) [65]	IC_{50}=1094 µg/mL (Shirazi, 2017) [65]
Ziziphus spina-christi	Alkaloid, flavonoid, tannin, saponin glycoside (Albakhit, 2016)	Essential oil IC_{50}=80 µg/mL Hydroalcoholic extract IC_{50}=60 µg/mL (Albakhit, 2016)

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mastigotes was 0.5 µg/mL and against the intracellular amastigotes was 24 µg/mL [34] (Table 2).

Discussion

Hojjati et al. stated that *Aloe vera* has multiple uses in medicine and examined the effect of the substance secreted from *Aloe vera* leaves on cutaneous leishmaniasis [43]. The promastigotes of the species causing cutaneous and visceral leishmaniasis were sensitive to *Aloe vera* leaf, and their IC_{50} ranged from 100-180 µg/mL. Such data revealed that *Aloe vera* leaf could improve the host macrophages function through direct anti-leishmaniasis activity and may be used as an effective antileishmanial agent in pharmaceutical research [43].

Soudi et al. examined the antileishmanial effect of the root extract of *Echinacea purpurea* cultivated in Iran. According to their results, the root extract of this plant had an irreversible leishmanicidal effect on *Leishmania major* promastigotes in vitro and could be used with a concentration of 50 mg/mL in clinical studies [25].

Taran et al. studied the effectiveness of *Pistacia atlantica* gum topically in the treatment of cutaneous leishmaniasis in an animal model (Balb/c mice). They did not provide the dilution. Their results indicated that the gum of this tree could be used to control rural cutaneous leishmaniasis and prevent the development of the sore [44].

Grecco et al. extracted two flavonoids, sakuranetin , and naringin, from the leaves of *Bacchari sretusa* plant and tested them in vitro against the promastigotes of various *Leishmania* species [45]. In the end, the second compound acted against *Leishmania amazonensis*, *Leishmania braziliensis*, *Leishmania major*, and *Leishmania chagasi* with an IC_{50} value between 43 and 52 mg/mL, while the first compound showed no anti-parasitic activity in spite of having a chemical structural similarity [45]. There is an antioxidant component in this plant: 2, 2'-diphenyl-1-picrylhydrazyl [46].

Sawadogo et al. chose five plants from the central and western parts of Burkina Faso [19]. These plants were traditionally used to treat parasitic diseases and cancers. In previous studies, the antioxidant and antiproliferative activities of these plants have been examined. In this study, the alcoholic extract of these plants was evaluated to show their possible antileishmanial and antitrypanosomal activity. They used colorimetric and spectrophotometric methods and finally concluded that the extract of Lantana *ukambensis* had an antileishmanial activity with an IC_{50} of 9.6 mg/mL [19].

Feily et al. examined the green tea (*Camellia sinensis*) extract activity against *Leishmania major* promastigotes in vitro compared with glucantime, in which, the parasite promastigotes were exposed to 6 different concentrations of the extract [26]. The positive control group was treated with 85 mg/mL glucantime, and the control group received no medication. The green tea extract showed significant antileishmanial activity against parasite promastigotes in different concentrations, and with increasing the extract dose, the anti-parasitic effect increased, too. The average live promastigotes at a concentration of 12 mg/mL of green tea were approximately equal to the 85 mg/mL concentration of glucantime, and higher concentrations of green tea were more effective than glucantime. This study was merely done qualitatively by counting the number of parasites and the mortality rate of the parasites [26].

Ogeto et al. studied the antileishmanial activity of the extracts of *Aloe secundiflora* against Leishmania major promastigotes in vitro [47]. Among the extracts of this plant, the aqueous and methanolic extracts had the high-

est inhibitory effect on the growth of promastigotes. The IC_{50} values for the aqueous and methanolic extracts were 279.488 and 42.824 µg/mL, respectively [47].

Rodrigues et al. studied the cell-killing effects of *Croton cajucara* essential oil and one of its essential compounds, 7-hydroxy-calamenene, against *Leishmania chagasi* [48]. The minimum inhibitory concentration of parasite growth was 250 µg/mL for the essential oil and 15.6 µg/mL for the 7-hydroxy-calamenene. Transmission electron microscopy studies revealed significant nuclear and kinetoplastid changes in the promastigotes of *Leishmania chagasi*. The promastigotes and macrophages treated with essential oil had reduced by 52.8%, while the production of nitric oxide by parasite-infected macrophages had decreased by 80% [48].

Saleheen et al. studied the effect of the aqueous extract of *Allium cepa* on the promastigotes of *Leishmania major, Leishmania donovani, Leishmania tropica,* and *Leishmania mexicana* [27]. The extract concentration range tested for antileishmanial activity (0.7-10 mg/mL) was reported to be lethal for all the mentioned *Leishmania* species, while the concentration of 0.376 mg/mL killed, on average, 50% of all examined parasites after 72 hours. These researchers identified sulfur compounds in the plant, such as S-alkyl-L-cysteine sulfoxide, responsible for the antileishmanial effect [27].

In an experimental study, Shariatifar et al. examined the effects of Cassia fistula (known as the golden rain tree) on the promastigotes of leishmaniasis, causing agents in the culture medium [49]. To do this research, the fruit of Cassia fistula was obtained from the market and powdered. The aqueous extracts of the plant were prepared with different concentrations and added to the culture medium of the promastigotes, and their effects were evaluated. This extract was added at different concentrations on three *Leishmania*-inoculated culture media [49].

Counting the number of promastigotes showed that the plant extract had prevented the growth of *Leishmania major* in the culture medium at concentrations of 0.1, 0.2, 0.3 to 0.9 mg/mL, while the organism had proliferated in control culture media. In the next step, concentrations of 1, 2, 3 to 9 mg/mL were prepared and added to the culture medium. Again, no growth was observed in the media containing the plant extract at this stage. In the third stage, the concentrations of one-thousandth of the *Cassia fistula* fruit extract were studied, which revealed a small growth rate of the parasites at the concentrations of 0.001 and 0.002 mg/mL. However, no growth was seen at concentrations of 0.003 to 0.009 mg/mL.

Regarding the effect of the extract of this plant on cutaneous leishmaniasis, it was proposed that this herbal drug will be examined on laboratory mice after identifying its organic compound, and if proven to be useful, it can be used to treat cutaneous leishmaniasis in the living tissue [50].

Amanzadeh et al. studied the inhibitory effect of aqueous and alcoholic extracts of *Allium stipitatum* on the growth of *Leishmania infantum* in laboratory conditions and reported that the concentration of 0.01 to 0.1 mg/mL of this extract on the third day and the concentration of 0.2 mg/mL on the first day had inhibited the parasite's growth [50].

Sharif et al. examined the effect of methanolic extracts of tarragon (*Artemisia dracunculus*) and chamomile (*Matricaria chamomilla*) on *Leishmania major* under in vitro conditions. The mentioned extracts showed significant antileishmanial activity at different concentrations [28].

Mirzaii et al. evaluated the antileishmanial activity of Esfand or wild rue, with the scientific name of *Peganum harmala*, on the growth of promastigotes of the *Leishmania major* parasite in comparison with a trivalent antimony drug, potassium antimonyl tartrate, using MTT method in vitro. Both the extract and the antimony drug inhibited the growth of the parasite in the culture media after 72 hours. In other words, the power of both factors in controlling the growth was almost equal, so that their strength had increased by increasing the concentration. The IC_{50} values for the extract and antimycotic drug were 1832.65±89.72 µg/mL and 17.87±2.05 µg/mL, respectively. Regarding the side effects of antimony medications, the extract of this plant can be used as a drug against *Leishmania major* in laboratory conditions [4].

Ahmad et al. and Garcia et al. studied the effects of *Bidens pilosa* and pomegranate grains (*Punica granatum*) against promastigotes and amastigotes of *Leishmania amazonensis* and measured their toxicity against Balb/c mice peritoneal macrophages [51, 52]. These extracts showed considerable growth inhibitory effect against extracellular promastigotes and amastigotes. The IC_{50} values of these plants against extracellular amastigotes were calculated as 42.6 and 69.6 µg/mL, respectively. The antiparasitic activity of these plants has been reported against other parasitic agents, which is due to the presence of flavonoids (catechin and epicatechin) and epigallocatechin gallate. In

various studies, epigallocatechin gallate has been introduced as a potent antioxidant, an anti-cancer, and an anti-parasitic agent. Flavonol glycoside (quercine) is another antioxidant found in these plants [51, 52].

Barati et al. examined antileishmanial effects of the extracts of *Thymus vulgaris*, *Peganum harmala*, and *Myrtus communis* and control drug, tartar emetic, by MTT method in vitro and the results were calculated as IC_{50} for each extract. The IC_{50}s of *Thymus vulgaris, Peganum harmala,* and *Myrtus communis* extracts were obtained as 7.4 µg/mL, 7.2 µg/mL, and 5.8 µg/mL, respectively. The IC_{50} of tartar emetic was calculated to be 4.7 µg/mL. The extract of *Myrtus communis* with the lowest IC_{50} had a better effect than other extracts. All extracts showed significant antileishmanial impact [29].

Barati et al. studied the antileishmanial effects of the extracts of *Artemisia aucheri* Boiss, *Ferula assa-foetida L., Gossypium hirsutum,* and tartar emetic control drug on *Leishmania major* promastigotes by MTT method in vitro and the results were calculated as IC_{50} for each of the extracts individually. The IC_{50}s of the extracts of *Artemisia aucheri* Boiss, *Ferula assa-foetida L.*, and *Gossypium hirsutum* were estimated to be 5.9, 7.5, and 3.6 µg/mL, respectively. The IC_{50} of tartar emetic was calculated to be 4.7 µg/mL. Although the extract of *Gossypium hirsutum* showed a higher effect on the promastigotes than the other two extracts, all of these extracts had antileishmanial activity [53].

Maspi et al. sought to assess the lethal effects of alcoholic and aqueous extracts of *Calendula officinalis* on *Leishmania major* promastigotes (MRHO/IR/75/ER) under laboratory conditions [15]. They reported that the mentioned extracts killed all the parasites at a concentration of 500 µg/mL, and lower concentrations showed dose-dependent antileishmanial activity. The IC_{50} obtained from the alcoholic and aqueous extracts after 24 hours were 170 µg/mL and 215 µg/mL, respectively [15].

Asadi et al. evaluated the effect of hydroalcoholic extracts of *Hypericum perforatum* and *Mespilus germanica* on *Leishmania major* promastigotes under in vitro conditions. Different concentrations of the extracts were examined on the parasites. The results indicated that the number of promastigotes decreased with increasing the concentrations of the extracts [54].

Khademvatan et al. evaluated the cytotoxic effects of different concentrations of miltefosine on the promastigotes of *Leishmania major* and *Leishmania tropica* and observed the characteristics of programmed cell death or apoptosis [55]. They used the MTT colorimetric assay to determine the survival potential of these two parasites and reported the results as IC_{50}. Miltefosine induced death with apoptotic properties in both species, and the IC_{50} values of these two parasites were determined after 48 hours of incubation as 22 and 11 µmole, respectively.

In the same study, Khademvatan et al. assessed the possibility of inducing apoptosis by the extract of *Allium sativus* on *Leishmania major* promastigotes. They cultured the promastigotes of this parasite in the RPMI-1640 medium and treated them by different concentrations of garlic and calculated IC_{50} using the MTT method. They found that garlic had a dose-dependent cytotoxic effect, with approximately 100% death at a concentration of 93 µg/mL [55].

Shariatifar et al. examined the effect of the ethanolic extract of *Mespilus germanica* on the cutaneous leishmaniasis in the BALB/c mice. The extract could reduce the diameter of the ulcer and the number of *Leishmania major* parasites in the wound. The extract succeeded in reducing the wound diameter up to 20% in 3 mice at a concentration of 60%. At the same concentration, it had reduced the number of parasites to 66.4% in 8 mice. At 40% concentration, the number of ulcer parasites decreased by 26.7% in 4 mice and decreased by 82% in 9 mice [49].

Fani et al. studied the macrophages infected with *Leishmania major* exposed to the aqueous extract of garlic (*Allium sativum*), after incubation time and performing MTT test. They found that the garlic extract had macrophages destroyed promastigotes at a garlic dose of 37 µg/mL for 48 hours [30].

Barazesh et al. evaluated the antileishmanial activity of curcumin and its derivatives (*Curcumin, indium, Gallium curcuma*, and *Diacetyl curcumin*) against *Leishmania major* promastigotes by MTT method in vitro [56]. Curcumin is an active ingredient in plant therapy and is responsible for many biological effects of Curcuma longa. It has potent antioxidant, anti-inflammatory, and anti-cancer properties. The IC_{50} values for *Gallium curcuma*, and *Diacetyl curcumin*, and amphotericin B (control drug) were calculated as 38, 32, 26, 52, and 20 µg/mL, respectively. Having lower IC_{50}s than the *Diacetyl curcumin* analog, *Gallium curcumin* and *Curcumin idinum* were stronger agents against *Leishmania major* promastigotes [56].

Soozangar et al. studied the effects of *Achillea millefolium* on *Leishmania major* in vitro. All concentrations of this extract reduced the number of *Leishmania* parasites. They concluded that the extract of this plant could be used in further studies on *Leishmania* parasites and in developing herbal medicines [57].

Yektaian et al. designed and experimented to investigate the effect of hydroalcoholic extract of three herbs of *Achillea millefolium*, *Artemisia absinthium L.*, and walnut (*Juglans regia L.*) leaves and evaluate the synergism effect of the three mentioned extracts on *Leishmania major* parasites in vitro [58]. Based on the study objective, the extracts of all three plants were prepared at concentrations of 25 µg/mL. These concentrations were then injected into the parasite containing media in a PBS buffer solvent plus 2% DMSO and were examined and analyzed at intervals of 0, 6, 24, 48, and 72 hours in terms of the number of parasites. It was found that the extracts of plants increased the immobilization of parasites. This lack of mobility has a direct relation with time. For example, glucantime after 24 hours and amphotericin B after 30 minutes destroyed the parasites compared with the effect of plant extracts after 24 hours. The results of this study showed that the combination of the three plants' extracts has been effective on *Leishmania* parasite. However, further studies are needed to demonstrate this effect in laboratory animals and volunteer patients [59].

Naserifar et al. studied the effects of various concentrations of the aqueous extract of *Scophularia straiata* on the growth of *Leishmania* major in BALB/c mice peritoneal macrophages under in vitro conditions. The aqueous extract of this plant had a proper antileishmanial activity in eliminating this parasite in the macrophage and the culture medium. At the concentration of 25 µg/mL and on the third day, it removed the amastigotes within the macrophages, and it killed the promastigotes in the RPMI-1640 medium at the same concentration on the third day [16].

Artemisinin is one of the most prominent antileishmanial drugs. Artemisinin is a terpene lactone isolated from *Artemisia annua*, which is known as an anti-malarial and antileishmanial drug. In vitro, this drug had stopped the activity of the *Leishmania major*, strain Friedlin, changing the metabolites of various metabolic cycles, including galactose metabolism pathway, sphingolipid biosynthesis pathway as well as the biosynthesis pathways of valine, leucine, and isoleucine [60].

Yousefi et al. and Samarqandian and Borji studied the effects of *Crocus sativus* and its apoptotic activity against *Leishmania major* promastigotes in vitro. The chemical analysis of saffron extract showed that this plant contained antioxidant compounds such as anthocyanin, lycopene, flavonoids, carotenoids (crocin and crocetin), picocrocin, and safranal. The IC_{50} of saffron was 0.7 mg/mL after 48 hours of incubation, which indicated the high activity of this plant against the promastigotes of *Leishmania major* parasites [60, 61].

In an experimental study, Banyadian et al. first prepared the essential oil of the fresh plant of *Lavendula officinalis*, which was dried and powdered by the steam distillation method [31]. Then, the concentrations of 0.5%, 1.5%, 5%, 10%, 15%, and 20% of the essential oil and a concentration of 33.8% of the glucantime were separately added to the culture medium containing promastigotes of *Leishmania major* (106 parasites/mL). The number of live parasites after adding the essential oil and the drug were counted after 24, 48, and 72 hours by 10% trypan blue dye using the Neubauer chamber. The results showed that the promastigotes propagation rate significantly decreased after adding the plant essential oil compared with the control group. The lethal effect was also observed at a concentration of 10% and higher so that no alive parasites were seen in the groups after 72 hours. The results of this study indicated the inhibitory growth effect and the lethal impact of essential oil of lavender plant in laboratory conditions on the promastigote form of *Leishmania major*. Therefore, further studies are recommended to discover the antileishmanial effect of this plant on the amastigote form of the parasite .

Gharirvand-Eskandari and Doudi evaluated and analyzed the antileishmanial effects of the extract and essential oil of *Medicago lupulina* leaves on *Leishmania major* promastigotes (clinical isolate) by MTT method and reported that the IC_{50} of glucantime was equal to 19 µg/mL after 48 hours. The IC_{50} values for alcoholic extract and essential oil of this plant after 48 hours were equal to 130 and 340 µg/mL, respectively [62].

In another study, Gharirvand-Eskandari and Doudi examined the antileishmanial effect of alcoholic extract of *Medicago lupulina* leaves on the promastigotes of Leishmania major, the standard strain (MRHO/IR/75/ER) in vitro and obtained its IC_{50} after 48 hours as 98 µg/mL. The IC_{50} for glucantime was obtained 12 µg/mL in this study after 48 hours [62].

The results of Shahanipoor et al revealed that the glucose oxidase enzyme, together with ethanolic extract of propolis, not only had antimicrobial activity against gram-positive and gram-negative bacteria isolated from

cutaneous leishmaniasis ulcers but also managed to heal the wounds [63].

The results of Eskandari et al. research in 2016 suggested that the extract of *Portulaca oleracea L.* was effective on the promastigotes of *Leishmania major* (clinical isolates). Using the MTT standard method, the IC_{50}s for the alcoholic extract and essential oil of the plant leaves were obtained as 360 and 680 µg/mL, respectively, after 48 hours, while these values for glucantime were respectively 12 and 19 µg/mL after 48 hours [64].

The results of Shirazi and Doudi research demonstrated that applying the alcoholic extract of *Crataegus microphylla* leaves on the promastigotes of *Leishmania major* parasite (MRHO/IR/75/ER) by MTT method provided the glucantime IC_{50} value of 18.616 µg/mL, while the IC_{50} for alcoholic extract was obtained as 1094 µg/mL. Meanwhile, the results of the alcoholic extract of *Cichorium intybus* leaves revealed an IC_{50} of 1094 µg/mL [65].

The results of Albakhit et al. research showed that the IC_{50} of glucantime on the promastigotes of *Leishmania major* was equal to 21.96 µg/mL, while the IC_{50}s of methanolic extracts of the kernel and date fruit of *Phoenix dactylifera L.* were respectively 23 µg/mL and 500 µg/mL. Also, the IC_{50}s for the alcoholic and aqueous extracts of *Ziziphus spina-christi* were obtained as 60 and 80 µg/mL, respectively. Although glucantime was more effective than the extracts of the plants mentioned above, all extracts had significant effects on the promastigotes of *Leishmania major* [66].

Maroufi et al. investigated the effect of Juice (*Crataegus aronia*) on *Leishmania major* in vitro. The exposure was limited to 24, 48, and 72 hours by arranging (0/5-60 µg/mL), (20/94-20/11 µg/mL) and (55/14-35/19 µg mL) [67].

Conclusion

Medicinal plants have been the focus of attention since ancient times. The chemical drugs have many clinical complications, so medicinal plants can be considered as an alternative to synthetic drugs.

Ethical Considerations

Compliance with ethical guidelines

The study was reviewed by the Research Committee of Islamic Azad University of Falavarjan.

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Authors' contributions

Conceptualization and writing-original draft preparation: Monir Doudi; Data curation and validation: Elham Gharirvand Eskandari; Data analysis: Mahbubeh Setork; Visualization, supervision, project administration: All authors.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Mohseni N, Sajjadi SE, Eskandarian AA, Yousefi HA, Mansurian M, Shokoohinia Y, et al. [Natural anti leishmaniasis compounds in traditional Iranian medicine (Persian)]. J Islam Iran Tradit Med. 2012; 3(1):41-50.

[2] Lamidi M, Digiorgio C, Delmas F, Favel A, Eyele Mve-Mba C. In vitro products with antileishmanial activity. Phytomedicine. 2005; 12(6):514-35.

[3] Mosaddegh M, Naghibi F, Sadr M. [Leishmaniosis in Iranian traditional medicine (Persian)]. J Islam Iran Tradit Med. 2010; 1(1):59-61.

[4] Dutta A, Mandel G, Mandal C, Chatterjee M. In vitro antileishmanial activity of Aloe vera leaf exudates: A potential herbal therapy in leishmaniasis. Glycoconj J. 2007; 24(1):81-6. [DOI:10.1007/s10719-006-9014-z] [PMID]

[5] Verma NK, Dey CS. Possible mechanism of miltefosine-mediated death of Leishmania donovani. Antimicrob Agents Chemother. 2004; 48(8):3010-5. [DOI:10.1128/AAC.48.8.3010-3015.2004] [PMID] [PMCID]

[6] Taheri S, Vakili Z, Saffari M. [Effect of different types of blood on the growth of cutaneus leishmaniasis agent in vitro (Persian)]. J Shahid Sadoughi Uni Med Sci. 2007; 14(4):69-75.

[7] Chan-Bacab MJ, Pena-Rodriguez LM. Plant natural products with leishmanicidal activity. Nat Prod Rep. 2001; 18(6):674-88. [DOI:10.1039/b100455g] [PMID]

[8] UI Bari A. Chronology of Cutaneous leishmaniasis: An overview of the history of the disease. J Pak Assoc Dermatol. 2006; 16:24-7.

[9] Ramezani Y, Mousavi GA, Bahrami A, Fereydooni M, Parsa N, Kazemi B. [Epidemiological study of cutaneous leishmaniasis in Aran and Bidgol city from April to September 2009 (Persian)]. J Kashan Univ Med Sci. 2011; 15(3):254-8.

[10] Hashemi N, Hashemi M, Eslami G, Shirani-Bidabadi L, Hejazi H. [Detection of leishmania parasites from cutaneous leishmaniasis patients with negative direct microscopy using NNN and PCR-RFLP (Persian)]. J Isfahan Med Sch. 2012; 29(169):2613-9.

[11] Karami M, Doudi M, Setorki M. Assessing epidemiology of cutaneous leishmaniasis in Isfahan, Iran. J Vector Borne Dis. 2013; 50:30-7.

[12] Postigo JA. Leishmaniasis in the world health organization eastern mediterranean region. Int J Antimicrob Agents. 2010; 36(1):62-5. [DOI:10.1016/j.ijantimicag.2010.06.023] [PMID]

[13] WHO. Control of the leishmaniases. Report of a meeting of the WHO expert committee on the control of leishmaniases. Geneva: 2010; 949:22-6.

[14] Doudi M, Setorki M, Shirani-Bidabadi L. Genotyping of isolated cutaneous Leishmaniasis species by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis in endemic foci of Isfahan, Iran. Afr J Microbiol Res. 2011; 5(26):4607-14. [DOI:10.5897/AJMR11.702]

[15] Maspi N, Ghafarifar F, Bahrami AM, Bastaminezhad S, Shamsi M. Evaluation of leishmanicidal effect of watery & ethanolic flowers calendula officinalis extract on promastigotes of leishmania major (MRHO/IR/75/ER) in vitro. Sci J of Ilam Univ Med Sci. 2010; 18(1):28-33.

[16] Naserifard R, Dalimi Asl A, Ahmadi N. [Influence of aqueous extract Scophularia straiata on growth of Leishmania major in mice peritoneal macrophages (BALB /c) (Persian)]. Res Med. 2013; 36(5):12-8.

[17] Ben Salah A, Zakroui H, Zaatour AA, Ftaiti A, Zaafouri B, Garraoui A, et al. Randomized placebo controlled trial in Tunisia treating cutaneous leishmaniosis with paromycine ointment. AM J Trop Med Hyg. 1995; 55(2):162-6. [DOI:10.4269/ajtmh.1995.53.162] [PMID]

[18] World Health Organization, February. Report of the workshop of chemotherapy of old world cutaneous leishmaniasis.TDR/Leish/Cl-jer/73.3. Geneva, Switzerland: World Health Organization, February; 1983.

[19] Sawadogo WR, Le douaron G, Maciuk A, Bories C, Loiseau PM, Figadere B, et al. In vitro antileishmanial and antitrypanosomal activities of medicinal plants from Burkina Faso. Parasitolo Res. 2012; 110(5):1779-83. [DOI:10.1007/s00436-011-2699-3] [PMID]

[20] Berman JD. Chemotherapy for leishmaniasis biochemical mechanism clinical efficacy and future strategies. Rev Infect Dis. 1988; 10:560-86. [DOI:10.1093/clinids/10.3.560] [PMID]

[21] Chultav JD, Spencer HC, Mugambi M. Electerocardiographic changes during tredtment of leishmaniasis with pentavalent antimony (sodium stibogluconate). Am J Trop Med Hyg. 1985; 34(4):702-9. [DOI:10.4269/ajtmh.1985.34.702] [PMID]

[22] Berman JD, Badaro R, Thakur CP, Wasunna KM, Behbehani K, Davidson R. Efficacy and safety of liposomal amphotericin B for visceral leishmaniosis in endemic developing countries. Bull World Health Organ. 1998; 76(1):25-32.

[23] Martino LD, Daviason RN, Giaccbino R, Scotti S, Ramandi F. Treatment of visceral leishmaniasis in children with liposomal amphotericin B. J Pediate .1997 ;131(3):271-7. [DOI:10.1016/S0022-3476(97)70165-3]

[24] Calonge M, Johnson R, Balaña-Fouce R, Ordóñez D. Effect of cationic diamidines on polyamine content and uptake on Leishmania infantum in vitro cultures. Biochem Pharmacol. 1996; 52(6):835-41. [DOI:10.1016/0006-2952(96)00348-6]

[25] Soudi S, Hashemi SM, Zavaran-Hosseini A, Ghaemi A, Asghari-Jafarabadi M. Antileishmanial effect of echinacea purpurea root extract cultivated in Iran. Iran J Pharm Res. 2006; 6(2):147-9.

[26] Feily A, Saki J, Maraghi S, Moosavi Z, Khademvatan S, Siahpoosh A. In vitro activity of green tea against Leishmania major promastigotes. Int J Clin Farmacol Ther. 2012; 50(3):233-6. [DOI:10.5414/CP201571] [PMID]

[27] Saleheen D, Ali SA, Yasinzai MM. Antileishmanial activity of aqueous onion extract in vitro. Fitoterapia, 2004; 75(1):9-13. [DOI:10.1016/j.fitote.2003.07.010] [PMID]

[28] Sharif M, Ziaei H, Azadbakht M, Daryani A, Ebadattalab A, Rostami M. Effect of methanolic extracts of Artemisia aucheri and Camellia sinensis on Leishmania major (in vitro). Turk J Med Sci. 2006; 36(6):365-9.

[29] Barati M, Sharifi I, Sharififar F. [In vitro evaluation of anti-Leishmanial activities of zataria multiflora boiss, peganum harmala and myrtus communis by colorimetric assay (Persian)]. J Kerman Univ Med Sci. 2010; 17(1):32-41.

[30] Fani F, Gharavi M, Nobakht M, Bakhshayesh M, Khadem-Vatan S. [The Role of aqueous garlic extract (allium sativum) on interleukin 10 and 12 in leishmania infected macrophages (Persian)]. Qom Univ Med Sci J. 2011; 5(1):83-9.

[31] Bonyadian M, Hejazi H, Azizi H, Habibian S, Sayahi E. Antileishmania activity of Levandula officinalis essence against Leishmania major in in vitro media. J Shahrekord Univ Med Sci. 2015; 17(3):93-101.

[32] Gharirvand-Eskandai E, Doudi M, Abedi S. The study of antileishmanial effect of Medicago lupulina laves alcoholic extract on Leishmania major (MRHO/IR/75/ER) by MTT assay. Int Res J Appl Basic Sci. 2016; 10(1):59-65.

[33] Nilforoushzadeh MA, Hejazi H, Zarkoob H, Bidabadi LS, Asghari, GR, Hosseini M, et al. [Evaluation of effectivness of Nigella sativa extracts and topical honey application versus topical honey alone along with intralesional injection of Glucantime in the treatment of acute Cutaneous leishmaniasis (Persian)]. Dermatol Cosmet. 2010; 1(2):52-9.

[34] Torres-Santos EC, Moreira DL, Kaplan MA, Meirelles MN, Rossi-Bergmann B. Selective effect of 2′,6′-dihydroxy-4′-methoxychalcone isolated from Piper aduncum on Leishmania amazonensis. Antimicrob Agents Chemother. 1999; 43(5):1234-41. [DOI:10.1128/AAC.43.5.1234]

[35] Rana Virendra S. Chemical composition of the essential oil of cuminum cyminum L. seeds from western India. J Med Plants By-products. 2014; 3(2):207-10.

[36] Elasaed M. Cuminaldehyde: A potential drug candidate. J of Pharmacol & Clin Res. 2017; 2(2):001-004. [DOI:10.19080/JPCR.2017.02.555585]

[37] Tabeshpour J, Imenshahidi M, Hosseinzadeh H. A review of effects of Berberis vulgaris and its major component, berberine, in metabolic syndrome. Iran J Basic Med Sci. 2017; 20(5):551-68.

[38] Kuo Ping-Chung, Li Yue-Chiun, Wu Tian-Shung. Chemical constituents and pharmacology of aristolochia species. J Tradit Complement Med. 2012; 2(4):249-66. [DOI:10.1016/S2225-4110(16)30111-0]

[39] Kovaleva KS, Zubkov FL, Bormotov NI, Novikov RA, Dorovatovskii PV, Khrustalev VN, et al. Synthesis of D-(+)-camphor based N-Acylhydrazones and their antiviral activity. The Royal Society of Chemistry. 2013; 00:1-3.

[40] Guo Sh, Geng Zh, Zhang W, Liang T, Wang Ch, Deng Zh, et al. The chemical of essential oils from cinnamomum camphora and their insecticidal activity against stored product pets. Int J Mol Sci. 2016; 17(11):1-9. [DOI:10.3390/ijms17111836] [PMID] [PMCID]

[41] Fukuzumi Sh, Yamada Y, Karlin KD. Hydrogen peroxide as a sustainable energy carrier: Electrocatalytic production of hydrogen peroxide and the fuel cell. Electrochim Acta. 2012; 82:493-511. [DOI:10.1016/j.electacta.2012.03.132] [PMID] [PMCID]

[42] Al-Harrasi A, Rehman NU, Khan AL, Al-Broumi M, Al-Amri I, Hussain J, et al. Chemical, molecular and structural studies of Boswellia species: β-Boswellic Aldehyde and 3-epi-11β-Dihydroxy BA as precursors in biosynthesis of boswellic acids. PLoS One. 2018; 13(6):e0198666. [DOI:10.1371/journal.pone.0198666] [PMID] [PMCID]

[43] Hojjati M, Barzegar H. Chemical composition and biological activities of lemon leef. Nutr Food Sci Res. 2017; 4(4):15-24. [DOI:10.29252/nfsr.4.4.3]

[44] Taran M, Mohebali M, Esmaeli J. In vivo efficacy of gum obtained pistacia atlantica in experimental treatment of cutaneous leishmaniasis. Iran J Public Health. 2010; 39(1):36-41.

[45] Grecco Sdos S, Reimão JQ, Tempone AG, Sartorelli P, Cunha RL, Romoff P, et al. In vitro antileishmanial and antitrypanosomal activities of flavanones from Baccharis retusa DC. (Asteraceae). Exp Parasitol. 2012; 130(2):141-5. [DOI:10.1016/j.exppara.2011.11.002] [PMID]

[46] Rezaie M, Farhoosh R, Sharif A, Asili J, Iranshahi M. Chemical composition, antioxidant and antibacterial properties of Bene (Pistacia atlantica subsp. mutica) hull essential oil. J Food Sci Technol. 2015: 52(10):6784-90. [DOI:10.1007/s13197-015-1789-0] [PMID] [PMCID]

[47] Ogeto TK, Odhiambo RA, Shivairo RS, Muleke CI, Osero BO, Anjili C, et al. Antileishmanial activity of Aloe secandiflora plant extracts against Leishmnia major. Adv Life Sci and Technol. 2013; 13:2224-7181.

[48] Rodrigues IA, Azevedo MMB, Chaves FCM, Bizzo HR, Corte-Real S, Alviano DS, et al. In vitro cytocidal effects of the essential oil from Croton cajucara (red sacaca) and its major constituent 7-hydroxycalamenen against Leishmania chagasi. BMC Complement Altern Med. 2013; 13:249. [DOI:10.1186/1472-6882-13-249] [PMID] [PMCID]

[49] Shariatifar N, Rahimnia R, Jamshidi AM, Pirali Hamedani M, Shoeibi Sh. Effect of ethanolic extract of mespilus germanica on cutaneous leishmaniasis in BALB/c Mice. J Med Plants. 2011; 10(39):76-81.

[50] Amanzadeh Y, Izaddoost M, Soltanpoor A, Mahami-Oskouei M, Taheri M, Kalantari M, et al . [Inhibit effect of allium hirtifolium boiss. (Persian shallot) hydroalcoholic extract on the growth of leishmania infantum in vitro (Persian)]. J Med Plants. 2006; 4(20):48-52.

[51] Ahmad I, Zahin M, Aqil F, Hasan S, Khan MSA, Owais M. Bioactive compounds from Punica granatum, Curcuma longa and Zingiber officinale and their therapeutic potential. J Drugs Future. 2008; 33(4):329-39. [DOI:10.1358/dof.2008.033.04.1186159]

[52] Garcia M, Monzote L, Scull R, Herrera P. Activity of Cuban Plants Extracts against Leishmania amazonensis. ISRN Pharmacol. 2012; 2012:104540. [DOI:10.5402/2012/104540] [PMID] [PMCID]

[53] Barati M, Sharifi I, Sharififar F. [Antileishmanial activity of Artemisia aucheri, Ferula asa-foetid and Gossypium hirsutum extracts on Leishmania major promastigotes in vitro (Persian)]. J Kerman Univ Med Sci. 2010; 8(3):166-72.

[54] Asadi M, Bahrami S, Ansari-Samani R, Pakniat N. Effect of hydroalcoholic extracts of Stachys lavandulifolia Vahl and Mespilus germanica leaves on Leishmania major. Hormozgan Med. 2012; 15(4):e88498.

[55] Khademvatan SH, Gharavi MJ, Rahim F. MilteFosine induced apoptotic cell death on Leishmania major and L.Tropica strains. Korean J Parasitol. 2011; 49(1):17-23. [DOI:10.3347/kjp.2011.49.1.17] [PMID] [PMCID]

[56] Barazesh A, Fouladvand M, Farrokhzad F. Evaluation of in vitro anti-leishmanial activities of curcumin and its derivatives "Gallium curcumin, indium curcumin and diacetyle curcumin". Eur Rev Med Pharmacol Sci. 2013; 17(24):3306-8. [DOI:10.1016/j.ijid.2012.05.343]

[57] Sozangar N, Jeddi F, Reaghi S, Khorrami S, Arzemani K. [Abulkhalsa and Yarrow plant effect on Leishmania major in vitro (Persian)]. J N Khorasan Uni Med Sci. 2012; 4(3):329-33. [DOI:10.29252/jnkums.4.3.329]

[58] Yektaeian N, Rafeian M, Khalili-Dehkordi B, Hejazi SH, Shirani-Bidabadi L, Hosseini SA. [Effect of combination of achillea millefolium, artemisia absinthium & juglans regia leaves extracts on leishmania major (MRHO/IR/75/ER), in vitro (Persian)]. J Med Plants. 2012; 2(42):197-204.

[59] BeigiBoroujeni M, Arjmand M, Khalili G, Akbari Z, Najafi A, BeigiBoroujeni N, et all. [The metabonomic changes of Lishmania major, spromastigotes (fredlin strain) after in vitro artemisinin treatment at stationary phase (Persian)]. Koomesh 2014; 16(1):90-6.

[60] Yousefi E, Eskandari A, Gharavi MJ, Khademvatan Sh. In vitro activity and cytotoxicity of Crocus sativus extract against Leihmania major (MRHO/IR/75/ER). Infect Disord Drug Targets. 2014; 14(1):56-60. [DOI:10.2174/1871526514666140827101901] [PMID]

[61] Samarghandian S, Borji A. Anticarcinogenic effect of saffron (Crocus sativus L.) and its ingredients. Pharmacognosy Res. 2014; 6(2):99-107. [DOI:10.4103/0974-8490.128963] [PMID] [PMCID]

[62] Gharirvand-Eskandari E, Doudi M. [Antileishmanial effect of alcoholic extract and essential oils of medicinal plant leaf black alfalfa (Medicago lupulina), native to frieden of Isfahan, the number of clinical isolates of Leishmania major

promastigotes in vitro by mtt assay (Persian)]. J Shahid Sadoughi Univ Med Sci. 2016; 24(3):221-31.

[63] Shahanipoor K, Firoozi S, Doudi M, Naghavi NS, Setorki M. The effect of ethanolic extract of propolis and glucose oxidase on secondary infections of coutaneous leishmaniasis. Afr J Microbiol Res. 2012; 6(41):6884-7. [DOI:10.5897/AJMR11.1601]

[64] Eskandari EG, Doudi M, Abedi S. An in vitro study of antileishmanial effect of Portulaca oleracea extract. J Vector Borne Dis. 2016; 53(4):362-9.

[65] Shirazi S, Doudi M. Antileishmanial effect of Crataegus microphylla leaf extract on L. major (MRHO/IR/75/ER) promastigoes. Int J Mol Clin Microbiol. 2017; 7(1):761-8.

[66] Albakhit S, Khademvatan SH, Doudi M, Forutan-Rad M. Antileishmanial activity of date (phoenix dactylifera l) fruit pit extract in vitro. J Evid Based Complement Altern Med. 2016; 21(4):NP98-NP102. [DOI:10.1177/2156587216651031] [PMID]

[67] Maroufi Y, Dabirzadeh M,Hossein-pour-Mousavi SH. [Effect of methanolic extract of hawthorn (Crataegus aronia) ftuit on Leishmania major in vitro (Persian)]. J Kashan Uni Med Sci. 2016; 20(1):11-5.

[68] Manayi A, Vazirian M, Saeidnia S. Echinacea purpurea: Pharmacology, phytochemistry, and analysis methods. Pharmacogn Rev. 2015; 9(17):63-72. [DOI:10.4103/0973-7847.156353] [PMID] [PMCID]

[69] Abbas S. Epigallocatechin gallat (EGCG) from green tea (Camellia sinensis) increase life spam and stress resistance in Caenorhabditis. Planta Med. 2009; 75(3):216-21. [DOI:10.1055/s-0028-1088378] [PMID]

[70] Ajay KK, Satish S, Ibrahhim S, Karunakara H. Therapeutic Uses of Cassio fistula: Revioew. Int J Pharma Chem Res. 2017; 3(1):38-42.

[71] Sadoughi S, Zafar-Balanejad S, Baharara J, Nejhad Shahrokhabadi K, Sepehri-Moghadam H, Rahbarian R. [Effect of shoots of Allium sativum L. frula assa-foetida Aqueous Extract and Low Frequency Electromagnetic Field on Angiogenesis in Chick Chorioallantonic Membrane (in vivo) (Persian)]. J Med Plants. 2015; 4(56):149-60.

[72] Verma PK, Raina R, Agarwal S, Kour H. Phytochemical ingredients and Pharmacological Potential of Calendula officinalis Linn. Pharm Biomed Res. 2018: 4(2):1-17. [DOI:10.18502/pbr.v4i2.214]

[73] Borazjani R, Aminnia Sh, Rastegarian M, Hosseini M, Ghanbarianasab Z, Ashkani-Esfahani S, et al. Effects of hydroalcoholic extract of arnebia euchroma on the treatment of cutaneous leishmaniasis. J Clin Diagn Res. 2018; 12(8):21-3. [DOI:10.7860/JCDR/2018/35856.11906]

[74] Ozkan G, Ali-Koyuncu M. Physical and chemical composition of some walnut (Juglans regia L.) genotypes grown in Turkey. Grusas Y Aceites. 2005; 58(2):141-7. [DOI:10.3989/gya.2005.v56.i2.122]

[75] Amiri H, Lari-Yazdi H, Esmaeili A, Sasamnia F, Eghbali D, Viskarami Gh, et al. Essential oil composition and anatomical study of scrophularia striata boiss. Iran J Med Aromatics Plant. 2011; 27(2):271-8.

[76] Srivastava R, Ahmed H, Dixit RK, Dharamveer, Saraf SA. Crocus sativus L.: A comprehensive review. Pharmacogn Rev. 2010; 4(8):200-8. [DOI:10.4103/0973-7847.70919] [PMID] [PMCID]

[77] Afsharypour S, Azarbayejany N. Chemical constituents of the flower essential oil of lavendula officinalis chaix. Iran J Pharm Sci. 2006; 2(3):169-72.

[78] Nehdi IA, Sbihi HM, Tan CP, Rashid U, Al-Resayes SI. Chemical composition of palm (Phoenix doctylifera L.) Seed Oil from Six Saudi Arabian Cultivvars. J Food Sci. 2018; 83(3):624-30. [DOI:10.1111/1750-3841.14033] [PMID]

[79] Basta A, Tzakou O, Couladis M, Pavlovic M. Chemical composition of artemisia absinthium L. from Greec. J Essent Oil Res. 2007; 19(4):316-8. [DOI:10.1080/10412905.2007.9699291]

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