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Review

Medicinal plants with promising antileishmanial activity in Iran: a systematic review and meta-analysis

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HIGHLIGHTS

- We systematically reviewed all published papers regarding herbal medicine with antileishmanial activity in Iran among nine databases from 1999 to April 2015.
- Overall 68 articles including 140 in vitro and 48 in vivo, met our eligibility criteria. Also, 98 types of plants were examined against three genera of *Leishmania spp.*
- Our study shows, the most Iranian plants with anti-leishmanial activity were Artemisia species, Allium sativum, Achilleamille folium, Peganum harmala and Thymus vulgaris.

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ABSTRACT

Background: Leishmaniasis is a major public health problem worldwide. The aim of the present study was to investigate medicinal plants with anti-*Leishmania* activity which used in Iran.
Methods: Data were systematically gathered from five English databases including Ebsco, Science Direct, PubMed, Google Scholar and Scopus, four Persian databases including Magiran, Iran doc, Iran medex and the Scientific Information Database (SID) from 1999 to April 2015. Information obtained included plant family, extraction method, concentrations of extracts, animal models and parasite strains.
Results: A total of 68 articles including 188 experiments (140 in vitro and 48 in vivo) between 1999 and 2015, met our eligibility criteria. Thoroughly, 98 types of plants were examined against three genera of *Leishmania* spp. For the heterogeneity study conducted, it was showed that there was a great deal of variation among studies. Based on random effect, meta-analysis pooled mean of IC50 was obtained 456.64 (95% CI: 396.15, 517.12).
Conclusion: The most Iranian plants used as anti-leishmanial activity were *Artemisia species*, *Allium sativum*, *Achilleamille folium*, *Peganum harmala* and *Thymus vulgaris*. The present systematic and meta-analysis review provide valuable information about natural products with anti-*Leishmania* activity, which would be examined in the future experimental and clinical trials and herbal combination therapy.

Contents

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1. Introduction

Leishmaniasis is a parasitic disease caused by an obligate intracellular parasite of genus *Leishmania,* which is transmitted to human by the bite of a female sand fly [1]. The disease has wide clinical spectrums from self-limiting cutaneous to fatal visceral form which depends on both host immune response and the species of *Leishmania* parasite. The World Health Organization (WHO) emphasizes on leishmaniasis as one of the seven important infections [2]. Approximately, 350 million people in 98 countries are at the risk of infection. It is estimated that 12 million people are affected with the disease and about 1.5 million new cases of cutaneous leishmaniasis (CL) are reported annually. Approximately, 90% of the CL cases occur in eight countries of Afghanistan, Saudi Arabia, Syria, Iran, Algeria, Iraq, Brazil and Peru [3,4]. Pentavalent antimony is conventionally used from 1959 for leishmaniasis but it is toxic with side effects, which requires prolong injections. The efficacy of pentavalents has been decreased and the emergence of resistance limits their usage [5,6]. The first line drugs in leishmaniasis including meglumine antimoniate (Glucantime), pentamidine (Pentacarinat), and sodium stibogluconate (Pentostam) are not effective orally and require prolonged injections. The second line drugs such as amphotricine B and pentamidine are very toxic [5]. In the absence of an effective vaccine, there is an urgent need for new and more effective drugs to replace or supplement those in current use. Plant derivatives or plant extracts are likely to provide a valuable source of new medicinal agents. The urgent need for substituting treatments has led to a program for screening natural products in leishmaniasis. Actually, the WHO recommended the use of traditional medicine in societies with poor health services. Moreover, the data obtained from reviewing would lead to the emergence of natural products with anti-leishmanial activity and would be the way for the production of new effective synthetic compounds. It has been estimated that there are about 250,000 medicinal plant species in the world. Nevertheless, the biological activities of only about 6% of them have been evaluated. Besides, only around less than 1% of medicinal plant compounds have been assessed in clinical trials [6,7].

About 35% of approved drugs belong to natural products or semi synthetic derivatives, while 30% are synthetic molecules based on natural products or pharmacophore developed from natural compounds. It is noteworthy, out of 15 antiparasitic medications that have been approved by health authorities between January 1981 and June 2006, 65% are natural products or derivatives [8].

Medicinal plants are an effective source of pharmaceutical products in Iran [9,10]. A critical evaluation of the clinical data due to the adverse effects has shown that herbal medicine is generally accepted better than synthetic medications. However, potentially, serious adverse events including herbal drug interactions have been described. This suggests the need to be attentive when using herbal therapies, mainly in specific situations such as throughout pregnancy and in the children age group [11]. About 820 forms of herbal drugs are produced in Iran [12,13]. However, in different cultures and countries, indigenous medicinal plants are used to treat parasitic diseases such as leishmaniasis. Hence, clinical trials and empirical studies have been carried out about medicinal plants in different parts of the world especially in Asian countries including Iran [9,14]. Our study attempts to provide an overview on the native medicinal plants, which was investigated against *Leishmania* parasite in Iran.

2. Methods

2.1. Search method

An exclusive search was performed through all scientific databases from April 1999 to August 2015 including five English databases (Science Direct, Scopus, Ebsco, Pub Med and Google Scholar), four Persian databases (Iran medex, Magiran, Iran doc) and the Scientific Information Database (SID). All articles which related to the medicinal plants and leishmaniasis were chosen (Fig. 1). Additionally, reference lists of all articles were reviewed for prevention of missing relevant data. The search terms were: " *Leishmania,*" "plant extract," "herbal extract," "medicinal plants," "traditional medicine," and " herbal medicine" alone or in combination together. Furthermore, the synonyms of herbal medicines were considered as follow: herbal preparations, herbal medications, herbal products, herbal remedies, medicinal herbs and phytopharmaceuticals. Other relevant topics such as *Leishmania* parasite were also reviewed and included if the appropriate outcomes were retrieved. The search was performed both in English and Persian languages.

2.2. Paper selection

Papers selected for inclusion were studied carefully; repetitive papers, studies out of Iran and papers with poor methodology were excluded. (See Fig. 1). The following information was extracted: the year of publication, the first author, parasite species, herbal plant, type of extract, part of plant used for extraction, concentrations, exposure time, animal models, diameter of lesions and outcomes. Two reviewers independently screened studies identified for inclusion and determined study eligibility (Kapp index showed an agreement 89% between two reviewers). Disagreements were

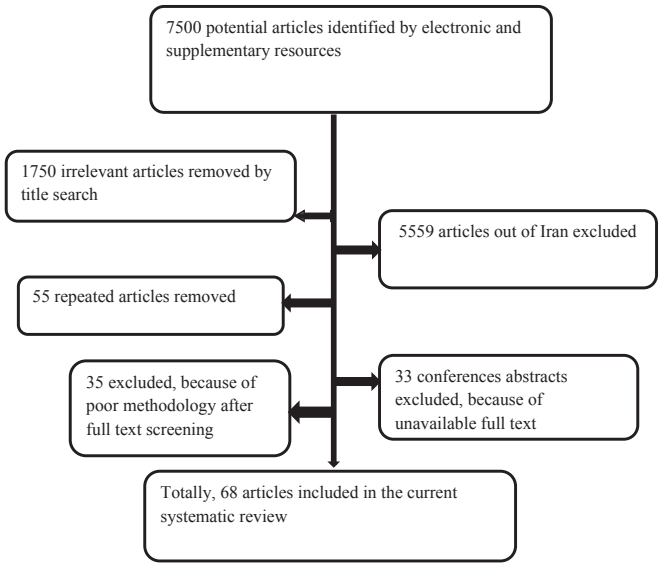

Figure 1. Flowchart describing the study design process.

resolved by the third opinion.

2.3. Statistical analysis

In this meta-analysis, the mean and 95% confidence intervals of the half-maximal inhibitory concentration (IC50) values were calculated for each individual study in order to estimate the pooled mean of herbal extract effect on *Leishmania* spp. in Iran. The results were reported using a random-effect model with 95% confidence interval (CI). Heterogeneity among studies was evaluated by the Q-Cochran test ($p < 0.1$ indicate heterogeneity) and I-square statistic [low (25%–49%), moderate (50%–74%) and high (≥75%) [12]. Subgroup analysis was performed to investigate potential sources of heterogeneity [14]. Publication bias was evaluated using the funnel plots and Egger test [15]. Statistical software Stata 11 (Stata Corp, College Station, TX, USA) was used to data analysis.

3. Results

Out of 7500 articles of literature searched from 1999 to 2015, 68 articles with 188 experiments (140 in vitro and 48 in vivo), met our eligibility criteria and included the current systematic review and meta-analysis. Unpublished data, duplicated papers, congresses proceeding abstracts were excluded from our systematic review and meta-analysis. Totally, data extracted comprised of 98 types of plants, their families, extraction methods, animal models IC50 and *Leishmania* species. In the in vitro studies, all of plant extracts were tested on three genera of Iranian strains of *Leishmania* spp including *L. tropica, L. major* and *L. infantom*. In the in vivo studies, most of *L. major* strains were including (MHOM/64/IR/ER75), (MRHO/IR/75/ER), (MRHO/SU/59/P), (MRHO/IR/76/ER) and also most *L. tropica* strains were (MHOM/IR/2002/Mash2) and (MHOM/TN/80/IPI1), which were maintained in Balb/c mice and human. Therefore, we attempt to summarize a list of various studies in the list of herbs and natural products with antileishmanial activity (Tables 1 and 2). Briefly, most leishmanicidal agents studied from natural sources in Iran were *Artemisia species, Allium sativum, Achillea millefolium* (Yarrow), *Peganum harmala* and *Thymus vulgaris*. Heterogeneity test was conducted and Q statistic was very large ($Q = 1945$, $df = 61$, I-square = 100%, $p < 0.001$), showing that there was a great variation among studies. Based on random effect model, the pooled mean of IC 50 was obtained 456.64 (95% CI: 396.15, 517.12). Begg's test showed that there was no publication bias among all studies ($t = 1.25$, $p = 0.215$). Subgroup meta-analysis of characters such as stem bark, preparation, family and botanical name was carried out. The results showed that IC50 was significantly different among the parts used (or stem bark) ($p < 0.001$) and the "Aerial" and "Leaves or twigs" parts were most parts used. Also subgroup analysis revealed that there was a significant difference in preparing characters including: hexane, dichloromethane, hydroalcoholic, ethyl acetate with higher IC50 values and aqueous or methanolic with lower IC50 values ($p < 0.001$) (Table 3). The IC50 values for *Allium* spp, *Alkanna* spp and *Artemisia* spp showed the significant difference ($p < 0.001$), so that it could be with the highest value for *Allium* spp. For details on the models or mechanism-based bioassays utilized for selecting crude plant extracts, fractions and pure compounds against the *Leishmania* parasite, the original references should be consulted (Fig. 2).

4. Discussion

Leishmaniasis is an important parasitic disease all around the world. For reducing the resistance in endemic areas, alternative strategies including the use of herbal plants are considered [84,85]. The present study showed a wide range of plant extracts with antileishmanial properties in vitro and in vivo experiments. Among all medicinal plants, the genus *Artemisia* (Astraceae) is a large, heterogeneous, and widely dispersed genus all over the world. These species are small shrubs biennial and perennial or annual herbs. The genus *Artemisia* has 30 species in Iran out of which two are endemic [86]. *Artemisia* plants contain chemical components such as sesquiterpenes, monoterpenes lactones, flavonoides, coumarins, sterols and polyacetylenes [86]. *Artemisis species* has cytotoxic and anti-inflammatory activity [86-88]. The results of a study carried out by Niloofarzadeh et al. (2008), showed that hydroalcoholic extracts of propolis *Thymus vulgaris* and *Achillea millefolium* were significantly more effective than systemic glucantime or alcoholic extract for the treatment of dermal leishmaniasis in Balb/c mice. The highest efficacy was observed for propolis, followed by *Achillea millefolium* and then *Thymus vulgaris* [65]. The efficacy of ethanol extract of the root leaves and stem of *Berberis vulgaris* were topically used on experimental dermal lesions of Balb/c mice. The result after two weeks statistically revealed a significant reduction of ulcer size in mice [89]. Doroodgar et al. (2008) reported the effect of various concentrations of *Artemisia* essence in Balb/c mice. They showed that cutaneous lesions in mice inoculated by *L. major* were enlarged after the application of higher concentration of the *Artemisia* essence. As a result, the lesions did not heal, and their size increased. In addition, parasitologic examination also remained positive [67]. The result showed that the size of lesion in mice received 40, 60, and 80% of *Rubia. tinctorum* extracts revealed no significant difference in comparison with the lesion size in control group [66]. *Seidlitzia rosmarinus (S. rosmarinus)* has been traditionally used in Mashhad and its suburbs for the treatment of CL. Despite little available data about the possible efficacy of this plant against leishmaniasis, the efficacy of herbal extracts of *S. rosmarinus* against cutaneous leishmaniasis in Balb/c mice was examined in this study. The natives in Khorasan Province used pure dried leaves' powder of *S rosmarinus* leaves on their cutaneous lesions. Therefore, alcoholic extract of stem and leaves, which is almost similar to the pure powder, was used in this study. In this study, Eucerine was used as a base for the extracts; however, the results could be different if the researcher used vaseline or lanoline as a base for transdermal delivery of herbal extract [61]. The ulcer size in Balb/c mice received Eucerine alone was significantly increased more than other groups which approved the

Table 1
Included publications of survey on the efficacy and activity of herbal medicines used against leishmaniasis in vitro in Iran.

Family and botanical name	Preparation	Organism (strain) tested	Stem bark	Concentration	Exposure time	Result	Reference
Allium hirtifolium	Hydro alcoholic	*L. infantum*	Fruit	0.01, 0.05, 0.1 and 0.2 mg/mL	For 7 days	Parasite growth at all concentrations was stopped after 3 days but at concentrations of 0.2 the first day was inhibited	[16]
A. aucheri	Methanolic	*L. major*	Aerial parts	150, 300, 450, 600, and 750 μg/mL	24, 48, and 72 h	750 μg/mL methanolic extract of *A. aucheri* was able to kill about 25% of both developmental stages of the parasite after 72 h	[17]
Camellia sinensis	Methanolic	*L. major*	Green leaves	150, 300, 450, 600, and 750 μg/mL hours	24, 48 and 72 h	Methanolic extract of *C. sinensis* inhibited the parasite multiplication	
Mimosa tenuiflora	Methanolic	*L. tropica*	NR	20,200,1000 and 2000 μg/mL	72 h	Concentration of 1000 and 500 μg/mL suppressed multiplication of promastigotes but at a concentration of 100 μg/mL it accelerated growth of promastigotes.	[18]
Perovskia abrotanoides Karel	Methanolic	*L. major (MRHO/IR/75/ER)*	Root	0.06, 0.12, 0.25, 0.5 and 1 mg/mL	2, 4 and 6 days incubation	IC50 = 926, 723 and 550 μg/mL after 2, 4 and 6 days Of incubation	[19]
P. abrotanoides Karel	Ethanolic	*L. major (MRHO/IR/75/ER)*	Root	0.06, 0.12, 0.25 0.5 and 1 mg/mL	2, 4 and 6 days incubation	IC50 = 213, 652 and 343 μg/mL after 2, 4 and 6 days of incubation,	
Peganum harmala	Unknown	*L. major (MRHO/SU/59/P)*	Seed	5000-20000 μg/mL and 62.5 −500 μg/mL	72 h	IC50° = 1832.65 ± 89.72 μg/mL	[20]
Ferula szowitsiana	Unknown	*L. major*	Root	10,100, 500 and 1000 μg/mL	48 h	IC50 = 4.9 μg/mL	[21]
Peganum harmala	Aqueous	*L. major (MRHO/IR/75/ER)*	Seeds	20,40,100 and 200 μg/mL	24, 48 and 60 h	IC50 *P. harmala* after 60 h = 0.7 μg/mL IC50 *A. tinctoria* after 60 h = 0.7 μg/mL IC50 combination of two extracts after 60 h = 0.6 μg/mL	[22]
Alkanna tincturia	Chloroformic	*L. major (MRHO/IR/75/ER)*	Stems and roots	20,40,100and 200 μg/mL	24, 48 and 60 h		
A. aucheri	Methanolic	*L. major (MRHO/IR/76/ER)*	Aerial parts	31.25, 62.5, 125, 250, 500 and 5000 μg/mL	NR	IC50 = 7.5 μg/mL	[23]
F. asafoetid	Methanolic	*L. major (MRHO/IR/76/ER)*	Gum	31.25, 62.5, 125, 250, 500 and 5000 μg/mL	NR	IC50 = 5.9 μg/mL	
Gossypium hirsutum	Methanolic	*L. major (MRHO/IR/76/ER)*	Boll	31.25, 62.5, 125, 250, 500 and 5000 μg/mL	NR	IC50 = 3.6 μg/mL (better effect)	
Echinacea purpurea	Ethanolic	*L. major (MRHO/IR/75/ER)*	Root	0.5, 2.5, 50 and 125 mg/mL	8, 16, 24, 48 and 72 h	LD50 for the promastigotes were determined as 22,300, 16,700, 36,600, 19,800 and 1230 μg/mL at 8, 16, 24, 48 and 72 h respectively. 125,000 and 50,000 μg/mL concentrations of this extract were able to kill 100% of the parasite after 48 h	[24]
Calendula officinalis	Aqueous	*L. major (MRHO/IR/75/ER)*	Flowers	500, 250, 125 and 62.5 μg/ml	24,48,72 h	IC50 was calculated for ethanolic & watery *C. officinalis*; 170 μg/mL, 215μg/mL after 24 h respectively. The extract at concentration of 500 μg/ml was found to kill all the parasites.	[25]
C. officinalis	Ethanolic	*L. major (MRHO/IR/75/ER)*	Flowers	500, 250, 125 and 62.5 μg/ml	24,48,72 h		
A. sativum	Aqueous	*L. major (MRHO/IR/75/ER)*	Small pieces	0, 10, 20, 40, 60, 80, 100 μg/mL	72 h	IC50 = 37 μg/mL. Cytotoxic effect in *L. major* with almost 100% death at a concentration of 93 μg/mL	[26]
Satureja khuzestanica	Ethanolic		Aerial parts	0.07−19.9 mg/ml	after 24 h		[27]

		L. major (MRHO/IR/75/ ER)				Ethanolic extract IC100 = 2400 μg/mL IC50 = 300 μg/mL.	
S. khuzestanica	Methanolic	*L. major (MRHO/IR/75/ ER)*	Aerial parts	0.07–19.9 mg/mL	after 24 h	Methanoic extract IC100 = 4800 μg/mL IC50 = 600 μg/mL.	
A. sativum	Aqueous	*L. major (MRHO/IR/75/ ER)*	Bulbs	(9.25, 18.5, 37, 74, 148 mg/mL	18, 24 and 48 h	IC50 = 37,000 μg/mL.	[28]
Arnebia euchroma	Alcoholic	*L. major (MRHO/IR/75/ ER)*	Root	0.78, 1.5, 3.2, 6.5 and 12.5 mg/ mL	0, 24, 48, 72 and 96 h	The results showed a significant decrease in the number of *Leishmania* parasites over time was due to the effect of the extract.	[29]
Achillea millefolium	Alcoholic	*L. major (MRHO/IR/75/ ER)*	Root	0.78, 1.5, 3.2, 6.5 and 12.5 mg/ mL	0, 24, 48, 72 and 96 h		
Green tea	Ethanolic	*L. major (MRHO/IR/75/ ER)*	Leaves	3, 6, 12, 24, 48 and 96 mg/mL	24,48,72 h	The effect of different concentrations of the plant extract on *Leishmania* revealed that all the concentrations of this extract can reduce the number of Leishmania parasites	[30]
A. millefolium	Alcoholic	*L. major (MRHO/IR/75/ ER)*	Leaves	3, 6, 12, 24, 48 and 96 mg/mL	0,24,48,72 h		
Wormwood	Alcoholic	*L. major (MRHO/IR/75/ ER)*	Flowers	25 mg/mL	0,24,48,72 h	The effect of different concentrations of the plant extract on *Leishmania* revealed that all the concentrations of This extract can reduce the number of *Leishmania* parasites. Plant extracts increased immobility parasite that this lack of mobility is directly related to time.	[31]
Walnut leaves	Alcoholic	*L. major (MRHO/IR/75/ ER)*	Leaves	25 mg/mL	0,24,48,72 h		
Verbascum thapsus	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 452 ± 4.47 μg/mL	[32]
Caparis spinosa	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 375 ± 2.96 μg/mL	
Amarusthus rutroflena	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 275 ± 7.45 μg/mL	
Sesamum indium	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 245 ± 3.78 μg/mL	
A. absintin	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 280 ± 5.96 μg/mL	
Tribulus terresttis	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 ≥ 625 μg/mL	
Ficus bengalensis	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 200 ± 23.14 μg/mL	
Prosropis juliflorea	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 312 ± 14.625 μg/mL	
A. dracunculus	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 ≥ 625 μg/mL	
Paliurus spina Christi	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 ≥ 625 μg/mL,	
Rhamnus persica boiss	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 75 ± 13.44 μg/mL	
Caesalpinia gilliesii	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 9.76 ± 1.27 μg/mL	
Acacia faresiana	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 625 ± 12.75 μg/mL	
Satureia hortensis	Hydro alcoholic	*L. major (MRHO/IR/76/ ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 15.625 ± 3.76 μg/mL	

(*continued on next page*)

Table 1 (*continued*)

Family and botanical name	Preparation	Organism (strain) tested	Stem bark	Concentration	Exposure time	Result	Reference
Carum copticum heirm	Hydro alcoholic	*L. major (MRHO/IR/76/ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 15.625 ± 3.76 μg/mL	
Thymus migricus	Hydro alcoholic	*L. major (MRHO/IR/76/ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50 = 31.25 ± 15.44 μg/mL	
A. vulgari	Hydro alcoholic	*L. major (MRHO/IR/76/ER)*	Leaves or twigs	5 to 500 μg/mL	After 28–30 h	IC50= >625 μg/mL	
Stachys lavandulifolia Vahl	Hydro alcoholic	*L. major (MRHO/75/IR)*	Aerial part	50, 100, 250, 500 and 1000 μg/mL	NR	With increasing concentrations of *S. lavandulifolia* and leaves *M. germanica* extract reduced the number promastigotes. Efficacy of the two extract were not significant difference and almost have same effect on the average number of *Leishmania* promastigotes	[33]
Mespilus germanica	Hydro alcoholic	*L. major (MRHO/75/IR)*	Leaves	50, 100, 250, 500 and 1000 μg/mL	NR		
Calotropis gigantea	Methanolic	*L. major*	Aerial parts	0.12, 0.25, 0.50 and 1.0 mg/mL	24, 48, 72 h	IC50 = 96.3 μg/mL	[34]
C. gigantea	Hexane	*L. major*	Aerial parts	0.12, 0.25, 0.50 and 1.0 mg/mL	24, 48, 72 h	IC50 = 92.5 μg/mL	
C. gigantea	Aqueous	*L. major*	Aerial parts	0.12, 0.25, 0.50 and 1.0 mg/mL	24, 48, 72 h	IC50 = 11.3 μg/mL	
C. gigantea	Butanolic	*L. major*	Aerial parts	0.12, 0.25, 0.50 and 1.0 mg/mL	24, 48, 72 h	IC50 = 58.7 μg/mL	
Artimisinin	Ethanolic	*L. major* (*MR HO/HR/75/ER)*	Leaves	10, 25, 50 and 100 μg/mL	incubated for 72 h	IC50 = 68.16 μg/mL	[35]
Artemisia annua	Ethanolic	*L. major*	Aerial parts	NR	NR	IC50 = 400 ± 0.8 μg/mL	[36]
A. annua	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 425 ± 1.5 μg/mL	
A. annua	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 850 ± 0.9 μg/mL	
A. annua	Hexane	*L. major*	Aerial parts		NR	IC50 = 1900 ± 2.4 μg/mL	
A. biennis	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 100 ± 0.9 μg/mL	
A. biennis	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 425 ± 0.5 μg/mL	
A. biennis	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 525 ± 1.1 μg/mL	
A. biennis	Hexane	*L. major*	Aerial parts		NR	IC50 = 1050 ± 2.0 μg/mL	
A. ciniformis	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 25 ± 0.4 μg/mL The ethanol extracts of *A. ciniformis* has one of the most potent leishmanicidal activity.	
A. ciniformis	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 340 ± 1.2 μg/mL	
A. ciniformis	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 450 ± 1.0 μg/mL	
A ciniformis	Hexane	*L. major*	Aerial parts		NR	IC50 = 790 ± 1.7 μg/mL	
A. sieberi	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 150 ± 1.0 μg/mL	
A. sieberi	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 265 ± 0.7 μg/mL	
A. sieberi	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 465 ± 0.8 μg/mL	
A. sieberi	Hexane	*L. major*	Aerial parts		NR	IC50 = 850 ± 1.5 μg/mL	
A. kulbadica	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 25 ± 0.5 μg/mL The ethanol extracts of *A. kulbadica has one of* the most potent leishmanicidal activity.	
A. kulbadica	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 275 ± 1.4 μg/mL	
A. kulbadica	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 440 ± 0.7 μg/mL	
A. kulbadica	Hexane	*L. major*	Aerial parts		NR	IC50 = 885 ± 1.8 μg/mL	
A. santolina	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 80 ± 0.8 μg/mL The ethanol extracts of *A. santolina* has one of the most potent leishmanicidal activity.	
A. santolina	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 375 ± 1.1 μg/mL	
A. santolina	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 675 ± 1.4 μg/mL	
A. santolina	Hexane	*L. major*	Aerial parts		NR	IC50 = 850 ± 1.4 μg/mL	
A. turanica	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 200 ± 1.3 μg/mL	

A. turanica	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 675 ± 2.1 μg/mL	
A. turanica	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 425 ± 0.9 μg/mL	
A turanica	Hexane	*L. major*	Aerial parts		NR	IC50 = 1120 ± 2.5 μg/mL	
A. absinthium.	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 500 ± 0.6 μg/mL	
A. absinthium.	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 425 ± 1.3 μg/mL	
A absinthium	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 600 ± 0.8 μg/mL	
A. absinthium.	Hexane	*L. major*	Aerial parts		NR	IC50 = 1050 ± 2.5 μg/mL	
A. fragrans	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 1000 ± 2.0 μg/mL	
A. fragrans	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 1375 ± 2.2 μg/mL	
A. fragrans	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 475 ± 1.0 μg/mL	
A. fragrans	Hexane	*L. major*	Aerial parts		NR	IC50 = 1150 ± 2.2 μg/mL	
A. khorassanica	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 400 ± 1.1 μg/mL	
A. khorassanica	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 435 ± 0.7 μg/mL	
A. khorassanica	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 500 ± 1.2 μg/mL	
A. khorassanica	Hexane	*L. major*	Aerial parts		NR	IC50 = 790 ± 1.5 μg/mL	
A. kopedaghensis	Ethanolic	*L. major*	Aerial parts		NR	IC50 = 50 ± 0.7 μg/mL	
A. kopedaghensis	Ethyl acetate	*L. major*	Aerial parts		NR	IC50 = 255 ± 0.8 μg/mL	
A. kopedaghensis	Dichloromethane	*L. major*	Aerial parts		NR	IC50 = 445 ± 0.5 μg/mL	
A. kopedaghensis	Hexane	*L. major*	Aerial parts		NR	IC50 = 925 ± 1.6 μg/mL	
A. seiberi	Aqueous	*L. major (MRHO/IR/75/ ER)*	Aerial parts and roots	5, 10, 25, 50 and 100 μg/mL	24,48 and 72 h	IC50 = 25 μg/mL *A. sieberi* has a higher growth inhibitory effect on promastigotes but The cytotoxic effect of seven concentrations of *Artemisia sieberi* on uninfected splenic macrophages of Balb/c mice has h very low cytotoxic effect on uninfected and healthy macrophages	[37]
A. sieberi	Aqueous	*L. major (MRHO/IR/75/ ER)*	Aerial parts & root	1, 5, 10,20 and 25%	24, 48 and 72 h	That promastigotes in RPMI culture were killed completely under concentrations of 20% and 25% of *Artemisia* in the first day. Concentrations of 20% of *Artemisia* in the second day led to the complete elimination of amastigote of *L. major* in macrophages	[38]
Scrophularia striata	Aqueous	*L. major (MRHO/IR/75/ ER)*	Aerial parts & root	1, 5, 10,20 and 25%	24, 48 and 72 h	The parasites were killed by *Scrophularia* at the concentration of 25% within three days. Concentrations of 25% of *Scrophularia* in the third day led to the complete elimination of amastigote of *L. major* in macrophages	
Indium curcumin	Unknown	*L. major (MRHO/IR/75/ ER)*	Turmeric plant extracts	NR	NR	IC50 = 26 μg/mL IC50 standard (Amphotericine B) = 20 μg/mL *I. curcumin* with IC50 values of 26 μg/mL was more effective than other three test agents against *Leishmania*.	[39]
Diacethyle curcumin	Unknown	*L. major (MRHO/IR/75/ ER)*	Turmeric plant extracts	NR	NR	IC50 = 52 μg/mL	
Gallium curcumin	Unknown	*L. major (MRHO/IR/75/ ER)*	Turmeric plant extracts	NR	NR	IC50 = 32 μg/mL	
G. curcumin	Unknown	*L. major (MRHO/IR/75/ ER)*	Turmeric plant extracts	NR	NR	IC50 = 38 μg/mL	
Alkanna frigida	Ethyl acetate	*L. major*	Root limb	62.5, 125, 250 and 500 μg/mL.	24, 48, and 72 h	The inhibitory effects = 46% IC50 = 106 μg/mL	[40]
A. frigida	Ethanolic	*L. major*	Root limb	62.5, 125, 250 and 500 μg/mL	24, 48, and 72 h	The inhibitory effects = 45% IC50 = 86 μg/mL	

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Table 1 (*continued*)

Family and botanical name	Preparation	Organism (strain) tested	Stem bark	Concentration	Exposure time	Result	Reference
A.frigida	Chloroformic	*L. major*	Root limb	62.5, 125, 250 and 500 μg/mL	24, 48, and 72 h	The inhibitory effects = 13% IC50 value after 48 and 72 h = 330 and 68 μg/mL	
A. frigida	Hexane	*L. major*	Root limb	62.5, 125, 250 and 500 μg/mL	24, 48, and 72 h	The inhibitory effects = 15% IC50 value= (384 μg/mL for 48 h) and (98 μg/mL 72 h).	
Nerium oleander, ricinus communis, capsicum, almond powder	Unknown	*L. major*	Leaves and stems	1/10, 1/100, 1/1000 and 1/10,000	For 7 weeks	In terms of quantity, the number of promastigotes of *Leishmania* in the face of the herbal combination reduced compared with the control group	[41]
Artemether	Unknown	*L. infantum (MHOM/TN/80/IPI1)*	Ointment and injection	0, 10, 25, 50, and 100 μg/mL.	72 h	IC 50 = 25 μg/mL after 24 h	[42]
aloe-emodin	Unknown	*L. major*	Powder	40, 80, 120 and 160 μg/mL	24, 48 and 72 h	IC50 = 52.79 μg/mL.	[43]
Scrophularia striata	Aqueous	*L. major*	Aerial parts and root	1, 5, 10,20 and 25%	72 h	In treatment of promastigotes of *L. major* with *S. striata* extract at the concentration of 25%, the parasites were killed at the day three	[44]
Nigella sativa	Essential oil	*L. major (MRHO/IR/75/ER)*	Aerial parts	0.1, 0.2, 0.4, 0.8, 1.2, 1.6 and 2%	24, 48 and 72 h	There was a significant difference in reducing parasites on groups receiving Satureia hortensis and *N. sativa* with Glucantime	[45]
S. hortensis	Essential oil	*L. major (MRHO/IR/75/ER)*	Aerial parts	0.1, 0.2, 0.4, 0.8, 1.2, 1.6, and 2%	24, 48 and 72 h		
A. cepa	Aqueous	*L. major*	Root	0.312, 2.5 and 5 mg/mL	24 and 48 h	The viability of the *L. major* promastigotes in the concentration of 312 μg/mL aqueous onion extracts was 80% and in the same concentration, 20% of the *L. major* promastigotes were unmovable. At the concentration of 2500 μg/mL aqueous *A. cepa* extracts, 70% of the *L. major* promastigotes were unmovable and the viability of promastigotes was 30%. Moreover, in the concentration of 5000 μg/mL of aqueous *A. cepa* extracts, 100% of the *L. major* promastigotes were unmovable and the viability of parasites in this concen-tration was 0%. IC50 = 1250 μg/mL IC100 = 5000 μg/mL	[46]
Ixora brachiata	Ethanolic	*L. major*	Root	0.312, 2.5 and 5 mg/mL	24 and 48 h	In addition, at the concentra-tion of 2500 μg/mL ethanolic and methanolic extracts of *I. brachiata* root, 100% of the *L. major* promastigotes were unmovable and the viability of the *L. major* promasti-gotes in the same concentration was 0%.in the concentration of 5000 μg/mL of aqueous *A. cepa* extracts, 100% of the *L. major* promastigotes were unmovable and the viability of parasites in this concen-tration was 0%. Ethanolic extract of *Ixora brachiata* root IC50 = 78 μg/mL IC100 = 2500 μg/mL Aqueous A. *cepa* = IC50 = 1250 μg/mL IC100 = 5000 μg/mL	
Hyssopus officinalis	Alcoholic		Leaves	0, 05, 0.1, 0.2, 0.4 and 1 μg/mL	24, 48 and 72 h	That extract was effective	[47]

		L. major (MRHO/IR/75/ER)					
Tussilago farfara	Alcoholic	*L. major (MRHO/IR/75/ER)*	Leaves	0, 05, 0.1, 0.2, 0.4 and 1 μg/mL	24, 48 and 72 h	That extract was effective	
Carum copticum	Alcoholic	*L. major (MRHO/IR/75/ER)*	Seed	0, 05, 0.1, 0.2, 0.4 and 1 μg/mL	24, 48 and 72 h	That extract was effective	
B. vulgaris	Methanolic	*L. tropica (MHOM/IR-/2002/Mash2)*	Aerial parts	Between 5 and 100 μg/mL and 1 −10 μg/mL	for 48 h at 37 °C	Inhibitory effects against promastigote forms IC50 = 16.1 μg/mL Inhibitory effects against amastigote forms IC50 = 39.4 μg/mL	[48]
B. vulgaris	Aqueous	*L. tropica (MHOM/IR-/2002/Mash2)*	Aerial parts	Between 5 and 100 μg/mL and 1 −10 μg/mL	for 48 h at 37 °C	Inhibitory effects against promastigote forms IC50 = 26.6 μg/mL Inhibitory effects against amastigote forms IC50 = 59.2 μg/mL	
B. vulgaris	Methanolic	*L. infantum (MCAN/IR/07/Moheb-gh)*	Aerial parts	Between 5 and 100 μg/mL and 1 −10 μg/mL	for 48 h at 37 °C	Inhibitory effects against promastigote forms IC50 = 13.2 μg/mL Inhibitory effects against amastigote forms IC50 = 52.8 μg μg/mL	
B. vulgaris	Aqueous	*L. infantum (MCAN/IR/07/Moheb-gh)*	Aerial parts	Between 5 and 100 μg/mL and 1 −10 μg/mL	for 48 h at 37 °C	Inhibitory effects against promastigote forms IC50 = 21.6 μg/mL Inhibitory effects against amastigote forms IC50 = 3.9 μg/mL	
Vinca major	Chloroformic	*L. major*	Leaves and stems	0,150, 300, 450, 600, 750 μg/mL	0,24,48,72 and 96 h	At a concentration of 750 mg/mL after 96 h led to destroy all parasites	[49]
A. sativum	Methanolic	*L. tropica (MHOM/IR/2002/Mash2)*	Bulbs	3.125, 6.25, 12.5, 25, 50, and 100 μg/mL	72 h incubation	The IC50 values methanolic extracts of *garlic* IC50 = 12.3 μg/mL The IC50 values aqueous extracts of *garlic* IC50 = 19.2 l μg/mL The IC50 values methanolic extracts of *garlic* CC50 = 291.4 μg/mL The IC50 values aqueous extracts of *garlic* CC50 = 348.2 μg/mL	[50] [51]
A. sativum	Aqueous	*L. tropica (MHOM/IR/2002/Mash2)*	Bulbs	3.125, 6.25, 12.5, 25, 50, and 100 μg/mL	72 h incubation		
Myrtus communis	Essential oil	*L. tropica (MHOM/IR/2002/Mash2)(pro&ama)*	Leaves	3.125, 6.25, 12.5, 25, 50, and 100 μg/mL	72 h incubation	The IC50 values for essential oil and methanolic extract was 8.4 and 28.9 μg/mL against promastigotes, respectively. These values were 11.6 and 40.8 μg/mL against amastigote forms,	
M.communis	Methanolic	*L. tropica (MHOM/IR/2002/Mash2)*	Leaves	3.125, 6.25, 12.5, 25, 50, and 100 μg/mL	72 h incubation		
N. sativa	Essential oil	*L. tropica*	Aerial parts	0−200 μg/mL	72 h incubation	Inhibitory effects against promastigote forms IC50 = 9.3 μg/mL Inhibitory effects against amastigote forms IC50 = 21.4 μg/mL	[52]

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Table 1 (*continued*)

Family and botanical name	Preparation	Organism (strain) tested	Stem bark	Concentration	Exposure time	Result	Reference
N. sativa	Methanolic	L. tropica	Aerial parts	0–200 μg/mL	72 h incubation	Inhibitory effects against promastigote forms IC50 = 14.8 μg/mL Inhibitory effects against amastigote forms IC50 = 30.8 μg/mL	
N. sativa	Essential oil	*L. infantum*	Aerial parts	0–200 μg/mL	72 h incubation	Inhibitory effects against promastigote forms IC50 = 11.7 μg/mL Inhibitory effects against amastigote forms IC50 = 26.3 μg μg/mL	
N. sativa	Methanolic	*L. infantum*	Aerial parts	0–200 μg/mL	72 h incubation	Inhibitory effects against promastigote forms IC50 = 15.7 μg/mL Inhibitory effects against amastigote forms IC50 = 34.6 μg/mL	
Kelussia odoratissim	Essential oil	*L. major (MRHO/IR/75/ ER)*	Aerial parts	7.5, 15, 25, 35.25 and 50 μl	24, 48 and 72 h	Higher concentrations (35.25 and 50 μl/mL had a stronger effect on promastigotes, causing total mortality.	[53]
Cordia myxa	Mucilage	*L. major*	Fruits	0.6,1.2,2.4,4.8,9.6,19.5,39,78 and 176 mg/mL	for 72 h	IC50 = 26,000 μg/mL	[54]
C. myxa	Mucilage	*L. infantum*	Fruits	0.6,1.2,2.4,4.8,9.6,19.5,39,78 and 176 mg/mL	for 72 h	IC50 = 35,000 μg/mL	
Caparis spinosa	Methanolic	*L. major (MRHO/IR/75/ ER)*	Root	0.1, 0.3, 0.5, 0.7 and 0.9 mg/mL	24, 48 and 72 h	It was determined that anti-protozoal activity of *Caparis* extract (900 μg/mL) was able to kill 97.8% of promastigotes after 72 h	[55]
Pistacia khinjuk	Alcoholic	*L. tropica (MHOM/IR/ 2002/Mash2)* & *L. major (MRHO/IR/75/ ER)*	Fruits	0–100 μ/mL	for 48 h	Promastigote: IC50 = 58.6 ± 3.15 μg/mL Amastigote: IC50 = 37.3 ± 2.51 μg/mL	[56]
Eucalyptus camaldulensis	Aqueous	*L. major (MRHO/SU/59/ P)*	Leaves	25, 50, 312.5, 625 and 1,250	72 h	IC50 = 1108.6 ± 51.9 μ/mL ,	[57]
E. camaldulensis	Methanolic	*L. major (MRHO/SU/59/ P)*	Leaves	25, 50, 312.5, 625 and 1,250	72 h	IC50 = 586.2 ± 47.6 μ/mL Methanolic extract was more effective than aqueous extract. This extract were less effective as compared to the control drμg	
A. absinthium,	Methanolic	*L. major (MROH/IR/75/ IR)*	Leaves	31.25–1000 μg/mL.	0-30 days	IC50 = 159.45 μ/mL Toxicity for macrophage cell line=10%	[58]
Vitex agnuscastus	Methanolic	*L. major (MROH/IR/75/ IR)*	Leaves	31.25 to 1000 μg/mL.	0-30 days	IC50 = 234.15 μ/mL Toxicity for macrophage cell line = 8%	
Phytolaca americana	Methanolic	*L. major (MROH/IR/75/ IR)*	Fruits	31.25 to 1000 μg/mL.	0-30 days	IC50 = 171.1 μ/mL Toxicity for macrophage cell line = 12%	

IC50: concentration of drμg that causes 50% growth inhibition of amastigote or promastigote forms of *Leishmania*.
IC100: concentration of drμg that causes 100% growth inhibition of amastigote or promastigote forms of Leishmania.
CC50: as the Cytotoxic concentration of the extracts to cause death to 50% of viable cells in the host.
LD50: (Lethal Dose, 50%) It is the amount of the substance required (usually per body weight) to kill 50% of the test population.
NR: Not reported.

Table 2
Included publications of survey on the efficacy and activity of herbal medicines used against leishmaniasis in vivo in Iran.

Family and botanical name	Preparation	Organism tested	Stem bark	Animals kind	Concentration	Result	Reference
Z-HE[a]	Crude extract	*L. major*	-	Human	Topical	In the group treated with Z-HE (group A), complete cure was observed in 74.4% (Figs 1 and 2), partial cure in 11.6%, and failure in 14.0%. In the group treated with meglumine antimoniate (Glucantime) (group B), complete cure was observed in 24.1%, partial cure in 14.1%, and failure in 58.8%	[59]
A. sativum	Aqueous	*L. major*	Bulbs	Mice (Balb/c)	Mices were subjected to 300,000 promastigotes. lesion was measured on days 1, 10, 20, 30 and 45	The diameter of lesion was reduced by aqueous extract of *garlic* within 30 days of treatment. However, the maximum reduction was induced when mice were subjected to vitamin A for 10 days before the administration of the aqueous extract for 30 days. A significant correlation between healing and the amount of NO release was also found.	[60]
Berberis vulgaris	Alcoholic	*L. major*	Leaves, stems and roots	Mice (Balb/c)	2.5, 4.0, 5.5 and 7.0%	The results showed that after 2 weeks, a statistically significant decrease of ulcer size of treated mice observed, while in the control group the lesion growth continued. The examinations showed that using higher concentration of the extract caused more decrease in surface area of CL lesions on day 15 and negative direct smear on day 20. Alcoholic extract of *B.vulgaris* root was more effective than leaves and stem extract.	[61]
Eucalyptus globulus	Essence	*L.major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Essence 10%	The essences reduced the diameter of lesions or caused small lesions to disappear completely.	[62]
Myrtus communis	Essence	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Essence 10%, 20%	No change was noticed in the size of the lesions or the number of parasites.	
Ferula gumosa	Essence	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Essence 10%, 20%	No change was noticed in the size of the lesions or the number of parasites.	
A. herbaalba	Essence	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Essence 10%, 20%	No change was noticed in the size of the lesions or the number of parasites.	
A. sativum	Tincture	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Tentor 50&100%	No change was noticed in the size of the lesions or the number of parasites.	
Urtica dioica	Crude extract	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Pure extract	No change was noticed in the size of the lesions or the number of parasites.	
A. dracunculus	Essence	*L. major (MRHO/IR/ 76/ER)*	NR	Mice (Balb/c)	Essence 10%	The essences of *A. dracunculus* reduced the diameter of lesions or caused small lesions to disappear completely.	
Cassia Fistula	Concentrated boiled	*L. major*	Fruits	Human	–	Mean healing time was 4.6 ± 3.7 weeks	[63]
C. Fistula	Hydro alcoholic	*L. major*	Fruits	Human	–	Mean healing time was 4.9 ± 3.8 weeks. There was no significant difference between the efficacy of concentrated boiled extract and that of the hydro alcoholic extract of the *Cassia fistula*	
Berberis vulgaris	Alcoholic	*L. major*	Stem skin	Mice (Balb/c)	20,40,80% for 30 days	With the 20% preparation: by the end of the treatment period, the mean diameter of the lesions had decreased, with complete healing in 5 mice (27.7%), ($p < 0.001$). by the time of the decrease in diameter, the mean weight of the animals had increased and the number of parasites in the lesions had declined (80%). Total elimination of the parasites was observed in 12 animals ($p < 0.001$). At a concentration of 40%: mean ulcer diameter decreased, with complete healing in 2 mice (11.1%, $p < 0.001$). By the time of the decrease in diameter, the mean weight of the mice had increased ($p < 0.05$). The mean number of parasites in lesions decreased (64.3%), with total elimination in 9 animals ($p< 0.05$).	[64]
Thymus vulgaris	Hydro alcoholic	*L. major (MRHO/IR/ 75/ER)*	NR	Mice (Balb/c)	NR	Mean of ulcer size reduction = 36.09% that *T. vulgaris*, hydro alcoholic extracts were significantly more effective in reduction of ulcer size as compared with Glucantim	[65]
Achillea millefolium	Hydro alcoholic	*L. major (MRHO/IR/ 75/ER)*	NR	Mice (Balb/c)	NR		

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Table 2 (*continued*)

Family and botanical name	Preparation	Organism tested	Stem bark	Animals kind	Concentration	Result	Reference
						Mean of ulcer size reduction = 43.29% that *A. millefolium* hydro alcoholic extracts were significantly more effective in reduction of ulcer size as compared with Glucantim	
propolis	Hydro alcoholic	*L. major (MRHO/IR/75/ER)*	NR	Mice (Balb/c)	NR	Mean of ulcer size reduction = 43.77% that *propolis* hydro alcoholic extracts were significantly more effective in reduction of ulcer size as compared with Glucantim	
Rubia Tinctorium	Dry extract	*L.major (MRHO/IR/76/ER)*	Roots	Mice (Balb/c)	40, 60 and 80%	The mean weight of the mice that received 40, 60 and 80% concentrations of *R. tinctorum* extracts showed a statistically significant difference compared to the control group the mean of lesion size of the mice extracts concentrations showed no statistically significant difference compared to the control	[66]
A.sieberi	Hydro alcoholic	*L. major (MHOM/64/IR/ER75)*	NR	Mice (Balb/c)	1,3,5% after 30 days	At the end of the 30 day treatment period with concentrations of *Artemisia*, any of the mice treated with complete remission were observed. And microscopic examination of samples taken from the animals tested were positive.	[67]
Thyme	Hydro alcoholic	*L. major (MRHO/IR/75/ER)*	NR	Mice (Balb/c)	NR	Observed significant difference between mean of lesion diameter before and after treatment in control, *Yarrow* and *Thyme* groups Paired *t*-test showed no significant difference between mean of lesion diameter after treatment between treatment and Glucantime groups	[68]
Thyme	Hydro alcoholic	*L. major (MRHO/IR/75/ER)*	NR	Mice (Balb/c)	NR		
A. millefolium	Hydro alcoholic	*L. major (MHOM/64/IR/ER75)*	NR	Mice (Balb/c)	NR	Ulcer dimeter Before treatment = 4/35 ± 0/5 mm Ulcer dimeter after treatment = 3/4 ± 0/67 mm The mean ulcer size in the group receiving *thyme* has been good impact on preventing The process of development of wound	[69]
T. vulgaris	Hydro alcoholic	*L. major (MHOM/64/IR/ER75)*	NR	Mice (Balb/c)	NR	Ulcer dimeter Before treatment = 5/39 ± 0/41 mm Ulcer dimeter after treatment = 4 ± 0/34 mm The mean ulcer size in the group receiving *yarrow* has been good Impact on preventing The process of development of wound	
Henna	Hydro alcoholic	*L. major (MHOM/64/IR/ER75)*	NR	Mice (Balb/c)	NR	Ulcer dimeter Before treatment = 5.77 ± 0/30 mm Ulcer dimeter after treatment = 7/11 ± 0/56 mm Were did not showen statistical significant difference between mean diameter of lesions after treatment with the treated group with Plant extracts and treated with Glucantime	
A. sativum	Hydro alcoholic	*L. major (MHOM/64/IR/ER75)*	NR	Mice (Balb/c)	NR	Ulcer dimeter Before treatment = 5.18 ± 0/47 mm Ulcer dimeter after treatment = 7/06 ± 1/09 mm Were did not showen statistical significant difference between mean diameter of lesions after treatment with the treated group with Plant extracts and treated with Glucantime	
Pistacia Atlantica	Unknown	*L. major (MHROM/IR/75/ER)*	Gum obtioned of trunk and branches	Mice (Balb/c)	0,4,8 week	Gum daily for 28 days decreased skin lesion size in the mice infected with *L.major* compared with that in the control. Treatment Balb/c mice with gum obtained *P. atlantica* var. *kurdica* and Glucantime causes decrease number of parasitologically positive mice	[70]
E. camaldulensis	Methanolic	*L. major (MRHO/IR/75/ER)*	NR	Mice (Balb/c)	NR	Amastigote number into the lesions, were significantly decreased, nanogold solutions were also decreased mortality rate in the mice	[71]
Satureja khuzestanica	Essential oil	*L. major MRHO/IR/75/ER*	Aerial parts	Mice (Balb/c)	0.01, 0.001, 0.0001% for 7 week	Lesions' size in SKEO treated groups was restrained but not significantly different from the control group the mortality rate in treated groups was clearly less than the control.	[71]
A. sativum	Aqueous	*L. major*	Bulbs	Mice (Balb/c & 57BL/6 and Suri)	Promastigote injection and evaluated For 8 week	The results showed that R10 had good therapeutic efficacy in treatment of lesions in mice ($P < 0.05$) that this efficacy was significant in sixth, seventh and eighth weeks after the treatment	[72]
Echinacea purpurea	Hydro alcoholic	*L. major*	Aerial parts	Mice (Balb/c)		The mean of lesion size in each group of mice were compared and analyzed. No significant differences in the lesions size were found between the three mice groups. Therefore, *E. purpurea* extract was not effective against *L. major* based on the findings of this study.	[74]
Mespilus germanica	Ethanolic	*L. major*	Leaves	Mice (Balb/c)	40, 60 and 80%		[75]

						Extract of *M. germanica* has the highest effectiveness in concentration of 40%, causing greater reductions in both ulcer diameter and the number of parasites in the lesions compared with other prepared concentrations	
A. aucheri Boiss	Methanolic	*L. major MRHO/IR/75/ER(IR/75)*	NR	Mice (Balb/c)	0.09, 0.36, 1.44, 6, 28 mg/kg for 30 days	The results indicated that herbal extract was able to affect on lesion size, its performance and to prevent visceralization of the parasite. This is the first report indicating visceralization caused by the cutaneous form of *L. major* in the Balb/c mice	[76]
N. oleander, r. communis, capsicum, almond powder	Unknown	*L. major*	Stem and seed	Mice (Balb/c)	1/10,1/100,1/1000,1/10,000	This skin lesion at the base of the tail of mice under investigation also indicate a significant effect on the composition of the herbal form wound and skin nodule at the base of the tail of mice treated with the control group.	[41]
Artemether	Unknown	*L. infantum (MHOM/TN/80/IPI1)*	Ointment and injection	Mice (Balb/c)	NR	In vivo experiments indicated that oral artemether treatment of mice, during 3 days and every 6 h (0.625 mg/kg) was more significant than parenteral (0.625 mg/kg IP) treatment	[42]
artemether	Unknown	*L. major*	Ointment and injection	Mice (Balb/c)	NR	Mean diameter of lesion in the infected group treated with ointment of *artemether* decreased from 1.294 to 0.214 cm mean diameter of lesion in the infected group treated with *artemether* injection decreased from 0.913 to 0.256 cm	[77]
Echium amoenum	Aqueous	*L. major (MRHO/75/IR)*	Flower	Mice (Balb/c)	0.1, 0.25, 0,50, 1, 2, 4 and 5 mg/mL	Increased the level of IFN-γ and lowered the parasite burden in the proximal lymph nodes and prevented the necrosis of the footpad as compared with the untreated infected mice.	[78]
E. amoenum	Alcoholic	*L. major (MRHO/75/IR)*	Flower	Mice (Balb/c)	0.1, 0.25, 0,50, 1, 2, 4 and 5 mg/mL		
Seidlitzia rosmarinus	Hydro alcoholic	*L. major (MRHO/75/IR)*	leaves	Mice (Balb/c)	5, 10 and 5 15%	Significant increase in the lesion size of treated mice compared with reference group except for treated group by 15% extract	[79]
Peganum harmala	Aqueous	*L. major (MRHO/IR/75/ER)*	Ground seed	Mice (Balb/c)	NR	In the aqueous extract group only 10% of mice healed.	[80]
P. harmala	Ethanolic	*L. major (MRHO/IR/75/ER)*	Ground seed	Mice (Balb/c)	NR	In the ethanolic extract group only 40% of mice healed. Results showed that ethanol extract of *P. harmala* had good therapeutic efficacy in treatment of lesions in mice	
V. major	Cloroformic	*L. major*	Leaves and stems	Mice (Balb/c)	NR	Injection was very effective By the prevention of ulcers caused by Leishmania major in Balb/c mice compared to untreated control	[49]
S. iastriata	Aqueous	*L. major*	Aerial parts& root	Mice (Balb/c)	1, 5, 10,20, 25% for 3 days	Extract concentration (25%) at the concentration at the first day, the extract led to a decrease in the parasite rate to 36 amastigotes. For all of the concentrations (10%, 20%, 25%) we observed completely elimination of amastigotes on the third day.	[44]
Hedera helix	Alcoholic	*L. major (MHOM/64/IR/ER75)*	Leaves	Mice (Balb/c)	20% and 70% for 30 days.	Study showed that the main lesion size did not decrease significantly, or the small lesions did not completely disappear after treatment by *H. helix* alcoholic extract. Amastigotes counts (mean ± SD) of the skin lesions decreased in control A and 20% concentration groups, but in negative control and 70% concentration groups the number of parasites did not reduce.	[81]
Pistacia khinjuk	Alcoholic	*L. tropica (MHOM/IR/2002/Mash2) & L. major (MRHO/IR/75/ER)*	Fruits	Mice (Balb/c)	NR	In vivo = after 30 days of treatment, 75 and 87.5% recovery were observed in the infected mice treated with 30% extract and meglumine antimoniate, respectively, while *P. khinjuk* extract at the concentration of 20% recovered 50% of the infected mice.	[82]
C. spinosa	Methanolic	*L. major MRHO/IR/75/ER*	Root	Mice (Balb/c)	0.1,0.3,0.5,0.7,0.9 mg/mL for 24, 48 and 72 h	It was determined that 700 μg/ml and 900 g/ml *Caparis* root extract concentrations were more effective than other concentrations on amastigotes of *Leishmania* in ulcers. The results were suggestive that *Caparis* root extract had significantly similar effect in reduction of ulcer size as compared to Glucantim	[55]
Matricaria chamomilla	Hydro alcoholic	*L. major*	Flower	Mice (Balb/c)	–	The comparison of these three groups revealed that wound healing in group one and group two were 58.3% and 80% respectively, which was significant whereas no healing was seen in the control group	[83]
A. absinthium	Methanolic	*L. major (MROH/IR/75/IR)*	Leaves	Mice (Balb/c)	daily for 30 days repeated 3 times	*A. absinthium* extract was statistically significant	[58]
						The lesion size in different groups mice after 30 day = 9.9 ± 2.4 μg/mL	
Vitex agnuscastus	Ethanolic	*L. major (MROH/IR/75/IR)*	Leaves	Mice (Balb/c)	daily for 30 days repeated 3 times	The lesion size in different groups mice after 30 day = 13.1 ± 2.8 μg/mL	
Phytolaca americana	Methanolic	*L. major (MROH/IR/75/IR)*	Fruits	Mice (Balb/c)	daily for 30 days repeated 3 times	The lesion size in different groups mice after 30 day = 15.3 ± 2.6 μg/mL	

[a] Mixture of Althaea rosa, Althaea officinalis, and Pharmacology, Pathology, and members of the families Leguminosae, Faliaceae, Malvaceae, and Lythraceae.

Table 3
Results of subgroup meta-analysis for the mean of IC50 separately characteristics.

Characteristics		n	IC50	95% CI		I-squared	P
				Lower	Upper		
Stem bark	Aerial parts	44	553.10	470.09	636.11	100.00%	P<0.001
	Root limb	8	123.43	23.18	247.07	98.7%	
	Bulbs	3	22.83	4.00	41.66	100%	
	Leaves or twigs	3	422.36	393.00	451.72	99.8%	
Preparation	Ethanol	9	251.33	137.64	365.03	89.32%	P<0.001
	Ethyl acetate	11	448.00	337.96	558.04	97.01%	
	Dichloromethane	10	531.82	457.96	605.68	100.00%	
	Hexane	11	910.92	781.92	1039.93	99.30%	
	Methanolic	3	59.75	16.12	103.38	93.28%	
	Aqueous	4	23.89	5.88	41.90	89.36%	
	Chloroformic	3	132.90	12.99	252.81	100.00%	
	Hydroalcoholic	3	510.00	490.77	529.23	100.00%	
Botanic name	Artemisia spp	49	8.0	7.4	8.6	97.1%	P<0.001
	Allium spp	4	14.2	13.7	14.6	99.7%	
	Alkanna spp	6	9.4	8.3	10.6	98.5	

n: sample size.

previous suggestion.

The administration form of a drug is also important. In the present study, the extracts were topically used as an ointment, but the results would be different if the extracts were administered intralesionaly. Recent studies have shown that nanoparticles of anti-leishmanial drugs are highly effective to treat CL. The important advantages of such drugs are low dosage and minimum adverse reactions [90].

In the present systematic review and meta-analysis, the Begg's test showed no publication bias among all studies ($t = 1.25$, $p = 0.215$). In addition, subgroup analysis revealed that there was a significant difference in extracting preparation including hexane, dichloromethane, hydroalcoholic and ethyl acetate with higher IC50 values, and aqueous or methanolic with lower IC50 values. ($p < 0.001$) (Table 3).

However, several studies have demonstrated that the hexane and ether acetate extracts present low or no toxicity to host cells at the effective concentrations [91,92]. Ribeiro et al. (2014) evaluated anti-leishmania activity of 44 extracts and fractions derived from 16 Brazilian plant species against *L. amazonensis*. Among them, the most potent extracts were the hexanic extract [92].

In general, the ethanolic extracts were less effective and more toxic than the hexanoic extracts and buthanolic, dichloromethane ethyl acetate and hexanic fractions in the mammalian cells [93]. Thus, the application of the hexanic extract against *Leishmania* parasites as a potent fraction is recommended in the in vivo experiments.

In the study of Hooshyar et al. (2014), a significant decrease was shown in the main lesion size, or the small lesions were not completely disappeared after treatment by *Hedera* helix (*H.helix*) alcoholic extract. Their results disagreed with those of Talari et al. who used, 100 and 50 mg/mL of *H. helix* extract and observed that all promastigotes of *L. major* were killed in vitro [94]. This difference of findings may be due to different preparation methods and concentration of the plant extract was used in two studies. Different extract was gathered from eleven Iranian *Artemisia* species. Their leishmanicidal activities against the growth of *L. major* showed that ethanol extracts especially those taken from *A. ciniformis, A. santolina* and *A. kulbadica* had the strongest effects [86]. In the present study, they demonstrated the inhibitory effect of different extracts from eleven *Artemisia* species on the growth of *L. major* promastigotes in vitro. It was previously reported that the aqueous extract and essential oil of *A. herbaalba* had antileishmanial activity against *L. tropica* and *L. major* promastigotes [37]. In addition, the aqueous extract of leaves of *A. indica* exhibited leishmanicidal activity (IC50 = 430 μg/mL) [95]. Here, some of tested *Artemisia* spp showed most strong antileishmanial activities. In this study, all tested extracts exhibited antileishmanial activity after incubation, however, ethanol extracts from *A. ulbadica* and *A. ciniformis* showed the stronger leishmanicidal activity at value of (IC50 = 25 μg/mL). Growth inhibitory effect of ethanol extract of other plants such as *Haplo phylum myrtifolium* against *L. tropica* promastigotes were previously reported (IC50 = 10.9 μg/mL) [96]. Comparing the antileishmanial effect of non-polar extracts revealed that ethyl acetate extract of *A. fragrans* had less antileishmanial activity against *L. major* promastigotes. Ethyl acetate extracts of studied *Artemisia* species (except for *A. turanica* and *A. fragrans*) were also more active in comparison with their dichloromethane extract. In vitro antileishmanial activity of ethyl acetate and dichloromethane extracts of *Ircinia spinosula* (IC50 = 16.09, 47.38 μg/mL) were reported against *L. major* promastigotes [97]. The lethal dose (LD50) of dichloromethane extract and hexane extract of *Calophyllum brasiliense* on *L. amazonensis* promastigotes were 40 mg/mL and 20 mg/mL, respectively [98]. In comparison with other extracts, *Artemisia* studying species hexane extracts (except for *A. fragrans*) were less active than *L. major*. Hexane extracts of *A. biennis, A. annua, A. turanica, A. fragrans* and *A. absinthium* were less effective than other species. Other investigators have also reported lower activity of hexane extracts of plants than *Leishmania* species in comparison with other extracts. For example, ethanol extracts of *Arbutus unedo* significantly decreased *L. tropica* promastigotes counts [99].

Leishmanicidal activity of *Allium sativum* (garlic extract) has been established against infection with *L. major*, so that it can induce a Th1-type response, stimulate INF-γ and NO production in macrophage and thus prevent the progression of the infection [73,28]. To improve the therapeutic efficacy and reduce toxicity, above mentioned natural molecules can be applied as either scaffold for producing and exploring new immune drugs or natural immunomodulators in synergy and in combination with existing drugs [100,101]. Targeting anti-leishmanial drugs to macrophages with drug delivery systems reflects a hopeful strategy overcoming the problems associated with the current treatment protocols.

Another important issue is the safety of natural remedies. Although natural immune therapy in different generations has been tested and approved, it is necessary to prove the overall pharmacological safety of the correction. Chemical agents in Iranian drug market have disadvantages such as high cost and side

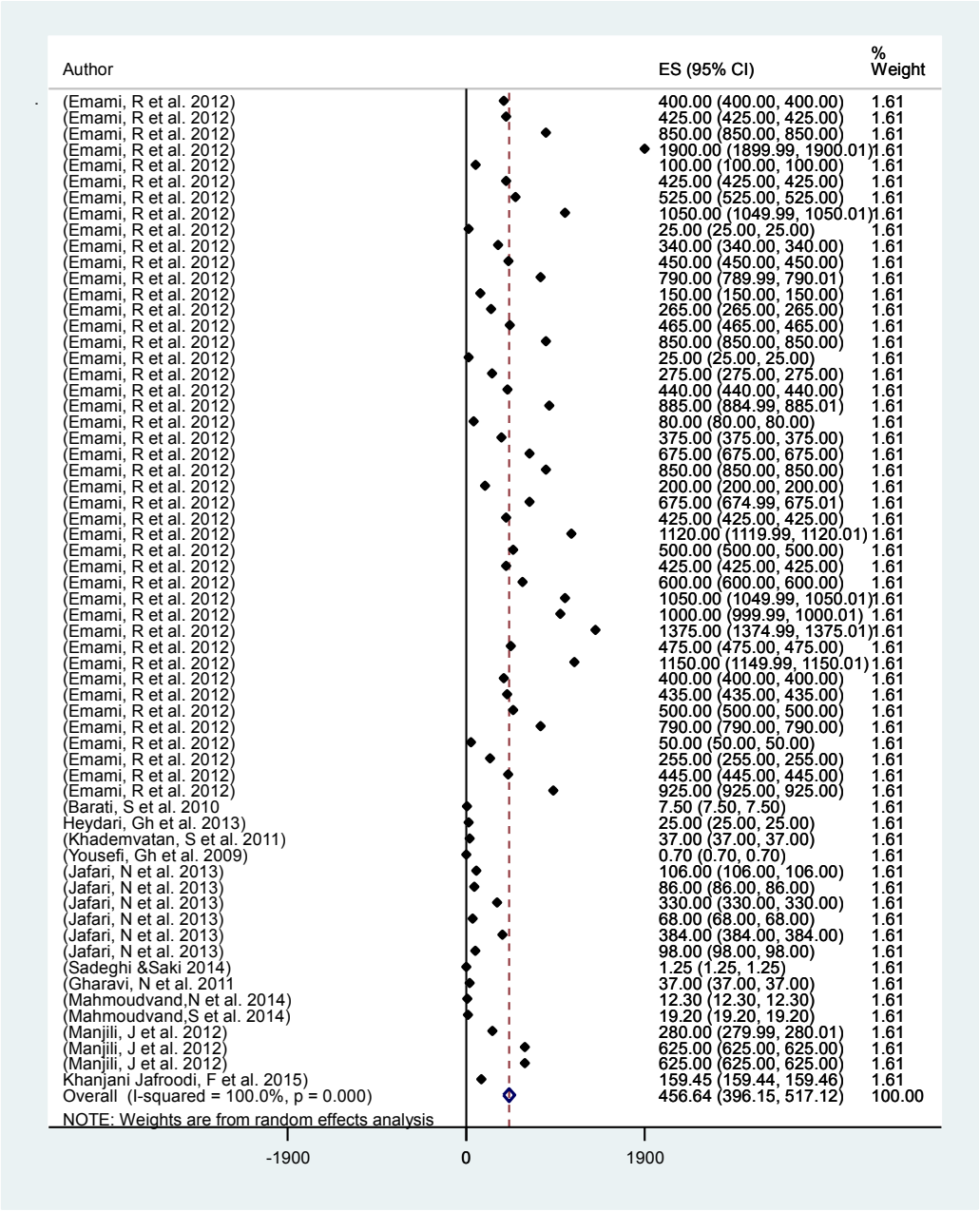

Figure 2. Based on random effect meta-analysis (Q = 1945, df = 61, I-square = 100%, p < 0.001) pooled mean of IC50 was obtained 456.64 (95% CI: 396.15, 517.12). Begg's test showed there is no evidence publishing bias among studies (t = 1.25, p = 0.215).

effects. Considering the effectiveness of these plants would make them as a source of natural and safe agents for the treatment of leishmaniasis. However, anti -leishmanial drugs or natural compounds are safe when their selectivity index is more than 10 [50].

5. Conclusion

In conclusion, the present review showed that a range of plant extracts had effects on promastigote stage of *Leishmania* and interesting antileishmanial properties exhibited in vitro and in vivo. Therefore, it might be possible to use the extracts instead of chemical drugs. However, almost all of the authors claimed successful results about their investigated plants, but their studies really had limitations which affected with the accuracy of their results. Some of defects included in these studies are described in detail as lacking of randomized double blind clinical trials in all of human based studies. Also some of investigations were performed in vitro and were not performed in vivo [102,103]. The period of exposure of extracts was not enough in some of the studies [104] and at last in one study, the toxicity level of the plant investigated was very high for testing in volunteer patients [105]. Most of data published were obtained from animal model and were not tested on human [106]. According to all documented data, phytotherapy has provided a large and hopeful vision to new, safe, and effective leishmaniacidal agents. Nevertheless, it needs to generalize all results obtained from in vitro and in vivo studies on the efficacy of plant extracts, metabolites or formulations against different *Leishmania* species to validate their activities. We

concluded that the mechanism of action was enhancing the hosts' cellular immunity.

The present systematic investigation on anti-leishmanial activity of the medicinal plants together with their toxicity, mechanism of action and chemical properties for improvement is the most favorable formulation urgently required to confirm their efficacy in the treatment of leishmaniasis.

As a whole, the present systematic review provide valuable information about the natural products with anti -leishmanial activity which would be very favorable for experimental and clinical trials and herbal combination therapy studies. Consequently, further clinical researches are needed to establish the effective and safe medicinal plants therapy. It is necessary to find their active components, and potential toxic effects would lead to producing the well-tolerated and safe drugs for leishmaniasis.

Ethical approval

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Guarantor

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