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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