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Review Article

Medicinal Plants Traditionally Used for the Treatment of Leishmaniasis in the World: A Systematic Review

Zohreh Akhoundi Meybodi [1] M.D., Akram Astani [1,2] Ph.D., Maryam Dehghan [3] Ph.D., Faezesadat Heidari [1] Ph.D., Hedayat Akhundimeybodi [4] M.D., Farzad Saremi [5] M.D., Razieh Nabimeybodi [6*] M.D, Ph.D.

[1] Infectious Diseases Research Center, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Internal Medicine, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4] Department of Urology, School of Medicine, Shahid Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran
[5] Department of Parasitology, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
[6] Department of Persian Medicine, School of Persian Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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A B S T R A C T

Leishmaniasis is a widespread parasitic disease and a major global public health challenge. No effective vaccines exist , and existing treatments are expensive and have numerous side-effects. Many medicinal plants show anti-leishmanial properties. This study systematically reviews and summarizes research done from 2000 to 2024 on the anti-leishmanial effects of medicinal plants and natural compounds. This systematic review included English-language studies published between March 2000 and March 2024. A comprehensive search was performed across Web of Science, Cochrane Library, ScienceDirect, PubMed, Scopus, and Google Scholar. Retrieved articles were screened using predefined inclusion criteria. Eligible studies were critically evaluated for research design, methodology, and overall quality. The search yielded 1353 articles. After removing duplicates, 650 articles were excluded, leaving 703. Title screening removed 186 unrelated articles, resulting in 517 for abstract review. At this stage, 356 articles were excluded, leaving 161 for full-text assessment. After full-text review, considering scientific quality and inclusion criteria, 44 articles remained. A wide variety of medicinal plants (117 species) from diverse geographical regions demonstrated promising anti-leishmanial activity *in vitro*, *in vivo*, and in some clinical settings. These plants represent a valuable source for developing new treatments against leishmaniasis. However, further *in vivo* and clinical studies are essential to confirm their efficacy, safety, and mechanisms of action.

* **Corresponding Author:** Department of Persian Medicine, School of Persian Medicine, Shahid Sadoughi University of Medical Sciences, Ardakan, Yazd, Iran. Tel: +989133564427; Email: R.nabimeybodi@gmail.cim

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Introduction

Leishmaniasis is one of the most important health problems in the world. It is currently endemic in 98 countries [1] and affects mainly low-income populations. Treatments that currently exist for the disease have high toxicity, reduced effectiveness, administration problems, and considerable costs. In such a situation, natural and traditional medicine can be an effective alternative to the existing leishmaniasis treatments [2]. Traditional medicine involves the use of a great variety of plants, and many people and communities worldwide use them to treat infections. Therefore, the medicinal plants of each region, due to their availability and lower cost, and in case they are effective and have no side effects, can be helpful in the treatment of this disease [3]. Medicinal plants have a wide range of pharmacological effects and can show analgesic, sedative, anti-inflammatory, anti-spasmodic, antimicrobial, anti-protozoal, and anthelmintic properties [4]. The vegetation in each region plays an essential role in providing the local people with food and medicine. The unique geographical, topographic, ecological, climatic, and physiographic conditions have resulted in many types of medicinal plants in the world. Local healers have great skills and knowledge in preparing traditional medicines to treat various diseases [5]. Considering these, this study aims to update and summarize the research conducted worldwide between 2000 and 2024 on the anti-leishmanial activity of medicinal plants and their natural compounds.

Materials and Methods

This work is part of secondary studies and is in the form of a systematic review. It was done based on studies conducted in the relevant field in different regions of the world until March 20, 2024; thus, it can be stated that the findings of this study are not limited to any country or region and include studies from around the world.

Search strategy and strategies

In this research, a comprehensive and complete search of the texts published between March 2000 and March 2024 in the databases Web of Science, Cochrane Library, Scopus, ScienceDirect, PubMed, and Google Scholar was carried out using the Boolean operators AND and OR. The search strategy was developed by using Medical Subject Headings (MeSH) terms and combinations of free-text keywords applied in the examined titles and abstracts (Table 1). The identified studies were screened using the Annotated software; duplicate and irrelevant titles and abstracts were removed, and the full texts were then checked for relevance and eligibility. The references of the selected studies were also examined to find more studies and increase the sensitivity of the present work.

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Table 1. Searched keywords and phrases

Sterategy	Search Terms
#1	("Leishmania" OR "Leishmania guyanensi" OR "Leishmania infantum" OR "Leishmania major" OR "Leishmania tropica")
#2	("Medicinal Plant" OR "Plants Medicinal" OR "Medicinal Herbs" OR "Pharmaceutical Plants" OR "Healing Plant" OR "Medicine Traditional")
#3	(#1 AND #2)

Inclusion criteria

This systematic review included studies evaluating the anti-leishmanial activity of herbal medicines and plant extracts published between March 2000 and March 2024. No restrictions were applied regarding geographical location. Eligible study designs included *in vitro* experiments, *in vivo* models, and clinical (human) trials. Only studies published in English were included.

Exclusion criteria

Lack of access to the full text of articles, articles published after March 2024, books and qualitative studies, Letter to Editor articles, proposals, review articles, meta-analyses, and ecological studies were excluded from the study.

Data collection

The required information was extracted from related articles using electronic forms in the Microsoft Excel (Excel) environment, which consisted of four parts and contained information about the article, i.e. title, first author's name, year of publication, country of origin, the study design, and materials.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. EndNote version 8 was used to facilitate reference management and study organization. Studies meeting the inclusion criteria and containing the required information were subsequently included in the analysis.

Validity and reliability of tests and data collection tools

The validity of the review results was ensured by using appropriate MeSH terms and by conducting a comprehensive search across Web of Science, Cochrane Library, ScienceDirect, PubMed, Scopus, and Google Scholar. Data reliability was enhanced by conducting literature searches and making study selection independently by each of the two reviewers, and the probable disagreements were resolved through discussion with a third reviewer. No artificial intelligence tools were used for data collection, screening, data extraction, or analysis.

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Results

To conduct this study, 1353 articles were collected by searching keywords. After removing duplicates, 650 were excluded, and 703 remained. Again, by examining the titles, 186 articles were removed because theirtitles were irrelevant to the present study's objective, and 517 article abstracts were reviewed. At this stage, 161 were considered relevant for full-text review. After reviewing the full text and checking the scientific quality of the works and the inclusion criteria, 44 articles remained for final analysis (Figure 1). Table 2 shows the characteristics of the final studies selected in the present work.

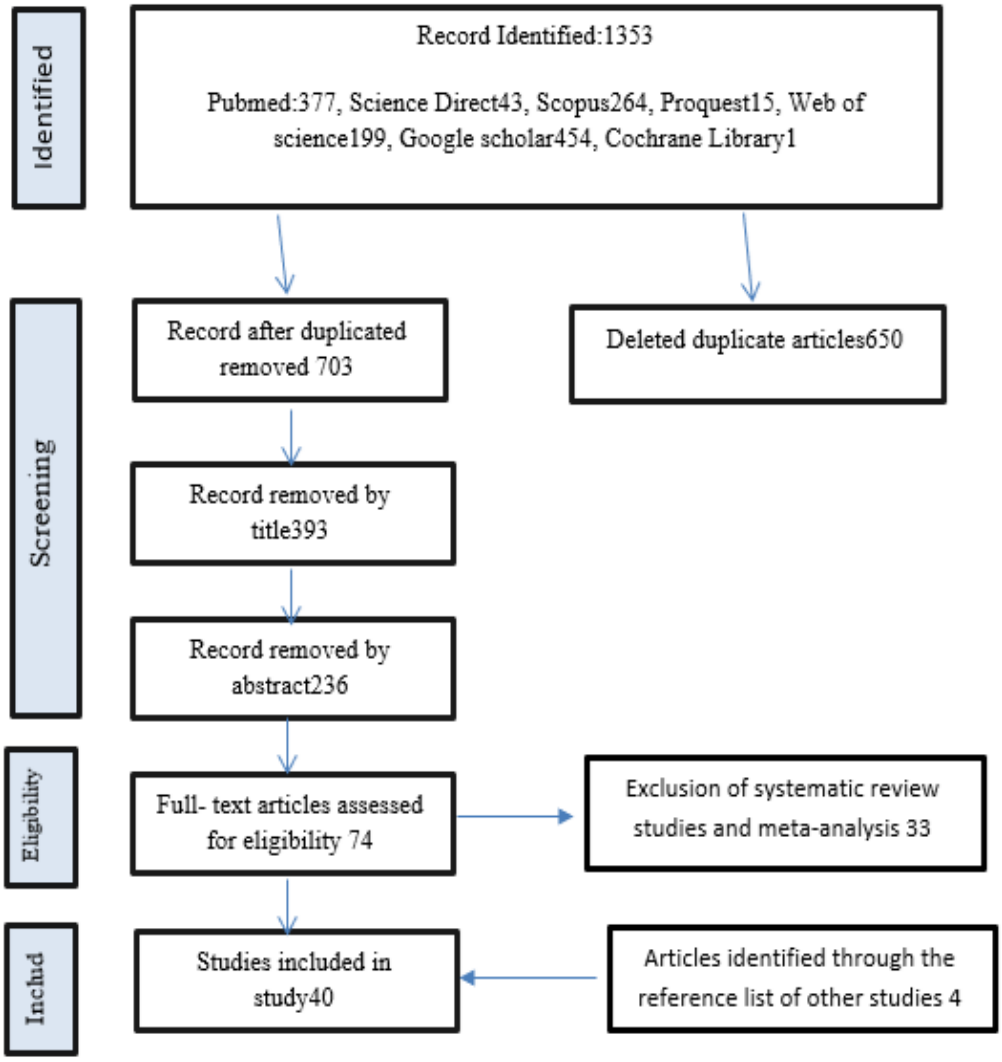


Fig. 1. The PRISMA graph of data retrieved from various databases based on inclusion and exclusion criteria

Table 2. Characteristics of the selected studies

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ID	Publication first author	Year	Country	Study design	medicinal plants	Part of plant used	Exposure time	Concentration	Result
1	Rguez [6]	2023	Tunisia	*in vitro*	*Cupressus sempervirens* *Tetraclinis articulate* *Pistacia lentiscus*	Aerial parts	-	-	The results showed *that C. sempervirens* is a very active anti-leishmania agent.
2	Alizadegan [7]	2023	India	*in vitro* and *in vivo*	*Nectaroscordum koelzi*	Leaves	-	-	Methanolic extract of *N. koelzi* has anti-leishmanial properties.
3	Ezenyi [8]	2023	Nigeria	*in vitro*	*Triumfettacordifolia*	Leaves	-	-	The results showed that the ethanolic extract of *T. cordifolia* has anti-inflammatory properties.
4	Bailén [4]	2023	Spain	*in vitro*	*Lamiaceae* *Asteracea*	-	-	-	Phytomonas can be used as alternative treatments or in combination with approved treatments for Leishmania.
5	Pyne [9]	2022	India	*in vitro*	*Ipomea aquatic* *Amaranthus viridis* *Ocimum sanctum* *Craniotome furcate* *Strobilanthes penstemonoides* *Garcinia cowa* *Mentha piperita* *Curcuma amada* *Ricinus communis* *Amaranthus gangeticus*	-	2-3 days	5 mg/ml	The results showed that *Garcinia cowa* has the potential to kill Leishmania.
6	Shaheen [10]	2021	Pakistan	*in vitro*	*Malus pumila* *Pyrus communis* *Diospyros lotus* *Prunus armeniaca* *Pyrus pashia* *Ficus glomerata* *Prunus persica*	-	3 days	m 0.5, 5, 25, 50, and 100µg/ml	The results showed that the *P. arminiaca* plant contains chemicals that can lead to the production of a cost-effective drug for Leishmania.
7	Najm [11]	2021	Iran		*Artemisia persica* *A. spicigera* *A. fragrance against*	Leaves	3 days	12.5, 25, 50, 100, 200, 400 and 800 µg/ml	The results showed that the herb has anti-leishmanial properties.
8	Ferreira [12]	2021	Brazil	*in vitro*	*Nectandra megapotamica* *Brunfelsia uniflora* *Myrcianthes pungens* *Anona muricata* *Hymenaea stigonocarpa* *Piper corcovandesis*	-	-	-	The results show that medicinal plants have the potential to be used as anti-leishmanial drugs.
9	Nigatu [13]	2021	Ethiopia	*in vitro*	*D. peninervium* *F. communis* *O. integrifolia* *U. simensis*	-	3 days	1, 0.50, 0.25, 0.125 and 0.065 mg/ml	*F. communis* and *O. integrifolia* exhibited the strongest anti-leishmanial activity against *L. aethiopica* and *L. donovani.*

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10	Balahbib [14]	2020	Morocco	*in vitro*	*Origanum compactum* *Lavandula stoechas L* *Mentha pulegium L* *Salvia officinalis L.* *Rosmarinus officinalis* *Myrtus communis* *Arbutus unedo L* *Cistus crispus L.* *Centaurium* *Pistacia lentiscus L.* *Salvia verbenaca* *Berberishispanica* *Lavandula dentate* *Cistus salviifolius* *Crataegus oxyacantha* *Ephedraaltissima*	Flowering top Flowering top Flowering top Leaf Leaf Leaf Leaf Leaf Flowering top Leaf Leaf Stem bark Flowers Leaf Leaf Tige	-	-	The results showed that medicinal plants with effective anti-leishmanial properties can be a valuable source for the treatment of leishmaniasis
11	Hammi [15]	2020	Tunisia	*in vitro*	Moringa oleifera	Leaves	-	-	The findings showed that *M. oleifera* extract can be used as a potential anti-protozoal drug.
12	Al Nasr [16]	2020	Saudi Arabia	*in vitro*	*Sonchus oleraceus* *Echinops spinosissimus* *Trichodesma Africana* *Pergularia tomentosa* *Teucrium oliverianum* *Blepharis ciliaris* *Citrllus colocynthis* *Cleome amblyocarpa* *Aerva javanica*	-	-	91 µg/mL	The results show that *T. oliverianum*, *P. tomentosa*, and *C. amblyocarpa* are the best anti-leishmanial plants.
13	Machado [17]	2019	Portugal		Lavandula luisieri Lavandula viridis	Flower Leaves	-	5 µg/mL	The results show that *L. luisieri* is a source of bioactive molecules to control leishmaniasis.
14	Tasdemir [18]	2019	UK	*in vitro* and *in vivo*	Origanum	-	5 days	150 ng/mL	*O. onites* derivatives have the potential to treat protozoan infections.
15	Mara Teles [19]	2019	Brazil	*in vitro* and *in vivo*	*Cinnamomum zeylanicum* *Curcuma longa* *Origanum vulgare*	Skin Stem Leaves	3 days	5–2000 µg/mL	The essential oil of three chemical compounds has anti-leishmanial properties, but the effects of *C. longa* are stronger.
16	Shokri [20]	2017	Iran	*in vitro*	*Lavandula angustifolia* *Rosmarinus Officinalis*	Flower Leaves	-	-	Investigations showed that both plants can have anti-leishmanial effects.
17	Bouyahya [21]	2017	Morocco	*in vitro*	*Lavandula stoechas*	Flower	-	-	The essential oil of *L. stoechas* has anti-leishmanial properties.

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18	Audrey R [22]	2017	Brazil	*in vitro*	Carvacrol Thymol Carene Eugenol Isoborneol Carvone Menthol Linalool Cineole	-	-	-	Further studies are needed to evaluate the effects of these compounds.
19	Mans [23]	2016	Netherlands	*in vitro*	*Allium sativum L.* *Aloe vera* *Anacardium occidentale* *Azadirachta indica A* *Bryophyllum pinnatum* *Cecropia peltata L* *Citrus aurantifolia* *Colocasia esculenta* *Crescentia cujete L* *Dieffenbachia seguine* *Eclipta prostrata (L.)* *Gossypium barbadense L.* *Abelmoschus esculentus* *Hymenaea courbaril L* *Inga alba* *Ipomoea batatas* *Mikania micrantha Kunth* *Morinda citrifolia L* *M Quassia amara L* *Quassia amara L.* *Senna alata* *Solanum lycocarpum A.St.-Hil* *Spondias mombin L* *Uncaria guianensis* *Vismia guianensis*	Cloves Leaves Bark Leaves Leaves Leaves Fruits Leaves Fruits Leaves Leaves Leaves Leaves Bark Bark Tubers Leaves Leaves Leaves Bark Leaves Leaves Bark Leaves Leaves	-	500–15,625 µg/mL	The results showed that *S. lycocarpum* can potentially be used to treat Leishmania.
20	Dey [24]	2015	India	*in vitro* and *in vivo*	*Croton caudatus* Geisel	stems and leaves	-	2.5-10 µg/mL	The results showed that *C. caudatus* Geisel has the potential to be used as an anti-leishmanial drug.
21	Nosratabadi [25]	2015	Iran	*in vitro*	*Eucalyptus camaldulensis*	Leaves	-	-	The results showed that *E. camaldulensis* extract has no effect on Leishmanial wounds.
22	Pastor [2]	2015	Cuba	*in vitro*	*Chenopodium ambrosioides*		3 or 4 days	250, 600 µg/mL	The combination of *C. ambrosioides* can be an alternative to monotherapy, relying on anti-leishmanial drugs.
23	Dashtpeima [26]	2015	Iran	*in vitro* and *in vivo*	*chamomile*	Flower	18 days	60 µg/mL	Chamomile tea can be recommended as an alternative medicine for leishmania.

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24	Morais [27]	2014	Brazil	*in vitro* and *in vivo*	*Thymol* *Eugenol*	-	3 days	100, 50, 25, 12.5 and 6.25 µg/ml	Synthesized derivatives of *Thymol* *Eugenol* had anti-leishmanial properties.
25	Ezatpour [28]	2014	Iran	*in vivo*	*Pistacia khinjuk*	Fruit	30 days	0–100 µg/mL	The results showed that this plant can be used to treat Leishmaniasis.
26	Ahmadi [29]	2014	Iran	*in vivo*	*Seidlitzia rosmarinus*	leaves and stems	10 days	5, 10& 15%	Hydroalcoholic extracts of *S. rosmarinus* with concentrations less than 15% had no therapeutic effect on Leishmanial wounds.
27	Khoshzaban [30]	2014	Iran	*in vivo*	*Peganum harala*	Seed	56 days	400 mL	*P. harala* extract is effective in the treatment of leishmaniasis
28	Hooshyar [31]	2014	Iran	*in vivo*	*Hedera helix*	Leaves	30 days	-	The results showed that *H. helix* does not have an anti-leishmanial effect.
29	Rodrigues [32]	2014	Brazil	*in vitro*	*Arrabidaea chica*	Leaves	7 days	37.2 and 18.6 µg/mL	The results support the effect of *A. chica* as an anti-leishmanial agent.
30	Ribeiro [33]	2014	Brazil	*in vitro*	*Bowdichia virgiloides Kunth* *Campomanesia lineatifolia Ruiz* *Cecropia pachystachya Trécul* *Chrysobalanus icaco L.* *Diospyros hispida D.C* *Dipteryx alata Vog* *Syzygium cumini Lam.* *Eugenia uniflora L* *Hymenaea courbaril L* *Hymenaea stignocarpa Mart* *Jacaranda caroba Vell* *Jacaranda cuspidifolia Mart.* *Jacaranda ulei Bureau* *Licania tomentosa Benth.* *Melacium campestre Naudin* *Vernonia phosphorea Vell*	Leaves Roots Leaves Stem bark Leaves Leaves	3 days	-	The results showed that the extracts of *D. alata* and *J. cuspidifolia* can have anti-leishmania effects.
31	Machado [34]	2013	Portuga	*in vitro*	*Thymus capitellatus*	Leaves	1 day	10 to 400 g/ml.	The results showed that *T. capitellatus* can be a source of treatment for Leishmaniasis.

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32	Sanchez [35]	2013	Colombia	*in vitro*	*Ocimum basilicum L* *Zingiber officinale Roscoe* *Citrus limon* *Cymbopogon citratus* *Mentha x piperita L* *Citrus sinensis* *Origanum vulgare L.* *Rosmarinus officinalis L.* *Thymus vulgaris L.* *Coriandrum sativum L.*	-	-	-	*O. basilicum* essential oil has anti-leishmaniasis properties.
33	Kahla-Nakbi [36]	2010	Tunisia	*in vitro*	*marine sponge*	-	3 days	1.39 to 264.67 µg/ml	The results showed anti-leishmania properties for this extract.
34	Honda [37]	2010	Brazil	*in vitro*	*Calophyllum brasiliense*	leaves	32 days	40, 20 µg/ml	*C. brasiliense* has leishmanicidal properties.
35	Kivçak [38]	2009	Türkiye	*in vitro*	*Arbutus unedo*	Leaves	2-3 days	100, 250, 500 µg/ml	Ethanol extract of *Arbutus unedo* leaves can be considered as an anti-leishmanial agent.
36	Ngure [39]	2009	Kenya	*in vitro*	*Warburgia ugandensis*	-			*W. ugandensis* has the potential to be used to treat Leishmaniasis.
37	Ozbel [40]	2007	Turkey	*in vitro* and *in vivo*	*Haplophyllum myrtifolium*	Flower		8.7, 9.4, 10.9, 25.7 and 25.8 µg/ml	The results showed that the acid extract of *Haplophyllum myrtifolium* has a limited effect on reducing the size of the lesion.
38	Dutta [41]	2007	India	*in vivo*	*Aloe vera*	Leaves			*A. vera* shows leishmanicidal properties.
39	Peraza-Sánchez [42]	2007	Mexico	*in vitro*	*Aphelandra scabra* *Byrsonima bucidaefolia* *Byrsonima crassifolia* *Clusia flava* *Cupania dentate* *Diphysa carthagenensis* *Dorstenia contrajerva* *Milleria quinqueflora* *Tridax procumbens* *Vitex gaumeri*	Leaves Bark Bark Leaves Bark Leaves Whole plant Roots Whole plant Bark			The results showed that these herbal medicines have a strong inhibitory effect on the growth of Leishmania.
40	Monzote [43]	2007	Cuba	*in vivo*	*Chenopodium ambrosioides*	Essential oil			This natural product is a start for the development of new and effective drugs against Leishmaniasis.
41	Ganguly [44]	2006	India	*in vitro*	*Artemisia indica*	Leaves	2days	10 mg/ml	The results showed that *A. indica* has anti-leishmania properties.

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42	Tiuman [45]	2005	Brazi	*in vitro*	*T.Parthenolide*	Not stated	The results showed that *T. parthenium* shows leishmanicidal pro[perties in laboratory conditions.
43	Torres-Santos [46]	2004	Brazil	semi experimental	*Kalanchoe pinnata*	leaves	*K. pinnata* stopped the growth and reduced Leishmania lesions. Additionaly, no adverse effects of this treatment were observed.
44	Teixeira [47]	2001	Brazil	*in vitro* and *in vivo*	lapachol	-	The results showed that Lapacol has a leishmanicidal function in laboratory conditions.

Discussion

Different parts of medicinal plants, such as leaves, roots, stems, flowers, and fruits are used in such different ways as infusion, soaking, tincture, and boiling to treat various infectious diseases like leishmaniasis. These herbal medicines, due to their availability and low costs, are widely used by affected populations [48]. Based on the results of this study and the available research worldwide on the effectiveness of Leishmania as a herbal remedy, the evidence is very scattered. In this study, 117 different plant species used in different countries to treat Leishmania were identified. Most of the cases were related to Brazil, Iran, India, and Pakistan. This can be due to the endemicity of the disease in these areas [49], or due to the high costs of industrial treatments, medicine shortages, lack of access to health and treatment services, and cultural acceptance of herbal medicines among native populations and tribes [50].

With the increasing global incidence of leishmaniasis, the need for effective and accessible treatments has become more urgent. The disease disproportionately affects socioeconomically disadvantaged populations, particularly those living in conditions associated with inadequate sanitation and limited access to healthcare, which may also contribute to delayed treatment and poor treatment adherence. On the other hand, the available treatments have side effects such as toxicity, liver damage, and anemia. Furthermore, their cost is also high, and this can cause the lower socio-economic class of people to be deprived of effective treatment [9]. Due to the limited availability of effective drugs, most people in areas where leishmaniasis is endemic seek indigenous treatments to reduce their symptoms. The treatment of Leishmania in endemic areas strongly depends on medicinal plants [51]. In

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some areas, plants and their extracts are the only available therapeutic options; therefore, it is necessary to conduct scientific studies on these plants to assess their efficacy and toxicity.

Given the wide diversity of medicinal plants traditionally used worldwide to treat leishmaniasis, a systematic review is needed to provide a concise assessment of their efficacy, toxicity, and potential side effects [50]. It should also be noted that many herbal remedies are less inhibitory than drugs/antibiotics. In addition, most studies on these plants have been conducted in laboratory settings, and the number of clinical trials confirming their effects is small. It would be better to conduct *in vivo* studies on plant extracts and pure compounds, especially when *in vitro* results are available.

There was limited access to some scientific literature, including gray literature, in this study. Additionally, given that most people tend to use native plants from their own regions as herbal treatments, it is possible that some studies might have been conducted on these plants and published in local journals to which the present researchers did not have access.

Conclusion

The results showed that medicinal plants from diverse geographical regions and vegetation zones contain bioactive compounds with promising anti-leishmanial activity. These plants can represent potential candidates for further preclinical and clinical studies aimed at developing effective anti-leishmanial drugs.

Ethical Considerations

This study is a systematic review of previously published literature; therefore, ethical approval was not required to conduct the study.

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This research received no specific funding.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Z.A.M. and R.N. contributed to the conception and design of the study, interpretation of the data, and preparation of the manuscript. A.A., M.D., F.H., H.A., and F.S. contributed to data collection, study screening, and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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