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Antileishmanial potential of medicinal plants: A global systematic and meta-analytic review of in vitro studies

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ABSTRACT

Introduction: Leishmaniasis is a major global health challenge with limited treatment options and rising drug resistance. Medicinal plants, traditionally used in many regions, offer a promising source of new antileishmanial agents. This study aims to systematically review global in vitro evidence on the antileishmanial activity of medicinal plants.

Methods: Data published between 2013 and 2025 were systematically retrieved from four databases: ScienceDirect, Scopus, PubMed, and Web of Science. The search used combinations of the keywords "plant extract," "*Leishmania*," "medicinal plants," "herbal extract," "traditional medicine," and "herbal medicine." A total of 29 studies met the inclusion criteria, encompassing 271 in vitro experiments. The difference in half-maximal inhibitory concentration (D-IC_{50}) was calculated to compare the efficacy of the tested extracts or compounds relative to the positive control, with negative values indicating stronger inhibitory activity.

Results: Seventy-two different plant species were thoroughly tested against *Leishmania* spp. On the other hand, the heterogeneity study revealed significant variations among studies (I-square greater than 75%). Linear regression analysis demonstrated significant antileishmanial activity for several medicinal plants and their bioactive compounds. *Myrtus communis* L., *Peganum harmala,* and *Ferula macrecolea* showed notable effects, with D-IC_{50} values of –20.315, –69.650, and –13.200 µg/mL, respectively ($P < 0.001$). Among the bioactive molecules, terpinolene (–262.570), plumericin (–241.850), and ergosterol peroxide (–240.470) exhibited the strongest inhibitory effects, all highly significant ($P < 0.001$).

Conclusion: This review highlights promising natural compounds with antileishmanial properties that warrant further investigation in upcoming laboratory and clinical studies.

Implication for health policy/practice/research/medical education:
This review highlights the global use of medicinal plants with antileishmanial properties through in vitro studies. Several plant species demonstrated significant inhibitory effects against *Leishmania* spp. The findings support further research into plant-based therapies as alternative treatments. They also underscore the value of traditional medicine in public health strategies and medical education.

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Introduction

Leishmaniasis is identified by the World Health Organization (WHO) as one of the neglected tropical diseases (1). It is a widespread zoonotic infection caused by protozoan parasites of the *Leishmania* genus, which are intracellular and flagellated in nature (2). Transmission typically occurs through the bite of an infected female *Phlebotomus* sand-fly during blood feeding, affecting

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both humans and animals (3). The disease manifests in four principal clinical forms: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis, and post-kala-azar dermal leishmaniasis (2). Clinical symptoms vary widely and may include localized skin ulcers at the point of parasite entry or systemic involvement of internal organs, which can lead to anemia, fever, leucopenia, and general weakness (4).

At the outset, the incidence and prevalence of this disease vary across the world. Leishmaniasis is a neglected disease in the global spectrum, and it largely affects people living in conditions of poverty in low and middle-income countries (5). Besides, each year, approximately 1.5 million new instances of CL are reported globally, highlighting the persistent public health burden posed by this parasitic disease. Moreover, twenty to thirty thousand cases of VL are reported yearly worldwide (6). The mortality rates also differ with the type of leishmaniasis and area; VL is more fatal than the cutaneous form of leishmaniasis, especially if it is not treated, and can kill more than 90% of patients (7,8). Furthermore, findings from a study suggest that in certain regions of Africa and South Asia, the death rates can be 20% of the cases diagnosed (6).

Cutaneous leishmaniasis is a significant public health issue in Latin American countries. It is also prevalent in the Northeast and Southeast regions of Brazil, and the incidence rate differs according to the state (5). However, VL is found predominantly in North Africa and South Asia; cut off from the rest of the world due to war and poor sanitation, incidence rates in Sudan remain very high (7). Additionally, awareness of prevention measures is necessary to control the incidence of the disease. Thus far, the improvement of health systems has enabled more at-risk populations to gain access to healthcare (8). Furthermore, the rates of incidence and mortality have been found to decrease over time in some areas, indicating that improved health systems can yield better outcomes (5).

First-line treatments include sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime), whereas second-line therapies comprise amphotericin B, paromomycin, pentamidine, and miltefosine (9). Nonetheless, the scarcity of available drugs and the growing problem of resistance remain significant barriers to effective leishmaniasis treatment. The high toxicity, elevated cost, and increasing resistance associated with current therapies have driven the search for novel treatment approaches (10). Additionally, the WHO has promoted the use of traditional medicine, particularly in communities where access to conventional healthcare is limited (11). Moreover, insights gathered from this review could contribute to the discovery of natural products with promising antileishmanial properties and stimulate the development of novel and effective synthetic agents.

While the global number of medicinal plant species is estimated to approach 250,000 (8), only around 6% have undergone evaluation for their biological activities. Furthermore, clinical trials have been conducted on merely 1% of compounds derived from these plants (12,13). Despite the widespread recognition of traditional plant-based medicines in many communities, few rigorous, globally synthesized evaluations have assessed the scientific evidence for their antileishmanial efficacy. While numerous laboratory studies over the past decades have identified promising activity of various plants against *Leishmania* species, the literature remains fragmented, inconsistently reported, and often inaccessible to policymakers and drug developers. This issue is further compounded by the lack of standardized methodologies, making it difficult to compare outcomes, identify the most effective candidates, or prioritize them for drug development. Moreover, with the number of studies on antileishmanial medicinal plants growing steadily each year, there is a pressing need for regularly updated systematic reviews and meta-analyses. Such efforts are essential for transforming traditional knowledge into evidence-based therapeutic strategies. In this context, our research provides a comprehensive, systematic, and meta-analytic review of medicinal plants evaluated worldwide against *Leishmania* parasites.

Methods

Search method

In this study, a comprehensive literature search covering the period from 2013 to 2025 was performed to investigate the antileishmanial activity of extracts and/or compounds derived from medicinal plants, assessed through various in vitro assays against different *Leishmania* species. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). Key scientific databases consulted included Scopus, ScienceDirect, Web of Science, and PubMed. The search strategy employed keywords such as "*Leishmania*," "plant extract," "herbal extract," "medicinal plants," "traditional medicine," and "herbal medicine," used individually or in combination. Searches were conducted in English, French, and Spanish.

Studies identification

The selected articles were analyzed based on the extracted data, including the year of publication, *Leishmania* species studied, plant species, type of extract, plant part used for extraction, active compounds, concentrations, exposure duration, and positive controls. Studies with repetitive content, abstracts, conference proceedings, expert opinions, reviews, and articles with insufficient information were excluded. Additionally, studies were omitted if they lacked essential experimental controls, failed to report IC_{50} values, did not perform statistical analyses, or did not include assay replications. Following

the application of the selection criteria, 29 studies were selected for in-depth analysis from an initial total of 3,108 records (Figure 1).

Statistical analysis

In this meta-analysis, the outcomes were continuous of a subgroup depending on the positive control used (meglumine antimoniate, amphotericin B, pentamidine, miltefosine), the 95% confidence intervals and the difference in half-maximal inhibitory concentration values (D-IC_{50}) were calculated to compare the efficacy of the experimental treatment relative to the positive control. For each tested extract or compound, the IC_{50} value, defined as the concentration required to inhibit 50% of parasite viability. A positive D-IC_{50} value indicates that the test compound is less potent than the positive control, while a negative value suggests higher potency. The D-IC_{50} (ug/mL) was then calculated as follows:

$$D\text{-}IC_{50} = IC_{50\ \text{Experimental}} - IC_{50\ \text{Positive Control}}$$

where IC_{50} (experimental) is the mean IC_{50} of the tested extract or compound; IC_{50} (Positive control) is the mean IC_{50} of the reference drug (Amphotericin B, miltefosine, etc).

A random-effects model with a 95% confidence interval (CI) was used to report the findings. Heterogeneity among studies was evaluated using Cochrane's Q test, with *P* values below 0.1 indicating significant heterogeneity, and further quantified using the I^2 statistic, classified as low (25–49%), moderate (50–74%), or high (≥75%) (15,16). Statistical analyses were carried out using JASP version 0.17.1.0 and RevMan 5.9.

Assessment of publication bias

Publication bias was assessed through visual inspection of a funnel plot, displaying effect sizes against their standard errors. To detect asymmetry, Egger's regression intercept and Kendall's rank correlation (tau) tests were applied. Additionally, Rosenthal's fail-safe N was computed to estimate the number of potential unpublished studies with null findings required to negate the observed effect. All analyses were conducted using Jamovi software.

Results

Applying the aforementioned inclusion and exclusion

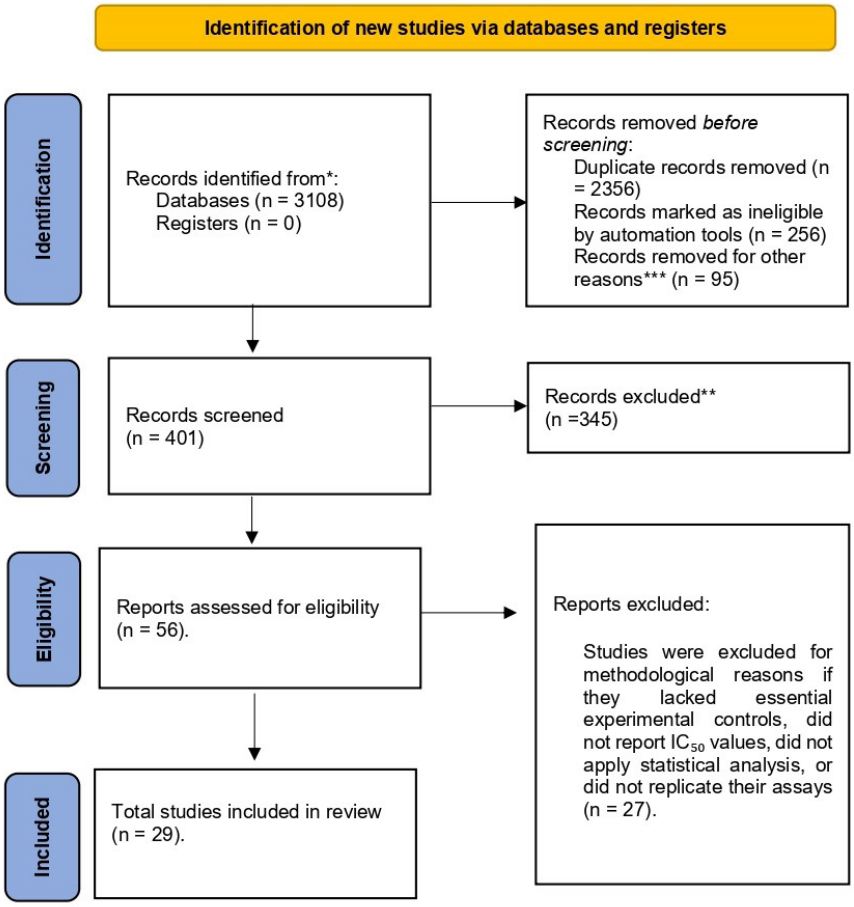

Figure 1. The PRISMA flow diagram illustrating the literature search and study selection process for in vitro studies on the antileishmanial potential of medicinal plants. * ScienceDirect, PubMed, Scopus, and Web of Science databases; ** Focused on a different disease/topic; *** Abstracts, conference proceedings, expert opinions, reviews, and articles with insufficient information.

criteria, a total of 29 publications comprising 271 in vitro experiments were deemed eligible for inclusion in the meta-analysis, selected from an initial pool of 3,108 research articles. These studies cover the period from 2013 to 2025, with a marked increase in publications observed in 2022. Geographically, 48% of the studies originated from Asia (including India, Indonesia, Iran, Malaysia, Saudi Arabia, and Pakistan), 45% from South America (Brazil, Cuba, and Suriname), while African countries (Morocco and Cameroon) represented only 7% of the total. The extracted data included plant species, their botanical families, preparation methods, active compounds, collection locations, exposure durations, half-maximal inhibitory concentrations (IC_{50}), and the *Leishmania* species tested. The studies evaluated plant extracts against seven different *Leishmania* genera, with *L. amazonensis*, *L. donovani*, *L. brasiliensis*, and *L. tropica* being the most frequently assessed species. Consequently, we aimed to compile and summarize various studies detailing herbs and natural products exhibiting antileishmanial activity (Supplementary file 1) (17-45).

Among the natural sources studied globally, *Allamanda schottii*, *Canarium patentinervium* Miq., *Diospyros gracilescens*, *Eugenia umbelliflora*, *Solanum sisymbriifolium*, and *Garcinia achachairu* were identified as the most potent leishmanicidal agents. Additionally, a heterogeneity test showed a considerable variability across studies, reflected by a high Q statistic (Tau^2 = 2280.07; Chi^2 = 27845.32, df = 28, $P < 0.00001$, I^2 = 100%). Based on the random-effects model, the pooled D-IC_{50} was estimated at 41.79 (95% CI: 22.07 to 61.51) with statistical significance (Z = 4.15, $P < 0.0001$) (Figure 2).

Moreover, the test for subgroup differences yielded a Chi^2 value of 46.03 with 3 degrees of freedom ($P < 0.0001$) and an I^2 of 93.5%, indicating substantial heterogeneity among subgroups. Within these, medicinal plants tested against meglumine antimoniate as the positive control showed the lowest D-IC_{50} values, suggesting higher efficacy. The statistical analysis of the D-IC_{50} values and exposure time revealed a significant negative correlation (r = -0.330, $P < 0.001$) between the two variables. Secondly, a linear regression analysis was conducted to explore the influence of various characteristics, including plant family, species, plant part used, preparation method, and active compound. The results indicated that D-IC_{50} values varied significantly depending on the plant part ($P < 0.001$), with "leaves", "fruit", and "stem" being the most commonly used parts. Furthermore, the regression analysis revealed significant differences in preparation methods ($P < 0.001$). Essential oil, methanol, and n-hexane extracts were associated with lower D-IC_{50} values, whereas chloroform and hydroalcoholic extracts showed higher D-IC_{50} values. In addition, hydrodistillation and percolation were the most efficient extraction methods for antileishmanial

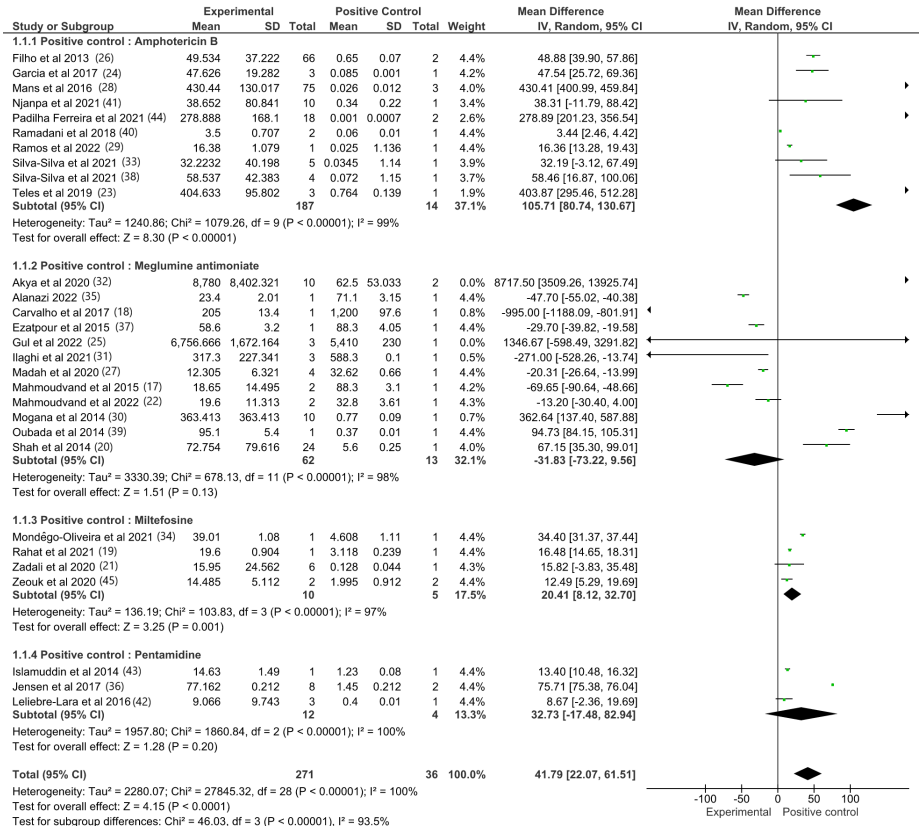

Figure 2. Forest plot displaying the D-IC_{50} values between medicinal plant extracts and standard positive controls.

activity. The D-IC_{50} values for medicinal plants showed a significant difference ($P < 0.001$), with *Myrtus communis* L., *Peganum harmala, Ferula macrecolea, Myracrodruon urundeuva, Nicotiana tabacum, Calotropis procera, Pistacia khinjuk, Quercus velutina,* and *Stachys lavandulifolia* having more efficacy against *Leishmania* spp. In addition, alkaloids, terpinolene, and plumericine were highly active compounds against *Leishmania* spp (Table 1).

The linear regression analysis revealed significant antileishmanial activity for most tested molecules, as indicated by their negative mean differences and highly significant *P* values (<0.001). Among the most potent compounds, terpinolene (-262.570), plumericin (-241.850), and ergosterol peroxide (-240.470) exhibited the highest mean differences, suggesting strong inhibitory effects. Conversely, vomifoliol (236.790), scoparone (87.760), and lioxin (60.660) showed positive mean differences, implying lower or potentially ineffective antileishmanial activity. Notably, Scopoletin (-78.840, $P = 0.094$) did not reach statistical significance, indicating weaker or variable effects (Table 2).

A residual versus predicted values plot was generated to explore the behavior of the D-IC_{50} data obtained from both the positive control and the medicinal plant tested against *Leishmania*. This plot offers a visual assessment of the residuals' distribution in the model, serving as a diagnostic tool for evaluating model assumptions. It revealed that most residuals were tightly clustered near zero, particularly for higher predicted values, with the presence of a few extreme residuals indicating potential outliers. In parallel, a Q-Q plot of the standardized residuals was also produced to evaluate whether the residuals followed a normal distribution. While most residuals were aligned near zero, strong deviations were observed at both tails of the distribution, indicating non-normality in the residuals (Figure 3).

Table 1. Subgroup meta-analysis results of D-IC_{50} stratified by plant family, plant name, plant part, preparation method, extraction method, and *Leishmania* species

Variables		N	D-IC_{50} value (µg/mL)	*P* value
Family of plant	*Apiaceae*	2	-13.200	0.819
	Fagaceae	1	-455.700	
	Menispermaceae	2	3.440	
	Nitrariaceae	4	-20.315	
	Polyporaceae	3	8.667	
	Tamaricaceae	4	12.500	
Name of plant	*Calotropis procera*	1	-340.200	< 0.001
	Ferula macrecolea	2	-13.200	
	Myracrodruon urundeuva	1	-995.000	
	Myrtus communis L	2	-69.650	
	Nicotiana tabacum	1	-17.100	
	Peganum harmala	4	-20.315	
	Pistacia khinjuk	1	-29.700	
	Quercus velutina	1	-455.700	
	Stachys lavandulifolia	1	-47.700	
Part of plant	Aerial	25	53.132	< 0.001
	Branch	2	90.150	
	Root	24	96.546	
	Stem	28	39.302	
	Whole plant	16	105.273	
Preparation	Dichloromethane	14	34.244	< 0.001
	Methanol	34	10.633	
	N-hexane	7	32.429	
Extraction methods	Decoction	75	430.414	< 0.043
	Hydrodistillation	7	32.087	
	Maceration	180	587.184	
	Percolation	8	-37.245	
Leishmania spp.	*L. amazonensis* promastigotes	68	77.041	< 0.001
	L. braziliensis promastigotes	42	98.355	
	L. donovani promastigotes	54	268.426	
	L. guyanensis promastigotes	29	409.469	
	L. infantum promastigotes	3	13.761	
	L. major promastigotes	34	1895.926	
	L. tropica promastigotes	41	918.830	

D-IC_{50} refers to the mean difference in IC_{50} values (µg/mL). n: number of comparisons or experiments analyzed in each subgroup. Subgroup analysis was conducted using linear regression; results were considered highly significant for $P < 0.01$, significant for $0.01 < P < 0.05$, and not significant for $P \geq 0.05$.

Table 2. Linear regression analysis of the association between plant-derived bioactive compounds and D-IC_{50} values in the in vitro antileishmanial studies

Molecules	Unstandardized	SE	T	*P* value
Terpinolene	-262.570	41.432	-6.337	<0.001
Plumericin	-241.850	35.881	-6.740	<0.001
Ergosterol peroxide	-240.470	41.432	-5.804	<0.001
Carajurin	-237.744	41.432	-5.738	<0.001
Cilistol A	-237.170	35.881	-6.610	<0.001
Anthocyanidins	-236.428	41.432	-5.706	<0.001
Trametenolic acid B	-235.870	41.432	-5.693	<0.001
Betulinic acid	-228.020	41.432	-5.504	<0.001
Guttiferone A	-227.620	35.881	-6.344	<0.001
Myrsinoic acid B	-226.920	35.881	-6.324	<0.001
Phomoxanthone A	-225.015	41.432	-5.431	<0.001
Stellasterol	-221.770	41.432	-5.353	<0.001
3′-hydroxycarajurone	-218.704	41.432	-5.279	<0.001
Lupeol	-218.490	41.432	-5.273	<0.001
Carajurone	-213.124	41.432	-5.144	<0.001

"Unstandardized" represents the change in D-IC_{50} associated with each bioactive compound. The standard error (SE) of the regression coefficient indicates the precision of the estimate. Smaller SE suggests more confidence in the coefficient. The t-statistic (t) was used to test whether the regression coefficient was significantly different from zero. The analysis was conducted using linear regression; results were considered highly significant for $P < 0.01$, significant for $0.01 \leq P < 0.05$, and not significant for $P \geq 0.05$.

To assess potential publication bias among the included studies, both graphical and statistical methods were employed. A funnel plot was generated to provide a visual representation of the distribution of study effect sizes about their standard errors (Figure 4). The Rosenthal Fail-Safe N was computed to determine the number of additional studies with null results required to bring the overall effect size to non-significance. This calculation resulted in a Fail-Safe N value of 120,409, with a *P* value less than 0.001. To complement this, Kendall's rank correlation test was applied to assess the correlation between effect sizes and their standard errors, yielding a Tau value of 0.512 with a *P* value below 0.001. Additionally, Egger's regression test was conducted to detect funnel plot asymmetry; the regression intercept was 1.713, with a *P* value of 0.087.

Discussion

In the present study, a total of 72 plant species were investigated through 271 in vitro experiments, revealing a broad spectrum of extracts with antileishmanial potential. The analysis of their effects showed substantial heterogeneity across studies, as indicated by a high I^2

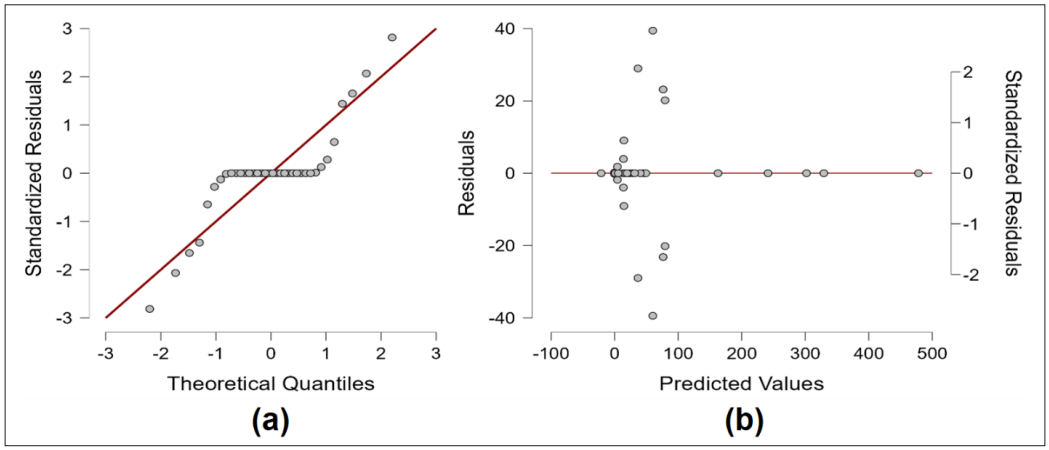

Figure 3. Diagnostic plots used to evaluate the regression model by analyzing D-IC_{50}. Plot (a) shows a Q-Q distribution of standardized residuals, indicating deviations from normality, especially at both tails. Plot (b) displays residuals against predicted values, with most residuals clustered near zero and a few outliers. Residuals: Differences between observed and predicted D-IC_{50} values. Predicted values: D-IC_{50} values estimated by the regression model. Standardized residuals: Residuals scaled to have a mean of 0 and standard deviation of 1. Theoretical quantile: Expected value from the normal distribution at a given percentile.

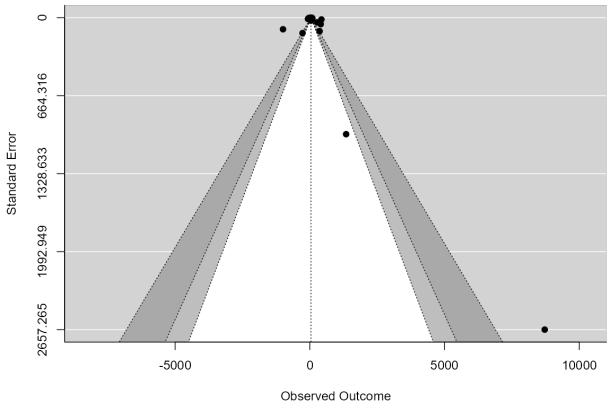

Figure 4. Funnel plot assessing publication bias in the in vitro studies on the antileishmanial activity of medicinal plants. This funnel plot visually assesses the presence of publication bias among the included studies. Each point represents a single study, plotting the D-IC_{50} on the horizontal axis against its standard error (SE) on the vertical axis.

value (≥75%) (15,16). A high I^2 statistic suggests that the variability in study outcomes is largely due to real differences between studies, such as variations in plant species, type of extract, plant part used, preparation method, concentration applied, and duration of exposure, rather than by chance alone. These factors likely contributed to the observed inconsistency in antileishmanial efficacy.

Among the *Leishmania* species included in this review, *L. amazonensis*, *L. donovani*, *L. braziliensis*, and *L. tropica* were the most frequently tested. Notably, *L. braziliensis* is a leading cause of the CL, while *L. amazonensis* is associated with both diffuse anergic CL and disseminated cutaneous lesions (2). However, species such as *L. amazonensis*, *L. infantum*, and *L. braziliensis* appear to be more susceptible and less resilient compared to *L. major*, *L. guyanensis, L. tropica*, and *L. donovani*.

Although most of the reviewed studies concentrated on plant families such as Apocynaceae, Asteraceae, Fabaceae, and Solanaceae, the families Apiaceae, Fabaceae, and Nitrariaceae exhibited lower D-IC_{50} values, indicating greater antileishmanial efficacy. Among them, the *Fabaceae* family stands out as one of the most important plant families due to both its frequent investigation and notable biological activity (46).

Additionally, the plants belonging to the Fabaceae family have antirheumatic, anti-inflammatory, antiulcer, antibacterial, analgesic, antimicrobial, antidiabetic, anticancer, and cytotoxic properties (47-49). Furthermore, it is important to note that, *Nitrariaceae* genus plants are common in Central Asia's steppe and desert regions, as well as in the mountainous regions of South Siberia, Southeastern Europe, North Africa, and Southeast Australia; moreover, species from the Apiaceae family are strongly recommended as alternative sources of bioactive compounds, as several offer a wide array of biopesticidal and synergistic agents, while others yield substantial amounts of bioactive extracts (50). In short, *Apocynaceae, Asteraceae, Fabaceae,* and *Solanaceae* plant groups indicate their importance in leishmaniasis studies (51-54). The different therapeutic characteristics of *Fabaceae* make it a valuable resource, while the extensive geographic distribution of *Nitrariaceae* underlines its potential value in various places. The motivation to look for bioactive chemicals in *Apiaceae* species indicates the need to diversify research methodologies. Focusing on these promising plant families for future leishmaniasis therapies is critical. After incubation, all tested extracts exhibited antileishmanial activity; however, the following plants, *M. communis, P. harmala*, and *F. macrecolea,* performed better (15). Even though there is a significant difference ($P<0.001$) between plant species and D-IC_{50} across all research papers.

The extracts and essential oils from *M. communis*, a member of the Myrtaceae family, have exhibited antimicrobial and antioxidant activities in vitro (55). Additionally, the results of a study conducted by (56) demonstrated that another advantage of the *M. communis* L. plant over glucantime is oral administration rather than injection, making the herb simpler and more useful. *P. harmala*, a member of the Zygophyllaceae family, is the most frequently utilized Iranian plant for antileishmanial purposes; its active alkaloids, especially harmine, are extracted from the seeds of this medicinal species (57). Its seeds, in particular, have held a prominent place in various cultural pharmacopeias due to their rich alkaloid content and therapeutic potential. Beyond its medicinal value, *P. harmala* has also been used in rituals and as a fumigant. These diverse traditional applications have prompted modern interest in exploring their pharmacological properties, despite concerns regarding their potential toxicity at higher doses (58,59). Moreover, harmine exhibits a broad spectrum of pharmacological activities, including anti-inflammatory, neuroprotective, antidiabetic, and antitumor effects (15,60).

Likewise, *F. macrecolea* essential oil, specifically terpinolene (77.72%), have exhibited strong antiparasitic activity against both the promastigote and amastigote stages of *L. tropica* (22,61). Additionally, *F. macrecolea* Boiss, one of the principal species within this genus, possesses a wide range of therapeutic properties, including analgesic, anti-inflammatory, antihypertensive, antibacterial, antiparasitic, antiviral, antifungal, insecticidal effects, and is used in traditional and modern medicine to treat cardiovascular and gastrointestinal diseases (62,63).

According to the results of a single experiment, *M. urundeuva, N. tabacum*, *C. procera*, *P. khinjuk*, *Q. velutina,* and *S. lavandulifolia* have high antileishmanial activities. Firstly, *M. urundeuva* essential oil exhibits a potent effect against *L. amazonensis*, particularly targeting the

intracellular amastigote forms, which are more directly linked to the clinical symptoms of leishmaniasis. Notably, *M. urundeuva* essential oil demonstrated low cytotoxicity toward host cells. These findings highlight it as a promising candidate for the treatment of leishmaniasis (18). Secondly, a lectin extracted from the heartwood of *M. urundeuva* exhibited high inhibitory activity against both Gram-positive and Gram-negative bacteria, outperforming several standard antimicrobial treatments (64). Additionally, it is worth highlighting that *N. tabacum* exhibits a notable level of bioactivity against *L. tropica* stages, as well as scolicidal capabilities, which may help develop hydatid cyst surgical protocols and address deficiencies in hydatosis treatment, such as recurrence (31,65). Also, *N. tabacum* methanol extract demonstrated both antibacterial and antileishmanial potential, with notable activity against *L. tropica* promastigotes (66). Likewise, it is worth noting that *N. tabacum,* renowned for its long-standing use, ranks among the most efficient plant-based pesticides (16,66). In addition, the phytochemical analysis of tobacco leaves revealed alkaloids, terpenes, steroids, flavonoids, cardiac glycosides, and Saponins; some of them have a strong efficacy antileishmanial (66). *C. procera* has been traditionally used as a purgative, anthelmintic, anticoagulant, anticancer, anti-inflammatory, antipyretic, analgesic, and antibacterial agent. It is also employed in the treatment of leprosy, leucoderma, ulcers, tumors, hemorrhoids, and disorders of the spleen, liver, and abdomen (67). The methanolic extract of *C. procera* leaves has exhibited significant antiparasitic activity against both promastigote and amastigote stages of *L. major*, with a high level of activity against *L. tropica* (31,68,69). For the first time, the phenolic composition of *P. khinjuk* fruit has been described as having the highest overall phenolic and flavonoid concentration in hull extract. Moreover, the researchers discovered a strong relationship between antioxidant activity and total phenolic and flavonoid levels (70). *P. khinjuk* leaf extracts have antibacterial and antifungal properties (71). According to a study (37), the mean width of lesions was considerably lesion size was significantly reduced following treatment of subgroups with 20% and 30% concentrations of *P. khinjuk* extract. Various crude extracts of *Q. velutina* have shown to possess potent antileishmanial properties, indicating their potential as natural candidates for developing novel leishmanicidal agents against CL (31). Moreover, *S. lavandulifolia*, a species from the Lamiaceae family, is recognized for its strong antioxidant activity and may serve as a supportive supplement in managing oxidative stress-related conditions (72). A study (35), reported that the methanolic extract of *S. lavandulifolia* effectively eliminated *Leishmania* parasites and contributed to lesion healing in BALB/c mice infected with *L. major*. Notably, the *S. lavandulifolia* plant is used to treat gastrointestinal and respiratory problems. The oil has a high inhibitory action against *Candida tropicalis*, growths of *Staphylococcus aureus,* and *Salmonella typhimurium* (35).

Accordingly, numerous plant extracts illustrate antileishmanial activity, with certain species such as *M. communis, P. harmala,* and *F. macrecolea* showing promising outcomes. These plants have a diverse set of pharmacological and therapeutic qualities, making them ideal resources for the development of anti-leishmanial medications. Other plants, including *M. urundeuva, N. tabacum, C. procera, P. khinjuk, Q. velutina*, and *S. lavandulifolia*, show strong antileishmanial activity, potentially providing a variety of therapeutic options.

The D-IC_{50} values of various naturally derived compounds revealed significant differences, as indicated by negative unstandardized coefficients and strong significance. These negative coefficients suggest that each of the selected molecules produced a lower IC_{50} than the control, indicating stronger antileishmanial activity under the tested conditions. Terpinolene, plumericin, ergosterol peroxide, carajurin, and cilistol A are the higher active compounds against *Leishmania* spp. A growing body of evidence highlights the leishmanicidal potential of diverse natural compounds, including metabolites such as quinones, naphthoquinones, lignans, neolignans, and various alkaloid subclasses (e.g., quinoline, isoquinoline, steroidal, and indole-based structures). In addition, phenolic compounds like flavonoids and chalcones, as well as different terpene groups, such as iridoids, sesquiterpenes, diterpenes, triterpenoids, and saponins, have demonstrated promising antiparasitic properties (73). Among these, terpinolene has been recognized for its anti-inflammatory and pain-reducing effects, possibly through modulation of serotonergic mechanisms within the central nervous system (74). Moreover, this compound has shown potent antileishmanial activity against *L. tropica* promastigotes, with a response that intensifies at higher concentrations (22). Taken together, the cytotoxic and oxidative characteristics of terpenes offer valuable prospects for developing novel therapeutic agents targeting cancer and parasitic infections; otherwise, terpinolene has antimicrobial and antioxidant activity (74,75).

In recent years, natural product research has opened new avenues for the discovery of effective antileishmanial agents, with alkaloids standing out as particularly potent candidates (76). Among these, carajurin has demonstrated noteworthy efficacy against the promastigote stage of *L. amazonensis*, suggesting its potential as a pharmacological marker for the species' leishmanicidal capacity (77). This compound exhibited an IC_{50} value of 3.66 μg/mL against promastigotes and showed significant selectivity toward intracellular amastigotes (SI > 10) (33). Additionally, plumericine, a compound with previously reported antibacterial, antifungal, antileukemic, anticancer, cytotoxic, and anti-inflammatory effects, has also been proposed as a candidate for treating protozoan infections,

including leishmaniasis (26,78,79). Furthermore, plumericine demonstrated antimycobacterial properties, showing inhibitory activity against various fungal pathogens including *C. albicans*, *C. krusei*, *C. glabrata*, *C. tropicalis*, and *Cryptococcus neoformans* (80,81).

Conflicting data have emerged from recent studies concerning the antibacterial properties of ergosterol peroxide against *M. tuberculosis*, along with its in vitro activity against *L. amazonensis* (42,82). Nonetheless, ergosterol peroxide has shown strong antileishmanial effects against *L. donovani*, coupled with moderate selectivity for infected macrophages (SI > 3.85) (49). In a separate study (26), cilistol A exhibited marked efficacy against both *L. amazonensis* and *L. braziliensis*, with IC_{50} values reported at 6.6 and 3.1 µg/mL, respectively.

Terpinolene, a small volatile monoterpene hydrocarbon, contrasts structurally with larger, more complex molecules such as plumericin, a reactive iridoid lactone, and ergosterol peroxide, a steroid derivative. Polyphenolic compounds, such as carajurin, cilistol A, and anthocyanidins, also showed substantial D-IC_{50} values, likely due to their hydroxylated aromatic structures, which may facilitate interaction with parasitic targets. Similarly, triterpenoids such as betulinic acid, lupeol, and trametenolic acid B demonstrated strong performance, with IC_{50} values significantly lower than the control, despite their bulky, lipophilic frameworks. This wide structural diversity, ranging from small terpenes to polyphenols and steroids, highlights the multifaceted nature of antileishmanial phytochemicals and underscores their potential as candidates for further pharmacological development (Figure 5). The consistency of statistically significant

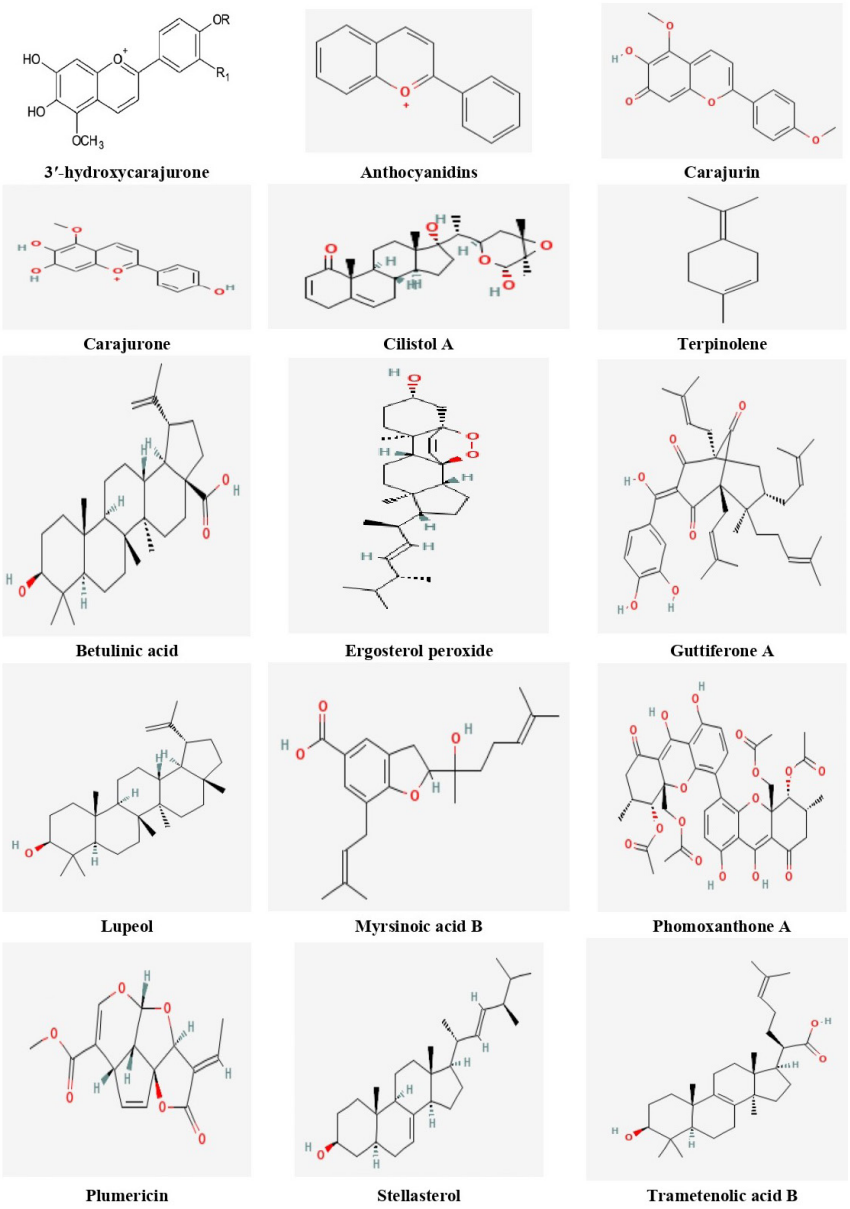

Figure 5. Chemical structures of potent antileishmanial phytochemicals from medicinal plants.

results across structurally distinct compounds reinforces the reliability of the observed effects and supports their biological relevance. Overall, this thorough analysis gives significant insights into prospective plant-based medicines, natural metabolites, and extraction methods for treating leishmaniasis. These findings underscore the necessity for further investigation and development in this area. Moreover, the evaluated plant species appear to hold significant potential as novel and effective antiparasitic candidates (26).

A drug administration form is also essential. If the extracts were administered intralesional, the results would be different. Moreover, the latest study (83) has shown that anti-leishmanial drug nanoparticles are extremely effective in treating CL. An additional benefit of these compounds lies in their effectiveness at low doses, along with a reduced risk of adverse effects (83–85).

The concentration of residuals around zero in the residual vs. predicted plot suggests limited variability or repeated measurements in certain cases. The few extreme residuals could reflect biological variability or measurement noise. Additionally, the strong deviations at both ends of the Q-Q plot indicate a significant departure from normality, which may be attributed to the biological characteristics of the tested compounds, limitations in measurement precision, or heterogeneity in treatment response. Although no statistical inference was applied subsequently, these graphical analyses serve as valuable diagnostic tools. They enhance understanding of the dataset's structure, highlight irregularities or patterns worth further exploration, and contribute to the transparency of the experimental process. Such assessments are especially useful for improving future study designs, refining experimental protocols, or considering data transformation or alternative modeling approaches when necessary. Ultimately, the publication bias analysis supports the robustness of our findings. While Kendall's test indicated some asymmetry, Egger's test did not confirm this statistically, and the funnel plot showed no substantial visual asymmetry. The very high Fail-Safe N value provides further confidence, suggesting that the observed effect is not likely to be overturned by unpublished null studies. These results collectively reduce concern about potential publication bias in our meta-analysis and reinforce the reliability of the synthesized evidence.

Our study provides a comparative evaluation of the efficacy of plant extracts and bioactive compounds against *Leishmania* spp. The inclusion of multiple databases enhances the scope and rigor of the search strategy, and the use of robust statistical tools strengthens the reliability of the findings. Despite the strengths, several limitations must be acknowledged. First, this review includes studies published through 2025, but the most recent publications could not be systematically assessed due to time and resource constraints. Future updates incorporating these studies may reveal additional promising plant candidates or modify the trends observed in this analysis. Second, the high heterogeneity among included studies limits the generalizability of the pooled estimates and may reflect variations in experimental design, extraction preparation, or the *Leishmania* species tested. Finally, the study is restricted to in vitro data, and the absence of in vivo and clinical validation limits the translational applicability of the findings to real-world treatment scenarios.

Conclusion

The current study is a systematic investigation into the anti-leishmanial activity of medicinal plants. Moreover, discovering new drugs from natural products will help to address global health issues. Therefore, further clinical investigations are essential to validate the safety and effectiveness of plant-derived therapies. Identifying their active constituents and assessing potential toxicities are crucial steps toward developing safe and well-tolerated treatments for leishmaniasis.

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Authors' contribution

Conceptualization: All authors.
Data curation: Takzima Mohammed-Yassine, Mounia Amane.
Formal analysis: Takzima Mohammed-Yassine, Mounia Amane.
Investigation: Takzima Mohammed-Yassine, Echchakery Mohammed.
Methodology: Takzima Mohammed-Yassine, Mounia Amane.
Project administration: El Fels Loubna, Echchakery Mohammed.
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Supervision: Echchakery Mohammed, El Fels Loubna, Hafidi Mohamed.
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Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

All ethical issues, including plagiarism, research misconduct, data fabrication, falsification, and duplicate or redundant publication, were carefully considered and fully avoided by the authors.

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Supplementary files

Supplementary file 1 contains Table A1.

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