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Review

Medicinal plants with antileishmanial activity on parasites responsible for new-world cutaneous leishmaniasis. A systematic review 2018-2022

[Plantas medicinales con actividad antileishmania sobre parásitos responsables de leishmaniasis cutánea del nuevo mundo. Una revisión sistemática 2018-2022]

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Abstract

Context: Cutaneous leishmaniasis is a disease of public health importance; treatment is based on the use of pentavalent antimonials with high toxicity and low efficacy; therefore, it´s necessary to search for therapeutic alternatives derived from natural products, based on the study of medicinal plants as a source of molecules with highly effective leishmanicidal potential.

Aims: To carry out a systematic review between 2018 and 2022 on medicinal plants with potential leishmanicidal activity on parasite strains from the New World causing cutaneous leishmaniasis.

Methods: The review study was conducted in four phases following the PRISMA methodology. First, research questions and objectives were formulated to establish the topic areas and construct the search algorithm. Second, a search was performed across different databases, including ScienceDirect, Scopus, PubMed, Web of Science, EBSCO, Taylor and Francis, and Scielo. Third, articles were chosen based on specific inclusion and exclusion criteria. Finally, the relevant information for the review was systematically organized.

Results: The search yielded 163 articles, and 12 of them were selected as the basis for the construction of the review. Ethanolic and aqueous extracts stand out, as well as biocompounds such as terpenes and flavonoids. Antioxidant activity on reactive oxygen species was the most frequently cited.

Conclusions: Promising terpene and flavonoid molecules with high antileishmanial activity (IC_{50} <2 µM or <10 µg/mL and SI >1) were identified in this study; these findings provide a scientific basis for the traditional use that communities have given to plants as a therapeutic source to treat cutaneous leishmaniasis in the New World.

Keywords: antiprotozoal agents; cutaneous; Leishmania; leishmaniasis; plant extracts.

Resumen

Contexto: La leishmaniasis cutánea es una enfermedad de importancia en salud pública; su tratamiento se basa en el uso de antimoniales pentavalentes con alta toxicidad y baja eficacia; por tanto, es necesaria la búsqueda de alternativas terapéuticas derivadas de productos naturales, a partir del estudio de plantas medicinales como fuente de moléculas con potencial leishmanicida.

Objetivos: Realizar una revisión sistemática comprendida entre los años 2018-2022 referente a plantas medicinales con potencial actividad leishmanicida sobre cepas parasitarias del nuevo mundo causales de leishmaniasis cutánea.

Métodos: La revisión se realizó en cuatro fases siguiendo la metodología PRISMA. En primer lugar, se formularon las preguntas de investigación y los objetivos para establecer las áreas temáticas y construir el algoritmo de búsqueda. En segundo lugar, se realizó una búsqueda en diferentes bases de datos, como ScienceDirect, Scopus, PubMed, Web of Science, EBSCO, Taylor and Francis y Scielo. En tercer lugar, se seleccionaron los artículos en función de criterios específicos de inclusión y exclusión. Por último, la información relevante se organizó sistemáticamente para la revisión.

Resultados: La búsqueda arrojó 163 artículos, definiendo 12 artículos base para la construcción de la revisión. Sobresalen los extractos etanólicos y acuosos; así como biocompuestos tipo terpenos y flavonoides. La actividad antioxidante sobre especies reactivas de oxígeno fue la más citada.

Conclusiones: Se identificaron moléculas promisorias con alta actividad antileishmania (CI_{50} <2 µM o <10 µg/mL y con IS >1) tipo terpenos y flavonoides; resultado que brinda una base científica para el uso tradicional que las comunidades le han dado a las plantas como fuente terapéutica para tratar la leishmaniasis cutánea en el nuevo mundo.

Palabras Clave: agentes antiprotozoarios; cutáneo; extractos de plantas; *Leishmania*; leishmaniasis.

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Abbreviations: ACAF: Anthocyanin-enriched fraction of *Arrabidaea chica*; AcEt: Ethyl acetate; CL: Cutaneous leishmaniasis; EC_{50}: Effective concentrations 50; H_2O_2; Hydrogen peroxide; IC_{50}: Inhibitory concentration 50; IL: Interleukins; Met: Methanol; ML: Mucocutaneous leishmaniasis; NO: Nitric oxide; ROS: Reactive oxygen species; SI: Selectivity index; STL: Sesquiterpene lactones; TNF-α: Interferon alpha; VL: Visceral leishmaniasis; ΔΨm; Mitochondrial membrane potential.

INTRODUCTION

Leishmaniasis is a group of neglected tropical and subtropical zoonotic diseases resulting from infection by protozoan parasites of the genus *Leishmania*, transmitted to humans and other animal species through the bite of infected phlebotomine insects. These pathologies are characterized by having a broad clinical spectrum associated with the infecting species of the parasite and the immune response of the host. The main three clinical manifestations are cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML), and visceral leishmaniasis (VL), with CL being the manifestation with the highest prevalence in the world. ML is the most incapacitating clinical manifestation, while VL is the most serious one and can be fatal if left untreated. On the other hand, according to its global distribution, the disease is classified into old-world leishmaniasis, spreading across the Eastern Hemisphere, mainly Asia, Africa, and southern Europe; and new-world leishmaniasis, existing in the Western Hemisphere, from Central and South Texas down to Central and South America (Kevric et al., 2015). In general terms, this disease mostly affects the poorest populations in Asia, Africa, and Latin America, making it one of the pathologies of interest in the Sustainable Development Goals agenda (Wamai et al., 2020).

According to the World Health Organization (WHO), this group of diseases has a broad worldwide distribution. It is estimated that between 50,000 and 90,000 new cases of VL, and between 600,000 and 1 million new cases of CL occur each year around the world (World Health Organization, 2022), with more than 1 billion people at risk of infection. Global Health Observatory records from 2021 indicate that 99 countries were categorized as endemic for some type of leishmaniasis (Fig. 1A-B), which is proof of its huge impact on global public health. In Latin America, Argentina, Bolivia, Brazil, Colombia, Paraguay, Uruguay, and Venezuela share the status of endemicity for CL and VL, with more than 97% of VL cases reported in 2020 in the Americas occurring in Brazil, while no autochthonous cases have been reported in Chile (World Health Organization, 2021; 2022).

More than 20 *Leishmania* spp. have been characterized to date, and they are classified into three subgenera: *Leishmania* (L.), *Viannia* (V.) and *Sauroleishmania*, with the difference being the place in the gut of the vector insect where they multiply (Dostálová and Volf, 2012; Klatt et al., 2019). To the first subgenus belong the spp. *L. (L.) donovani* and *L. (L.) infantum* (also known as *L. chagasi* in the New World), causative agents of VL; *L. (L.) tropica, L. (L.) major,* and *L. (L.) mexicana*, causative agents of CL, are also part of this subgenus. On the other hand, the spp. *L. (V.) guyanensis, L. (V.) panamensis* and *L. (V.) brazilienzis* belong to the second subgenus and are responsible for most of the CL and ML cases reported in Latin America (Guerra et al., 2011; Saravia et al., 1985).

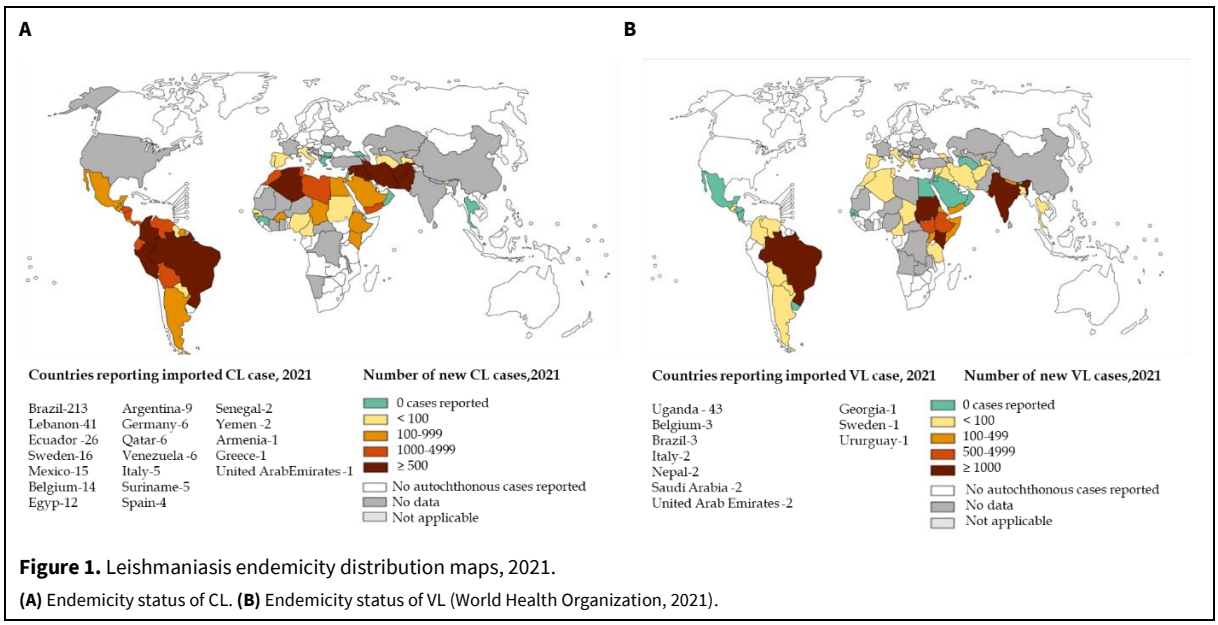

Figure 1. Leishmaniasis endemicity distribution maps, 2021.

(A) Endemicity status of CL. **(B)** Endemicity status of VL (World Health Organization, 2021).

Colombia stands out as one of the countries with the largest diversities of circulating *Leishmania* spp., including *L. (V.) panamensis, L. (V.) braziliensis, L. (V.) guyanensis, L. (L.) infantum, L. (L.) amazonensis, L. (L.) mexicana, L. (V.) colombiensis, L. (V.) lainsoni* and *L. (V.) equatorensis* (Salgado-Almario et al., 2019). It is important to highlight that geographical and weather conditions in tropical and subtropical regions favor the life cycle of the insect vector, whose spp. belong to two genera: *Phlebotomus* in Africa, Asia, and Europe (Old World); and *Lutzomyia* in Central and South America (New World) (Kato et al., 2010; Mann et al., 2021). These insects are characterized by their small size of 2 to 3 mm, body covered with fine bristles and long hairy wings, with nocturnal hematophagous activity (Claborn, 2010). In Latin America, about 54 different vector spp. have been identified that are potentially involved in the transmission of CL and VL (Pan American Health Organization—PAHO, 2022).

The diseases occur when parasites of the genus *Leishmania* are injected as promastigotes by the bite of infected phlebotomine sandflies into a vertebrate host, where they are phagocytozed by macrophages and dendritic cells, and compartmentalized in the parasitophorous vacuole (Alexander et al., 1999). The parasite is confined there to be controlled, but at the same time it differentiates into its infective form, known as amastigote, and multiplies thanks to the conditions in the organelle.

At the moment of infection, the parasite generates an immune response of susceptibility or resistance, which, together with the type of infecting strain, determines the type of clinical manifestation. In the resistance response, the macrophage is stimulated to control replication of the parasite in amastigote form; in the susceptible response, on the other hand, the disease develops progressively as the parasite resists all the phagocyctosis and cell digestion mechanism, manages to divide in the parasitophorous vacuole, and once differentiated in amastigotes, it proliferates and is capable of infecting other cells.

In the clinical manifestation known as VL or kala-azar, the parasite proliferates at a systems level, making it the most severe manifestation of the disease with a mortality rate of 95% when it is not diagnosed and treated in due time. Patients may suffer weight loss, fever, hepato- and splenomegaly, hypergammaglobulinemia and pancytopenia (de Araújo et al., 2012). VL affects mostly young children aged 0–5 years and is associated with malnutrition and immunosupressive conditions, which socioeconomically correspond to poor, disadvantaged populations with little access to health services (World Health Organization, 2022).

The clinical manifestation with the highest number of cases worldwide is CL; in this form of the disease, an exacerbated pro-inflammatory response occurs, initiating at the bite site as erythema that progressively ulcerates. Resolution takes several months, leaving permanent scars that cause psychological effects on those who suffer this manifestation (anxiety, psychological discomfort, lack of confidence and self-esteem, and frustration, among others) and that also have a psychosocial impact (stigma, rejection, social and professional discrimination (Chahed et al., 2016). ML, on the other hand, evolves as a complication of CL that occurs when the parasites migrate from the initial skin wound, via lymphatic or blood vessels, to the mucus membranes of the respiratory tract, causing partial or total destruction of the nose, mouth and throat cavities, and surrounding tissues. This situation affects the quality of life of patients and increases the risk of mental health problems (Pires et al., 2019).

As mentioned before, leishmaniases are diseases associated with particular socioeconomic conditions and highly dependent on the weather. This is a relevant factor for the occurrence of the disease, even more so considering the frequent fluctuations in temperature, relative humidity, and precipitations associated with climate change. These climate variables have a significant influence on the distribution, growth, and prevalence patterns of vector insect populations (Fouque and Reeder, 2019). It is important to highlight these socioeconomic variables associated with the propagation of the disease (such as poverty and malnutrition), along with increasing urbanization of areas where the vector and its reservoirs are naturally present, are at the origin of deforestation processes that favor the development of unplanned human settlements. Other variables to consider are the migration of human populations from rural into urban areas (Alvar et al., 2006b), also known as forced displacement, together with the limitations for obtaining adequate treatment, associated with specific drug use restrictions, inadequate or late diagnoses, and association of leishmaniasis with HIV infection (Desjeux, 1999). Moreover, the emergence of drug-resistant strains and the slow development of vaccines have turned these diseases into a public health concern of global dimensions (Docampo, 2000).

Thus, correct identification of the spp. that causes leishmaniasis is essential for establishing the clinical prognosis and initiating the appropriate treatment (Arevalo et al., 2007; Llanos-Cuentas et al., 2008; Romero et al., 2001). The current therapeutic approach, however, is very broad and not specific to the infecting species or the type of clinical spectrum present in the patient (Uliana et al., 2018). In general terms, the first line of treatment for the different clinical mani-

festations of leishmaniasis is the use of pentavalent antimony compounds such as meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®), which are highly toxic compounds with a narrow therapeutic window. Pentamidine isethionate, miltefosine, and amphotericin B have been used as a second-line treatment, with adverse effects including cardiovascular, gastrointestinal, kidney, and liver disorders; thus, before starting the treatment, it is necessary to perform a clinical assessment to determine the general condition of the patient, with frequent clinical and paraclinical checkups being needed, considering the toxicity of these drugs (Alvar et al., 2006a; World Health Organization, 2022). Additionally, the use of these drugs requires frequent parenteral administration and long courses of treatment (Frézard et al., 2009), which favor treatment failure with severe clinical complications and the probability of inducing the development of drug-resistant strains, mainly in populations with no easy access to health centers to receive treatment (Ponte-Sucre et al., 2017).

These problems make it necessary to search for new therapeutic alternatives with acceptable profiles of efficacy, safety, and accessibility. In this context, the search for bioactive compounds with antileishmanial activity is relevant, and research on medicinal plants becomes an invaluable source of possible solutions through the use of bioactive molecules, which represent a first-hand alternative for vulnerable populations that perceive them as harmless, of easy access, preparation, and consumption to control the disease. Information about traditional uses of plants is recognized as a source for the discovery of new bioactive compounds and essential for the development of drugs aimed at treating neglected diseases. Moreover, the study of essential oils, plant extracts and fractions rich in metabolites can give place to the development of phytotherapeutics that can potentially aid in the treatment of different diseases and, in particular, of clinical manifestations of leishmaniasis.

Considering all the above, this systematic review between 2018 and 2022 aimed to identify highly active extracts, oils and metabolites from medicinal plants of traditional use and with antileishmanial activity against new-world strains of this parasite causative of CL, taking into account that this is the most recurring manifestation in this region of the planet. This inquiry is also supported by the interests of various international organizations that aim to consolidate actions to reduce the morbidity and mortality of this disease in the Americas, including a reduction in cutaneous leishmaniasis cases in children under 10 years of age (Pan American Health Organization-PAHO, 2017). It is hoped that the research reported here will become a basis for the development of new antileishmanial chemotherapies.

MATERIAL AND METHODS

Study design

The construction process of the present review comprised four stages according to the PRISMA protocol (McInnes et al., 2018). First, the objectives were identified to limit the scope in order to create the search algorithm; then, the most relevant articles were retrieved, filtered and analyzed to present the findings.

Stage 1: The objectives and research question were prepared and structured to answer on the nature of the metabolites found in medicinal plant extracts or oils of traditional use that have shown high leishmanicidal activity against new-world strains causative of CL. Thus, the main thematic axes were identified and defined in order to start the search for information in different databases.

Stage 2: The search for papers was carried out in the Scielo, Scopus, Web of Science, PubMed, SpringerLink, Tylor and Francis, and EBSCO Academic Search databases. The keywords and search expressions used are presented in Table 1.

Table 1. Search strategy and algorithm of the review.

Search resources
Databases: Scielo, Scopus, Web of Science, PubMed, SpringerLink, EBSCO Academic Search.
Scope: Articles written and published in English.
Period of time: Articles published between 2018 and 2022.
Search algorithm
1# AND #2 AND #3 AND #4
#1 (“Leishmania”)
#2 (“Antileishmanial activity”) OR (“Leishmanicidal activity”)
#3 (“Medicinal plants”) OR (“plant extract”)
#4 (“cutaneous leishmaniasis”)

Table 2. Inclusion and exclusion criteria for article selection.

Inclusion criteria	Exclusion criteria
Research articles published between 2018 and 2022. Articles dealing with plants or plant-derived compounds with high activity (IC_{50} <2 µM or <10 µg/mL) and with SI >1 on *Leishmania* strains causative of CL in the New World.	Review articles or papers written in languages other than English. Papers not about medicinal plants or plant-derived compounds with antileishmanial activity or using *Leishmania* strains causative of CL in the Old World.

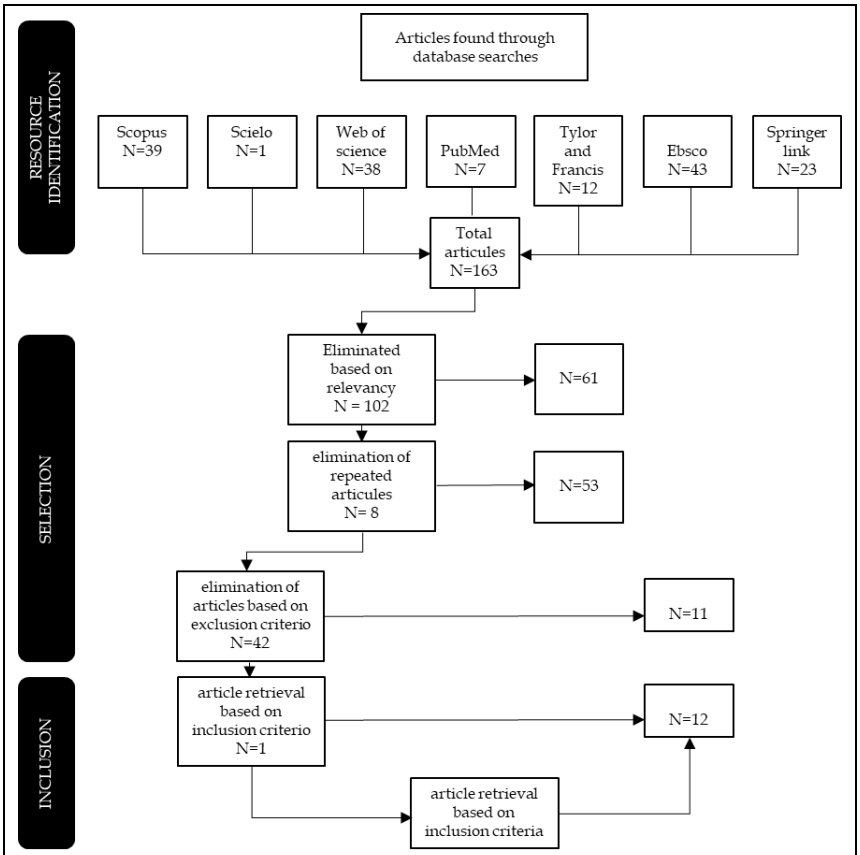

Figure 2. PRISMA flow chart for the systematic review of the literature.

Stage 3: Article selection was carried out according to the criteria presented in Table 2. A total of 163 papers were retrieved, which were then reviewed by all the authors (title, abstract and content), taking into account the inclusion and exclusion criteria. As a result of this process, 12 papers were selected for the review process. In case of finding a paper that, after selection, did not match the inclusion criteria, one of the eliminated papers was then chosen; this process is presented in Fig. 2.

Stage 4: The articles selected were analyzed in detail to obtain relevant information for the review, making emphasis on the activity of the extract, oil, or biocompound with inhibitory concentration 50 (IC_{50}) <2 µM or <10 µg/mL) (Boniface and Ferreira, 2019; Lima et al., 2012) and selectivity indexes (SI >1), indicative of high leishmanicidal activity and low cytotoxicity in mammalian cells (Koutsoni et al., 2019).

Quality of the studies

Each author independently assessed the quality of the selected articles using the AXIS tool, which evaluates both the quality of evidence within the studies and the risk of selection bias. This evaluation was conducted through a Delphi panel process composed of four components: introduction, methods, results, discussion, and others, totaling 20 questions (Downes et al., 2016).

The articles were subsequently categorized in terms of quality as high, moderate, or low based on criteria that included "Meets," "Does not meet," "Not measurable," and "Not applicable" (N/A). Articles were considered to have high quality if they scored

more than 15 points, moderate quality if they scored between 12 and 15 points, and low quality if they scored less than 12 points. Only articles belonging to the high and moderate quality categories were included (Table S1), following a similar approach to previous studies (Mat Sharil et al., 2022; Pérez-Loyola et al., 2022).

Qualitative analysis and data extraction

The selected papers were reviewed and analyzed by all the authors to carry out a qualitative synthesis. The following data were extracted: last name of the first authors, year and study site, medicinal plant, type of extract(s) or essential oil or metabolite studied, vegetable drug (part of the plant evaluated), *Leishmania* strain studied, $IC_{50,}$ and SI.

RESULTS AND DISCUSSION

A total of 12 articles were examined as the central axis of this review (Fig. 2, Table 3); most of them are from Latin America, mainly Brazil, while only two papers are from North African countries, with *L. (L.) amazonensis* being the most frequently studied infecting species.

The search for therapeutic alternatives based on plants is rooted in the beliefs and experiences of communities with plants that are attributed healing properties. These are perceived as an effective alternative to conventional medicine, since they have fewer adverse effects and are easy to obtain at a low cost, being in many cases the only therapeutic source for patients with low economic resources (Lozano et al., 2022). Exploration of new bioactive molecules, on the other hand, is also supported by our current economic and climate conditions, where environmental policies are aimed at using sustainable resources to minimize environmental impact; in this line, the WHO backs and supports the use of herbal medicine when it has proven therapeutic benefits, with minimum risk for both the patients and the environment.

The need to identify new compounds with leishmanicidal activity, reduced toxicity, and adequate safety and efficacy profiles has led to the search for new bioactive compounds in plants with promising results; thus, some extracts, fractions, essential oils and isolated compounds obtained from different parts of medicinal plants of traditional use are a subject of research interest given their high antileishmanial activity (Luize et al., 2005; Oryan, 2015; Weniger et al., 2001).

Extracts and compounds with potential leishmanicidal activity against new-world spp. causative of CL

One of the plants that has exhibited therapeutic applications for the control of CL is *Arnica montana* L., family *Compositae (Asteraceae)*, also known as mountain tobacco, leopard's bane, and mountain arnica (Jha et al., 2018). This plant belongs to the *Asteraceae* family, *Arnica* L. genus, with 32 spp; it is endemic to central and southern Europe (Alps and Pyrenees), northern Spain, and the south of Scandinavia. Its habitat is at altitudes ranging from 500 to 2500 m above sea level (Kriplani et al., 2017; Waizel-Bucay and Cruz-Juárez, 2014). It is widely used in homeopathic medicine as part of the treatment for various conditions; traditionally, the plant material is macerated or boiled, and it is administered as plasters, washings, rubbing, or by direct application of the plant (Obón et al., 2012). Dried flowers are used as tincture or ointment for the topical treatment of contusions and bruises, and to control pain (Klaas et al., 2002). At the phytochemical level, *A. montana* has a large amount of organic compounds such as flavonoids, carotenoids and lignans, among others (Kriplani et al., 2017); phenolic acids and flavonoids from ethanolic extracts of flowers stand out for their good antioxidant activity evidenced by free radical scavenging by Trolox equivalent antioxidant capacity (TEAC), ORAC Oxygen Radical Absorbance Capacity (ORAC) and 2, 2-diphenyl-1-picrylhydrazyl (DPPH), as well as for its protective activity against oxidative stress studied in fibroblasts (pretreated with 10 mg/L of ethanolic extract) exposed to H_2O_2, a precursor compound of reactive oxygen species (Craciunescu et al., 2012).

Sesquiterpene lactones (STLs) are among the biologically active compounds present in *A. montana*, and in general in the *Asteraceae* family. STLs are a diverse group of terpenoids that contain a lactone ring conjugated to an exomethylene group (α-methylene-γ-lactone) (Fig. 3).

Cytotoxicity results reported by the group of Robledo et al. (2022) evidenced the antileishmanial activity of arnica tincture against intracellular amastigotes of *L. (V.) braziliensis*, as well as of several compounds isolated from STL, most notably isobutyrate and helenalin acetate with effective concentrations 50 (EC_{50}) of 1.85 ± 0.03 µg/mL and 1.86 ± 0.01 µg/mL, respectively; the same was found for 11α, 13-dihydrohelenalin acetate and isovalerate, with EC_{50} of 2.44 ± 0.10 µg/mL and 3.04 ± 0.16 µg/mL, respectively. On the other hand, using as animal model golden

hamster specimens infected intralesionally with *L. (V.) braziliensis*, it was found that the optimal dose per lesion is 19.2 g of total STL, with an administration frequency of twice daily for 60 days, generating a cure rate of 87.5% (Robledo et al., 2022). This result can be explained by considering that compounds with a (potentially reactive) carbonyl group α,β-unsaturated as pharmacophore usually show significant antiprotozoal and cytotoxic activity (Schmidt et al., 2009).

Table 3. Articles selected for the review between 2018 and 2022.

No.	Title	Authors	Journal	Database	Country of origin
1	Therapeutic efficacy of arnica in hamsters with cutaneous leishmaniasis caused by *Leishmania braziliensis* and *L. tropica*	Robledo et al. (2022)	Pharmaceuticals	Scopus	Colombia
2	Antioxidant and leishmanicidal evaluation of *Pulicaria inuloides* root extracts: A bioguided fractionation.	Fadel et al. (2019)	Pathogens	Scopus	Algeria
3	The *in vitro* antileishmanial activity of essential oil from *Aloysia gratissima* and guaiol, its major sesquiterpene against *Leishmania amazonensis*	Garcia et al. (2018)	Parasitology	Scopus	Brasil
4	*Caryocar coriaceum* extracts exert leishmanicidal effect acting in promastigote forms by apoptosis-like mechanism and intracellular amastigotes by Nrf2/HO-1/ferritin dependent response and iron depletion: Leishmanicidal effect of *Caryocar coriaceum* leaf exracts.	Tomiotto-Pellissier et al. (2018)	Biomedicine and Pharmacotherapy	Web of Science	Brasil
5	Carajurin: A anthocyanidin from *Arrabidaea chica* as a potential biological marker of antileishmanial activity. Biomedicine and Pharmacotherapy	Silva-Silva et al. (2021)	Biomedicine and Pharmacotherapy	Scopus	Brasil
6	Leishmanicidal activity of α-bisabolol from *Tunisian chamomile* essential oil	Hajaji et al. (2018)	Parasitology Research	Springer Link	Túnez
7	Selective *in vitro* antileishmanial activity of *Mimosa caesalpiniifolia* stem barks and its main constituent betulinic acid against *Leishmania amazonensis*.	Brito et al. (2021).	South African Journal of Botany	EBSCO Academic research	Brasil
8	*Eugenia piauhiensis* Vellaff. essential oil and γ-elemene its major constituent exhibit antileishmanial activity, promoting cell membrane damage and *in vitro* immunomodulation	Nunes et al. (2021).	Chemico-Biological Interactions	EBSCO Academic research	Brasil
9	Leishmanicidal activity of *Piper marginatum* Jacq. from Santarém-PA against *Leishmania amazonensis*	Macêdo et al. (2020).	Experimental Parasitology	EBSCO Academic research	Brasil
10	Antileishmanial activity evaluation of a natural amide and its synthetic analogs against *Leishmania (V.) braziliensis*: an integrated approach *in vitro* and *in silico*	da Silva et al. (2021)	Parasitology Research	EBSCO Academic research	Brasil
11	Chemical constituents with leishmanicidal activity from a pink-yellow cultivar of *Lantana camara* var. *aculeata* (L.) collected in Central Mexico	Delgado-Altamirano et al. (2019)	International Journal of Molecular Sciences	Web of Science	Mexico
12	Cinnamic acids derived compounds with antileishmanial activity target *Leishmania amazonensis* arginase	da Silva et al., (2019)	Chemical Biology and Drug Design	EBSCO Academic research	Brasil

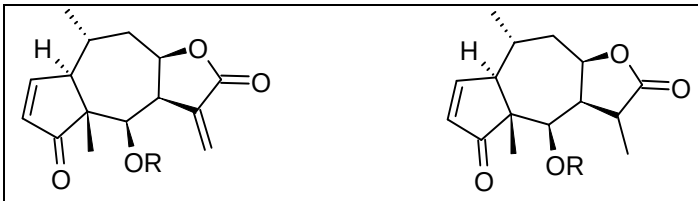

Figure 3. Sesquiterpene lactones (STLs) found in *Arnica montana* L.

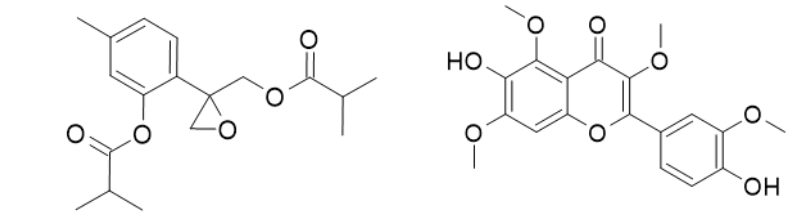

Figure 4 Compounds with leishmanicidal potential isolated from *P. inuloides.*
(A) Thymol derivative 10-isobutyryloxy-8,9-epoxythymol isobutyrate. **(B)** Quercetagetin-3,5,7,3'-tetramethyl ether.

Another plant of the *Asteraceae* family that exhibits antileishmanial activity is *Pulicaria inuliodes* (Poir.) DC, known in Yemen as anssif; its main area of distribution includes Morocco, Egypt, Eritrea, Ethiopia, Arabia, and Yemen (Chhetri et al., 2015). This plant is part of Yemeni medicine, being employed for its antibacterial and antioxidant activity (Qaid et al., 2017); additionally, it is traditionally used to repel insects, to reduce symptoms of the common cold, and to treat back pain, intestinal disorders, and inflammation (Qaid et al., 2017). At the phytochemical level, *P. inuliodes* has a wide range of bioactive compounds identified by chemical analysis of its essential oil, in which the presence of monoterpenes, diterpenes, sesquiterpenes, among others, has been found (Qaid et al., 2017).

Studies from chloroplast subfractions of the roots of *P. inuloides* evidenced its leishmanicidal activity on promastigotes of *L. (L.) amazonensis* with an IC_{50} of 5.03 ± 0.29 µM, with respect to the reference drug miltefosine with an IC_{50} of 6.48 ± 0.24 µM. Similarly, activity assays against intracellular amastigotes of *L. (L.) amazonensis* evidenced that this subfraction is more potent (IC_{50} of 2.87 µM) than the reference drug, miltefosine (IC_{50} of 3.12 µM). Notably, compound (8R:8S)-(75:25 er)-10-isobutyryloxy-8,9-epoxy-thymol isobutyrate (Fig. 4A) was isolated as the one responsible for the leishmanicidal activity, with a good selectivity index (SI) evaluated in murine macrophages (Fadel et al., 2019). This was the first report of a thymol derivative with leishmanicidal activity in root extracts from *P. inuliodes*.

On the other hand, studies with chloroplast fractions of the aerial parts of *P. inuloides* evidenced their leishmanicidal potential, starting with the isolation of the flavone quercetagetin-3,5,7,3'-tetramethyl ether (Fig. 4B), which demonstrated moderate leishmanicidal activity with IC_{50} of 0.483 mM (Fadel et al., 2018).

Another extract that has shown high leishmanicidal activity comes from *Caryocar coriaceum* Wittm., a plant species belonging to the *Caryocaraceae* family, mainly distributed in northeastern Brazil, where it is popularly known as pequi, piquiá, marañón, piquárana, among others, and whose fruit has a high commercial value, as does the oil extracted from the seed (Sousa Júnior et al., 2013). In popular medicine, fruit pulp and seed oil have been used for their healing and anti-inflammatory effects, for bronchial affections, cough, and asthma, among others (de Oliveira et al., 2010).

Studies conducted by the group of Tomiotto-Pellissier in 2018 with leaves of *C. coriaceum* indicated that ethyl acetate and methanol extracts inhibited the proliferation of *L. (L.) amazonensis* promastigotes and showed no toxicity on macrophages derived from mouse peritoneum, which is evidence of the selective potential of the extract on the parasites (Tomiotto-Pellissier et al., 2018). Likewise, tests performed on infected macrophages showed a reduction in the in-

fection rate, as well as in the number of amastigotes per macrophage at concentrations of 25-100 µg/mL, a result comparable to that obtained with the reference drug (amphotericin). It is suggested that the majority presence of catechins, steroids in the ethyl acetate extract and flavonoids in the methanol extract, could explain the results obtained. The study of the biological activity of these extracts showed that their activity generates depolarization of the mitochondrial membrane, with increased production of reactive oxygen species (ROS), a result suggesting parasite death through a mechanism similar to apoptosis (Tomiotto-Pellissier et al., 2018).

Similarly, studies with extracts of pulp and peel of ripe fruits of *C. coriaceum* have shown moderate leishmanicidal activity on *L. (L.) amazonensis* promastigotes with IC_{50} of 30 ± 5 and 38 ± 3 µg/mL, respectively; this activity is attributed to the presence of the flavonoids quercetin, rutin, and isoquercitrin, and to their antioxidant and anticholinesterase mechanisms (Alves et al., 2017).

Another plant of interest in Brazilian traditional medicine is *Arrabidaea chica* (Humb. and Bonpl.) B. Verlot (Ministério da Saúde, 2022) or *Fridericia chica* (Bonpl.) L.G. Lohmann, known as crajiru, carajuru, pariri and cipó cruz in Brazil; it belongs to the family *Bignoniaceae* and is native to tropical forests, being distributed mainly in Central America and the Amazon region. It is used in popular medicine for its anti-inflammatory, healing, anti-anemic and anticancer properties, among others (Matias et al., 2021). Leaf extracts and their fractions have shown antifungal and trypanocidal activity (Barbosa et al., 2008; Höfling et al., 2010), as well as antioxidant capacity, attributed, especially, to the presence of a mixture of flavonoids (Siraichi et al., 2013).

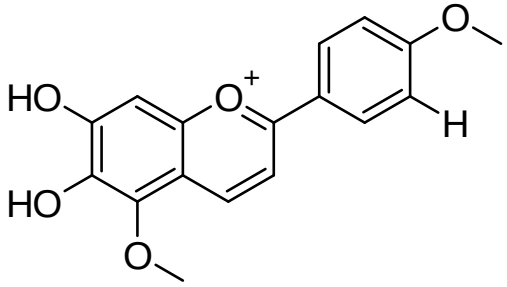

Figure 5. Anthocyanin carajurin (3-deoxycyanthocyanidin) isolated from *Arrabidaea chica*.

Studies of the anthocyanin-enriched fraction of *Arrabidaea chica* (ACAF) and its compound carajurin (3-deoxyanthocyanidin) (Fig. 5) evidenced high leishmanicidal activity on promastigotes of *L. (L.) amazonensis*, with IC_{50} values of 4.976 ± 1.09 µg/mL for ACAF and 3.66 ± 1.16 µg/mL for carajurin; the latter showed higher selectivity (SI of carajurin 34.8; SI of ACAF 10.2), with low cytotoxicity against macrophages and activity against intracellular forms of promastigotes and amastigotes of the parasite (Silva-Silva et al., 2021).

The study suggests that the leishmanicidal activity of ACAF and carajurin could be associated with the ability to induce nitric oxide (NO) production in macrophages, promoting their microbicidal response (Silva-Silva et al., 2021), thus making this anthocyanidin a promising candidate for therapeutic use against *Leishmania* parasites.

Other studies performed with hexane extracts of leaves of *A. chica* showed leishmanicidal activity against strains of *L. (L.) amazonensis* and *L. (L.) infantum*, with a minimum inhibitory concentration of 37.2 and 18.6 µg/mL, respectively. Ultrastructural analysis evidenced alterations in mitochondrial size due to loss of matrix content, alterations in the Golgi complex and cytoplasmic vacuolization, with fatty acids and sterols being the molecules potentially involved in this activity (Rodrigues et al., 2014); these findings make it necessary to conduct studies that contribute to the identification of the nature of the molecules responsible for this activity.

Another study carried out with *Arrabidaea brachypoda* (D.C.), a plant belonging to the same genus, allowed the isolation of the compound brachydin B (extracted from the root) with leishmanicidal activity *in vitro* against intracellular amastigotes of *L. (L.) amazonensis*. Exposure of the compound to promastigotes also generated alterations in the Golgi apparatus and accumulation of vesicles inside the flagellar sac; however, topical administration of the compound on infected mice did not show leishmanicidal effects (Rocha et al., 2018), a result that evidences the importance of the use of models that validate the biological activity of the metabolites of this plant.

The species *Mimosa caesalpiniifolia* Benth, popularly known as sansao-do-campo, unha-de-gato or sabia (de Sousa et al., 2013), is a shrub native to northeastern Brazil that belongs to the *Fabaceae* family; it is characterized by its rapid growth, high regeneration capacity, and climate resistance, which facilitate its use for reforestation purposes (Silva et al., 2022). In popular medicine, its bark is used to wash wounds as an antibacterial and anti-inflammatory agent; additionally, the consumption of bark infusion is used as a treatment for bronchitis (do Nascimento Silva et al., 2016; Ramalho Carvalho, 2007). Extracts of *M. caesalpiniifolia* have vasorelaxant (Santos et al., 2015), antioxidant, antimicrobial (Silva et al., 2012), and antitumor (Mororó et al., 2018) effects, among others. At the phytochemical level, the ethanolic extract of the

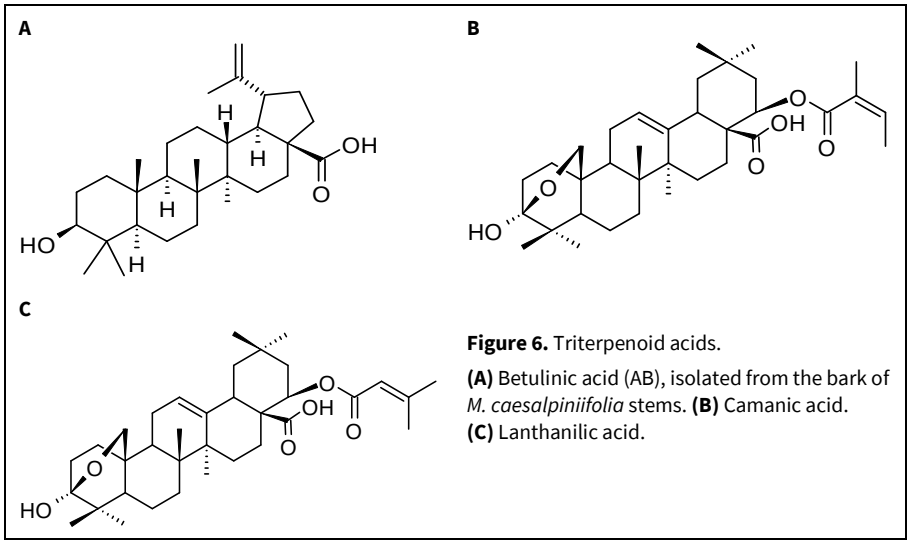

Figure 6. Triterpenoid acids.
(A) Betulinic acid (AB), isolated from the bark of *M. caesalpiniifolia* stems. **(B)** Camanic acid. **(C)** Lanthanilic acid.

leaves showed the presence of acids, alcohols, isoprenoids, and phenolic compounds, among which and as major constituents were recorded phytol, lactic acid, α-tocopherol and β-sitosterol (Monção et al., 2014).

Studies with the ethanolic extract, the dichloromethane fraction, and the isolated compound betulinic acid, a pentacyclic triterpenoid (Fig. 6) obtained from the bark of the stems of *M. caesalpiniifolia*, evidenced leishmanicidal activity on the promastigote and amastigote forms of *L. (L.) amazonensis*. For promastigotes, the ethanolic extract, dichloromethane fraction and betulinic acid showed activity at IC_{50} of 4.63 ± 0.69, 0.38 ± 0.42, and 29.63 ± 4.63 µg/mL, respectively; for axenic amastigotes, the activity was obtained at IC_{50} of 4.8 ± 1.27, 0.56 ± 0.39 and 14.2 ± 2.01 µg/mL, respectively, with SI higher than 20 for the dichloromethane fraction and for betulinic acid (Brito et al., 2021); these results underline the safety and efficacy profile of both the fractions and the isolated compound, making them promising candidates for treating leishmaniasis.

Another study related to *M. caesalpiniifolia* revealed its promising antileishmanial potential by presenting an inhibitory effect also on the growth of promastigotes of *L. (L.) amazonensis*. The ethanolic extract obtained from the flowers and the isolated compound lupeol exhibited moderate activity after 48 hours of exposure to the parasite at an IC_{50} of 74.52 µg/mL for the extract and of 15.40 µg/mL for lupeol, with the extract standing out for exhibiting a better SI against murine macrophages. Chemical characterization of the extract showed the presence of lupeol acetate, lupeol, β-amyrin, a mixture of steroids, and triterpenyl esters of fatty acids (Quirino et al., 2020).

Other molecules belonging to the group of pentacyclic triterpenoids that have shown leishmanicidal activity are camarinic acid (Fig 6B) and lanthanilic acid (Fig 6C). Studies from extracts obtained from the aerial parts (leaves, stems, flowers and fruits) of *Lantana camara* var. *aculeata* (L.) showed leishmanicidal activity on promastigotes of *L. (L.) mexicana*, with values for lanthanilic acid and camarinic acid of IC_{50} of 9.50 ± 0.28 and 2.52 ± 0.08 µM, respectively. Particularly, the mixture of these compounds in a 79%/21% ratio of lanthanilic acid and camarinic acid exhibited high leishmanicidal activity with values of 12.02 ± 0.36 µM (Delgado-Altamirano et al., 2019). These results demonstrate the potential for the development of phytomedicines from *Lantana camara* var. *aculeata* (L.), a plant native to South America, whose essential oils, composed mainly of mono- and sesquiterpenes, have also shown high antileishmanial activity against CL-causing species (Barros et al., 2016; Ghadimi et al., 2020; Machado et al., 2012).

The recent study of biocompounds with antileishmanial activity has been oriented to the isolation of metabolites capable of inhibiting parasite enzymes, which act as effective defense systems against oxidative stress induced by ROS and reactive nitrogen species (RNS) released by macrophages to eliminate them. Among these enzymes are trypanothione reductase and triparedoxin peroxidase (Manta et al., 2013).

Da Silva et al. (2021) evaluated the antileishmanial activity of the natural amide piplartine (Fig. 7) against *L. (V.) braziliensis*, also performing some experiments that allowed a closer understanding of its mechanism of action (da Silva et al., 2021). Piplartine was isolated from the roots of *Piper tuberculatum* Jacq. (*Piperaceae*), a species used in traditional Brazilian medicine, according to previous studies (Araújo-Vilges et al., 2017).

While in the assay of antileishmanial activity on promastigote forms piplartine achieved an IC_{50} value

of 8.58 ± 2.1 µM, in the *in vitro* assay against amastigotes of *L. (V.) braziliensis* it achieved an IC_{50} value of 1.46 ± 0.28 µM, showing a more potent activity compared to the activity of its analogues. In the molecular docking study, piplartine showed a favorable binding energy (-7.13 kcal/mol), confirming its affinity for the trypanothione reductase enzyme of *L. (V.) braziliensis* with an IC_{50} of 91.1 µM, a concentration that generates 50% inhibition of enzyme activity. Preliminary results showed that inhibition of the enzyme promoted increased ROS levels, induced loss of cell membrane integrity, and caused accumulation of lipid bodies after 24 h of incubation at their lowest effective concentration (da Silva et al., 2021).

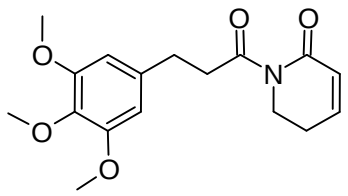

Figure 7. Piplartine (1-[3-(3,4,5-trimethoxyphenyl) propanoyl]-5,6-dihydropyridin-2(1H)-one). Natural amide extracted from *P. tuberculatum*.

Leishmanicidal activity of essential oils against new-world strains causative of CL

Essential oils are defined by the European Pharmacopoeia (7th edition) as an odorant product, generally of complex composition, obtained from a botanically defined vegetable raw material, either by steam conduction, dry distillation or by a suitable mechanical method without heating. An essential oil is generally separated from the aqueous phase by a physical method that does not entail significant changes in its chemical composition (El Asbahani et al., 2015). At the chemical level, they are characterized by being a complex mixture of lipophilic compounds enriched with monoterpenes and sesquiterpenes, standing out for their broad bactericidal (Mayaud et al., 2008; Rhayour et al., 2003), virucidal (Ocazionez et al., 2010; Reichling et al., 2005), fungicidal (El-Mougy, 2009; Sitara et al., 2008) and leishmanicidal activity (Monzote et al., 2006; 2014; Rodrigues et al., 2013; Santin et al., 2009).

One of the essential oils that has exhibited high activity against *L. (L.) amazonensis* is that from *Aloysia gratissima* (Gill. et Hook) Tronc., also known as cidron del rio de la plata in Ecuador and as erva-santa in Brazil. It is a shrub of the genus *Aloysia*, belonging to the *Verbenaceae* family, which is native to southern Brazil and widely distributed in tropical and subtropical regions including Mexico, Brazil, Paraguay, and Argentina (Souza and Wiest, 2007). Its importance lies in being a melliferous, aromatic plant of medicinal use. Its oil shows antiviral activity against Herpes simplex virus type 1 (HSV-1) at an IC_{50} of 65 ppm (Garcia et al., 2003; Reichling et al., 2009), as well as antifungal activity associated with the presence of oxygenated sesquiterpenes in its oil (Dellacasa et al., 2003). On the other hand, the aqueous extract of the aerial parts of the plant has demonstrated antidepressant and neuroprotective effects in mice (Zeni et al., 2011). It is also traditionally used for colds, bronchitis and ear pain (Souza and Wiest, 2007). As regards phytochemicals, the essential oil of *A. gratissima* leaves has terpenes, among which isopinocamphone (trans-3-pinanone) (25.4%), limonene (15.1%) and guaiol (12.7%) stand out as the most abundant (Trovati et al., 2009).

Studies conducted by the group of Garcia et al. (2018) showed the high activity of the sesquiterpene guaiol (Fig. 8A), present in the essential oil of leaves and branches of *Aloysia gratissima* (Gill. et Hook) Tronc. (AgEO). The result obtained with AgEO on macrophages infected with amastigotes of *L. (L.) amazonensis* was highlighted, where exposure to the oil reduced the parasite survival rate in a dose-dependent manner, with amastigote survival inhibition percentages of 35.5, 50 and 61% at essential oil concentrations of 0.01, 0.1 and 1 µg/mL, respectively. In particular, the guaiol molecule inhibited amastigote survival with an IC_{50} of 0.01 µg/mL, without generating a cytotoxic effect on uninfected macrophages at the highest concentration evaluated (100 µg/mL). Moreover, its effect is independent of NO production, suggesting that the activity of AgEO and guaiol is direct on amastigotes, with these results demonstrating its potential leishmanicidal activity (Garcia et al., 2018).

Another essential oil that has exhibited high activity against *Leishmania* promastigotes is the one obtained from the leaves of *Cryptocarya aschersoniana* Mez. (*Lauraceae* Juss.), that belongs to the family *Lauraceae*, one of the most widely distributed throughout the world. In Latin America, it is present in Brazil, Argentina, Chile, Ecuador, Peru, Colombia and Uruguay (Rodrigues de Moraes, 2007; Vargas, 2021). The leishmanicidal potential of the essential oil of *C. aschersoniana* was evidenced on promastigotes of *L. (L.) amazonensis* with an IC_{50} of 4.46 µg/mL, by inhibiting parasite growth in a dose-dependent manner. Amphotericin B (IC_{50} = 1.88 µg/mL) was used as a positive control; however, the oil showed high toxicity to mouse peritoneal macrophages (IC_{50} = 7.71 µg/mL).

Analysis of *C. aschersoniana* leaf essential oil showed a complex mixture of monoterpenes (48.8%), oxygenated monoterpenes (13.4%) and oxygenated sesquiterpenes (26.7%), with the main constituents

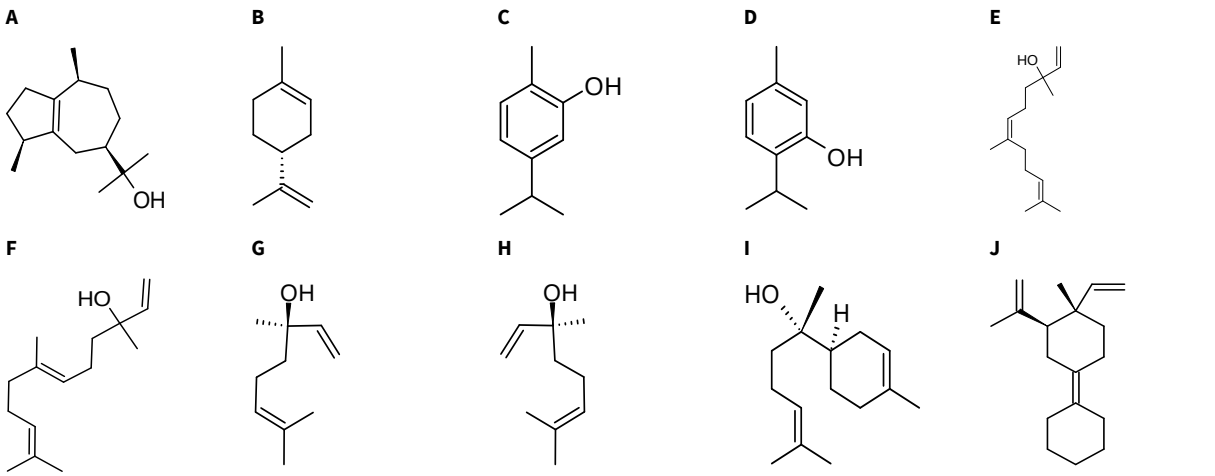

Figure 8. Terpene compounds of *Aloysia gratissima* and *C. aschersoniana* essential oils.

(A) Guaiol: (2-[(3*S*,5*R*,8*S*)-3,8-dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl]propan-2-ol). **(B)** Limonene: (4R)-1-methyl-4-(prop-1-en-2-yl) cyclohex-1-ene. **(C)** Carvacrol: 2-methyl-5-(propan-2-yl) phenol. **(D)** Thymol: 5-methyl-2-(propan-2-yl) phenol. **(E)** Nerolidol: (6Z)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol. **(F)** Nerolidol: (6E)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol. **(G)** Linalool: (3R)-3,7-dimethylocta-1,6-dien-3-ol. **(H)** Linalool: (3S)-3,7-dimethylocta-1,6-dien-3-ol. **(I)** (-)-α-Bisabolol: (2S)-6-methyl-2-[(1R)-4-methylcyclohex-3-en-1-yl]hept-5-en-2-ol. **(J)** γ-Elemene: (3S,4S)-4-ethenyl-4-methyl-3-(prop-1-en-2-yl)-1,1'-bi(cyclohexylidene).

being limonene (42.3%), linalool (9.7%) and nerolidol (8.6%), compounds that together with thymol and carvacrol (Fig. 8B-H) have shown leishmanicidal activity (Arruda et al., 2005; 2009; Youssefi et al., 2019). Although the oil is highly active on promastigotes, its toxicity on macrophages is a parameter that requires further studies, especially in models that can replicate their physiological architecture, as well as in three-dimensional models (Andrade et al., 2018).

Another essential oil that showed high leishmanicidal activity was obtained from the plant *Matricaria recutita* L., an annual herbaceous species belonging to the *Asteraceae* family. This plant is native to Europe and western Asia, and is known as German chamomile, Hungarian chamomile, false sweet chamomile, or wild chamomile. It has been used as a traditional herbal remedy for its calming effect (Amsterdam et al., 2012), as an antioxidant, antimicrobial (Roby et al., 2013), antifungal (Jamalian et al., 2012), anti-inflammatory, antiplatelet aggregation and anticancer agent, among other applications (McKay and Blumberg, 2006; Singh et al., 2011). It is also marketed in products such as soaps, perfumes, lotions and, at the food level, in bakery products and infusions (McKay and Blumberg, 2006).

The biological activity of the molecules present in this plant has been shown in studies of cytotoxicity and antioxidant activity, where the ethanolic extract of dried flowers exhibited antiproliferative activity against the human liver cancer cell line (HepG2) attributed to the high concentration of polyphenols and flavonoids (Al-Dabbagh et al., 2019). Another important activity of the whole chamomile extract is that it has been shown to have antidepressant and anti-anxiolytic activity in patients (Amsterdam et al., 2012), where the flavone apigenin 5,7,4′-trihydroxyflavone, present in the dried flowers, has shown anxiolytic and sedative effects (Viola et al., 1995). At the phytochemical level, the essential oil is mainly composed of bisabolol oxides A and B, (Z)-β-farnesene, α-bisabolol, chamazulene and chamo-spiroether (Matos et al., 1993).

Studies conducted by the group of Hajaji et al. (2018) with the essential oil of *M. recutita* evidenced high leishmanicidal activity on promastigotes of *L. (L.) amazonensis* and *L. (L.) infantum*, with an IC_{50} of 10.8 ± 1.4 and 10.4 ± 0.6 µg/mL, respectively. Bioguided fractionation allowed the identification of (-)-α-bisabolol (monocyclic sesquiterpene alcohol, Fig. 8I) as the most active molecule, with an IC_{50} of 5.9 ± 1.2 and 4.8 ± 1.3 µg/mL for amastigotes of *L. (L.) amazonensis* and *L. (L.) infantum*, respectively. Additionally, the determination of the SI for intracellular amastigotes was 5.5 for *L. (L.) amazonensis* and 6.7 for *L. (L.) infantum* (Hajaji et al., 2018); these results evidence the therapeutic potential of (-)-α-bisabolol.

The leishmanicidal potential of (-)-α-bisabolol was also corroborated by the group of Corpaz-López et al. (2016) in a study of a murine model of CL produced by *L. (L.) tropica*; the results showed a reduction in the thickness of the plantar pad with more efficacy than the reference drug, meglumine antimoniate (Corpas-López et al., 2016). The same group also showed that the molecule was active in an *in vivo* model of VL caused by *L. (L.) infantum* with a reduction of the parasitic load in the spleen and liver (Corpas-Lopez et al., 2015); these results confirm the therapeutic potential of this compound.

Another essential oil with promising antileishmanial properties is obtained from *Eugenia piauhiensis* O.Berg, commonly known as goiabinha, a little studied plant belonging to the family *Myrtaceae* with a wide and predominant distribution in tropical and subtropical regions (de Araujo et al., 2012; 2019; de Souza et al., 2018). In traditional medicine, plants of this genus have been used to treat a wide variety of ailments such as infectious diseases, as anti-inflammatory and antihypertensive agent, in gastrointestinal disorders, as well as in the treatment of wounds or as repellents (de Souza et al., 2018; Quirino et al., 2020).

Studies carried out with the essential oil of *E. piauhiensis* have shown insecticidal effect on *Aedes aegypti* larvae (Dias et al., 2015). At the phytochemical level, the oil extracted from its leaves is mainly composed of sesquiterpene-type metabolites (Dias et al., 2015), whose main compounds are γ-elemene, (E)-β-caryophyllene and germacrene D (Nunes et al., 2021); thus, the study of the extracts of aerial parts allowed the identification of triterpenes, flavonoids, tannins and cyanidins (de Souza et al., 2018).

The essential oil of *E. piauhiensis* (EpEO) and the isolated compound γ-elemene (monocyclic sesquiterpene, Fig. 8J) exhibited leishmanicidal activity on the promastigote and amastigote forms of *L. (L.) amazonensis*. For promastigotes, EpEO and γ-elemene showed an IC_{50} of 6.43 ± 0.18 and 9.82 ± 0.15 µg/mL, respectively, while for intracellular amastigotes IC_{50} values of 4.59 ± 0.07 and 8.06 ± 0.12 µg/mL were obtained. EpEO presented an SI of 35.11, while γ-elemene showed an SI of 21.7, with EpEO being safer for macrophages. EpEO and γ-elemene also participated in the stimulation of macrophage activity with increased production of IL-12, TNF-α, ROS and nitric oxide (Nunes et al., 2021).

On the other hand, the essential oil of *E. uniflora* L. (EuEO), a plant belonging to the same genus, evidenced antileishmanial activity against promastigotes (IC_{50} of 3.04 µg/mL) and amastigotes (IC_{50} of 1.92 µg/mL) of *L. (L.) amazonensis*, with low cytotoxicity in macrophages (SI >20) and erythrocytes. The mechanism of action of EuEO was independent of NO production, with increased phagocytic capacity and lysosomal activity, essential immunomodulatory functions in the macrophage. Chemical analysis of EuEO indicated the presence of oxygenated sesquiterpenes and sesquiterpene hydrocarbons, with curzerene, γ-elemene and trans-β-elemene being the major constituents (Rodrigues et al., 2013). The data from these studies demonstrate the high leishmanicidal activity of the essential oils of *E. piauhiensis* and *E. uniflora*; however, further studies are required to define both the molecules that may be involved in the bioactivity and the additional mechanisms of action present in the antileishmanial activity.

Another species native to the Amazon rainforest with leishmanicidal activity is *Piper marginatum* Jacq., known as pimento do mato or mavaisco (Autran et al., 2009). This plant belongs to the genus *Piper* of the family *Piperaceae*, and it is broadly distributed from Mexico to Brazil, including Cuba, Suriname, and Trinidad and Tobago (POWO, 2022); it grows mainly in humid and shady places at elevations below 1500 m above sea level (Brú and Guzman, 2016). This plant stands out for its wide therapeutic potential, since it is used in traditional medicine for the treatment of gastrointestinal problems, urinary ailments, as an analgesic, anti-inflammatory, hemostatic and antimicrobial agent, among others (Autran et al., 2009; Brú and Guzman, 2016; D'Angelo et al., 1997). Studies carried out with the essential oil showed activity against *Aedes aegypti* larvae (Autran et al., 2009), as well as acaricide (Ribeiro et al., 2016), antimicrobial and antifungal (Sánchez et al., 2011) effects. At the phytochemical level, this species is characterized by containing anethole, estragole, isoeugenyl methyl ether, phenylalkanoic acids 3-farnesyl-4-hydroxybenzoic and 3-farnesyl-4-methoxybenzoic and the glucosides marginatoside and vitexin, among other metabolites (Brú and Guzman, 2016).

Studies carried out with the essential oil, the ethanolic extract and the hexanic, dichloromethane, ethyl acetate fractions and the residual methanolic fraction from the leaves of *P. marginatum* exhibited the ability to inhibit the growth of promastigotes of *L. (L.) amazonensis*, with the hexanic and methanolic fractions being the most active with IC_{50} values of 1 and 0.9 µg/mL, respectively. On the amastigote form, the essential oil and the ethanolic extract were the most active with IC_{50} of 0.6 and 1.2 µg/mL, results that suggest a synergistic activity of the compounds. On the other hand, all the samples evaluated presented an SI >1, with the essential oil and the ethanolic extract standing out with SI values of 57.5 and 415.8, respectively; this indicates that as a mechanism of action, there is no evidence of NO increase, suggesting that the antileishmanial effect is independent of macrophage activation or that it could be the result of a direct effect on the parasite (Macêdo et al., 2020).

Other studies carried out with species of the genus *Piper*, such as *Piper angustifolium* Lam., *Piper betle* L., *Piper regnellii* (Miq.) C. DC., *Piper tuberculatum Jacq.*, and *Piper aduncum* L. (Bosquiroli et al., 2015; Goretty et al., 2010; Misra et al., 2009; Nakamura et al., 2006; Oliveira et al., 2018; Peixoto et al., 2021; Torres-Santos

Table 4. Leishmanicidal activity of raw extracts, fractions or essential oils.

Plant (Part)	Extract/fraction/ compound	Leishmania species	IC_{50} promastigotes (µg/mL)	IC_{50} amastigotes (µg/mL)	SI*	Reference
Azadirachta indica A. Juss (Leaves)	Ethanolic extract	*L. (L.) amazonensis*	38	9.8	>1	(Carneiro et al., 2012)
	Dichloromethane fraction		3.9	1.1		
	Chloroformic fraction		1.2	0.6		
Azadirachta indica A. Juss. (Nut tegument)	Ethanolic extract		2.7	0.4		
	Chloroformic fraction		2.1	0.6		
Piper ovatum Vahl. (Leaves)	Dichloromethane: ethyl acetate fraction (1:1)	*L. (L.) amazonensis*	2.1	24	>1	(Rodrigues-Silva et al., 2009)
Dipteryx alata Vog. (Leaves)	Hexane extract	*L. (L.) amazonensis*	0.08 ± 0.04		129	(Ribeiro et al., 2014)
Hymenaea stigonocarpa Hayne (Leaves)	Ethanolic extract		4.69 ± 0.77		7.4	
Jacaranda cuspidifolia Mart. (Leaves)	Ethanolic extract		10.96 ± 0.76		69.6	
Physalis angulata L. (Stem)	Ethanolic extract	*L. (L.) amazonensis*	5.35 ± 2.50	1.23 ± 0.11	5	(Nogueira et al., 2013)
		L. (V.) braziliensis	4.50 ± 1.17			
Tetradenia riparia (Hochstetter) Codd (Leaves)	Essential oils	*L. (L.) amazonensis*	0.03	0.03	5.67	(Demarchi et al., 2015)

*Selectivity index, calculated as the CC_{50}/IC_{50} ratio. For values higher than 1 the evaluated activity of the extract/fraction/molecule is more selective against parasites than against cells (Koutsoni et al., 2019).

et al., 1999) have demonstrated their efficacy against different *Leishmania* spp., making this genus a promising group for the development of leishmanicidal phytomedicines.

Table 4 presents other extracts, fractions or essential oils with high leishmanicidal activity (IC_{50} <2 µM or [<10 µg/mL]) (Boniface and Ferreira, 2019; De Lima et al., 2012) and SI >1 against new-world spp. causative of CL.

According to this review, the bioactivity of the molecules is mostly generated by sesquiterpenes and monoterpenes, belonging to the terpene family. These secondary metabolites function as attractant or repellent substances and are responsible for the typical fragrance of many plants (Paduch et al., 2007). They act as protective molecules against biotic and abiotic stress, and as thermoprotectants, among others (Cox-Georgian et al., 2019), and due to their lipophilic nature they make up a major part of essential oils from plants. The biosynthesis of terpenes occurs via two routes: the mevalonic acid pathway, which takes place in the cytosol and is responsible for the synthesis of sterols, specific sesquiterpenes; and the non-mevalonate pathway or methylerythritol phosphate pathway, which takes place in chloroplasts and produces monoterpenes, specific sesquiterpenes, diterpenes and carotenoids (Cox-Georgian et al., 2019). At the chemical level, these compounds are also called isoprenoids due to the presence of isoprene units (C_5H_8) in their molecular structure; therefore, they are classified according to the number of isoprene units into hemiterpenes, monoterpenes, iridoids, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes; there are also polyterpenes, with more than eight isoprene units, and irregular terpenes (Raimundo et al., 2022). Terpenes can exist as hydrocarbons or have oxygen-containing compounds such as hydroxyl, carbonyl, ketone, or aldehyde groups, which are termed terpenoids (Paduch et al., 2007).

The second type of compounds studied in this review are flavonoids, which are secondary metabolites with a polyphenolic structure of low molecular weight; they are used by plants as a defense mechanism against pests, and are responsible for the color and aroma of flowers, among other characteristics and functions (Ioset, 2008). They are synthesized from acetic acid/phenylalanine derivatives via the shikimic

acid pathway. Traditionally, flavonoids are classified by degree of oxidation, C-ring annularity and B-ring connecting position. At the chemical level, they are subdivided into flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins and chalcones (Boniface and Ferreira, 2019). The biological activity of flavonoids depends mainly on the nature of the chemical groups (-OH, -Me, -MeOH, -glycosyl, among others) present in their backbone (Boniface and Ferreira, 2019); in particular, the presence of methoxyl (-O-CH_3) and hydroxyl (-OH) groups in one of the rings has been found to be related to better leishmanicidal activity (Silva-Silva et al., 2021).

The biological activity of these compounds is associated with lipophilic components that can interact with the hydrophobic parts of the cell, affecting the polysaccharides, fatty acids and phospholipids present in the plasma membrane of promastigotes and amastigotes of *Leishmania* spp. (Rodrigues et al., 2013; Sikkema et al., 1995). By the same mechanism, essential oils cause alterations in the permeability of the mitochondrial membrane, with deterioration of its potential (ΔΨ m) (Rottini et al., 2015). In particular, the inhibitory effect of the sesquiterpene nerolidol on isoprenoid biosynthesis via the mevalonic acid pathway has been shown to be potentially responsible for the effect of *Copaifera reticulata* Ducke essential oil on amastigotes and promastigotes of *L. (L.) amazonensis* (Arruda et al., 2005); moreover, due to the complex nature of essential oils, their bioactivity might be related to a synergistic effect, where the fractions are more active than the isolated compounds (Nunes et al., 2021).

Table 5 presents some studies of flavonoids and terpenes that are highly active (IC_{50} <2 µM or [<10 µg/mL]) against parasites of the *Leishmania* genus.

Research outlook on oils, extracts and compounds with leishmanicidal activity

Ethnobotanical studies have allowed the identification of species with antileishmanial activity that have been employed by the communities as part of the ancestral knowledge linked to their traditional medicine. Thus, the study of these species generates scientific knowledge that can contribute to the sustainable use of natural resources and improve the bioeconomy and health of the populations.

Among the plants that stand out for their growing economic value is *Cannabis sativa* L., a herbaceous plant of the *Cannabaceae* family, important in popular medicine for its analgesic, anti-depressive, stimulating, anti-inflammatory, anxiolytic, and immunosuppressive properties, among others (Russo, 2007), and whose essential oils have shown strong antimicrobial activity (Ali et al., 2012; Nissen et al., 2010).

In terms of phytochemicals, approximately 500 compounds have been identified in the plant, including cannabinoids, sesquiterpenes, flavonoids, nitrogenated compounds, stilbenes, phenols, lignanamides, and aminoacids, among others (ElSohly and Slade, 2005). As regards its anti-parasitic effect, its use has shown evidence of activity against *Trypanosoma brucei* (Nok et al., 1994). Among the specific studies on the genus *Leishmania*, the group of Radwan identified two compounds with moderate inhibition on the growth of promastigotes of *L. (L.) donovani* (Radwan et al., 2008); similarly, studies conducted in Colombia by Robledo et al. (2017) showed the antileishmanial activity of ethanolic extracts of *Cannabis* Nicole Kush (75% *C. indica* and 25% *C. sativa*), being a therapeutic alternative to be explored for the management of CL.

Among the wide range of compounds present in the *Cannabis sativa* plant, there are some that have been identified as having potential antileishmanial activity in other plants; this is the case of sesquiterpenes, present in the essential oils of several plants (Machado et al., 2010; Pérez et al., 2012; Rodríguez-Chaves et al., 2018; Sosa et al., 2016). Notably, the presence of β-sitosterol (Radwan et al., 2009), a chemical compound of the phytosterol family, has shown activity against *L. (L.) donovani* and *L. (L.) tropica*, causative agents of VL and CL, respectively (Majid et al., 2019; Pramanik et al., 2020), thus confirming the importance of studying this plant for the development of new antileishmanial therapies.

Both *Cannabis sativa* and other plants that express secondary metabolites with potential antileishmanial activity are the subject of research interest; therefore, it is necessary to use tools such as chemotaxonomy, that allows the classification of plants at the phylogenetic level from the difference or similarity of their metabolites (Liu et al., 2017). From its methodological utility, chemotaxonomy has the potential to group plant families, genera and species on the basis of characteristic chemotaxonomic markers (Elzinga et al., 2015; Emerenciano et al., 2001; Johnson et al., 1997); sesquiterpene lactones (STL), for instance, are chemotaxonomic markers of the *Asteraceae* family (Da Costa et al., 2005; Zhao et al., 2015), with high leishmanicidal potential (Barrera et al., 2013; Caldas et al., 2019; de Toledo et al., 2014; Odonne et al., 2011; Tiuman et al., 2005; Wulsten et al., 2017). A similar result was observed with the oxygenated sesquiterpene spatulenol, considered as a chemotaxonomic marker of the *Annonaceae* family (Costa et al., 2009), which together with other sesquiterpene molecules exhibits antileishmanial activity (Costa et al., 2009; Siqueira et al., 2011).

Table 5. Antileishmanial activity and cytotoxicity of flavonoids and terpenes against new-world *Leishmania* strains.

Plant	Molecule studied	Species evaluated	IC $_{50}$ promastigotes	IC$_{50}$ intracellular amastigotes	SI*	Mechanism of action	Reference
Selaginella sellowii Hieron.	Amentoflavone**	*L. (L.) amazonensis*	-	0.1 µg/mL	22 in J774.A1. 30 in NIH/3 T3.	Defense mechanisms independent of NO release	(Rizk et al., 2014)
	Robustaflavone**		-	2.8 µg/mL	9.1 in NIH/3T3 1.1 in J774.A1		
Pluchea carolinensis (Jacq.) D.Don	Quercetin**	*L. (L.) amazonensis*	0.2 µg/mL 0.7 µM	1.3 µg/mL 4.3 µM	10 in macrophages	-	(Montrieux et al., 2014)
Camellia sinensis (L.) Kuntze; Theaceae	(−)-Epigallocatechin 3- O-gallate (EGCG)**	*L. (L.) amazonensis*		1.6 µM	129.4 in macrophages	-	(Inacio et al., 2013)
Croton cajucara Benth.	Linalool*** (Enriched oil)	*L. (L.) amazonensis*	LD_{50}: Essential oil: 8.3 ng/mL Purified linalool: 4.3 ng/mL	Amastigotes in culture LD_{50}: Essential oil: 22.0 ng/mL Purified linalool: 15.0 ng/mL	Non-cytotoxic to Vero cells and macrophages	Destruction of nuclear chromatin and kinetoplast, followed by cell lysis.	(do Socorro et al., 2003)
Lophanthera lactescens Ducke	6a, 7a, 15b, 16b, 24-pentacetoxy-22a-carbometoxy-21b,22b-epoxy-18bhydroxy-27,30-bisnor-3,4-secofriedela-1,20 (29)-dien-3,4 R-olide (LLD-3)***	*L. (L.) amazonensis*		0.41 µg/mL	Not cytotoxic in peritoneal macrophages or B cells	Defense mechanisms independent of NO release	(Danelli et al., 2009)
Salacia madagascariensis (Lam.) DC.	Isoiguesterine***	*L. (L.) mexicana*	-	0.082 µM	-	-	(Thiem et al., 2005)
Ambrosia tenuifolia Sprengel.	Psilostaquiine***	*L. (L.) mexicana*	0.12 µg/mL	0.43 µM	25.7 in T lymphocytes from BALB/c mice	-	(Sülsen et al., 2008)
	Peruvine***		0.39 µg/mL		35.0 in T lymphocytes from BALB/c mice	-	
Jatropha grossidentata Pax & K.Hoffm.	Jatrogrossidione***	*L. (V.) braziliensis/ L. (L.) amazonensis/ L. (L.) chagasi*	IC100 0.75 µg/mL	0.8 µM			(Schmeda-Hirschmann et al., 1996)

*SI: selectivity index. CC_{50} for macrophages/IC_{50} for intracellular amastigotes (µg/mL). **Flavonoids. ***Terpens.

Taken together, these results contribute to the predictive value of secondary metabolites in the bioprospecting of medicinal plants, a scenario that has contributed to the development of computational tools aimed at the search for drug candidate molecules or the identification of pharmacophore groups that enhance biological activity on *Leishmania* parasites (Herrera-Acevedo et al., 2017; 2021; Moraes Neto et al., 2019).

On the other hand, it is necessary to take into account that biotic and abiotic factors influence the synthesis, accumulation and expression of secondary

metabolites among species of the same genus (Moghaddam and Mehdizadeh, 2017). This has become evident for the genus *Piper* after studying the chemical profile of essential oils of eleven species from different areas of southeastern Brazil, with the results showing variation in their chemical composition according to the area of provenance (Perigo et al., 2016). A similar effect was described for *Cannabis sativa*, with variation in environmental, genetic, ontogenetic factors and cultivation techniques changing the expression of phytocannabinoids and their potential use (Giraldo Escobar, 2022). These results guide the research approach towards the study of variation in the expression of metabolites due to biotic and abiotic factors and the implications on their antileishmanial activity.

From another perspective, it has been found that the antileishmanial effect is enhanced by the combined use of extracts and/or isolated compounds, generating a synergistic or additive effect (Peixoto et al., 2021). These results have been observed for some essential oils whose antileishmanial activity presents greater efficacy than their isolated compounds (Macêdo et al., 2020; Nunes et al., 2021; Santin et al., 2009), making them a low-cost and easily accessible therapeutic option (Monzote et al., 2019), with reduced adverse effects and without losing therapeutic efficacy, taking into account that many of the species studied have been used as a constituent part of traditional medicine.

The intracellular localization of infective forms of *Leishmania* becomes a challenge for disease control. With increasing evidence of the antileishmanial activity of secondary metabolites, there is a need to develop controlled release systems that demonstrate effects at the intracellular level for disease control. Recently, studies conducted by the group of Higuita-Castro et al. (2021) demonstrated the efficacy of the use of chitosan soft capsules incorporating a mixture of benzoic acid 2-(2,3-dihydro-4H-1-benzopyran-4-ylidene) hydrazide (TC2), a compound previously synthesized and studied (Zapata et al., 2020), together with compounds present in *Sapindus saponaria* L. (SS) extract in a 1:1 ratio, against an *in vivo* model of cutaneous leishmaniasis produced by *L. (V.) braziliensis*. The results showed a reduction in lesion size by 93% at 30 days of treatment (Higuita-Castro et al., 2021), which shows the technological potential of incorporating extracts and mixtures of secondary metabolites, among others, in new delivery systems for topical use.

Another study conducted by the group of Aragão evidenced the antileishmanial utility of poly(lactic-co-glycolic acid) (PLGA) polymeric microparticles in the encapsulation of a hexane eluate subfraction of *Maytenus guyanensis* Klotzsch ex Reissek (HEMg) bark; the results showed a reduction in the parasite load in the plantar pad of mice infected with *L. (L.) amazonensis*, as well as an activation of the microbicidal mechanisms IL-12 and TNF-α at the site of lesions and lymph nodes (Aragão et al., 2019), results that demonstrate the potential of microparticles as an optimal delivery system for biocompounds.

Considering the clinical characteristics of CL, the use of topical formulations is an alternative that offers multiple advantages over systemic therapies. Due to the simplicity of its application and greater adherence to treatment, its localized action reduces complications generated by the use of oral drugs and is usually more economical. However, in the case of some bioactive compounds with antileishmanial activity, their lipophilic nature becomes a barrier to topical administration; therefore, it is necessary to develop drug delivery systems, such as water-in-oil (w/o) micro- and nanoemulsions capable of increasing the penetration of lipophilic compounds. Additionally, technologies such as hydrogels, including nano- and microgels, could be contemplated to encapsulate extracts or metabolites of medium to high polarity.

Studies conducted by the group of Kawakami evidenced the promising effect of nanoemulsions loaded with oleoresin from *Pterodon emarginatus* Vogel, as a treatment for ulcerated lesions of BALB/c mice infected with *L. (L.) amazonensis*. Topical administration showed a significant reduction in lesion size compared to the control, while the application of this nanoemulsion in combination with injectable meglumine antimoniate generated a significant reduction in parasite load, as well as a reduction in lesion size; therefore, the use of bioactive compounds in nanoemulsion or in combination with traditionally used drugs may be a promising new strategy for the treatment of CL (Kawakami et al., 2021).

Finally, in the search for bioactive metabolites with antileishmanial activity, the enzymes of the parasite are being recognized as new therapeutic targets in drug development. Recently, phenolic compounds derived from hydroxycinnamic acid that are present in extracts of *Pluchea carolinensis* (Jacq.) D.Don and *Stachytarpheta cayennensis* (Rich.) Vahl showed inhibitory activity on arginase from *L. (L.) amazonensis*. The compounds caffeic acid, rosmarinic acid and isoverbascoside (Fig. 9) achieved the lowest IC_{50} in the *in vitro* inhibition assay, with 1.5 ± 0.3, 2.1 ± 0.3 and 2.3 ± 0.3 μM, respectively (da Silva et al., 2019).

The arginase enzyme of *Leishmania* is critical in the metabolism of polyamine precursors. The polyamine pathway gives rise to spermidine, a substrate for trypanothione synthesis which neutralizes ROS and

RNS produced by macrophages to attack the parasite (Colotti and Ilari, 2011), which broadens the spectrum of search and inquiry on the different ways to contribute to the control of leishmaniasis.

Limitations of the study

Ninety percent of the studies reviewed evaluate the effect of biocompounds on *L. (L.) amazonensis* species, ignoring the diversity of *Leishmania* species causing CL in the New World. In Colombia, cutaneous leishmaniasis has been reported to be mainly caused by *L. (V.) panamensis* (Marcondes and Day, 2019), just as in Ecuador (Kato et al., 2019), while *L. (V.) braziliensis* is one of the most widely recorded strains in reported cases in Peru (Lucas et al., 1998), with this same species being predominant in some states of Brazil (Marlow et al., 2013).

On the other hand, some studies do not specify the geographical and environmental conditions of the starting plant material, which is a limitation considering that these parameters directly influence the composition of the metabolites present in the extracts, fractions and/or essential oils.

Another limitation is the lack of information related to the mechanisms of action of the evaluated compounds; however, this limitation becomes a research opportunity that is suggested to be approached from the chemical structure of the metabolites and their relationship with cellular metabolic pathways, as well as based on the visible effects caused in the processes of healing or reduction of the symptoms and signs of the disease. The above can be used as a guide to orient the research questions to be asked.

One of the most important limitations is associated with the lack of financial resources allocated to the study of this type of disease, since it affects isolated population groups in low socioeconomic conditions, which are not of priority interest to government agencies responsible for the welfare of the population. Therefore, this type of research is not especially addressed in the calls for funding.

CONCLUSION

The identification of plants with leishmanicidal activity opens new perspectives in terms of plant species that may have secondary metabolites with some type of therapeutic potential. In this study, terpenes and flavonoids stand out as those with higher biological action against the various parasite forms of *Leishmania*. There is evidence showing that the biological activity of these compounds depends on the nature of the chemical groups found in the central chemical structure, which opens a line of inquiry on the structure-activity relation.

Both ethanolic extracts and essential oils were of interest in this review study, since they are promising for the development of herbal products with leishmanicidal activity, whether they are considered in phytotherapy or as adjuvants in drug therapy for the treatment of infection caused by parasites of the genus *Leishmania*.

With respect to the study of extracts from plants with potential leishmanicidal effects, those distributed in the South American continent stand out, especially in Brazil, where they have been traditionally used for different purposes according to the needs of the population, with the potential to become an option for the treatment of leishmaniasis and other diseases, and also as a source of sustainable development for rural communities.

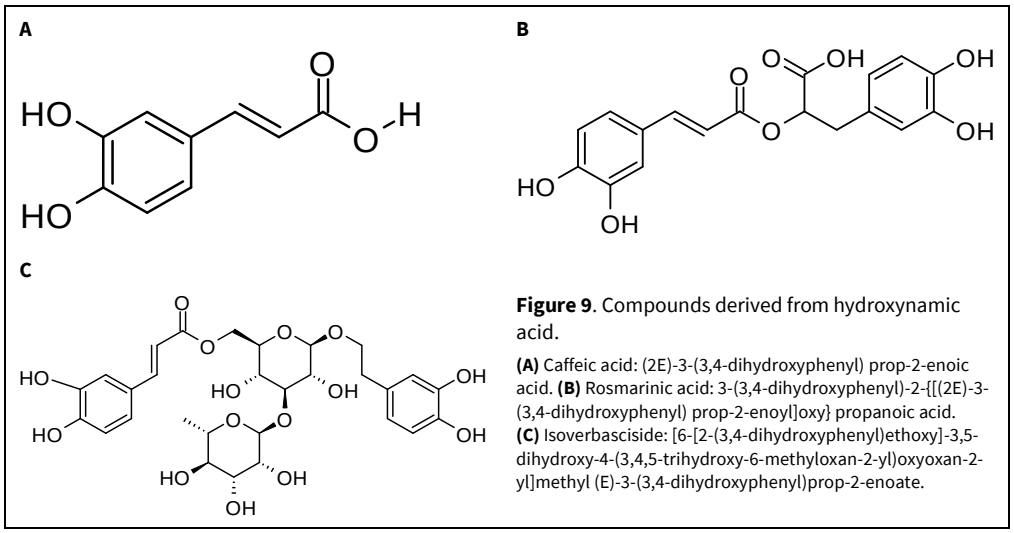

Figure 9. Compounds derived from hydroxynamic acid.

(A) Caffeic acid: (2E)-3-(3,4-dihydroxyphenyl) prop-2-enoic acid. **(B)** Rosmarinic acid: 3-(3,4-dihydroxyphenyl)-2-{[(2E)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]oxy} propanoic acid. **(C)** Isoverbasciside: [6-[2-(3,4-dihydroxyphenyl)ethoxy]-3,5-dihydroxy-4-(3,4,5-trihydroxy-6-methyloxan-2-yl)oxyoxan-2-yl]methyl (E)-3-(3,4-dihydroxyphenyl)prop-2-enoate.

Many research groups have identified secondary metabolites isolated from plants with promising activity against amastigotes, but their intracellular location hinders therapeutic efficacy; therefore, it is necessary to search for new release systems of antileishmanial compounds for topical use with high efficacy and low probability of generating adverse effects.

Finally, ethnobotanical research contributes to the identification of molecules with biological activity, in addition to endorsing the traditional use of plants as a viable and complementary alternative to treat neglected diseases or as adjuvants in their treatment, contributing to the preservation of the intangible cultural heritage of the communities and becoming an economic option for the populations that cultivate them.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Lozano YY	Giraldo SG	Zapata AC	Escobar JE	Sánchez RM
Concepts or ideas	x				
Design	x	x			
Definition of intellectual content	x	x	x		x
Literature search	x	x	x	x	x
Data acquisition	x	x	x	x	x
Data analysis	x	x	x	x	x
Manuscript preparation	x	x	x	x	x
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x

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Supplementary data

Table S1. Quality assessment of the selected studies.

Authors	AXIS tools questions																				Score	Quality	Positive answers (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20			
Robledo et al. (2022)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	17	High	85
Fadel et al. (2019)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
Garcia et al. (2018)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
Tomiotto-Pellissier et al. (2018)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	n/a	yes	no	no	yes	yes	yes	yes	no	n/a	14	medium	70
Silva-Silva et al. (2021)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
Hajaji et al. (2018)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
Brito et al. (2021)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	no	no	n/a	14	medium	70
Nunes et al. (2021)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
Macêdo et al. (2020)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
da Silva et al. (2021)	yes	yes	yes	yes	n/a	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	16	medium	80
Delgado-Altamirano et al., (2019)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75
da Silva et al., (2019)	yes	yes	yes	yes	n/a	yes	yes	yes	n/a	yes	yes	yes	no	no	yes	yes	yes	yes	no	n/a	15	medium	75

Introduction

1. Were the study objectives/aims clear?

Methods

2. Was the study design appropriate for the objectives?
3. Was the sample size justified?
4. Was the target/reference population clearly defined? /Is it clear about whom the research was conducted?
5. Was the sample taken from an adequate population base to represent closely the target population under investigation?
6. Did the selection process allow selecting representative subjects/participants of the target/reference population or under investigation?
7. Were measures taken to address and categorize non-respondents?
8. Were the risk factors and result variables appropriate measurements for the study objectives?
9. Were the risk factor and result variables correctly measured by using instruments/measurements that had been previously tested, experimentally implemented or published?
10. Is it clear what was used to determine statistical significance and/or precision? (i.e., p values, IC)
11. Are the methods sufficiently described (including statistical methods) so that they can be replicated?

Results

12. Were the basic data adequately described? SD, mean and error.
13. Does the response rate raise concerns of non-response bias?
14. If applicable, was there information describing non-respondents?
15. Were the results internally consistent?
16. Were the results of the analyses described in the methods presented?

Discussion

17. The authors' discussion and conclusions were justified by the results?
18. Were the limitations of the study discussed?

Other aspects

19. Are there funding sources or conflicts of interest that can affect the authors' interpretation of results?
20. Was the ethical approval or consent of participants obtained?

Response criteria: Yes: it complies; No: it does not comply; N/M: non- measurable (not detailed); and N/A: not applicable. *Question 19: Yes = 0 points; No = 1 point.

[b] Papers with a score lower than 12 were considered of low quality, from 12 to 15 of medium quality, and higher than 15 of high quality (Mat Sharil et al., 2022; Pérez-Loyola et al., 2022).