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Natural Compounds and Extracts from Mexican Medicinal Plants with Anti-Leishmanial Activity: An Update

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Additional information is available at the end of the chapter

Abstract

Leishmaniasis is considered an emerging, uncontrolled disease, and is endemic in 98 countries. Annually, about 2 million cases of cutaneous and 500,000 cases of visceral type leishmaniasis are recorded, and 60,000 persons die from the disease. In Mexico, cutaneous leishmaniasis is known as chiclero's ulcer and is reported in 22 states; it is considered a health problem. For its treatment, pentavalent antimonial drugs are administered; these drugs cause severe side effects, are costly, and drug-resistant cases have been reported and have been developing for >70 years. One alternative to the drugs that are currently available is to find active molecules in medicinal plants; dihydrocorynantheine, corynantheine, and corynantheidine are active against *Leishmania major*, while harmane, pleiocarpin, buchtienin, luteolin, and quercetin are active against *L. donovani*. In Mexico, about 20 medicinal plants have been evaluated against *L. mexicana*, among which the most active are *Tridax procumbens, Tridax procumbens, Pentalinon andrieuxii, Lantana camara, Schinus molle,* and *Prosopis laevigata*. From some of these plants, active compounds with $IC_{50} \leq 30$ μg/mL or μM have been isolated, such as 3(S)-16,17-didehydrofalcarinol or Oxylipin, cholestra-4,20,24-trien-3-one or pentalinosterol, 24-methylcholest-4-24(28)-dien-3-one, cholest-4-en-3-one, 6,7-dihy-droneridie-none, neridienone, cholest-5,20,24-trien-3β-ol, and isocordoin. Today, the only pentalinonsterol has been synthesized and assayed in the visceral leishmaniasis experimental model using BALB/c mice infected with *L. donovani*. Liposome formulation of this compound administered by intravenous route at 2.5 mg/kg showed a significant reduction of parasite load in mouse liver and spleen.

Keywords: active extracts, leishmaniasis, leishmanicidal activity, natural compounds, Mexican medicinal plants

1. Introduction

Leishmaniasis is caused by about 20 species of the protozoan parasite of the genus *Leishmania*. It is classified by the World Health Organization (WHO) as an emergent category one, uncontrolled disease, and it comprises one of the six most important tropical diseases, with 0.9–1.6 million new cases annually and 20,000–30,000 deaths. The *Leishmania* infection exhibits three main clinical manifestations: cutaneous, mucocutaneous, and visceral. It is endemic in 98 developing countries (tropical and subtropical regions) and is more frequent in males. Today, it is estimated that there are 12 million infected persons (all forms), 350 million of people are at risk, and an incidence has been reported of 1.5–2 million new cutaneous cases annually [1–4]. Each year, 500,000 cases of the visceral type are reported and 50,000 individuals die from the latter [4]. In Mexico, cases of leishmaniasis has been reported in 22 states, and it is considered endemic in the states of Coahuila, Nuevo León, Tamaulipas, Veracruz, Tabasco, Campeche, Yucatán, Quintana Roo, Chiapas, Oaxaca, Guerrero, Michoacán, Jalisco, Nayarit, San Luis Potosí, Morelos, Puebla, and Hidalgo, where it is commonly known *as* chiclero's ulcer [5–8]. For example, in one municipality of the state of Campeche, over a 2-year period, 76% of persons had skin lesions, and were diagnosed with cutaneous leishmaniasis. In this study, about 89% of cutaneous leishmaniasis is caused principally by *Leishmania mexicana* [9]. The most serious clinical manifestation of leishmaniasis is the visceral form (VL), which it is endemic in Guerrero and Morelos; and 921,273 people are considered at risk to be infected [10]. Recently, cases of leishmaniasis co-infection with HIV/AIDS have been reported, which have a poor prognosis. This co-infection has worldwide distribution and has been recorded in 35 countries. Infection by this parasite depends in great measure on the state of the host's immune system. Other risk factors that favor its dissemination are socioeconomic condition, migration, deforestation, and urbanization [3, 8].

Currently, treatment of leishmaniasis employs first-line drugs such as sodium stibogluconate (commercially known as Pentostam) and meglumine antimoniate (commercially known as Glucantime), and other options (second-line drugs) are pentamidine isothionate (commercially known as Pentamidine), amphotericin B, (Fungizone or Ambisome), miltefosine, and paramomycin sulfate (Aminosidine), although this latter option is not widely utilized in Mexico and is not effective when administered orally [11]. Even when administered in combination, the effectiveness of the drugs is less than optimal [12, 13].

Antimonial pharmaceuticals (pentostam, glucantime, and pentamidine) were developed >70 years ago, and are continue to be used to treat leishmaniasis. Some of these have not been effective due to the drug resistance developed by the parasite [2, 8, 14, 15], in addition to the scarce development of this drug type. These substances have severe side effects, such as kidney failure, acute pancreatitis, myalgia, teratogenicity, peripheral neuropathy, hepatotoxicity, and cardiotoxicity (cardiac arrhythmia), in addition to the fact that treatment is prolonged (>30 days) depending on the patient's immunity. Drug administration is by the parenteral route, some of these drugs are expensive, and they are not always effective due to the parasite's resistance. Sometimes, the patient has no access to health systems, and these drugs cannot be utilized in patients with kidney, hepatic, or cardiac failure, or in those with tuberculosis [8]. An alternative for the treatment of leishmaniasis is to find molecules active in medicinal plants that serve as active principles for the development of new pharmaceutical preparations.

In the present text, an exhaustive bibliographic research (from 2001 to 2018) was carried out on leishmanicidal activity from the extracts and/or compounds obtained from Mexican medicinal plants against several *Leishmania* spp. in *vivo* and *in vitro* assays. The main scientific sources consulted were the Scopus and PubMed databases. Regarding this subject, we found 56 references. The keywords employed included: medicinal plants, Mexican medicinal plants, anti-leishmanial activity, and natural compounds.

2. An overview of the leishmanicidal potential of medicinal plants and compounds isolated from these

The development of drugs to treat parasitic diseases such as leishmaniasis has been scarce, due to the fact that these diseases are more often present in developing countries, and because the pharmaceutical industry does not receive high profits since it must develop low-cost medication that will be accessible to a population with a low socioeconomic condition [7, 15]. In this regard, the WHO has emphasized the urgent need to develop new drugs for the treatment of leishmaniasis [4]. An alternative to synthetic drugs is the search for active molecules from natural sources, such as the medicinal plants used in the treatment of leishmaniasis in ancient times. In this regard, medicinal plants biosynthesize several secondary metabolites, which constitute an important source of leishmanicidal agents [7, 16].

Natural products have been an important role in current therapy; between the years 1981–2006, 1184 novel drugs with a natural origin were obtained, and 28% of these derived from plants. On the other hand, 24% of the new synthetic drugs have as a base molecule or are derived from, active molecules obtained from medicinal plants [8–17]. Another report states that between the years 2000–2005, 23 new natural-origin drugs were introduced into the market, all of which exhibited structural and biological diversity. Therefore, natural products constitute an immeasurable wealth of chemical structures that has been and continues to be an important source of new drugs and that constitutes prototype molecules for the development of new active substances [18–20]. Some examples of the active agent obtained from medicinal plants utilized in current therapy are paclitaxel (isolated from *Taxus brevifolia*), camptothecin (isolated from *Camptotheca acuminata*), and vinblastine and vincristine (isolated from *Catharanthus roseus*); artemisinin, isolated from *Artemisia annua*; this compound is employed in malaria treatment.

Regarding the development of active compounds against *Leishmania* spp., to date only four molecules are potential candidates for the development of anti-leishmanial drugs (these substances are in phase I/II research) and include the following: miltefosine (an alkylphospholipid) that has been used in India since 2002, that was authorized for use in Colombia in 2005, and is in clinical phase research to determine its possible global use [2]; paromomycin (an aminoglycoside); 8-aminoquinoline; sitamaquine, and berberine (the latter, an alkaloid of vegetable origin, isolated from *Beberis vulgaris*). This latter compound has been utilized against this disease for >50 years and has demonstrated its activity both *in vitro* and *in vivo* [8, 20–24].

Recently, some secondary metabolites, such as quinones, naphthoquinones, lignans, neolignans, alkaloids (quinolines, isoquinoline, steroidal, and indole analogs), phenolic derivatives (chalcones and flavonoids), and terpenes (iridoids, sesquiterpenes, diterpenes, triterpenoids, and saponins) have been reported to possess leishmanicidal activity [23, 25–28]. Among these,

some alkaloids isolated from plant species have exhibited significant *in vitro* leishmanicidal activity. Some examples of these are isoguattouregidine, an indole alkaloid isolated from *Guatteria foliosa*, with a mean inhibitory concentration (IC_{50}) = 100 μg/mL against *L. donovani* and *L. amazonensis*, and coronaridine (isolated from *Peschirea australis*), which an IC_{50} = 12 μg/mL against *L. amazonensis*. In addition, indole alkaloids (dihydrocorinanteine, corinanteine, and corinanteidine), which were isolated from *Corynanthe pachyceras*, were active against *Leishmania major* with an IC_{50}~30 μM. Other indole alkaloids, including harmane, pleiocarpin, and buchtienin, which are isolated from the bark and leaves of *Kopsia griffithii*, were active against promastigotes of *L. donovani*, demonstrating IC_{50} = 6.25, 2, and 1.56 μg/mL, respectively [26–29]. The main disadvantage is that these alkaloids have been evaluated against different strains of *Leishmania* and on different growth stages, and none of these compounds, to our knowledge, is currently under clinical investigation. Other active alkaloids, such as ramiflorines A and B (isolated from *Aspidosperma ramiflorum*) showed a median lethal dose (LD_{50}) = 16.3 and 4.9 μg/mL against *L. amazonensis* promastigotes, respectively [26]. The alkaloid 4-hydroxy-1-tetralone (isolated from *Ampelocera edentula* bark) was active against *L. braziliensis*, *L. amazonensis*, and *L. donovani* promastigotes, with an IC_{50} = 10 μg/mL [30].

In addition, the *in vitro* activity of other two medicinal plant extracts, such as *Ambrosia miratima* and *Acacua nilotica* with IC_{50} < 8 μg/mL [31] have been reported; however, no compounds responsible for activity have been isolated from these active plant species. The ethanol extract and the dichloromethane and chloroform fractions from the leaves of *Azadirachta indica* presented IC_{50} = 38, 3.9, and 1.2 μg/mL against promastigotes of *L. amazonensis,* respectively, and against amastigotes, IC_{50} was 9.8, 1.1, and 0.6 μg/mL [16].

The tormentic acid-rich fraction, 2α,3β-dihydroxyursan-12-in-28-oic acid,2α,3β-dihydroxyolean-12-in-oic acid, ursolic acid, and oleanolic acid from *Pourouma guianensis* were active against *L. amazonensis* promastigotes, showing an IC_{50} = 100 μg/mL; in addition, ursolic acid, and oleanolic acid were also very active against intracellular amastigotes (IC_{50} = 27 and 11 μg/mL, respectively). These compounds were more active than glucantime (IC_{50} = 83 μg/mL) [23]. In addition, review described that the flavones luteolin and quercetin (isolated from *Vitex negundo* and *Fagopyrum esculentum*, respectively) were active against *L. donovani* amastigotes, with IC_{50} = 12.5, and 45.5 μM; the chalcone identified as licochalcone A (isolated from *Glycyrrhiza* spp.) showed an IC_{50} = 0.9 μg/mL (2.7 μM) against *L. donovani* amastigotes and against *L. major* promastigotes, demonstrating an IC_{50} = 7.2 μg/mL (21 μM). Also, 2′,6′-dihydroxy-4′-methoxy chalcone (isolated from *Piper aduncum*) inhibited the growth of promastigotes and intracellular amastigotes of *L. amazonensis*; median effective doses were 0.5 μg/mL (1.9 μM) and 24 μg/mL (89 μM), respectively. The nanoparticle polymeric formulation of this compound (440 μg) was administered during 42 days to BALB/c mice infected with *L. amazonensis*; the results revealed that this formulation reduced their skin ulcers by 53%, while the pure compound reduced ulcers by only 23% [27, 32]. A glucosecoiridoid, identified as amarogentin (isolated from *Swertia chirata*), was tested in an *in vivo* model (hamster), together with two formulations (liposomal and niosomal) in mice infected with *L. donovani*; the niosomal-amarogentin formula reduced the parasitic load by 90% in the spleen of the treated animals and was more efficacious than the liposomal amarogentin. Both of these formulations can be good candidates for developing leishmanicidal drugs [27, 33].

Plumbagin, a naphthoquinone isolated from the bark of *Pera benensis* and from some species of the genus *Plumbago*, resulted active against *L. donovani* promastigotes and intracellular

amastigotes (IC_{50} = 0.21 μM); also, against intracellular amastigotes of *L. donovani* and *L. amazonensis*, with IC_{50} = 0.42 and 1.1 μg/mL, respectively. *In vivo* studies have demonstrated that plumbagin delayed the development of *L. amazonensis* and *L. venezuelensis* infection and exhibited good activity at 2.5–5 mg/kg/day, respectively. Local treatment of a simple lesion with 8,8′-biplumbagin resulted in a better treatment than that of glucantime (reference drug). In addition, plumbagin and 8,8′-biplumbagin were very active against *L. amazonensis* amastigotes and against *L. brazilensis* (2903), *L. amazonensis* (PH8, H-142), and *L. donovani* (2682 and HS70) promastigotes, demonstrating values of IC_{90} = 5 μg/mL [27, 34–37].

Saponins mesabalide III and mesabalide VI (obtained from *Maesa balansae*), were very active against intracellular amastigotes of *L. infantum* (IC_{50} = 7 and 14 ng/mL, respectively) but, despite exhibiting significant leishmanicidal activity, these compounds are highly cytotoxic; thus, they are not candidates for continued research. The steroidal saponin racemoside A (isolated from *Asparagus racemosus*) induced apoptosis in *L. donovani* promastigotes and amastigotes and showed values of IC_{50} = 1.31 and 0.61 μg/mL, respectively [27]. α- and β-Hederine and hederacholchiside A (obtained from *Hedera helix*) demonstrated leishmanicidal activity; hederacholchiside A was more active, with an IC_{50} = 1.2 and 0.053 μM against *Lleishmania infantum* promastigotes and intracellular amastigotes, respectively [26]. Diospyrin (isolated from *Euclea natalensis*) was active against *L. donovani* promastigotes at 0.1 μg/mL. This compound is a specific inhibitor of the parasitic topoisomerase [38, 39].
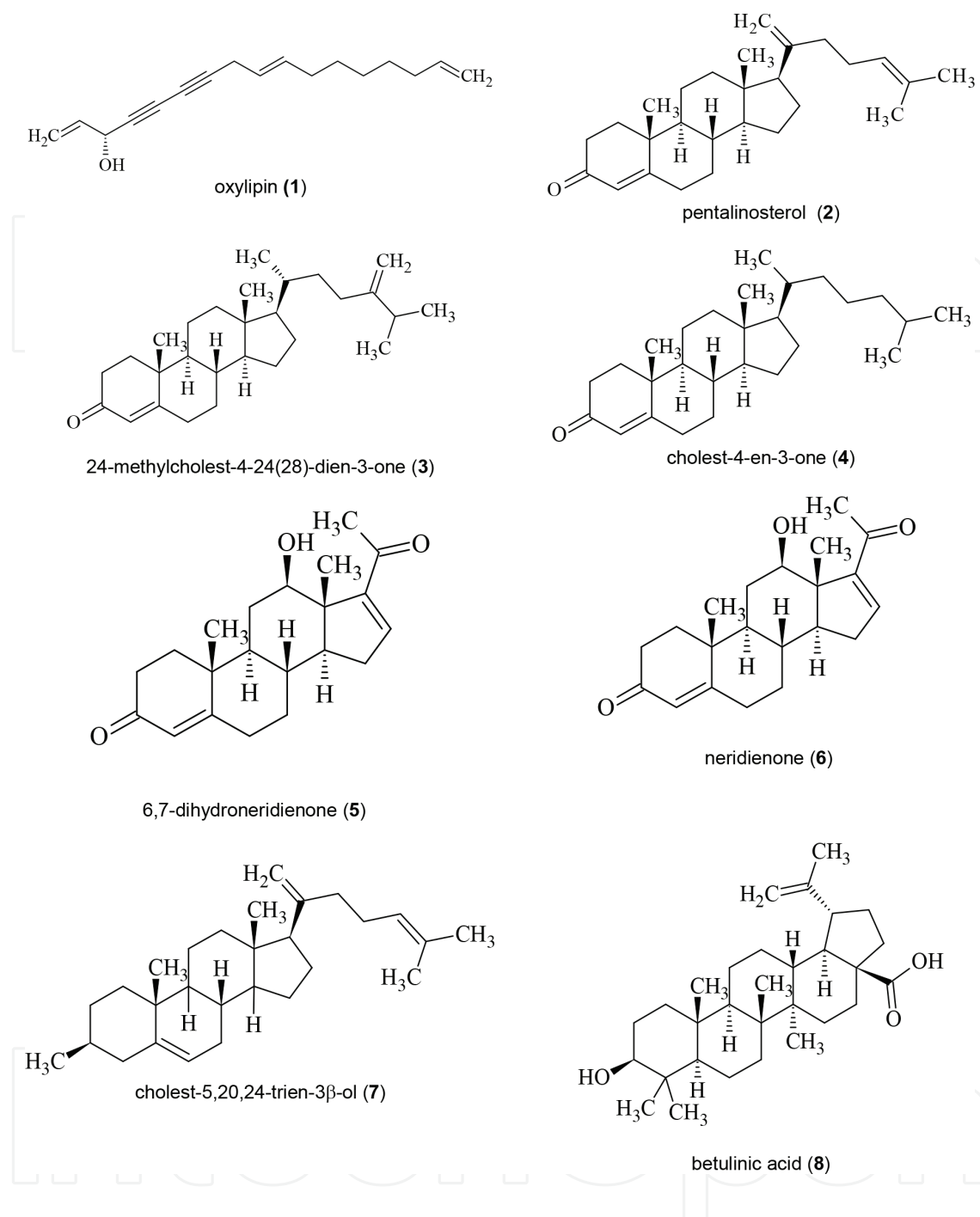
3. Extract and pure compounds obtained from Mexican medicinal plants active against *Leishmania* spp.

In Mexico, some unconventional treatments as cauterization with copper sulfate are routinely used to treat leishmaniasis. Employing hot automobile engine oil, red-hot coins, red metal utensils, hot animal bones, or a hot light bulb directly applied as thermotherapy are on the ulcer as thermotherapy; also, cryotherapy, which consists of placing ice on the wound is applied. Both therapies are used in Mexico and in some regions worldwide [22]. Antibacterials as penicillin or antifungal creams (such as miconazole, ketoconazole, or itraconazole) are applied on the lesion [40]. Mexican patients have also used acetic acid, boric acid, sulfuric acid (car battery acid), formalin, alcohol, hydrogen peroxide, wire and copper sulfate, among other remedies [22, 42]. While these methods only deform and accentuate the inflammation, patients continue to employ these approaches without knowing that they are dealing with a parasitosis, which requires professional medical care.

On the other hand, some plants are routinely used in Mexico to treat the skin lesions caused by *Leishmania* [22, 41, 42]. To date, there are scarce studies that explore theirs *in vitro* and/or *in vivo* leishmanicidal activity. Peraza-Sánchez et al. [42] described an *in vitro* evaluation of the methanolic extracts from 18 medicinal plants from the southeastern state of Yucatán, Mexico against *L. mexicana* promastigotes; these authors found that the extracts of *Aphelandra scabra* (leaves), *Byrsonima bucidaefolia* (bark), *Byrsonima crassifolia* (bark), *Clusia flava* (leaves), *Cupania dentata* (bark), *Diphysa carthagenensis* (leaves), *Dorstenia contrajerva* (complete plant), *Milleria quinqueflora* (root), *Tridax procumbens* (complete plant), and *Vitex gaumeri* (bark) were the most active, exhibiting IC_{50} values of <50 μg/mL. The same investigation group assayed 15 samples

(extracts, fractions, and some pure compounds) obtained from *Urechites andrieuxii* (syn. *Pentalinon andrieuxii*), *Colubrina greggii*, *Dorstenia contrajerva*, and *Tridax procumbens*. One compound, identified as NCG-5C, and the fraction DCG-3A (with low polarity) obtained from *C. greggii* and the low-polarity fraction TPZ-24 obtained from *T. procumbens*, were the most active against *L. aethiopica* promastigotes; these samples demonstrated LD_{50} = 62.4, 7.2, and 18.5 µg/mL, respectively, while LD_{50} against amastigotes was 94.2, 27.1, and 95.2 µg/mL, respectively. In this study, it is also evaluated the same extracts and pure compounds against *L. major* and *L. tropica*, but these samples exhibited poor activity [1]. The methanol extract of *T. procumbens* and the compound identified as 3(S)-16,17-didehydrofalcarinol or oxylipin (1) inhibited the growth of *L. mexicana* promastigotes, showing IC_{50} = 3 and 0.478 µg/mL, respectively. In addition, pure oxylipin (1) was active against the intracellular amastigotes of *L. mexicana* [43, 44]. Gamboa-León et al. [45] described that the methanol extract of the *T. procumbens* (complete plant) mixed with the lyophilized aqueous extract of *Allium sativa* (bulbs) significantly reduced skin lesions caused by *L. mexicana* promastigotes (Hd18-MHET/MX/97/Hd18) in female CD-1 mice treated during 2 weeks with this mixture. Individually, these extracts also reduced the formation of lesions in a lower percentage than the mixture. These authors also described that the methanol extract from *U. andrieuxii* (syn. *P. andrieuxii*) leaves and roots, collected in Champotón, Mexico (Collection I), was the most active against promastigotes of *L. braziliensis*, of *L. amazonensis*, and of *L. donovani* [42] and was also active against *L. mexicana* promastigotes [46, 47]. The hexane fraction obtained from the methanol extract of *P. andrieuxii* roots was evaluated in an *in vivo* model for cutaneous leishmaniasis in male C57BL/6 mice infected with *L. mexicana* promastigotes. Topical application of 10 µg of the hexane fraction for 6 weeks significantly reduced the size of the lesions with respect to the vehicle. This fraction also inhibited the growth of *L. mexicana* in *vitro* condition, showing an IC_{50} = 43.04 µg/mL, while against macrophages infected with *L. mexicana* amastigotes, it exhibited an IC_{50} = 4.1 µg/mL, and in dendritic cells infected with *L. mexicana* amastigotes the IC_{50} value was 11.06 µg/mL [48].

From the active hexane fraction (obtained by partition from active methanol extract) of the *U. andrieuxii* roots (syn. *P. andrieuxii*), the following compounds were isolated: cholestra-4,20,24-trien-3-one or pentalinosterol (2); 24-methylcholest-4-24(28)-dien-3-one (3), cholest-4-en-3-one (4),6,7-dihydroneridienone (5), and neridienone (6). All compounds (2–6) inhibited the growth of *L. mexicana* promastigotes, showing an IC_{50} of <30 µM; pentostam was used as positive control (IC_{50} = 346.1 µM). All of these compounds, together with cholest-5,20,24-trien-3β-ol (7), were active against *L. mexicana* amastigotes (IC_{50} < 14.5 µg/mL) in the *in vitro* assay [49]. The most active compound was cholest-4-en-3-one (4), which exhibited an IC_{50} value of 0.03 µM; all active compounds were non-cytotoxic in healthy bone marrow-derived macrophages (C57BL16 mice), demonstrating an IC_{50} of >100 µg/mL [48]. In addition, recently, pentalinonsterol (2) was synthesized and was tested in the visceral leishmaniasis experimental model using BALB/c mice infected with *L. donovani*. Pentalinonsterol (2.5 mg/kg) was administered by intravenous (IV) route in liposome formulation; this compound showed a significant reduction of parasite load in mouse liver and spleen, and it is a candidate for the development of a new leishmanicidal drug [50]. In addition, betulinic acid (8) has been isolated from the ethanol extract of *P. andrieuxii* leaves, but this was inactive against *L. amazonensis* and *L. brazilensis*, exhibiting an IC_{50} of >200 µM [1].

oxylipin (**1**)

pentalinosterol (**2**)

24-methylcholest-4-24(28)-dien-3-one (**3**)

cholest-4-en-3-one (**4**)

6,7-dihydroneridienone (**5**)

neridienone (**6**)

cholest-5,20,24-trien-3β-ol (**7**)

betulinic acid (**8**)

The hexane extract from *P. andrieuxii* roots at 10 μg/mL was very active against *L. mexicana* promastigotes (MHOM/MX/84/ISETGS). The effect observed was similar to that of glucantime (positive control); the parasites were completely destroyed after 100 h of exposure (LD$_{50}$ = 6.10 vs. 173.9 μg/mL, respectively). In addition, the extracts of ethyl acetate and ethanol of this medicinal plant were also tested against *L. mexicana* but were inactive [51].

The flavone 5, 4-dimethoxy-(6, 7)-2′,2′-dimethyl-pyrano-favone (9), isolated from *Lonchocarpus xuul* and *Lonchocarpus yucatanensis* leaves) was active against promastigotes of *L. brazilensis* (MHOM/BR/75/M9203), *L. donovani* (MHOM/BR/74/PP75), and *L. amazonensis* (IFLA/BR/67/PH8), showing the similar value, an IC$_{50}$ = 5.6 μg/mL. Also, 3β,4β-dihydroxy-5-methoxy-(7,6)-2,

2-dimethylpyranoflavan (10) was isolated from both *Lonchocarpus* spp. and was tested against promastigotes of same *Leishmania* strain. Compound 10 was less active than compound 9, it showed an IC_{50} = 26.7–40 µg/mL against *L. brazilensis* and *L. amazonensis*, respectively, and was inactive against *L. donovani*. From *Lonchocarpus xuul* roots was isolated 2',4'-dihydroxy-3'-(3-methyl-but-2-enyl) chalcone or isocordoin (11), this compound was active against promastigotes of the same *Leishmania* strains (*L. brazilensis*, *L. donovani*, and *L. amazonensis*), showing an IC_{50} values of 10, 40, and 26.7 µg/mL, respectively, also, this compound was active against the P-388 cell line with IC_{50} = 34–57 µM [52]. Isocordoin (11) and 2',4'-dihydroxy-3'-(γ,γ-dimethylallyl)-dihydrochalcone or dihydroisocordoin (12), isolated from *Lonchocarpus xuul* roots were tested against *L. mexicana* promastigotes. These compounds showed an IC_{50} = 7.7–66.5 µM, respectively. In this study, some semisynthetic derivatives of these natural compounds were tested; the acetylated and methoxylated derivative [2',4'-diacetoxi-3'-(3-methyl but-2-enyl)-chalcone (13) and 2',4'-dimethoxy-3'-(3-methyl but-2-enyl)-chalcone (**14**)] were the most active, exhibiting an IC_{50} = 3.10–11.70 µM against *L. mexicana* promastigotes, these semisynthetic derivates were more active than natural compounds [53].
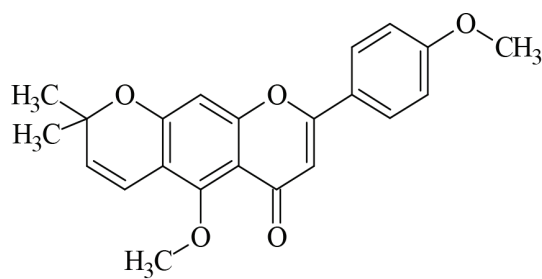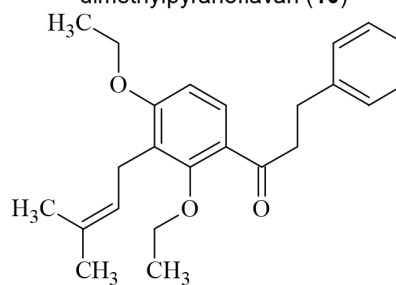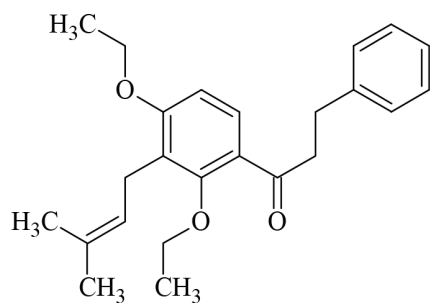

5,4-dimethoxy-(6,7)-2′,2′-dimethyl-pyrano-favone (**9**)
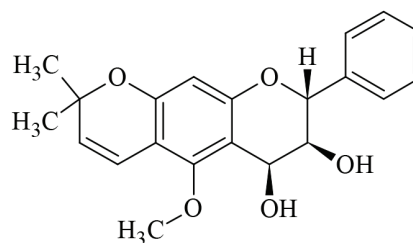
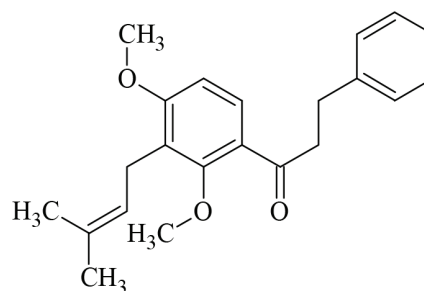3β,4β-dihydroxy-5-methoxy-(7,6)-2,2-dimethylpyranoflavan (**10**)
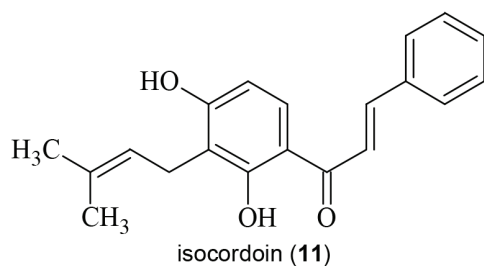
isocordoin (**11**)

dihydroisocordoin (**12**)

2′,4′-diacetoxi-3′-(3-methylbut-2-enyl)-chalcone (**13**)

2′,4′-dimethoxy-3′-(3-methylbut-2-enyl)-chalcone (**14**)

On the other hand, the chloroform and aqueous extracts (successive extracts) from *Laennecia confusa* aerial parts and the primary fraction of the chloroform extract demonstrated leish-manicidal properties. These extracts and fraction presented good activity on *L. donovani* promastigotes, with IC_{50} = 20, 20, and 200 µg/mL, respectively, after 72 h of exposure. However,

these samples (the aqueous and chloroform extracts and the primary fraction from chloroform extract) exhibited a cytotoxic effect on human-derived monocyte (THP-1) cells, with IC_{50} values of 24.8, 25, and 24.2 µg/mL, respectively [54]. The chloroform extract from *Lopezia racemosa* (aerial parts) and the hexane and methanol fractions demonstrated good activity against *L. donovani* promastigotes after 72 h incubation. The extract and hexane and methanol fractions reduced parasitic growth by approximately 88% (1×10^6 promastigotes/well). In addition, the chloroform extract was cytotoxic in macrophages (THP-1) cells, showing an IC_{50} = 28.58 µg/mL [55]. The author did not describe the active compounds.

The primary fractions (HE 5 and HE 14b) obtained from the hexane extract from the aerial parts of *gallium mexicanum* were active against *L. donovani* promastigotes (1×10^6 promastigotes/well). The HE 5 sample inhibited the growth of the parasites at 333 µg/mL after 72 h of exposure, and HE 14b was active at 999 µg/mL. The HE 5 fraction was not cytotoxic (IC_{50} = 1398 µg/mL), and the HE 14b fraction was cytotoxic (IC_{50} = 228.5 µg/mL) on the THP-1 cell line [56].

The chloroform and methanol extracts from *Echeveria leucotricha* reduced the growth of *L. donovani* promastigotes in 64–52%; however, these extracts were toxic in the human-derived monocyte-cell line THP-1. It is important to mention that the author did not describe the concentration of the extracts that they evaluated or their LD_{50} values [57].

Recently, 10 medicinal Mexican plants were evaluated against *L. amazonensis* (MHOM/77BR/LTB0016) promastigotes and amastigotes. Three of it showed a good activity (with IC_{50} < 30 µg/mL) against *L. amazonensis* promastigotes; being the most active *Lantana camara* (dichloromethane extract), *Schinus molle* (dichloromethane and dichloromethane:methanol 1:1 extracts) (SI = 5; SI = 6, respectively), and *Prosopis laevigata* (aqueous extract) (SI = 7). The SI = 5; SI = 6 extracts of *S. molle* showed IC_{50} = 15.4 and 29.4 µg/mL, respectively. The dichloromethane extract of *L. camara* exhibited IC_{50} = 11.7 µg/mL, and the aqueous extract of *P. laevigata* showed an IC_{50} = 22.8 µg/mL. The qualitative screening of the extracts revealed the presence of terpenoids in *S. molle*, the most active species. In addition, these extracts were cytotoxic against peritoneal macrophages Balb/c mice with CC_{50} > 186.8 µg/mL. In addition, both extract (dichloromethane and dichloromethane: methanol) of *S. molle* was active against *L. amazonensis* amastigotes with IC_{50} = 25.9 and 21.8 µg/mL, respectively. Also, the dichloromethane extract of *L. camara* and aqueous extract from *P. laevigata* exhibited IC_{50} = 21.8 and 35.2 µg/mL, respectively, against amastigotes of *L. amazonensis* [58].

Alamilla-Fonseca et al. [59] evaluated *Cleoserrata serrata* dichloromethane: methanol (1:1) extract. This Mexican medicinal plant is used in South-Central Mexico to treat skin infections and wounds. The extract showed activity against the *L. mexicana* amastigotes at the concentration of 10 µg/mL; and against *L. mexicana* promastigotes, the effect was dose-dependent; in this case, the author observed 60% of inhibition at 100 µg/mL and 85% of inhibition at 200 µg/mL. The LD_{50} doses were 23.5 µg/mL for promastigotes, and 6.11 µg/mL for the amastigotes [59]. This extract at 10 µg/mL showed leishmanicidal activity on amastigotes after 4 days of culture and at 100 µg/mL was leishmanicidal on promastigotes.

4. Conclusion

To date, there are few medicinal species in Mexico that have been evaluated to determine their leishmanicidal potential; from the studies performed, only seven medicinal species (*Tridax*

procumbens, *Lonchocarpus xuul*, *Pentalinon andrieuxii*, *L. camara*, *Schinus molle*, *Prosopis levigate*, and *Cleoserrata serrata*) have demonstrated significant activity *in vivo* against *L. mexicana* and can be considered potential candidates as leishmanicidal sources. From these species, eight active compounds have been isolated [Oxylipin, Isocordoin, 2′,4′-dihydroxy-3′-(γ,γ-dimethylallyl)-dihydrochalcone, cholesta-4,20,24-trien-3-one or pentalinosterol, 24-methyl-cholesta-4-24(28)-dien-3-one, cholest-4-en-3-one, 6,7-dihydroneridienone, neridienone, and cholest-5,20,24-trien-3β-ol], which have shown an IC_{50} of >30 μg/mL against *L. mexicana*; however, the real potential of these are not known, because only pentalinosterol has been synthesized and was tested in an *in vivo* experimental model using BALB/c mice infected with *L. donovani*. In addition, some organic extracts have demonstrated activity against other species of *Leishmania* (*L. brazilensis*, *L. donovani*, and *L. amazonensis*), but the compounds responsible for this activity, to our knowledge, have not been reported. Leishmaniasis is a global health problem, coupled with drug resistance and the side effects caused by current drugs, which makes it necessary to redouble efforts to continue investigating other medicinal species in order to find active compounds that contribute to the treatment of the disease or that serve as prototype molecules to develop drugs with different mechanism of actions from those currently employed.

Conflicts of interest

All authors have read and approved the final version of the manuscript. The authors declare that they have no competing interests.

Ethical responsibilities concerning the protection of people and animals

This manuscript is a bibliographic review and no persons or animals were used.

Confidentiality of data

This review does not describe patient data.

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