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Natural compounds and extracts from Mexican medicinal plants with anti-leishmaniasis activity: An update

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ABSTRACT

Leishmaniasis is considered as an emerging, uncontrolled disease and is endemic in 98 countries. Annually, about 2 million cases of cutaneous and 500000 cases of visceral-type leishmaniasis are recorded and 60000 persons died from the disease. In Mexico, cutaneous leishmaniasis is known as chiclero's ulcer and is reported in 22 states, it is considered as a health problem. For its treatment, pentavalent antimonial drugs are administered. These drugs cause severe side effects, are costly. Drug-resistant cases have been reported and have been developing for over 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 *Leishmania donovani*. In Mexico, about 20 medicinal plants have been evaluated against *Leishmania mexicana*, among which the most active are *Tridax procumbens*, *Lonchocarpus xuul* and *Pentalinon andrieuxii*. From 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-dihydroneridie-none, neridienone, cholest-5,20,24-trien-3β-ol, and isocordoin. Today, only pentalinonsterol has been synthesized and assayed in the visceral leishmaniasis experimental model using BALB/c mice infected with *Leishmania 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.

1. Introduction

Leishmaniasis is caused by about 20 species of *Leishmania*, and is classified by the World Health Organization as an emergent category one, uncontrolled disease. It is one of the six most important tropical diseases. The *Leishmania* infection exhibits several manifestations, such as cutaneous, diffuse cutaneous or disseminated, mucocutaneous, visceral, and recidivans manifestations. 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 of 1.5–2.0 million new cutaneous cases has been reported annually [1–4]. Each year, 500000 cases of the visceral type are reported and 50000 individuals died from the recidivans [4]. In Mexico, its presence 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 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* (*L. mexicana*) [9].

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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 paromomycin sulfate (Aminosidine), although this latter option is not widely utilized in Mexico and is not effective when administered orally [10]. Even when administered in combination, the effectiveness of the drugs is less than optimal effect [11,12].

Antimonial pharmaceuticals (Pentostan, glucantime, and pentamidine) were developed over 70 years ago, and continue to be used to treat leishmaniasis. Some of these have not been effective due to the drug-resistance developed by the parasite [2,8,13,14], in addition to the scarce development of this drug type. These substances have severe side effects, such as kidney failure, acute pancreatitis, myalgia, teratogenic, peripheral neuropathy, hepatotoxicity, and cardiotoxicity (cardiac arrhythmia), in addition to the fact that treatment is prolonged over 30 d that depends on the patient's evolution. Drug is administrated by 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.

2. Methods

In the present paper, an exhaustive search (from 2001 to 2017) was carried out on antileishmanicidal activity from the extracts and/or compounds which were obtained from Mexican medicinal plants against several *Leishmania* spp. *in vivo* and *in vitro* assays. The main scientific consulted sources were the Scopus and PubMed databases. This review does not describe patient data, and this manuscript is a review and no persons or animals were used.

3. Overview of antileishmanicidal potential of medicinal plants and their isolated compounds

The development of drugs to treat parasitic diseases such as leishmaniasis has been scarce, due to the fact that these diseases are more often presented in developing countries, because the pharmaceutical industry does not receive high profits. It must develop low-cost medication that will be accessible to a population with a low socioeconomic condition [7,14]. In this regard, the World Health Organization has emphasized the urgency that needs 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 which were 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 [7,15].

Natural products have been an important role in current therapy, the years between 1981 and 2006, 1 184 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 base molecule, or are derived from, active molecules which were obtained from medicinal plants [8–16]. Another report stated that the years between 2000 and 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 [17–19]. 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*), vinblastine and vincristine (isolated from *Catharanthus roseus*) and artemisinin (isolated from *Artemisia annua*), and 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 antileishmanial drugs (these substances are in phase I/II research) and include the following: Miltefosine (an alkylphospholipid) that has been used in India since 2002, which 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 *Berberis vulgaris*). This latter compound has been utilized against this disease for over 50 years and has demonstrated its activity both *in vitro* and *in vivo* [8,19–23].

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 [22,24–27]. 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 *Leishmania donovani* (*L. donovani*) and *Leishmania amazonensis* (*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* (*L. 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 μg/mL, 25.00 μg/mL and 1.56 μg/mL, respectively [25–28]. The main disadvantage is that these alkaloids have been evaluated in different strains of *Leishmania* and in 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 μg/mL and 4.9 μg/mL against *L. amazonensis* promastigotes, respectively [25]. The alkaloid

4-hydroxy-1-tetralone (isolated from *Ampelocera edentula* bark) was active against *Leishmania braziliensis* (*L. braziliensis*), *L. amazonensis*, and *L. donovani* promastigotes, with an IC_{50} = 10 μg/mL [29].

In addition, the *in vitro* activity of other medicinal plant extracts, such as *Ambrosia miratima* and *Acacia nilotica* with IC_{50} < 8 μg/mL [30]; however, no compounds responsible for activity have been isolated from these active species. The ethanol extract and the dichloromethane and chloroform ($CHCl_3$) fractions from the leaves of *Azadirachta indica* presented IC_{50} = 38.0 μg/mL, 3.9 μg/mL, and 1.2 μg/mL against promastigotes of *L. amazonensis*, respectively, and against amastigotes, IC_{50} was 9.8 μg/mL, 1.1 μg/mL, and 0.6 μg/mL [15].

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 μg/mL and 11 μg/mL, respectively). These compounds were more active than glucantime (IC_{50} = 83 μg/mL) [22]. An additional 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 μM 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′-methoxychalcone (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 d 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 these by only 23% [26,31]. 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 antileshmanicidal drugs [26,32].

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*, it showed IC_{50} = 0.42 μg/mL and 1.10 μg/mL, respectively. *In vivo* studies have demonstrated that plumbagin delayed the development of *L. amazonensis* and *Leishmania venezuelensis* infection and exhibited good activity at 2.5 mg/kg/d and 5 mg/kg/d, respectively. Local treatment of a simple lesion with 8,8′-biplumbagin resulted a better treatment than that of Glucantime (reference drug). In addition, plumbagin and 8,8′-biplumbagin were very active *in vitro* against *L. amazonensis* amastigotes and against *L. braziliensis* (2903), *L. amazonensis* (PH8, H-142), and *L. donovani* (2682 and HS70) promastigotes, demonstrating values of IC_{90} = 5 μg/mL [26,33–36].

Saponins mesabalide III and mesabalide VI (obtained from *Maesa balansae*), were very active against intracellular amastigotes of *Leishmania infantum* (IC_{50} = 7 ng/mL 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 μg/mL and 0.61 μg/mL, respectively [26]. α- and β-Hederine and Hederacholchiside A (obtained from *Hedera helix*) demonstrated leishmanicidal activity; Hederacholchiside A was more active, with an IC_{50} = 1.200 μM and 0.053 μM against *Leishmania 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 [37,38].

4. Extract and pure compounds obtained from Mexican medicinal plants active against *Leishmania* spp.

In Mexico, some unconventional treatments are routinely used to treat leishmaniasis. For example, cauterization with copper sulfate, and thermotherapy is also employed; in this case, hot automobile-engine oil, red-hot coins, red metal utensils, hot animal bones, or a hot light bulb are directly applied on the ulcer. Also, cryotherapy which consists of placing ice on the wound is used. Both therapies are used in Mexico and in some regions worldwide [21]. On some occasions, Penicillin powder or antifungal creams (such as Miconazole, Ketoconazole, or Itraconazole) are applied on the lesion. 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 [21,39,40]. 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* [21,40,41]. To date, there are scarce studies that explore their *in vitro* and/or *in vivo* leishmanicidal activity. Peraza-Sánchez *et al.* described an *in vitro* evaluation of the methanolic (MeOH) 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 [40]. The same investigation group assayed 15 samples (extracts, fractions, and some pure compounds) obtained from *Urechites andrieuxii* [syn. *Pentalinon andrieuxii* (*P. andrieuxii*)], *Colubrina greggii*, *Dorstenia contrajerva*, and *Tridax procumbens* (*T. 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 *Leishmania aethiopica* promastigotes; these samples demonstrated LD_{50} = 62.4 μg/mL, 7.2 μg/mL, and 18.5 μg/mL, respectively,

while LD_{50} against amastigotes was 94.2 μg/mL, 27.1 μg/mL, and 95.2 μg/mL, respectively. In this study, these authors also evaluated the same extracts and pure compounds against *L. major* and *Leishmania tropica*, but these samples exhibited poor activity [2]. The MeOH 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} = 3.000 μg/mL and 0.478 μg/mL, respectively. In addition, pure oxylipin (**1**) was active against the intracellular amastigotes of *L. mexicana* [42,43]. Recently, Gamboa-León *et al.* [44] described that the MeOH extract of the *T. procumbens* (complete plant) mixed with the lyophilized aqueous extract of *Allium sativa* (bulbs) significantly reduced skin lesions which caused by *L. mexicana* promastigotes (Hd18-MHET/MX/97/Hd18) in female CD-1 mice treated during 2 wk 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 MeOH extract from *U. andrieuxii* (syn. *P. andrieuxii*) leaves and roots which were collected in Champotón, Mexico (Collection I), was the most active against promastigotes of *L. braziliensis*, of *L. amazonensis*, and of *L. donovani* [40] and was also active against *L. mexicana* promastigotes [45,46]. The hexanic fraction obtained from the MeOH 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 hexanic fraction for 6 wk significantly reduced the size of the lesions with respect to the vehicle. This fraction also inhibited the growth *in vitro* of *L. mexicana*, showing an IC_{50} = 43.04 μg/mL, while in macrophages infected with *L. mexicana* amastigotes, it exhibited an IC_{50} = 4.10 μg/mL, and in dendritic cells infected with *L. mexicana* amastigotes the IC_{50} value was 11.06 μg/mL [47].

From the active hexanic fraction (obtained by partition from active MeOH 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 [48]. 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 (*i.v.*) 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 [49]. In addition, betulinic acid (**7**) has been isolated from the ethanol extract of *P. andrieuxii* leaves, but this was inactive against *L. amazonensis* and *L. braziliensis*, exhibiting an IC_{50} of >200 μM [1].

The hexanic 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} = 6.1 μg/mL *vs.* 173.9 μg/mL, respectively). In addition, the extracts of EtOAc and EtOH of this medicinal plant were also tested against *L. mexicana* but were inactive [50].

The flavone 5,4-dimethoxy-(6,7)-2′,2′-dimethyl-pyranoflavone [**9**, isolated from *Lonchocarpus xuul* (*L. xuul*) and *Lonchocarpus yucatanensis* leaves] was active against promastigotes of *L. braziliensis* (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 that compound (**9**), it showed a IC_{50} = 26.7 μg/mL and 40.0 μg/mL against *L. braziliensis* and *L. amazonensis*, respectively and was inactive against *L. donovani*. From *L. 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. braziliensis*, *L. donovani*, and *L. amazonensis*), showing IC_{50} values of 10.0 μg/mL, 40.0 μg/mL, and 26.7 μg/mL, respectively; also, this compound was active against the P-388 cell line with IC_{50} = 34 μM and 57 μM [51]. Isocordoin (**11**) and 2′,4′-dihydroxy-3′-(γ,γ-dimethylallyl)-dihydrochalcone or dihydroisocordoin (**12**), isolated from *L. xuul* roots were tested against *L. mexicana* promastigotes. These compounds showed an IC_{50} = 7.7 μM and 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-methylbut-2-enyl)-chalcone (**13**) and 2′,4′-dimethoxy-3′-(3-methylbut-2-enyl)-chalcone (**14**)] were the most active, exhibiting an IC_{50} = 3.1 μM and 11.7 μM against *L. mexicana* promastigotes, these semisynthetic derivates were more active than natural compounds [52].

On the other hand, the $CHCl_3$ and aqueous extracts (successive extracts) from *Laennecia confusa* aerial parts and the primary fraction from the $CHCl_3$ extract demonstrated leishmanicidal properties. These extracts and fraction presented good activity on *L. donovani* promastigotes, with IC_{50} = 20 μg/mL, 20 μg/mL, and 200 μg/mL, respectively, after 72 h of exposure. However, these samples (the aqueous and $CHCl_3$ extracts and the primary fraction from $CHCl_3$ extract) exhibited a cytotoxic effect on human-derived monocyte (THP-1) cells, with IC_{50} values of 24.8 μg/mL, 25.0 μg/mL, and 24.2 μg/mL, respectively [53]. The $CHCl_3$ extract from *Lopezia racemosa* (aerial parts) and the hexanic and MeOH fractions demonstrated good activity against *L. donovani* promastigotes after 72 h of incubation. The extract and hexanic and MeOH fractions reduced parasitic growth by approx. 88% (1×10^6 promastigotes/well). In addition, the $CHCl_3$ extract was cytotoxic in macrophages (THP-1) cells, showing an IC_{50} = 28.58 μg/mL [54]. The author did not describe the active compounds.

The primary fractions (HE 5 and HE 14b) obtained from the hexanic 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} = 1 398 μg/mL) and the HE 14b fraction was cytotoxic (IC_{50} = 228.5 μg/mL) on the THP-1 cell line [55].

The $CHCl_3$ and MeOH extracts from *Echeveria leucotricha* reduced the growth of *L. donovani* promastigotes in 64% and 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 [56].

5. Conclusions

To date, there are few medicinal species in Mexico that have been evaluated to determine their leishmanicidal potential; among the studies performed, only three medicinal species (*T. procumbens*, *L. xuul*, and *P. andrieuxii*) have demonstrated significant activity *in vivo* against *L. mexicana* and can be considered potential candidates as leishmanicidal sources. From these active species, eight active compounds have been isolated [Oxylipin, Isocordoin, 2′,4′-dihydroxy-3′-(γ,γ-dimethylallyl)-dihydrochalcone, cholestra-4,20,24-trien-3-one or pentalinosterol, 24-methylcholesta-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 been described that demonstrated activity against other species of *Leishmania* (*L. braziliensis*, *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 statement

The authors declare that they have no conflict of interests.

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