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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 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 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, 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 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

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