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REVIEW ARTICLE

Conventional Versus Natural Alternative Treatments for Leishmaniasis: A Review

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Abstract: Leishmaniasis is a neglected disease caused by protozoan belonging to the *Leishmania* genus. There are at least 16 pathogenic species for humans that are able to cause different clinical forms, such as cutaneous or visceral leishmaniasis. In spite of the different species and clinical forms, the treatment is performed with few drug options that, in most cases, are considered outdated. In addition, patients under classical treatment show serious side effects during drug administration, moreover parasites are able to become resistant to medicines. Thus, it is believed and well accepted that is urgent and necessary to develop new therapeutic options to overpass these concerns about conventional therapy of leishmaniasis. The present review will focus on the efficacy, side effects and action mechanism of classic drugs used in the treatment of leishmaniasis, as well as the importance of traditional knowledge for directing a rational search toward the discovery and characterization of new and effective molecules (*in vivo* assays) from plants to be used against leishmaniasis.

Keywords: Leishmaniasis, Conventional drugs, Ethnopharmacology, New drugs, Molecules, Amphotericin.

1. INTRODUCTION

The parasite responsible to cause human leishmaniasis was firstly noticed by the Scottish doctor David Douglas Cunningham in 1885, and important discoveries have been made so far, such as the spectrum of immunological responses and how immune cells respond to the different *Leishmania* species and antigens [1-8]. Moreover, every time has been depicted the importance of new vectors and wild or domestic animals during the life cycle of *Leishmania* sp., and how they can impact the human disease. Thus, it is possible to track and understand each step of *Leishmania* survival in vertebrate and invertebrate hosts.

In spite of the huge accumulated knowledge about all aspects of host-pathogen interplay in leishmaniasis, surprisingly, the treatment of leishmaniasis has been neglected for almost one century, because it is carried out with few outdated drug options, being the major ones the antimonials-based medicines and amphotericin B [9]. The most recent one is an oral-based medicament, the miltefosine that is primarily used to treat breast cancer. Other drugs that have been used as repurposed ones include anti-mycotics [10], but some of them present limitations to treat leishmaniasis [11]. In addition, the therapeutic options for the treatment of leishmaniasis are considered toxic for human use, in addition, the emergence of parasites resistant mainly to antimonials, the most common drug used in the therapy, have been constantly published and indeed is a concern [12].

Therefore, the characterization of new drugs directed to the treatment of leishmaniasis is urgent. There are different forms to search for leishmanicidal molecules, such as drug repurposing, that ultimately lead to the use of amphotericin B, an anti-fungal drug, and search of new compounds based on ethnopharmacology, that deals with traditional knowledge about natural resources as remedies for different medical conditions [9]. Noteworthy, this type of method aids the discovery of drugs used in the therapy of different diseases.

There are traditional populations around the world that use plants to treat different diseases [13], including leishmaniasis, and in order to save this knowledge, researchers re-

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cord the medicinal uses of this natural resource [14]. In this regard, published ethnopharmacological surveys showed the richness of the traditional folk [15], because lots of plants have been used around the world to treat leishmaniasis as well as other skin problems, but unfortunately, few works progressed toward to the isolation of the active molecule, analyze the action mechanism on *Leishmania* sp., analyze the toxicity in animal models, and more importantly, investigate the therapeutic potential in experimental models or in clinical trials of leishmaniasis.

At the same time we could progress towards the understanding of the relation between parasites and hosts, we are not progressing in the development of new potent leishmanicidal molecules, capable to replace the current drugs. Thus, we are neglecting all data published so far, because after pointing out the leishmanicidal effect of the given molecule, no progress has been made. In part, it occurs because the majority of human cases occurred in poor areas of the world and also because pharmaceutical industries do not have interest to develop new drugs direct for leishmaniasis as well as other neglected tropical diseases.

Thus, this manuscript will summarize information about medical importance of leishmaniasis, current medicines used in the therapy as well as their action mechanisms and side effects for vertebrates; the importance of ethnopharmacology in the discovering of active plants; and recent published works about the therapeutic effect of molecules purified from plants traditionally used in leishmaniasis or correlated symptoms, such as skin disease or infection. It is also important to highlight that interesting articles dealing with molecules purified from different plant species with leishmanicidal activity were already published and reviewed [9,16-18]; however, few of them reviewed works dealing with plants popularly used in folk communities and associated these observations with scientific works.

2. LEISHMANIASIS

Leishmaniasis affects humans and several species of wild and domestic animals. The infection is initiated by a protozoan belonging to the *Leishmania* genus and Trypanosomatidae family. The biological life cycle of this protozoan alternates between vertebrate and invertebrate hosts which belong to the Psychodidae family and to the genera *Lutzomyia* (New World) or *Phlebotomus* (Old World).

Infection with *Leishmania* sp. occurs during the sand fly blood feeding of an infected vector in a vertebrate host. At this moment, promastigote forms are injected in the skin of the vertebrates and they will be rapidly phagocytized by macrophages, the main host cells for *Leishmania* sp. Following this step, the parasite will differentiate in the amastigote stage, establishing cutaneous or visceral infection in vertebrates. In cutaneous leishmaniasis, parasites will infect cells from the skin or mucosa producing benign or serious disfiguring lesions in patients. On the other side, in visceral leishmaniasis, parasites will colonize mainly spleen, liver, bone marrow and lymph nodes.

Concerning Cutaneous Leishmaniasis (CL), it has been estimated that around 12 species of *Leishmania* are pathogenic to humans. Furthermore, clinically, CL is divided into Localized Cutaneous Leishmanaisis (LCL), Mucocutaneous Leishmaniasis (MCL), Disseminated Cutaneous Leishmaniasis (DCL) and Anergic Diffuse Leishmaniasis (ADL). LCL can be caused by any dermatotropic leishmania species, such as *L. (L.) amazonensis*, *L. (V.) guyanensis* or *L. (V.) shawi* [19]. However, MCL is mainly caused by *L. (V.) braziliensis*, but *L. (V.) panamensis* or *L. (V.) peruviana* can also induce this clinical manifestation; and ADL is caused by *L. (L.) amazonensis, L. (L.) mexicana* or *L. (L.) aethiopica* [20].

The visceral leishmaniasis has been considered as the most severe and fatal form of the disease and can be caused by *L. (L.) infantum* or *L. (L.) donovani* and comprises a broad range of clinical manifestations [21]. Parasites are able to infect and replicate into macrophages from the spleen, liver and bone marrow. The most common symptoms are related to prolonged and irregular fever, splenomegaly, lymphadenopathy, hepatomegaly, pancytopenia, progressive anemia and weight loss.

In spite of the diversity of parasites causing serious lesions and the different clinical forms of leishmaniasis, the treatment is based on very few drug options.

3. CLASSICAL TREATMENT OF LEISHMANIASIS

A few years after the discovery of leishmaniasis as a disease caused by the protozoa of the genera *Leishmania*, the efficacy of antimonials to cure this disease was reported [22, 23]. The Brazilian physician Gaspar Vianna described the use of the antimony tartar emetic for treatment of mucocutaneous leishmaniasis [24] and the scientist and physician Upendranath Brahmachari used urea stibamine for the treatment of Indian patients with visceral leishmaniasis [25]. With the passage of time, these drugs were progressively replaced by less toxic antimony compounds and nowadays, a century later, a few more drugs are available for the treatment of this parasitic disease, but antimonials still are the front-line drugs applied in the majority of leishmaniasis clinical forms.

Sodium stibogluconate and N-methyl-glucamine antimoniate formulations are extensively used for more than seven decades in leishmaniasis treatment. In the last decades, cheaper generic compounds with equivalent results of the branded drugs have emerged, wide spreading the use of pentavalent antimonials and presenting similar efficacy. Depending on the sensitivity of the infecting species of *Leishmania* [26] and the patient immune status, clinical cure rate can reach 80-100% [27]. However, cure levels are often limited by treatment failure. In some areas, like Nepal and especially in North of Bihar (India) the failure rate can reach more than 50% of patients mainly due to parasite resistance [28-30], which is a major concern, owing to the absence of vaccines and sustainable strategies to prevent vector transmission. Furthermore, pentavalent antimonials are also highly toxic and responsible for life-threatening adverse side effects, including cardiac arrhythmia and acute pancreatitis.

When injected in the infected patient, pentavalent antimony pro-drug is biologically reduced to the trivalent form (Sb^{III}). Although the reduction mechanism still remains unclear, it seems that it can occur inside the parasite and within the parasite host cell. Furthermore, experimental evidences indicate that sensitivity to antimony is specific of parasite

stage, being the intracellular amastigote form more susceptible than the extracellular promastigote [31].

Pentavalent antimonials are internalized by the parasite through an unidentified transporter, while trivalent antimony enters *via* the aquaglyceroporin pore, which are implicated in osmotic balance and in the bidirectional flux of glycerol and urea. Inside the parasite, pentavalent antimony can be reduced by a nonenzymatic antioxidant system thiol-dependent or by enzymatic processes that involve arsenate reductase 2 and thiol-dependent reductase 1 [32, 33], which have been found to be highly abundant in the amastigote form [34, 35]. Thus, trivalent compound directly acts on the parasite causing a redox imbalance. Trypanothione Reductase (TR) along with trypanothione ($T(SH)_2$) maintains the redox potential low. In the presence of the trivalent compound occurs TR inhibition and the generation of $T(SH)_2$ and glutathione conjugates, raising the redox potential [35, 36] and leading to parasite dead. Inside macrophage (MØ), drug reduction also requires glutathione that is present in the cytosol and, cysteine and cysteinyl-glycine that can be found in lysosomes [37, 38]. Furthermore, the acidic pH of phagolysosome and the high temperature of mammal are two additional factors that also seem to favor antimony reduction. By inhibiting TR, trivalent compounds interfere with T(SH)2 metabolism, inducing the influx of MØ T(SH)2 and glutathione into *Leishmania* amastigotes [35, 39], causing oxidative stress.

Despite the higher antileishmanial activity of trivalent antimony, it has been reported that pentavalent form can also have parasite activity by inhibiting glycolysis and fatty acid oxidation pathways [40], reducing the available energy in the amastigote and troubling the biosynthesis of macromolecules [41] and, by generating ribonucleoside complexes obstruct parasite DNA and compromise parasite viability [42, 43].

Additionally, antimony also seems to interfere with the host immune system by activating MØ. This drug also can induce the expression of class I molecules of major histocompatibility complex on MØ [44], probably stimulating $CD8^+$ T cells that can provoke the apoptosis of infected cells, promote the generation of reactive oxygen species [45], causing oxidative damage, and drive the production IL-12 and nitric oxide [46], leading to parasite death. Altogether, these findings indicate that antimony can have a multifactorial activity, directly disturbing the parasite or, on the other hand by modulating the host immune response, indirectly affects parasite survival.

The reduced number of antileishmanial drugs available, associated with the adverse side effects of antimony formulations and the concern on cumulative drug-resistance lead to a continuing research of new compounds and formulations. These efforts give origin to other drugs with antileishmanial activity. Pentamidine is a diamidine compound with efficacy ranging between 70-100%. However, its high toxicity limits the use of this drug [47]. Paromycin is an aminoglycoside antibiotic that affects the parasite machinery of protein synthesis causing changes in membrane permeability [48]. This affordable drug that has been applied in VL and CL cases since 1980s presents adverse side effects and variable efficacy. Antifungals like fluconazole and ketoconazole have been mainly administered to CL cases and, amphotericin B and miltefosine were commonly used in the most severe cases of disease and in patients resistant to conventional treatment [49, 50].

Amphotericin B deoxycholate that has been initially used to treat fungal infections also exhibits antileishmanial activity, presenting a high cure rate (~97%). This compound has a high affinity to sterols, including *Leishmania* ergosterol, causing the formation of pores in cell membranes that allow the leakage of intracellular components [51], promoting parasite death. Affinity to sterols, as is the case of cholesterol, also account for the high toxicity observed in mammals, from which nephrotoxicity is the more representative side effect. Liposomal encapsulation of amphotericin B reduces the toxicity and maintained similar cure rates, even at short courses. This formulation has progressively replaced the use of antimony. Despite its high efficacy even in immunosuppressed patients and reduced side effects, liposomal amphotericin B is still prohibitively expensive, particularly in very poor countries where antimony resistances are increasing and this drug is needed most.

Furthermore, amphotericin B presents a low solubility profile, being almost completely insoluble in water [52] and consequently exhibiting reduced bioavailability when administered by oral route. Currently, some research groups are developing formulations that increase amphotericin B solubility, and consequently its therapeutic effect in experimental visceral leishmaniasis [53]. Moreover, these type of formulations reduce nephrotoxicity by complexing amphothericin B with nanoparticles [54, 55]. These delivery nanosystems seem to be efficient in retaining the drug and, when tested *in vivo* exhibit increase oral absorption, improve bioavailability, and present reduce kidney accumulation, being recognized as a promising avenue in leishmaniasis treatment.

Miltefosine (hexadecylphosphocholine) is an alkyl phospholipid developed in the early 1980s as an anti-cancer drug. This drug, which exhibits a wide antimicrobial spectrum and also demonstrated activity against *Leishmania* is currently the only recognized oral agent used to treat visceral (*L. (L.) donovani*), cutaneous (*L. (V.) braziliensis, L. (V.) guyanensis* and *L. (V.) panamensis*), and mucosal (*L. (V.) braziliensis*) clinical forms of leishmaniasis. It has a cure rate of about 70-90% [56-59], including the immunosuppressed patients [60]. It can be administered topically or orally and is indicated for patients older than 12 years, although its teratogenic potential hampers its general use. When orally administered, mild gastrointestinal adverse reactions are common, such as vomiting, nausea, diarrhea or abdominal pain. Furthermore, concerns on increase resistance have already been reported [61].

Miltefosine pharmacokinetics are mainly characterized by its long high accumulation and extended half-life [62]. A general consensus on the mechanism of action of miltefosine has not yet been achieved. But it is known that not all Leishmania species are equally susceptible to miltefosine. Therefore, it is possible that this drug has a multifactorial effect. Disturbance of lipid content on parasite membrane and modulation of macrophage activity are regarded as the more consensual mode of action. However, it has been reported that miltefosine interferes with choline transport [63], probably leading to changes in the normal amount of different class of phospholipids [64] of parasite membrane and consequently, interfering in membrane architecture. Addi-

tionally, a more recent study [65] suggests that miltefosine causes parasite lysis by altering the internal lipid metabolism and increase the levels of alkanes, sugars and nucleotides.

4. THE IMPORTANCE OF ETHNOPHARMACOLOGY TO DIRECT THE SEARCH FOR NEW DRUGS

Ethnopharmacology is a sub-area of Ethnobotany and a recent discipline in the academic sphere. It was defined by Holmsted [66] as the "*interdisciplinary scientific exploration of biologically active agents and traditionally employed or observed by man*." This concept includes, in addition to plants, other substances, such as animal, mineral, fungi and algae. In an even more contemporary approach, our group has been dedicated to unraveling the relationship between these substances, such as the study that shows the mixed composition of a home remedy involving a plant resin and an amphibian secretion [67].

One of the applications of ethnopharmacology is the development of new drugs and thus, it is necessary for the ethnopharmacologist to collaborate with researchers in areas such as phytochemistry and pharmacology. According to Balick [68], 6% of randomly collected samples that was sent to the US NCI (United States, National Cancer Institute), were bioactive, whereas the collected samples directed by ethnopharmacological researches indicated 25% of bioactive plants. According to Kate and Laird [69], 80% of the pharmaceutical laboratories that use ethnopharmacological research for the development of their products, obtain such information either from literature or databases, instead of sending researchers to the field so they can record the traditional knowledge of local medicine of a particular culture.

Some examples of drugs derived from traditional knowledge are: galegine extracted from *Galega officinalis* L., which later served as a model for the synthesis of antidiabetic metformin; *Papaver somniferum* from which was extracted the morphine, codeine and papaverine used for the development of antihypertensive verapamil; reserpine isolated from *Rauwolfia serpentina* used for hypertension; ephedrine extracted from *Ephedra sinica* used as feedstock/basic element for the synthesis of beta agonists such as salbutamol; the muscular relaxant tubocurarine isolated from species of *Chondrodendron sp*. and *Curarea sp*.; vinca alkaloids (vincristine and vinblastine) used for the treatment of cancer and extracted from *Catharanthus roseus*; the antimalarial quinine extracted from species of the genus *Cinchona sp*.; and other examples [70].

Oliveira and Szczerbowski [71] reported the curious history of the development of quinine dating back to 1638 when a countess from Chinchón, wife of the Spanish viceroy in Peru, was afflicted with a severe third-degree fever. After drinking a potion made by the Indians called "quina-quina", the fever subsided and the continuity of the treatment left her cured. Afterwards, the Jesuit fathers of the Spanish mission brought the powder to Europe to sell it as a medicine, which later became known as "Jesuit powder". In 1820, its active principle, the alkaloid quinine, was isolated and has been used in the treatments of malaria until today.

For the accomplishment of the fieldwork, Ethnofarmacology uses methods of at least two areas of the knowledge: anthropology and biology. The methods of the first one favor the coexistence of several cultures and the second one, the collection of plants and animals cited by the experts of local medicine. During the field work, it is necessary to register, in details, the use of plants, animals, fungus, used part, dose, duration of use, route of administration and contraindications. The more detailed information is greater the chance of revealing a pharmacological activity in the laboratory, consistent with traditional knowledge. In addition to this, the Ethnofarmacology aims to interpret local terms used by the traditional/popular medicine, termed as "emic" in comparison to the "Etic" term used by the conventional medicine. This is not always possible, since different cultures use their own perceptions to identify and denominate the diseases of their daily life. In the Amazon rainforest, for example, some “Caboclos River-Dwellers” refer to the furuncle (etic term) as a tumor (emic). Sometimes, the correlation is totally misunderstood due to the translation difficulties, been compared to an "Ethnopharmacological Puzzle", even more when a physician is not present in the field work team. This difficulty applies to cases of neglected diseases, since rarely a certain community refers to their diseases as being: leishmaniasis or schistosomiasis. This difficulty can be explained, in part, by the lack of access to clinical tests that would confirm the diagnosis, especially in remote locations with great geographic isolation from hospital or clinics.

Between 1995 and 2012, we conducted ten ethnopharmacological studies in the following cultures that inhabit five Brazilian biomes, with great geographical isolation in relation to conventional medical care: “caboclos river-dwellers” of the Rio Unini and Rio Jaú (Amazon Equatorial rain forest biome); “Quilombolas” (Pantanal wetlands); Indians and immigrants (cerrado savannahs); immigrants (Atlantic forest) and Sertanejos (“caatinga” - semiarid scrublands). From the 992 plants species cited only three were indicated directly for the treatment of leishmaniasis, as follows: the leaf' juice of the plant *Dysphania ambrosioides* (L.) Mosyakin and Clemants (Amaranthaceae) are used as compresses to treat wounds *"pus-filled made by mosquitoes"*; the decoction of leaves or barks of *Lafoensia pacari* A. St.-Hil. (Lythraceae) *"should be ingested 2 times a day";* finally, "the bark of mango tree, *Mangifera indica* L (Anacardiaceae), is used *“to make a compress in place of the wound to treat leishmaniasis”*. However, many other plants were indicated for indirect symptoms of this disease, like: wounds, fever and among other indications; that may be clues for investigating new drugs in the future for different clinical forms of leishmaniasis.

5. ETHNOPHARMACOLOGICAL SURVEYS ASSOCIATED WITH THE CHARACTERIZATION OF LEISHMANICIDAL MOLECULES

Ethnopharmacology studies about plants used for leishmaniasis have been performed within traditional communities around the World and these studies showed that plants as well as their molecules can be considered interesting targets to develop new leishmanicidal compounds. Thus, this section will summarize works performed in different continents, where leishmaniasis is endemic and communities used plants as the alternative medicines.

In an ethnopharmacological survey of antiparasitic medicinal plants used in Ivory Coast (Africa) 17 plants were collected and evaluated *in vitro* against *L. (L.) donovani*. In this case, extracts produced with different organs of *Lippia multiflora***,** *Aframomum sceptrum* and *Uvaria afzelii* were active against promastigote forms (IC_{50} of 12.5 μg/mL). In spite of that, no cytotoxic tests were carried out in this study, making it difficult to classify the selectivity of these plants concerning their leishmanicidal activities [72].

Muganza and colleagues [73] also performed an ethnopharmacological survey with traditional healers in the Bolongo-area, Mai-Ndombe district, Bandundu province in the Democratic Republic of Congo. They directed the survey on plants traditionally used for the treatment of parasitic diseases. Antiprotozoal and cytotoxic activities of 33 extracts from different parts of plants were reported. As a result, 8 plant extracts presented low to high activity against *L. (L.) infantum* amastigotes. Among them, *Napoleona vogelii* stem bark extract was the most active with an IC_{50} value of 5.66 μg/mL and selective index of 11.3. *N. vogelii* is an evergreen shrub with a dense crown growing up to 15 meters tall. Usually, seashore grows near west tropical Africa. Traditionally, its stem bark decoction is used topically against skin infection [73].

In Brazil, it is possible to find different traditional populations or communities living inside the biomes, and their knowledge about plants frequently is used against different diseases. In this respect, an interesting ethnopharmacological study was carried out with plants used in the treatment of leishmaniasis [74]. In this study, information was collected about plants used by the rural population of a cocoa-producing coastal area of Bahia state, Brazil, in two villages: Três Braços and Corte de Pedra, to treat American cutaneous leishmaniasis. Among all plants, the most commonly mentioned by the interviewees were: *Anacardium occidentale, Clidemia hira, Plectrantranthus amboinicus, Chenopodium ambrosioides, Solanum americanum, Plantago major*. In literature, two of them have already been analyzed in order to evaluate its antileishmanial potential. *A. occidentale* is a small common tree original from South America, and its bark hydroalcoholic extract was studied by França and colleagues [75] and presented leishmanicidal effect *in vitro* against promastigote of *L. (V.) braziliensis*. However, this extract did not present therapeutic efficacy in experimental model of cutaneous leishmaniasis caused by *L. (V.) braziliensis*. Additionally, *C. ambrosioides* is a shrub up to a meter high originally from Mexico and widespread in Central and South America. It has been well studied about its leishmanicidal effect in the literature. Monzote *et al.* [76] firstly noticed the antileishmanial activity of the essential oil produced with the aerial parts of *C. ambrodioides,* in addition, this oil showed *in vivo* activity in BALB/c mice experimentally infected with *L. (L.) amazonensis*. In spite of that, it was recently showed that this essential oil failed to heal skin lesions of BALB/c mice infected by *L. (V.) braziliensis*. According to this study, absence of *in vivo* activity could be related with the concentration of active molecules into the essential oil, the route of administration and the cycle of treatment [77]. On the other side, BALB/c mice infected with *L. (V.) braziliensis* could not represent the best experimental model to test new drugs, since this mouse lineage is resistant to *L. (V.) braziliensis* infection [78].

In Pantanal, an important biome from Brazil, an interesting ethnopharmacology study was performed in order to record the traditional uses about medicinal plants [79]. These communities are relatively isolated and they have developed their own medicinal knowledge. To collect this information a total of 262 informants were interviewed. A total of 3,289 citations were recorded corresponding to 376 different plant species. In this sense, a few were indicated to wound healing and others symptoms that could be related to leishmaniasis clinical forms. Among them, *Himatanthus obovatus* showed to be a very important plant, being cited for 13 different ailments, including dermatological problems. Interestingly, a previous study already demonstrated that ethanol extract produced with the root of this plant was active against promastigote forms of *L. donovani* (IC_{50} 7,5 μg/mL) [80].

Another ethnobotanical survey was undertaken with the agreement of the Chayahuitas ethnic group in the North Eastern of Peru [81]. As this group is highly exposed to leishmaniasis [82], the survey was directed to their phytomedicines used to treat or to alleviate symptoms associated with leishmaniasis. Among 12 plant species indicated for treating leishmaniasis only two showed interesting leishmanicidal activity. The first one was *Piper hispidum,* a shrub-like tree natural from America, in which its leaves are traditionally crushed and used on the affected skin. When tested against promastigote and amastigote forms of *L. (L.) amazonensis*, *P. hispidum* ethanol extract showed leishmanicidal activity against amastigote forms with an IC_{50} 5μg/mL, but moderate activity against promastigotes (IC_{50} 69 μg/mL), suggesting the efficacy of this plant to treat leishmanial lesions. On the other hand, *Tabernaemontana sananho* another indication, showed a strong activity against promastigote forms (IC_{50} 9 μg/mL), but it was moderated against amastigote forms (IC_{50} 58 μg/mL). Additionally, previous studies [83] showed that dihydrochalcones isolated from *Piper* elongatum presented low cytotoxicity and high activity against different species of *Leishmania*. In this regard, it was also showed that adunchalcone, a prenylated dihydrochalcone from *Piper aduncum* presented leishmanicidal activity against different species of leishmanias, but it failed to eliminate intracellular amastigotes of *L. (L.) amazonensis* [84]. Therefore, these reports demonstrated that *Piper* genus, as well as its metabolites, can be an interesting group of plants that can be molecularly explored in order to afford potent and effective leishmanicidal molecules. On the other hand, several dimeric indolic alkaloids produced by *Tabernaemontana* species [85] were active against *L. (L.) amazonensis in vitro* and *in vivo* models. Additionally, an ethnobotanical study conducted in the northeastern of Peru [86] suggest that traditional community uses *Tabernaemontana* species against leishmaniasis, showing its importance for the ethnical communities in Peru.

In areas located between Guiana Francesa and Brazil interviews were conducted in traditional communities in the upper Oyapock and Camopi basins about plants used as remedies for treating leishmaniasis as well as other dermatological problems [87]. In this survey, 54% of interviewed cited, at least, one specimen of plant used to treat leishmani-

asis, all indications totalize 38 plant species. Among the eight most cited species used for leishmaniasis treatment, it was scientifically proved that *Caricaca papaya* presented leishmanicidal activity [88], as well as extracts produced with plants from genera *Arrabidaea* sp and *Cecropia* sp [89, 90]. In spite of that, plants with less number of citations can possess important leishmanicidal activity (*in vivo*), as is the case of *Bixa orellana*. It has been demonstrated that the ethanol extract of seeds as well as the essential oil from *B. orellana* presented therapeutic effect in BALB/c mice infected with *L. amazonensis* [91, 92]. Further experiments showed that geranylgeraniol, one of the major constituents of essential oil from *Bixa orellana*, was active against amastigote forms of *L. (L.) amazonensis* (IC_{50} = 17.5 μg/mL) and interferes with parasite mitochondria as well as superoxide anion production, altering parasite viability [93].

Another interesting plant genus that has been frequently indicated for dermatological problems by traditional populations is *Jacaranda* [94], that belongs to the Bignoniaceae family, and is widespread in South America, is endemic to Brazil. Studies already showed the traditional or popular uses of *Jacaranda* species to treat diseases, such as wounds, ulcer, healing and infections. As is possible to observe that, there are many references about the use of this genus for dermatological problems that can be interpreted as leishmaniasis, but few communities could identify the disease "leishmaniasis" and indicate plants to treat it. In this respect, the use of *J. cuspidifolia* and *J. glabra* to treat leishmaniasis was cited by the Bolivian communities of Chinane Indians, Colonos [95] and Tacana [96] as well as by Ecuadorian Amazon community Kichwas [97]. *J. hesperia* was also indicated in Chocó region of Colombia [98]. In spite of that, there are few works investigating the action of these species concerning their molecular diversity and leishmanicidal effect *in vitro* and *in vivo*, and in fact we can be neglecting interesting classes of molecules that can be pharmacologically explored, because very few works investigating the leishmanicidal action of *Jacaranda* genus [99-101] have been published so far. Table **1** summarizes data regarding *in vitro* activity of extracts produced with plants traditionally used by folk populations.

The traditional populations spread around the world have a vast knowledge about medicinal uses of plants, as demonstrated in these elegant works reviewed herein. In spite of that, few works, indeed, reported phytochemical profile of plants with medicinal indications along with biological investigations *in vivo*. The translation of *in vitro* to *in vivo* studies, in fact, is a limitation in such studies, and it possibly occurs due to the difficulties inherent to the process of purification or even the concentration of active compounds. Furthermore, investigations involving experimental animals are time-consuming, expensive, and require different types of reagents, that could not be feasible for countries with low investments in science or even in groups of research in initial phase of establishment.

6. NATURAL PRODUCTS ISOLATED FROM PLANTS USED IN POPULAR MEDICINE TO TREAT LEISHMANIASIS *IN VIVO*

Despite the use of several plant species in traditional medicine to treat leishmaniasis, there are few studies demonstrating the *in vivo* activity of molecules derived from plants used in traditional communities. In this respect, some secondary metabolites with potential antileishmanial activity have been isolated such as alkaloids (**1 - 4**), coumarins (**5** and **6**), terpenoids (**7 - 12**), and naphtoquinone derivatives (**13 - 16**), as showed in Fig. (**1**). The discovery of these metabolites represents potential tools to study new drug candidates for leishmaniasis treatment.

Extracts from stem bark from *Zanthoxylum chiloperone* var. *angustifolium* (Rutaceae) were used in traditional medicine to treat cutaneous leishmaniasis in America. Based on this evidence, two bioactive alkaloids were isolated from this plant - canthin-6-one (**1**) and 5-methoxycanthin-6-one (**2**) which were tested *in vivo* at 10 mg/kg daily for 14 days (oral route) and four days (intralesional route) using the murine model of *L. (L.) amazonensis* infection. Animals treated with compound **1** showed a trend to reduce the tissue parasite (77.6%), while compound 2 displayed reduced activity (21.6% of reduction of parasite loads) which could be directly associated to the presence of methoxyl group at C-5, affecting the antileishmanial potential *in vivo* [102].

Peganum harmala (Zygophyllaceae) is a medicinal plant used in Indian folk medicine to the treatment of parasitic diseases, including leishmaniasis. The crude extract from seeds of this plant was subjected to bioactivity-guided fractionation, that leads to the purification and identification of the alkaloid peganine hydrochloride (**3**). This compound was administered orally (three different dosages of 50, 100 and 200 mg/kg) in *L. (L.) donovani*-infected hamsters during five days. The highest dose of compound **3** inhibited by 87.5% the splenic parasite burden of treated animals, in contrast, the dose of 50 mg/kg did not present therapeutic activity in infected hamsters. Miltefosine, a standard drug used during the therapy of leishmaniasis, was tested at 40 mg/kg and inhibited 95.5% of parasites [103].

Helietta apiculata (Rutaceae) is a shrub found in South America, where it is used to treat several parasitic diseases. Phytochemically, this plant is composed of some alkaloids being γ-fagarine (**4**) responsible for the antileishmanial activity of this plant. BALB/c mice infected with *L. (L.) amazonensis* were treated for 15 days with 10 mg/kg of compound **4** or glucantime (standard drug) by oral route. [104]. Additionally, BALB/c mice infected with *L. (L.) amazonensis* were also treated with coumarins 3-(1'-dimethylallyl)-decursinol (**5**) or (-)-heliettin (**6**) by subscutaneous route for 14 days at 10 mg/kg daily. In these conditions, compounds **4**, **5** and **6** showed the same efficacy as the reference drug, reducing by 97.4, 95.6 and 98.6 % the parasite loads in the lesion, respectively. Furthermore, reduced toxicity was observed in the tested animals [91].

Chenopodium ambrosioides (Chenopodiaceae) is an important medicinal plant used in traditional medicine to treat

Table 1. Leishmanicidal activity of crude extracts, produced with different plant organs, traditionally used by folk populations to treat leishmaniasis.

Plant Species (Family)	Part Used	Leishmania Specie (EC_{50})	Country of the Ethnopharmacology Survey	Refs.
Aframomum sceptrum (Zingiberaceae)	Leaves Root	*L. donovani* (**12.5** μg/mL) - promastigote	Ivory Coast	[72]
Anacardium occidentale (Anacardiaceae)	Bark	*L. braziliensis* (NC*) - promastigote	Brazil	[75]
Arrabidaea chica (Bignoniaceae)	Leaves	*L. amazonensis* (31.8 μg/mL) - promastigote *L. infantum* (14.7 μg/mL) - prosmastigote	Brazil	[89]
Bixa orellana (Bixaceae)	Seed	*L. amazonensis* (8.5 μg/mL) - amastigote	Guiana Francesa	[91,92]
Carica papaya (Caricaceae)	Leaves	*L. amazonensis* (11 μg/mL) - amastigote	Peru	[88]
Cecropia pachystachya (Urticaceae)	Leaves	*L. amazonensis* (17 μg/mL) - promastigote	Brazil	[90]
Chenopodium ambrosioides (Amaranthaceae)	Essential Oil	*L. amazonensis* (3.7 μg/mL) - promastigote *L. amazonensis* (4.6 μg/mL) - amastigote	Brazil	[76]
Himatanthus obovatus (Apocynaceae)	Root	*L. donovani* (7,5 μg/mL) - promastigote	Brazil	[80]
Jacaranda puberula (Bignoniaceae)	Leaves	*L. amazonensis* (88 μg/mL) - promastigote	NM**	[94]
Lippia multiflora (Verbenaceae)	Bark, Leaves and Root	*L. donovani* (**12.5** μg/mL) - promastigote	Ivory Coast	[72]
Napoleona vogelli (Lecythidaceae)	Bark	*L. infantum* (5.66 μg/mL) - amastigotes	Democratic Republic of Congo	[73]
Piper hispidum (Piperaceae)	Leaves	*L. amazonensis* (69 μg/mL) - promastigote *L. amazonensis* (5μg/mL) - amastigote	Peru	[82]
Tabernaemontana sananho (Apocynaceae)	Root	*L. amazonensis* (9 μg/mL) - promastigote *L. amazonensis* (58 μg/mL) - amastigote	Peru	[85]
Uvaria afzelii (Anonnaceae)	Leaves	*L. donovani* (**12.5** μg/mL) - promastigote	Ivory Coast	[72]

*NC - Not Calculated.
**NM - Not Mentioned.

rheumatism and skin problems. The aerial parts of this plant produce an essential oil, which has been used by native population of South America against parasitic diseases, including leishmaniasis. The chemical profile of essential oil was composed, mainly, by the terpenoids ascaridole (7), carvacrol (**8**) and caryophyllene oxide (**9**). Crude oil and purified compounds **7 - 9** were tested at 30 mg/kg (intralesional route) on a four days interval during 14 days in BALB/c mice infected with *L. (L.) amazonensis*. In this case, it was observed that exclusively the crude essential oil prevented lesion development with a superior potential when compared with standard treatment (Glucantime), suggesting that a combination of compounds **7 - 9** is important to get protection [105].

Matricaria chamomilla (Asteraceae) is an important medicinal plant used for the treatment of parasitic diseases. Chemically, this plant is composed by the monocyclic sesquiterpene (-)-α-bisabolol (**10**) which displayed potent activity against *L. (L.) infantum* in *in vivo* model. BALB/c mice infected with *L. (L.) infantum* were treated with 200 mg/kg of compound **10,** by oral route, and meglumine antimoniate (104 mg/kg) by intraperitoneal route during 14 days. In this case, it was observed that compound **10** at 200mg/kg showed comparable efficacy than the standard drug. Interestingly, compound **10** was not toxic for BALB/c mice, because plasmatic levels of urea, creatinine, alkaline phosphatase, and transaminase were normal. Studies of drug combination were also performed, and in this case, it decreased only the parasitism in the liver [106].

Baccharis uncinella (Asteraceae) has been used in some regions of Brazil, to treat dermatological problems and infections [107]. The phytochemical characterization of ethanol

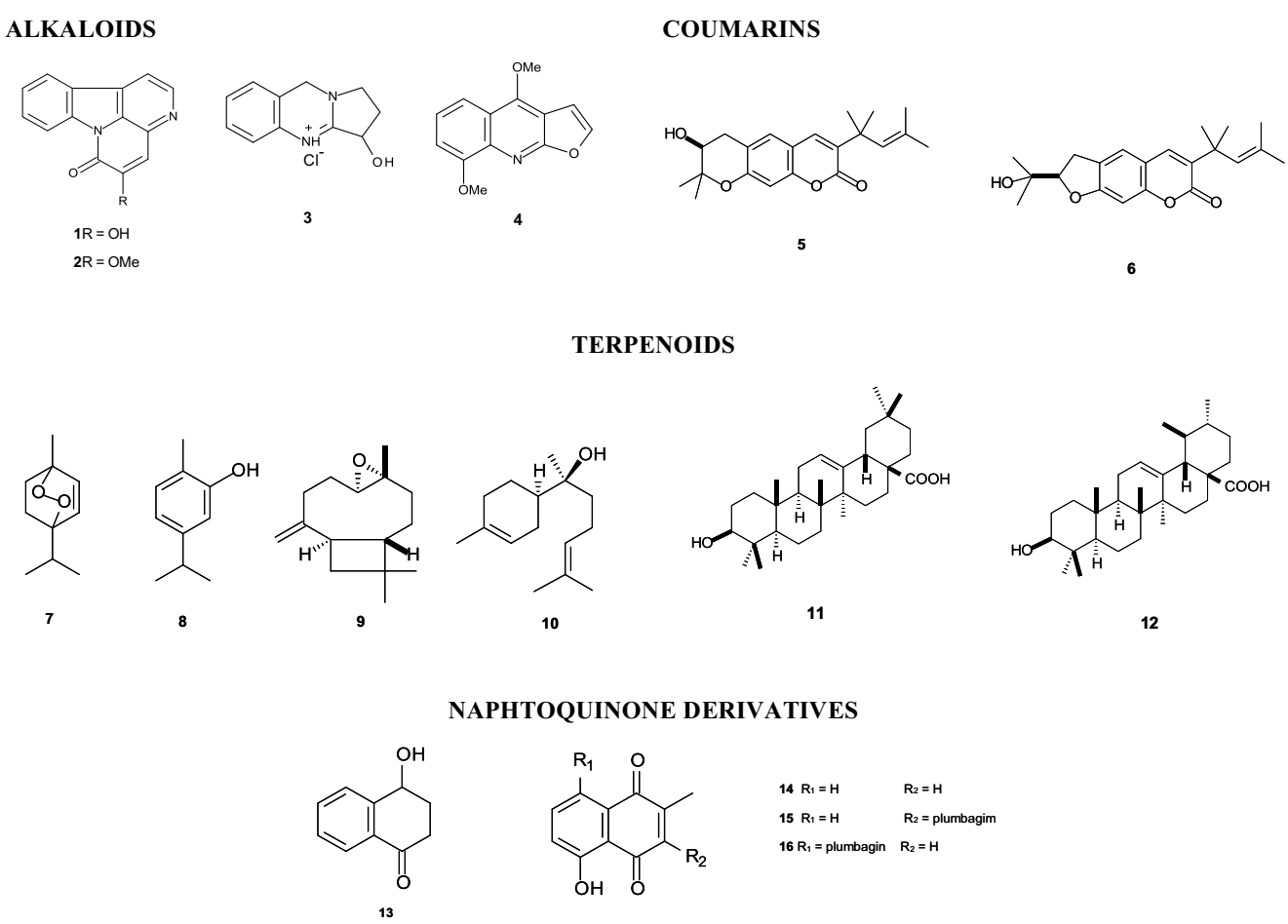

Fig. (1). Structures of natural products **1 - 16** with *in vivo* antileishmanial activity isolated from plants used in traditional medicine to treatment of antiparasitic diseases.

extract from aerial parts of *B. uncinella* led to the identification of oleanolic (**11**) and ursolic (**12**) acids, two related triterpenes. *In vivo* studies showed that BALB/c mice infected with *L. (L.) amazonensis* and treated with compound **12** (1.0 and 2.0 mg/kg) or glucantime (100.0 mg/kg) presented decreased lesion size and skin parasitism in comparison with infected control ($p < 0.05$), further experiments also showed that the triterpene **12** presented therapeutic effect in experimental visceral leishmaniasis, and it was associated with increased Th1 immune response [108, 109], in contrast, ursolic acid isomer, the oleanolic acid (**9**) was inactive *in vitro*. Importantly, seric levels of creatinine, urea, aspartate aminotransferase and alanine aminotransferase were normal in UA-treated hamsters in comparison with control animals, in contrast amphotericin B - treated hamster had signs of renal toxicity [109].

Ampelocera edentula (Ulmaceae) has been used by indigenous population in Bolivia to treat cutaneous leishmaniasis caused by *L. (V.) braziliensis*. Extract produced with the stem bark of this plant was purified and the bioactive compound 4-hydroxy-1-tetralone (**13**) was isolated. Compound **13** was tested *in vivo* in BALB/c mice infected with *L. (L.) amazonensis* and *L. (L.) venezuelensis*. After 14 days of the treatment (50 mg/kg) with compound **13** through subcutaneous route, it was observed that the natural product presented superior activity at inhibited lesion development in BALB/c mice when compared with the standard treatment (Glucantime - 112mg Sb^{V}/kg) [110].

Popularly used to treat cutaneous leishmaniasis caused by *L. braziliensis,* extracts from *Pera benensis* (Euphorbiaceae) was subjected to phytochemical studies in which the naphtoquinones plumbagin (**14**), 3,3'-biplumbagin (**15**) and 8,8'-biplumbagin (**16**) were isolated. These compounds displayed activity in BALB/c mice infected with *L. (L.) amazonensis* and *L. (L.) venezuelensis*. Comparatively, compound **14** showed higher potential after eight weeks of treatment at 2.5 and 5 mg/kg/day, a similar result found to animals treated with Glucantime. Additionally, compound **14** showed reduced toxicity, an important feature to development of new drugs to treatment of leishmaniasis [111]. Table **2** summarizes data regarding *in vivo* activity of plant-derived molecules.

Therefore, based in the ethnopharmacological interviews, studies performed with medicinal plants used in traditional medicine to treat parasitic diseases consist in a rational and important method to prospect bioactive secondary metabolites, such as the ones described herein, that showed therapeutic activity. These compounds could be used as tools to develop new prototypes to leishmaniasis treatment.

Table 2. Leishmanicidal activity of compounds purified from plants traditionally used by folk populations to treat leishmaniasis.

Plant Species (Family)	Molecule (Number)	Clinical Form, Host	Dose, Route, Duration	Parasite Reduction %	Refs.
Ampelocera edentula (Ulmaceae)	4-hydroxy-1-tetralone (13)	CL, BALB/c	50 mg/kg, Intralesional, 14 days	ND	110
Baccharis uncinella (Asteraceae)	Ursolic acid (12)	VL, BALB/c	1.0 and 2.0 mg/kg, Intralesional, 14 days	Spleen 93.3 - 92.7 Liver 96.9 - 96.7	109
Helietta apiculata (Rutaceae)	γ-fagarine (4) 3-(1'-dimethyllallyl)- decursinol (5) Heliettin (6)	CL, BALB/c	(4) 10 mg/kg, Oral, 15 days (5) 10 mg/kg, Subcutaneous, 15 days (6) 10 mg/kg, Subcutaneous, 15days	97.4% 95.6% 98.9%	104
Peganum harmala (Zygophyllaceae)	Peganine hydrochloride (3)	VL, Gold Hamster	50 mg/kg, Oral, 5 days 100 mg/kg, Oral, 5 days 200 mg/kg, Oral, 5 days	0 79.6 87.5	103
Pera benensis (Euphorbiaceae)	Naphtoquinones plumbagin (14) 3,3'-biplumbagin (15) 8,8'-biplumbagin (16)	CL, BALB/c	(14) 5mg/kg Subcutaneous 14 days (15) 25mg/kg Subcutaneous, 14 days (16) 25mg/kg Subcutaneous, 14 days (14) 10 mg/kg, Intralesional, 14 days (15) 50 mg/kg, Intralesional, 14 days (16) 50 mg/kg, Intralesional, 14 days	NM*	111
Matricaria chamomilla (Asteraceae)	α-bisabolol (10)	VL, BALB/c	200 mg/kg, Oral, 14 days	85% - 89%	106
Zanthoxylum chiloperone var. *angustifolium* (Rutaceae)	Canthin-6-one (1) 5-methoxycanthin-6-one (2)	CL, BALB/c	10 mg/kg, Intralesional, 4 days (2) 10 mg/kg, Intralesional, 4 days	77.6 21.6	102

CL -Cutaneous Leishmaniasis
VL - Visceral Leishmaniasis
*NM - the parasitism was not mentioned, but significant reduction in lesion size was detected.

CONCLUSION

Leishmaniasis therapy is considered outdated and drugs are able to induce serious side effects in patients, furthermore, parasites are able to become resistant to the conventional therapy. Therefore, each single step performed towards the characterization of new, effective and less toxic molecules can be considered an important advance to the chemotherapy of leishmaniasis, and in this regard, ethnopharmacological surveys can give important clues to do that. In spite of the important and elegant works published so far, few of them were able to show *in vivo* potential of purified molecules, the toxicity activity as well as their efficacy in other models of leishmaniasis, or even in clinical trials in naturally infected humans or animals. This is alarming, because we are, in fact, neglecting all knowledge gathered about medicinal plants.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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