

Current Treatment of Leishmaniasis: A Review

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Abstract: The World Health Organization has classified the leishmaniasis as a major tropical disease. An effective vaccine against leishmaniasis is not available and chemotherapy is the only effective way to treat all forms of disease. However, current therapy is toxic, expensive and the resistance has emerged as a serious problem, which has compelled the search for new antileishmanial agents. The aim of this article is to review the current aspects of the pharmacology of leishmaniasis, giving an overview from current agents clinically used to new compounds under development. Pentavalent antimonials are still the first choice among drugs used for the treatment of leishmaniasis. Alternatively, amphotericin B, pentamidine, miltefosine and paromomycin can be used. The search for new drugs is a perpetual process; including synthetic products and compounds isolated from natural sources. The current scenario of antileishmanial drugs constitute the results of effort by academics, researchers and sponsorships in order to obtain drugs available, efficient and less toxic to people infected by *Leishmania* parasites.

Keywords: Leishmaniasis, treatment, drug, pharmacology, parasite.

1. INTRODUCTION

Leishmania are protozoan parasites belonging to the family *Trypanosomatidae* that causes high morbidity and mortality levels with a wide spectrum of clinical syndromes [1]. The World Health Organization has identified leishmaniasis as a major public health problem [2]. The control of leishmaniasis remains a serious problem. As a zoonotic infection, transmission is difficult to interrupt, although some attempts to reduce vector and mammalian reservoir populations have been successful. There are currently no vaccines for leishmaniasis. The drugs available for leishmaniasis treatment are toxic, expensive and frequently ineffective [3, 4].

The problems previously exposed emphasize the importance of the development of new drugs against leishmaniasis [3]. During the last decades has been seen a significant increase in our basic knowledge of parasite, as well as a revolution in chemical techniques and several advances in bioinformatics tools that have motivated the search of new antileishmanial agents. The present article reviews the current status of chemotherapy and the advances in the development of new drugs against the leishmaniasis.

2. THE LEISHMANIASIS

Leishmania parasites were independently described by Willian Leishman and Charles Donovan in 1903, but were previously observed by David D. Cuningham in 1885 and Peter Borovsky in 1989. The genus *Leishmania* was proposed by James Wright in 1903 [1].

The leishmaniasis are a complex of diseases caused by at least 17 species of protozoan parasite *Leishmania* [4]. The

disease affects around 12 million people worldwide, with an annual incidence of approximately two million new cases and 350 million are living at risk to be infected. Reported from 88 subtropical and tropical countries has been recorder from Indian subcontinent, Southern Europe and Western Asia to America, including rural and periurban areas [2]. Multiple factors such as the human immunodeficient virus (HIV) epidemic, increase of international travel, a lack of effective vaccines, difficulties in controlling vectors, international conflicts and the development of resistance to chemotherapy could increase the cases of leishmaniasis [5].

The transmission of *Leishmania* occurs through hematophagus vectors from *Phlebotomus* genus in the Old World and *Lutzomyia* in the New World [6]. Parasites multiply in the vector digestive tract, and they are transmitted to the mammalian host during vector blood feeding. Inside the vectors, *Leishmania* are in promastigotes form, which are long, elongated and extracellular. In the vertebrate host, the parasite multiplies inside the macrophages as amastigotes, which are spherical, with an internalized flagellum. *Leishmania* parasite is able to survive to stress conditions, lyses the macrophage and are phagocyted by new host cell [7, 8].

Leishmaniasis has traditionally been classified in three different clinical forms according of parasite tropism: cutaneous (CL), mucocutaneous (ML) and visceral (VL) leishmaniasis; ranging from simple cutaneous ulcers to massive destruction in CL and subcutaneous tissues in ML. Other cutaneous manifestation can occur, including diffuse cutaneous (DCL), recidivans (RL) and post-kala azar dermal (PKDL) leishmaniasis. When the infection involve the liver and other organs in the VL can be fatal, if left untreated [2, 4]. More than 90% cases of VL occur in 5 countries: India, Sudan, Bangladesh, Nepal and Brazil; while more than 90% cases of CL occurs in Afghanistan, Saudi Arabia, Algeria, Brazil, Iran, Iraq, Syria and Sudan [4, 9]. Nevertheless, clinical features of the leishmaniasis are highly variable due

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to the interplay of numerous factors in the parasites, vectors, host and environments involved [10].

Primary prevention relies on managed control of the maintenance host and sandfly bite prevention measures. Secondary and tertiary prevention are dependent of the medical assistance using the clinical guidelines and adequate treatments. Currently, there is no immunoprotection available, although prospects for a vaccine remain high [11].

Around 25 compounds and formulations showing antileishmanial effects in clinical uses, but only a few have been proven worthy. The primary treatment against leishmaniasis includes pentavalent antimonials. In some cases, other drugs, such as amphotericin B, pentamidine, miltefosine and aminosidine can be used. The drugs used in leishmaniasis treatment present several problems, including high toxicity and many adverse effects, leading to patients withdrawing from treatment and emergence of resistant strains. In addition to these problems, the high cost of the compounds makes the treatment far from suitable and, regrettably, it has been increasing gradually through the years [9]. The treatment of leishmaniasis probably seldom eradicates all parasites in tissue macrophages; nevertheless, most T cell-intact patients show long-lasting clinical cure after treatment, despite residual intracellular infection, which can provoke the post-treatment relapse of infection [10].

3. CURRENT CHEMOTHERAPY

3.1. Derivatives of pentavalent antimonial

Pentavalent antimonials (Sb^V) become the drug of choice for the treatment of all types of leishmaniasis. Pentostam, sodium stibogluconate¹, manufactured by Wellcome Foundation was first used; following the Glucantime, meglumine antimoniate², is manufactured by Rhone Poulenc in France [12] can be used.

The drug can be administered intramuscularly or intravenously, which is distributed in high concentration in the plasma, liver and spleen. Mean total apparent volume of distribution is 0.22 ± 0.057 L/Kg of body weight and the half-life is 2 hours. In liver, it biotransforms to its trivalent state (Sb^{III}) and about 50% of antimony is excreted from 24 hours to 76 hours through urine [13].

To date, the precise mechanism of action of antimonials remains an enigma and their antileishmanial action probably depend on the *in vivo* reduction of Sb^V form to a more toxic Sb^{III} form, due to that only amastigotes are susceptible to the Sb^V [14]. A general consensus is that Sb^V acts upon several targets that include influencing the bioenergetics of *Leishmania* parasite by inhibiting parasite glycolysis, fatty acid beta-oxidation and inhibition of ADP phosphorylation [15]. It has also been reported to cause non specific blocking of SH groups of amastigote proteins and cause inhibition of DNA topoisomerase I [16]. More recently, it was demonstrated that antimony can alter the thiol-redox potential in both forms of parasite by actively promoting efflux of thiols, glutathione and trypanothione, thus rendering the parasite more susceptible to oxidative stress [17].

The recommended dose is 15-20 mg Sb^V /Kg of body weight per day for 21-28 days by intramuscular or intravenous route. Intralesional administration of the drug

has shown promising results by injection of 0.2-1 mL of Sb^V [18].

The long course treatment allows antileishmanial levels of the drug to accumulate in tissues, particularly in liver and spleen. The treatment with antimonials has been caused several side effects, such as: nausea, abdominal pain, myalgia, pancreatic inflammation, cardiac arrhythmia and hepatitis, leading to the reduction or cessation of treatment [19].

Currently, several limitations have decreased the use of antimonials: the variable efficacy against CL and VL, as well as the emergence of significant resistance has been increased [4]. The recommendations have replaced the antimonials by amphotericin B in refractory zones [20]. Second, new generic of Pentostam have been produced with the aim to decrease the high cost of the treatment. However, caution must be exercised before using Sb^V from new manufactures as bad batches because of caused fatal cardiotoxicity [21]. Intralesional administration can be a choice but each lesion has to be injected individually and do not prevents the potential dissemination of infection [9].

3.2. Amphotericin B

Amphotericin B³ is a macrolide polyene antifungal antibiotic agent, discovered in 1956, from a bacterium: *Streptomyces nodusus*, actinomycetes obtained from the soil of Orinoco River in Venezuela. In early 1960s it was demonstrated its antileishmanial activity [9, 22].

The drug is poorly absorbed by gastrointestinal tract. Amphotericin B exhibits multicompartmental distribution and is found to be present in low concentrations in aqueous humour, pleural, pericardial, peritoneal and synovial fluids. The elimination in adult is approximately 24 hours and can be found in blood for up to 4 weeks and in urine for 4-8 weeks in case of discontinuation of therapy [12].

The antileishmanial activity of amphotericin B is attributable to its selectivity for 24 substituted sterols, namely ergosterol *vis-a-vis* cholesterol, the primary sterol counterpart in mammalian cells eventually helping to increase drug selectivity towards the microorganism. However, higher concentrations ($>0.1 \mu M$), it triggers cationic and anionic influx *via* formation of aqueous pores resulting in cell lyses [22].

Therapeutic doses of amphotericin B deoxycholate of 0.5 to 1mg/Kg by endovenous bolus daily for 20 days can be administered or alternate days and with a total dosage between 1.5 to 2.0 g [11, 23].

Serious adverse reactions have been displayed by the treatment with amphotericin B, including fever with rigor and chills, thrombophlebitis and occasional serious toxicities like myocarditis, severe hypokalaemia, renal dysfunction and even death. Its use requires prolonged hospitalization and close monitoring [23].

Amphotericin B has excellent leishmanicidal activity and constitutes an option in patients that showed resistance to treatment with antimonials. The major limiting factor about the use of this drug is due to their toxicity. Currently, toxic effects of amphotericin B have been largely ameliorated with the advent of lipid formulations. In these formulations,

deoxycholate has been replaced by other lipids that mask amphotericin B from susceptible tissues, thus reducing toxicity, and facilitating its preferential uptake by reticuloendothelial cells. Thus, this drug delivery result in increasing efficacy and reduced toxicity. Three lipid-associated formulations of amphotericin are commercially available: liposomal amphotericin B (AmBisome), amphotericin B lipid complex (Abelcet) and amphotericin B colloidal dispersion (Amphocil). These compounds has been considered between the most striking advances in leishmaniasis therapy [23, 24].

Among the lipid formulations, AmBisome is the best tested and some studies demonstrated the successful in patients with CL and VL, particularly in areas where antimonials resistance has been detected. AmBisome have been considered as a high effective, non-toxic form of treatment for VL when administered in a short course [25, 26]. The optimal regimen have been recommended with a total dose of 20 mg/Kg, given in 5 doses of 3-4 mg/Kg over 10 days [27].

3.3. Pentamidine

Aromatic diamidines were first synthesized as hypoglycemic drugs and their chemotherapeutic profile against antiprotozoal therapy was early discovered. Chemically, pentamidine 4 is 4-[5-(4-carbamimidoylphenoxy)pentoxyl benzenecarboximidamide, synthesized in the late 1930s. It was originally used in the treatment of African Trypanosomiasis and since 1939 it was demonstrated its activity against *Leishmania* infections [23].

This drug can be administered parenterally, by intramuscular or intravenous route. It has a half-life is 5 to 15 minutes and 54 minutes, respectively. Drug distribution shows their concentration to be considerable higher in the liver, kidneys, adrenal glands and spleen, while only a small amount is found in lungs [12, 23].

Pentamidine acts on the genome of parasite by hampering replication and transcription at the mitochondrial level. Polyamines are substituted at nuclei acid binding sites, which preferentially bind to kinetoplast DNA [26].

The regimen consist of 4 mg/Kg three times a week for 3-4 weeks (10–12 injections) [12].

Commonly, the treatment with pentamidine causes myalgias, pain at the injection site, nausea, headache and less frequently result in a metallic taste, a burning sensation, numbness and hypotension. Reversible hypoglycemia occurs in about 2% of cases. It causes irreversible insulin dependent diabetes mellitus and death [28].

Pentamidine is one of the drugs for clinical use in all forms of leishmaniasis. However, different studies concerning to efficacy of pentamidine have been reported In Colombia, the efficacy of the drug was demonstrated in patients infected with *L. panamensis* [29]. However, Andersen *et al.* 2 reported a low cure rate for pentamidine (35%) in patients infected with *L. braziliensis* in Peru [30]. The cure rate associated with low dose of pentamidine, given for a short period, makes it an attractive alternative for CL in antimonies treatment failure cases. In general, the use of this drug has declined due to their low efficacy and toxicity [28].

3.4. Miltefosine

Lysophosphatidylcholine was found to have immunomodulatory activity in 1960s. More stable derivatives including etherphospholipids and structurally related alkylphosphocholines were made in the 1970s and 1980 [4]. One of them was the miltefosine5 and their *in vitro* activity on amastigotes of *L. donovani* was reported in 1987 [31]. In 2002, miltefosine was registered to be used in visceral leishmaniasis cases in immunocompetent patients from India and in 2004, it was approved in Germany, including their use in immunocompromised patients [32].

The antileishmanial mechanism of action of this compound can be extrapolated from its effect on mammalian cells, where it causes modulation of cell surface receptors, inositol metabolism, phospholipase activation, protein kinase C and other mitogenic pathways, eventually culminating in apoptosis [33].

Depending on the individual weight, the recommended therapeutic regimen for patients weighing less than 25 Kg is a single oral dose of 50 mg for 28 days by oral route, whereas individuals weighing more than 25 Kg require a twice daily dose of 50 mg for 28 days [28].

Adverse effects of miltefosine include gastrointestinal disturbances and renal toxicity. Fortunately, these symptoms are reversible and they are not a major cause for concern. As miltefosine is teratogenic, it is contraindicated in pregnancy and women of child bearing age group, not observing contraception [28].

Miltefosine has been hailed as a novel oral drug for treatment of VL, with successful in immunocompetent and immunocompromised patients and perhaps the most significant recent advances [34]. However, some studies have demonstrated the insensibility of *Leishmania* species from the New World; including: *L. braziliensis*, *L. guyanensis* and *L. mexicana* [35]. These results were disappointing given that it was hoped that miltefosine would provide a better alternative to drug therapy in America [17]. For other hand, the efficacy of miltefosine against *L. infantum* infection have been conducted in animals; needing a validation in clinical trials [36].

3.5. Paromomycin

Paromomycin 6 (aminosidine) is an aminoglycosidic aminocyclitol produced by *Streptomyces riomonus* var. *Paromomycinus*, which was isolated in 1956. It is effective against a wide range of bacteria and protozoa [12]. Antileishmanial activity of paromomycin was demonstrated by Neal *et al.* in the 1960s [37].

The drug is poorly absorbed into systemic circulation after oral administration, but rapidly absorbed from intramuscular sites of injection. Peak concentration in plasma occurs in 30-90 min and its apparent volume of distribution is 25 % of body weight. The half-life varies between 2 and 3 hours in patients with normal renal function. Their clearance is almost entirely by glomerular filtration [12].

The mechanism of action of paromomycin in *Leishmania* requires further elucidation and it inhibits protozoan protein synthesis. It binds to the 30S ribosomal subunit, interfering with

initiation of protein synthesis by fixing the 30S-50S ribosomal complex at the start codon of mRNA, leading of accumulation of abnormal initiation complex [38]. In parallel, experimental evidences have shown that paromomycin promoted ribosomal subunit association of both, cytoplasmatic and mitochondrial forms, following low Mg^{2+} concentration, induce dissociation and also cause dysfunction in respiratory systems [39].

Three preparations of paromomycin ointments have been used for CL: paromomycin 15% plus methylbenzethonium chloride 12%, paromomycin 15% with urea 10% and paromomycin plus gentamicin 0.5%. These formulations have shown variable results according to the specie of *Leishmania* involved and the epidemiologic situation [38].

The most common side effect associated with the paromomycin is the ototoxicity, as well as problems in liver function [40]. In patients treated with the ointment formulation skin rashes, local pruritus and burs have been the side effects encountered [23].

3.6. Other Drugs Clinically Used

3.6.1. Azoles

The imidazoles and triazoles are well known oral antifungal agents that are well tolerated. They also have antileishmanial activity against certain species as they inhibit 14 α -demethylase, a key enzyme in the sterol biosynthesis pathway, thereby interfering with *Leishmanial* cell membrane biosynthesis. Among them, Fluconazole⁷ have been used against *L. major* in Old World [41] and Ketoconazole⁸ in the New World against *L. panamensis* and *L. mexicana* [42]. Itrakonazole⁹ have been used in Old and New World, but a low efficacy has been demonstrated [43]. Posaconazole¹⁰ has shown activity against experimental *L. amazonensis* infection, but has not been evaluated yet in clinical trials [44].

3.6.2. Allopurinol

The antileishmanial activity of the purine analogue allopurinol¹¹ was identified over 30 years ago. Because it had oral bioavailability and it was widely used for other clinical indications, the drug was investigated in clinical trials for CL and VL. However, the results were disappointing. Allopurinol is used as a substrate by various enzymes of the purine salvage pathway of trypanosomatids, and it is selectively incorporated into nucleic acid in the parasite. In recent years, allopurinol was considered as part of a maintenance therapy for canine leishmaniasis [45].

3.6.3. Sitamaquine

Sitamaquine ¹² is an orally active 8-aminoquinoline analogue (8-aminoquinoline (8-[6-(diethylamino)hexyl] amino)-6-methoxy-4-methylquinoline) known as WR 6026. This new primaquine was originally developed by Walter Reed Army Institute of Research (Unite States) for malaria. Animal studies showed very encouraging results against VL; although in clinical trials it did not shows high efficacy after treatment during 28 days [46].

3.7. Antiretroviral drugs

The coinfection *Leishmania*-HIV is frequent and the most common specie involved is *L. infantum*. In general, the treatment in these cases is similar to that of immunocompetent patients, using primarily antimonials or amphotericine B

(standard or lipid or liposomal forms). However, the relapses are very frequent. Therefore, it is important to perform a secondary prophylaxis. Currently, no treatment has been completely effective and the mortality rate is high (approximately 25%) during the first month after diagnosis [47].

Recently, the use of antiretroviral drugs has been a considerable impact in coinfecting patients. Indinavir and saquinavir, two HIV protease inhibitors, have shown pharmacological activity against *L. major* and *L. infantum*. These results add new insights into the wide-spectrum efficacy of protease inhibitors and suggest studying their action on amastigote forms of *Leishmania* in order to validate their potential contribution against opportunistic infections in treated seropositive patients [48].

3.8. Immunomodulators

Cure of leishmaniasis appears to be dependent upon the development of an effective immune response, that activates macrophages to produce toxic nitrogen and oxygen metabolites top kill the intracellular amastigotes. This process is suppressed by the infection itself, which downregulates the requisite signaling between macrophage and T cell such as the interleukin (IL) 12, the interferon (IFN) γ and the presentation of major histocompatibility complex (MHC). One alternative in leishmaniasis treatment is the association of antileishmanial drugs with products that stimulate the immune system. The purpose is to enhance the immune response by the activation of macrophages and the increase of the nitric oxide production among other mechanisms to eliminate the infection [4, 49].

The first report about the use of immunomodulators was the superiority of human IFN- γ as an adjunct antimony therapy for VL, which was demonstrated in Kenya and India [50]. Amphotericin B in conjunction of IL-12 or IL-10 was more efficient than monotherapy and led to a reduction of the amphotericin dose [49]. Other studies have been reported, using immunomodulators like BCG [51] and protein A [52]. Nevertheless, the price of immunomodulators is exorbitantly high for poor population [53].

Recently, a new generation of synthetic immunomodulator drugs has shown potential for *Leishmania* treatment. A Schiff-base forming compound, Tucaresol ¹³, enhance TH1 response and the production of IL-12 and IFN- γ in mice and human in patients with viral infections and cancer. Tucaresol also has activity against infection caused by *L. donovani* in BALB/c mice and C57BL/6 at a dose of 5 mg/Kg [54]. Iminoquimod ¹⁴, an imidazoquinoline, is the ingredient of a cream (AldaraTM) used for the treatment of genital warts. This drug has shown to induce nitric oxide production in macrophages and it was effective *in vitro* against *L. donovani* [55].

This field can be more explored with new products, aiming to validate the use of immunomodulator for treatment of leishmaniasis, particularly in patients infected with strains that can develop ML or other complications.

3.8. Combined Therapy

After increasing unresponsiveness to most of the monotherapeutic regimens, the combination therapy has found new scope in the treatment of leishmaniasis. The combination of antileishmanial drugs could reduce the potential toxic side effects and prevent drug resistance.

Several works have shown that some drugs increase their antileishmanial effect in conjunction [56].

Paromomycin have been used extensively in Sudan in combination with sodium stibogluconate for the treatment of VL in a period of 17 days [57]. The superiority of this combination has been demonstrated in several studies [58, 59]. Combined chemotherapy against VL in Kenya was evaluated using oral allopurinol (21 mg/Kg, three times a day for 30 days) with endovenous pentostam (20mg/Kg once a day). The therapy was efficient, but relapses were found in the first month after treatment [60]. This clinical evidence demonstrated the superiority of the combination therapy and can be a hope to develop new formulations.

3.9. Remarks of Treatment of Leishmaniasis in Categories of Patients

Leishmaniasis, particularly the visceral form, is generally associated with severe immunodeficiency (AIDS; renal, liver, and heart transplantations; haemopoietic malignancies). More rarely it can be related to an immunotolerance status such as pregnancy. In these patients, differences in the response to treatment of leishmaniasis have demonstrated the complexity of managing infections between different individuals [61].

Treatment of leishmaniasis in HIV patients encounters inefficacy and relapse due to drug resistance, toxicity and immunodepression. Treating patients with *Leishmania* and HIV co-infection requires close monitoring for effectiveness of treatment, especially because of the high relapse rates. For immunosuppressed patients, AmBisome has been recommended in a total dose of 40 mg/Kg spread over 38 days [62].

Infection with *Leishmania* during pregnancy is rare and deserves special attention since little information is available regarding the occurrence of visceral leishmaniasis during gestational period and the real possibility of vertical transmission of this disease. Because specific areas in the world are endemic for the disease and considering the continuous growth of the population, cases of pregnant women with visceral leishmaniasis are becoming more frequent. Unfortunately, textbooks on infectious diseases do not include this specific group of patients, and studies in the literature on aspects related to pregnancy and leishmaniasis are scarce. Currently, amphotericin B is strongly recommended as the first choice drug due to their activity and its fewer maternal-fetal adverse effects [63].

4. DEVELOPMENT OF NEW DRUGS

During the past decades have given new impetus to antileishmanial drug discovery; including (i) knowledge of biology, biochemical pathway and genome of parasite, (ii) a revolution in chemical techniques, (iii) several advances in bioinformatics tools and (iiii) a higher number of networks, partnerships and consortia to support the development of new antileishmanial agents. Currently, the developments of both synthetic and natural drugs have relevant importance in the search of new therapeutic alternatives.

4.1. Antileishmanial Synthetic Compounds

The medicinal chemistry is a recent applied science directed to the development of new drugs that evolved significantly due to recent technological advances, mainly in

molecular, structural biology and computational chemistry areas. The generation of structural modifications in an initial molecule (called leading compound) to obtain new derivatives has been one successful approach for the design of new drugs based in known and validated molecular targets in the parasite [64].

The knowledge about the physic-chemical and structural properties of the leading compound and its relation to the pharmacological target or action have provided evidences about the initial pharmacophore group, which is essential to activity [64]. Derivatives with pharmacophore group can be obtained with the aim to increase the activity and modulate toxic and pharmacokinetic characteristics of the compound. This approach together with bioinformatics tools has possibilities the *virtual search* or *in silico* of potential drugs.

In parallel, the design of specific inhibitors has been explored as a possible means for controlling the parasites growth without damaging the host [8]. A review about potential targets in *Leishmania* parasite has been written [65]. Some of the most promising targets are: topoisomerases [66], kinetoplast [67], mitochondria [68], trypanothione reductase [69], cysteine protease [70], fatty acid and sterol pathways [71].

Several synthetic products have demonstrated their antileishmanial potentialities. Per example: azasterols are inhibitors of 24-methyltransferase, which showed activity against promastigotes of *L. donovani* and axenic amastigotes of *L. amazonensis* [72]; edelfosine and ilmofosine, new alkyl-lysophospholipid derivatives, demonstrated high *in vitro* activity against *L. donovani* promastigotes and amastigotes [73]; nicotinamide is an inhibitor of certain III NAD-dependent deacetylase that caused *in vitro* inhibition of *L. infantum* promastigotes and amastigotes [74]; n-acetyl-l-cysteine, a precursor of glutathione, showed *in vivo* activity against *L. amazonensis* in BALB/c mice [75] and 3-substituted quinolines have been demonstrated their potential as activators of macrophages and *in vitro* activity against *L. chagasi* promastigotes and amastigotes was observed [76]. Others examples are listed in Table 1.

On the other hand, the screening of library compounds has been reported. Per example, St. George and col. screened a chemical library of 15000 compounds. Three compounds (NSC#: 13512, 83633 and 351520) were identified to be active against amastigotes of *L. major* and safe to mammalian host, which represent possible candidates for drug development [77]. The analyzed of library is an advance technology since several compounds can be search and gain information on the chemical class of leaders.

The synthetic products have been considered successfully, and some advantages are mentioned such as: cost, time of obtention, novelty and scale-up and low intellectual property complications [78]. However, the synthetic molecules can display a high toxicity and only a low of compounds have been evaluated in clinical studies.

4.2. Promising Antileishmanial Natural Products

Many people in rural areas depend largely on popular treatments to alleviate the symptoms, particularly the use of medicinal plants [79, 80]. The natural products are potential sources of wide chemistry with a remarkable diversity and

Table 1. Synthetic Products that Showed Antileishmanial Activity

Compound	Drug Design	Antileishmanial Activity	References
3-substituted quinolines	Potential activators of macrophages	Antileishmanial <i>in vitro</i> effects against <i>L. chagasi</i> promastigotes and amastigotes was observed.	[76]
9, 9-dimethylxanthene tricyclics	Inhibitors of trypanothione reductase	Caused <i>in vitro</i> inhibition of amastigotes of <i>L. donovani</i> .	[90]
Azasterols	Inhibitors of 24-methyltransferase	Showed activity against promastigotes of <i>L. donovani</i> and axenic amastigotes of <i>L. amazonensis</i>	[72]
Edelfosine and Ilmofosine	New alkyl-lysophospholipid derivatives	Demonstrated high <i>in vitro</i> activity against <i>L. donovani</i> promastigotes and amastigotes.	[73]
N-acetyl-L-cysteine	Precursor of glutathione	Showed <i>in vivo</i> activity against <i>L. amazonensis</i> in BALB/c mice	[75]
Nicotinamide	Inhibitor of certain III NAD-dependent deacetylase	Caused <i>in vitro</i> inhibition of <i>L. infantum</i> promastigotes and amastigotes.	[74]
Perifosine	New alkylphospholipid derivatives	Displayed significant activity against promastigotes of <i>L. braziliensis</i> , <i>L. amazonensis</i> , <i>L. major</i> and <i>L. infantum</i> .	[91]
Triazole SCH 56592	Inhibitor of ergosterol synthesis pathway	Exhibited <i>in vitro</i> and <i>in vivo</i> activity against <i>L. amazonensis</i> and <i>L. donovani</i> .	[44]

accessibility in nature. Recently, the Tropical Diseases Program of the World Health Organization (TDR/WHO) with the Drug Discovery Research Program has considered a priority the pharmacological investigation of plants [80]. Extensive studies of activity of natural products against *Leishmania* during the last years have been accumulated. Recently, the most advances in this field have been excellent reviewed [79-81], which have listed plants and natural-product derived that showed some level of antileishmanial activity.

Some studies revealed the search of new products in microorganism or marine sources, such as a glycoprotein isolated from the sponge *Pachymatisma johnstonii*, which showed a high activity *in vitro* against *L. donovani*, *L. braziliensis* and *L. mexicana* [82], and aphidicolin a fungal metabolite isolated from *Nigrospora sphaerica*, which inhibited the growing of promastigotes and amastigotes of *L. donovani* [83]. Nevertheless, the plants have been the source

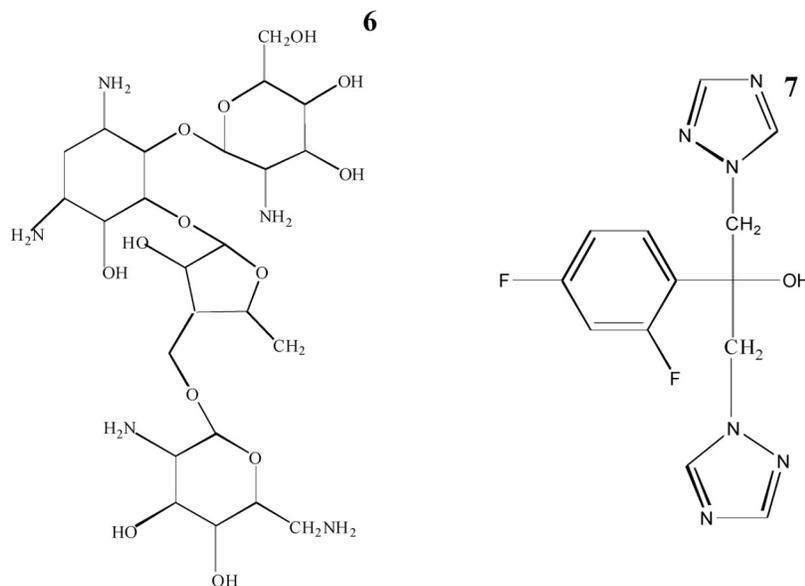
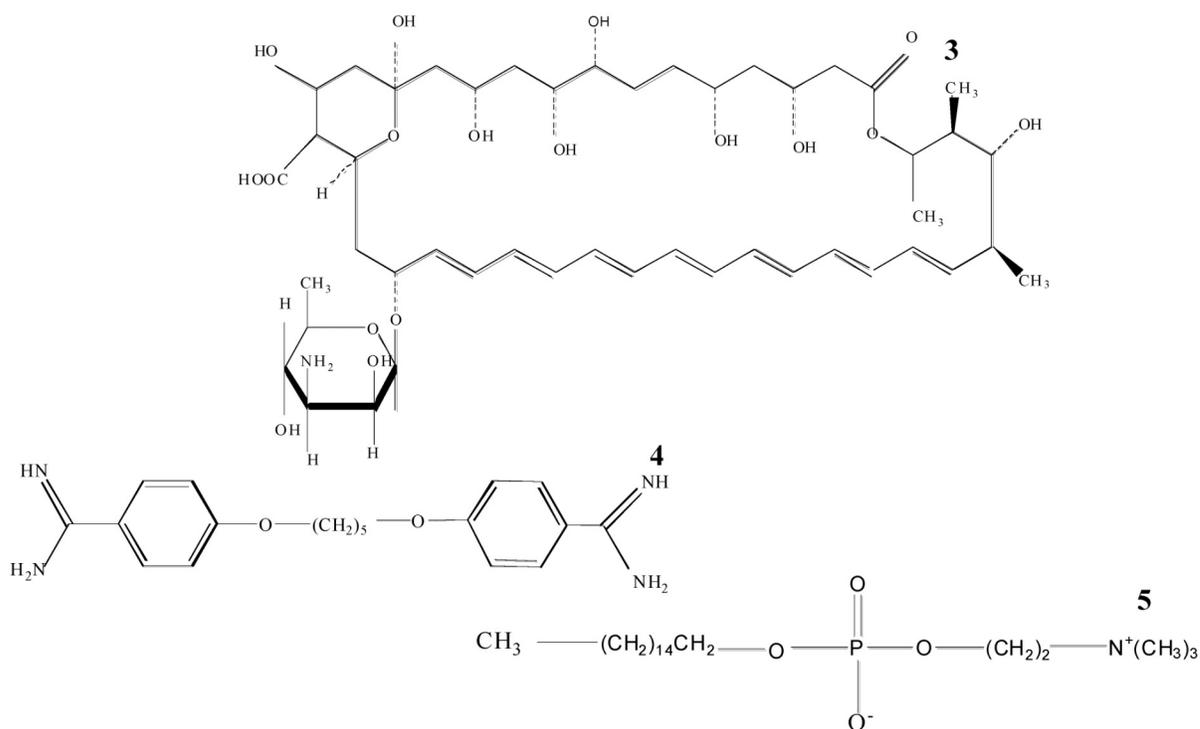
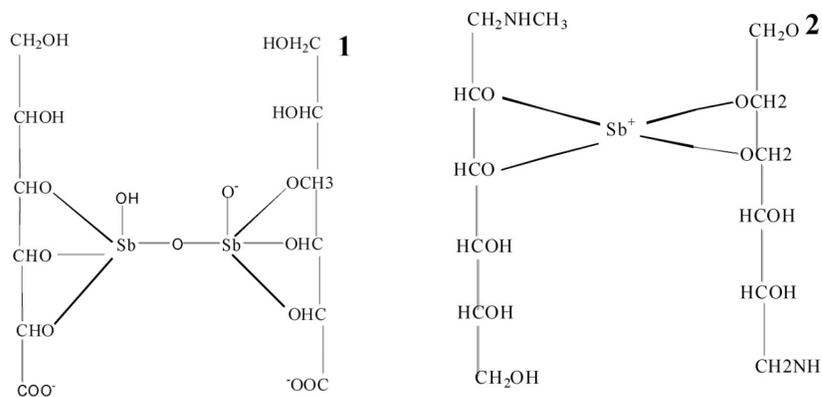
more explored. Studies about the evaluation of plants extract from different geographic areas have been reported. Brazilian [84], Mexican [85], Colombian [6] and Peruvian [86] flora extracts showed the antileishmanial activity of plants used by people from endemic areas of Latin America.

The antileishmanial activity of essential oil have been evaluated and details have been reviewed by Antony and col. [87]. The oil of *Croton cajucara*, a plant used in folk Brazilian medicine, causes the inhibition of *L. amazonensis* and increased the nitric oxide production [88]. Nerolidol is a compound present in the essential oils of some plants and inhibits the *in vitro* growing of *L. amazonensis*, *L. braziliensis* and *L. chagasi*. Their mechanism of action could be the inhibition of earlier steps of ergosterol synthesis [89].

Other advanced studies have been evaluated potential compounds isolated from natural source, which displayed antileishmanial activity. Table 2 recompiles some of the most promising products isolated from natural sources.

Table 2. Natural Product that Showed Antileishmanial Activity

Compound	Natural Source	Antileishmanial Activity	References
2', 6'- dihydroxy-4' methoxychalcone	<i>Piper aduncum</i>	Exhibited <i>in vitro</i> activity against promastigotes and amastigotes of <i>L. amazonensis</i> .	[92]
Canthin-6-one alkaloids	<i>Zanthoxylum chiloperone</i>	Demonstrated <i>in vivo</i> activity in BALB/c mice infected with <i>L. amazonensis</i>	[93]
Coronaridine	<i>Peschiera australis</i>	Showed <i>in vitro</i> activity against promastigotes and amastigotes of <i>L. amazonensis</i>	[94]
Licochalcone A	<i>Chinese licorice</i>	Exhibited activity <i>in vitro</i> and <i>in vivo</i> against <i>L. major</i> and <i>L. donovani</i>	[95]
Maesabalide III	<i>Maesa balansae</i>	Caused <i>in vitro</i> and <i>in vivo</i> activity against <i>L. donovani</i>	[96]
Parthenolide	<i>Tanacetum parthenium</i>	Displayed activity against promastigotes and amastigotes of <i>L. amazonensis</i>	[97]
Plumbagin	<i>Pera benensis</i>	Demonstrated <i>in vivo</i> activity in BALB/c mice infected with <i>L. amazonensis</i> and <i>L. venezuelensis</i>	[98]
Trichothecenes	<i>Holarrhena floribunda</i>	Exhibited antileishmanial activity against promastigotes and amastigotes of <i>L. donovani</i>	[99]



(Fig. 1) contd....

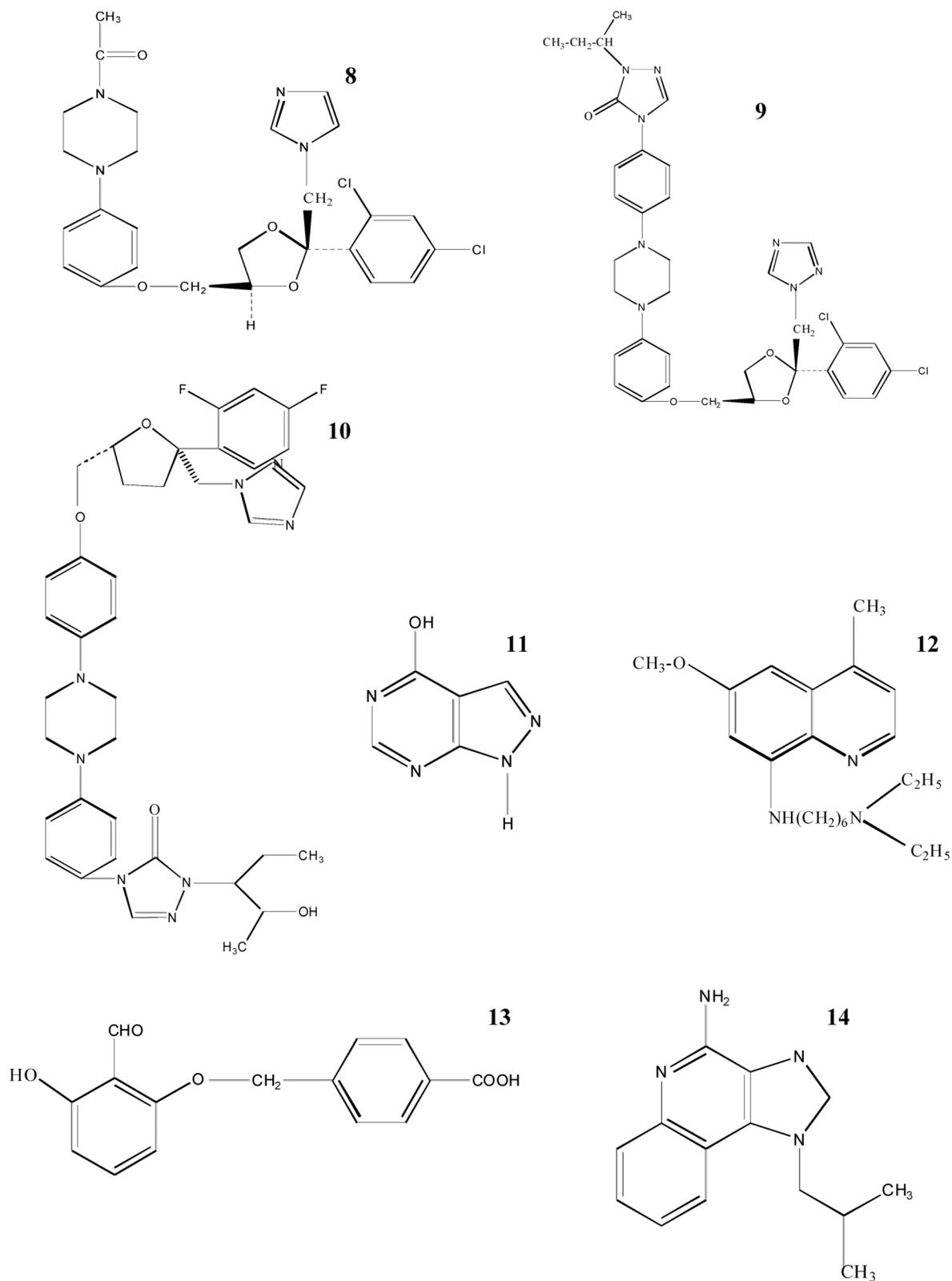


Fig. (1). Antileishmanial compounds clinically used. **1:** Sodium stibogluconate; **2:** Meglumine antimoniate; **3:** Amphotericin B; **4:** Pentamidine; **5:** Miltefosine; **6:** Paromomycin; **7:** Fluconazole; **8:** Ketoconazole; **9:** Itrakonazole; **10:** Posaconazole; **11:** Allopurinol; **12:** Sitamaquine; **13:** Tucaresol; **14:** Iminoquimod.

Unfortunately many studies failed due to the toxicity of the compounds against mammalian cells, low tractability or it's complicate to obtain or modify by synthetic ways [78].

CURRENT & FUTURE DEVELOPMENTS

The leishmaniasis is a public health problem in many countries of the World. Currently, the chemotherapy is the main weapon to combat the infection. Some drugs are commercially available such as pentavalent antimonial, amphotericin B, pentamidine, miltefosine, aminosidine, azole derivatives, lloporinol, sitamaquine and immunomodulators. New formulations of lipid-associated of amphotericin B and ointments with aminosidine have been under evaluation in clinical trials that has given promising therapeutic options together with the combination of recommended drugs. However, the advances in the pharmacology of leishmaniasis are under constant change due to the needing to search better drugs. The research based on (a) knowledge about genome of parasite, (b) information of drug used for other infection or pathologies, (c) the synthesis of new compounds using rational design of drugs and (d) compounds isolated from new natural sources; can give a solution more efficient and available to treatment of leishmaniasis.

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