Acta Tropica 221 (2021) 105988

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

An appraisal of the scientific current situation and new perspectives in the treatment of cutaneous leishmaniasis

C.A. Briones Nieva [a], Alicia Graciela Cid [a], Analía Irma Romero [a], María Fernanda García-Bustos [b], Mercedes Villegas [a], José María Bermúdez [a,*]

[a] Instituto de Investigaciones para la Industria Química, Universidad Nacional de Salta - Consejo Nacional de Investigaciones Científicas y Técnicas, Av. Bolivia 5150, (4400) Salta, Argentina

[b] Instituto de Patología Experimental, Universidad Nacional de Salta - Consejo Nacional de Investigaciones Científicas y Técnicas, Salta, Argentina

ARTICLE INFO

Keywords:
Cutaneous leishmaniasis
Improved treatment
Current therapy
In vivo assay

ABSTRACT

Leishmaniasis is a Neglected Tropical Diseases caused by protozoan parasites of the genus *Leishmania*. It is a major health problem in many tropical and subtropical regions of the world and can produce three different clinical manifestations, among which cutaneous leishmaniasis has a higher incidence in the world than the other clinical forms. There are no recognized and reliable means of chemoprophylaxis or vaccination against infections with different forms of leishmaniasis. In addition, chemotherapy, unfortunately, remains, in many respects, unsatisfactory. Therefore, there is a continuing and urgent need for new therapies against leishmaniasis that are safe and effective in inducing a long-term cure. This review summarizes the latest advances in currently available treatments and improvements in the development of drug administration. In addition, an analysis of the *in vivo* assays was performed and the challenges facing promising strategies to treat CL are discussed. The treatment of leishmaniasis will most likely evolve into an approach that uses multiple therapies simultaneously to reduce the possibility of developing drug resistance. There is a continuous effort to discover new drugs to improve the treatment of leishmaniasis, but this is mainly at the level of individual researchers. Undoubtedly, more funding is needed in this area, as well as greater participation of the pharmaceutical industry to focus efforts on the development of chemotherapeutic agents and vaccines for this and other neglected tropical diseases.

1. Introduction

According to a conservative estimate, there are more than 65000 species of protozoa (Pelczar et al., 1993). Although only a few species cause diseases in humans, they can produce considerable damage to human health. In particular, in the low-income population, parasitic diseases are one of the main causes of human misery and death in the world. In response to this critical situation, the World Health Organization (WHO) has established a special research program on the most important parasitic diseases such as leishmaniasis, malaria, schistosomiasis, and trypanosomiasis. Regarding leishmaniasis, the main objectives of the scientific working group are strongly oriented towards epidemiology and development of vaccines, without neglecting the study of new effective drugs along with improving therapeutics with existing ones (Croft and Coombs, 2003; WHO, 1975).

Leishmaniasis is a Neglected Tropical Disease caused by kinetoplastid protozoan parasites belonging to the genus *Leishmania* (Fraga et al., 2013; WHO, 2010), being a major health problem in many tropical and subtropical regions of the world. This disease is endemic in 98 countries and represents a serious threat to approximately 310 million people living in endemic regions of affected countries (Información general: Leishmaniasis. WHO). It is one of the main parasitic diseases in the developing world, as well as in underdeveloped countries. In the Americas, in particular, it occurs with great magnitude and wide distribution. In addition, the main risk factors, which are the result of local social, economic and environmental processes, increase exponentially the number of the population at risk of infection. As a consequence of the medical complexity of this disease, the general tools and guidelines for the management of cases of leishmaniasis, from clinical suspicion to follow-up after therapy, are scarce or incomplete, and when available, can only be applied regionally. For this reason, leishmaniasis is not recognized and prioritized at the level of public health policy, and its visibility is eventually not proportional to its true impact.

Since leishmaniasis is classified as a zoonosis, animal vectors

* Corresponding author.
E-mail addresses: josemariabermudez@gmail.com, jbermudez@unsa.edu.ar (J.M. Bermúdez).

https://doi.org/10.1016/j.actatropica.2021.105988
Received 24 February 2021; Received in revised form 23 May 2021; Accepted 24 May 2021
Available online 28 May 2021

transmit the parasites causing most forms of the disease, however, some have been reported to be transmitted between humans (Torres-Guerrero et al., 2017). Its complex biological cycle (Fig. 1) includes different stages of the parasite, both in reservoirs and in vectors, which cause a set of clinical syndromes in the infected human that compromise the skin, mucous membranes and viscera.

Leishmaniasis includes a group of diseases, which are often classified according to the world regions in: Old World (OW) leishmaniasis, existing in the Eastern Hemisphere and endemic in Asia, Africa, and southern Europe; and New World (NW) leishmaniasis, endemic in the Western Hemisphere, extending from south-central Texas to Central and South America (except Chile and Uruguay) (Kevric et al., 2015). *Leishmania* parasites are transmitted by infected female sandflies of the genus *Lutzomyia* in the New World, and *Phlebotomus* in the Old World. Out of 53 described species of *Leishmania* parasites, 20 are known to cause human pathogenesis (Fig. 2) and may produce three different clinical manifestations, which are cutaneous (CL), mucocutaneous (MCL), and visceral (VL) leishmaniasis that differ in their immunopathologies and degree of morbidity and mortality. It is estimated that approximately 0.7–1.2 million of new CL and 0.2–0.4 million of new VL cases occur each year in endemic countries (Tiwari et al., 2019). According to the global analysis of the burden of infectious diseases, leishmaniasis in its different clinical forms is responsible for 2.35 million years of life adjusted for disability (DALYs).

Effective, affordable and easy-to-use medications for leishmaniasis treatment are currently lacking. Until its appearance as a co-infection of HIV / AIDS, leishmaniasis was not perceived as a direct threat to industrial countries (Dujardin et al., 2008). There are no recognized and reliable means of chemoprophylaxis or vaccination against infections with different forms of leishmaniasis. In addition, chemotherapy, unfortunately, remains, in many respects, unsatisfactory (Leishmaniases and World Health, 1990). It is necessary to emphasize that leishmaniasis have the characteristic of being a hidden problem since many patients live in remote areas with poor access to health services and urbanization.

The typical clinical presentation of CL is a localized, non-healing, often ulcerative skin lesion. Less common CL presentations include nodular, psoriasiform, and verrucous forms. Other unusual cutaneous syndromes include diffuse CL, disseminated CL, post–kala-azar dermal leishmaniasis (PKDL), and leishmaniasis recidivans (LR). In the New World, a primary cutaneous lesion that may be co-existent with or followed months to years later by destructive nasopharyngeal lesions ("espundia") characterizes MCL. VL (Kala-azar) is classically

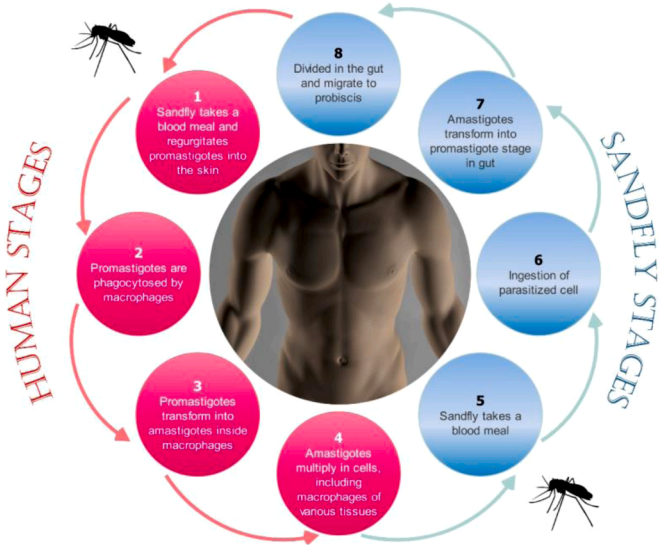

Fig. 1. The *Leishmania* life cycle.

Fig. 2. Species of *Leishmania* parasite that cause human pathogenesis.

characterized by fever, wasting, pancytopenia, hepatosplenomegaly (especially splenomegaly), and hypergammaglobulinemia. With "incomplete," or atypical, syndromes, in which one or more of these clinical features are missing, sub-clinical and asymptomatic VL are common (Aronson and Magill, 2020).

The process of development, progression and resolution of the lesions varies according to the species of infection and the immune status of the patient, but generally, it involves the next steps. A macula initially appears at the bite site, which then evolves into a papule. The lesion continues growing and a nodule develops, produced by dermal mass containing vacuolated macrophages with abundant *Leishmania* parasites and a lymphocytic infiltrate. The nodule grows in size and necrosis occurs at the center of the granulomatous reaction, causing ulceration. Finally, when the body eliminates parasites, because either the immune response was effective or through the action of a specific treatment, the process of resolving the lesion (scarring) involves the production of collagen and metalloproteases of the extracellular matrix. In this way, tissue regeneration occurs by the migration and proliferation of fibroblasts and keratinocytes to the affected tissue (Reithinger et al., 2007b).

Although not fatal, CL is treated to accelerate healing and reduce scarring, especially in cosmetic sites, and to prevent parasite dissemination or relapse. The WHO divides its recommendations according to OW and NW CL, and in turn subdivides them into local and systemic treatment, identifying the type of host-parasite (WHO 2010). Treatment is commonly given for persistent (>6 months' duration), multiple or large lesions, and for lesions located in joints or face. However, treatment should be considered for NW CL, since the disease has a low spontaneous cure rate and late treatment could possibly lead to an increased risk of late mucosal involvement. The main challenges in the treatment of CL are that clinical diagnosis is difficult in the absence of microscopy at the basic healthcare level and that pentavalent antimonial (PA) drugs, the first-line treatment, in addition to being very expensive, can have serious, although usually reversible, side-effects, and are of variable efficacy against MCL (Reithinger et al., 2007a). Other current therapies for CL include pentamidine (PMD), miltefosine (MLF), paromomycin (PMM), and amphotericin B (AmpB) and treatment approaches range from local therapy, including topical treatments and

intralesional injections, to systemic therapy. Molecular structures of some of the most common drugs used in CL treatment are shown in Fig. 3.

These drugs are associated with various shortcomings like toxicity, efficacy, side effects, drug resistance, high cost, and requirement of prolonged administration (Tiwari et al., 2019). The Table 1: Therapeutic regime, administration route and side effects of drugs currently used for CL. summarizes the drugs, their therapeutic regimen, administration route and most relevant side effects.

Although local therapy still lacks sufficient evidence to support its widespread use in public health, it is recommended in specific situations and when the treating health professional considers that benefit to the patient outweighs the risk. Local therapies, including thermotherapy or cryotherapy with or without local infiltration with antimonials, as well as PMM ointment, are options with less systemic toxicity but variable efficacy. Treatments based on local infiltration using PAs reach the highest concentrations at the lesion site, but unfortunately, they are not effective for metastatic leishmaniasis. Moreover, intralesional infiltrations are painful and can produce local irritation and inflammation. Localized methods are usually recommended for patients with *L. mexicana* or *L. major* infections, or with small and few lesions. On the other hand, systemic treatments, such as MLF, PA, PMD, or AmpB formulations, are generally recommended for more complicated cases, for those who do not respond to topical treatments, for immunosuppressed patients, and for cases in areas where progression to mucosal leishmaniasis is prevalent (Caridha et al., 2019).

Emerging resistance mechanisms in well-established key targets are affecting the use of current drug treatment options, leading to treatment failure. The reasons for the emergence of resistance may be explained by the widespread misuse of the drugs, including smaller doses at the beginning of the treatment or drug-free periods to minimize toxicity, which leads to subtherapeutic drug levels and increased tolerance of parasites (Chakravarty and Sundar, 2010). Therefore, the development of new anti-leishmanial compounds with alternative and efficient mechanisms of actions is required to eradicate this disease (Kapil et al., 2018).

In recent years' improvements have been made in the treatment of CL. New drug delivery systems and new treatment regimens have been designed and applied. This review summarizes the latest advances in currently available treatments and improvements in the development of drug administration. In addition, an analysis of the *in vivo* assays was performed and the challenges facing promising strategies to treat CL are discussed.

2. Literature analysis and search design

An advanced literature search was performed in three of the most relevant scientific databases, ScienceDirect, Wiley and PubMed, using the search terms: "cutaneous leishmaniasis" AND "treatment" or "cutaneous leishmaniasis" AND "therapy" in the fields "Title, abstract or author-specified keywords" or "Title", according to the database. Articles in English, French and Spanish since 2015 were selected.

The scientific articles were selected by applying a three-steps procedure. Articles without abstract were excluded in the first step. After that, publications were classified into five topics: 1) Improve current drugs; 2) Photodynamic therapies; 3) Natural products; 4) Molecular targets; and 5) Others. Articles classified as "Others" and repeated publications were excluded, arriving at the summary shown in Fig. 4. Finally, all the literature was reviewed and the information was reorganized and descriptively summarized.

3. Improvements of current treatments

Treatment options for CL are selected taking into account several aspects such as clinical manifestations, number and location of lesions, *Leishmania* species, geographic location, general condition of the patient, availability of medications, among other factors that must be carefully evaluated. The treatment scheme used for these pathologies is often long and painful, which can lead to abandonment of treatment. In addition, if we consider that the cure is difficult to achieve in many cutaneous and mucocutaneous forms, the result will probably be therapeutic failure.

In this section, the improvements of the current therapies mentioned in the introduction are reviewed, such as the encapsulation of drugs, the combination of therapies, the supplementation with different complex, the combination with natural products like essential oils, or the

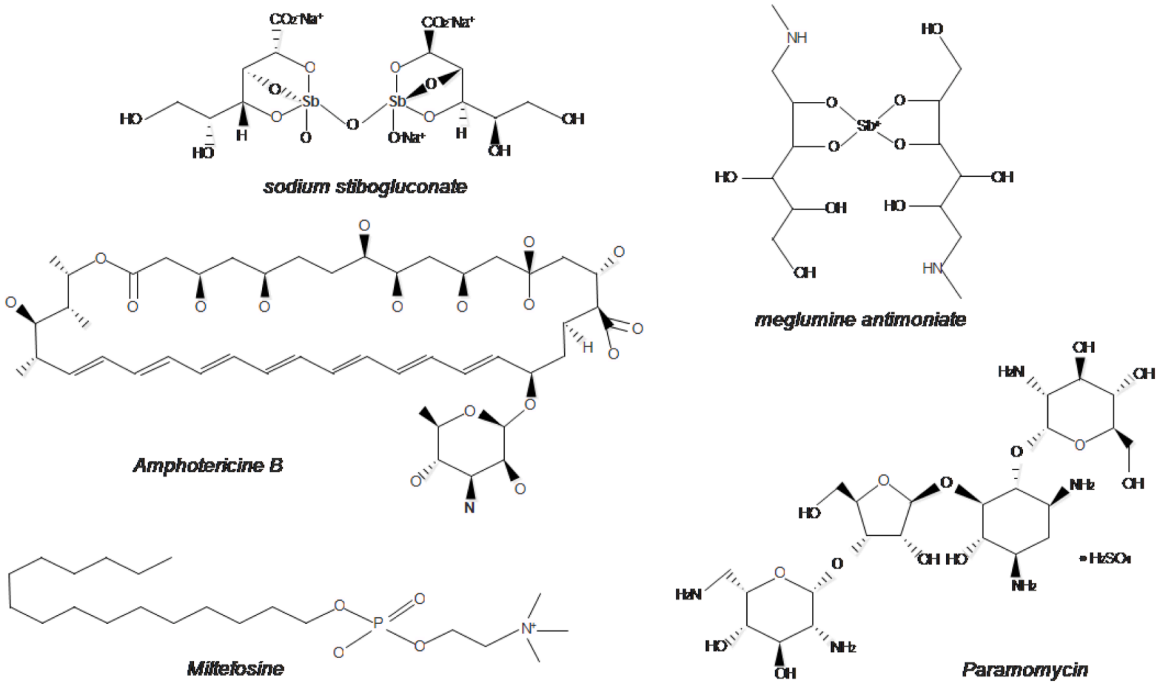

Fig. 3. Chemical structure of drugs used for the treatment of leishmaniasis

Table 1
Therapeutic regime, administration route and side effects of drugs currently used for CL.

Drug	Therapeutic regimen	Administration route	Species	Side effects
Pentavalent antimonials	Intralesional: 1–5 ml per session every 3–7 days (1–5 infiltrations). 20 mg Sb^V/kg per day intramuscularly or intravenously for 10–20 days (for 60 days or longer to treat diffuse cutaneous leishmaniasis).	Intralesional Intravenous or intramuscular	All species. All species but *L. mexicana*	Cardiotoxicity, hepatotoxicity, pancreatitis, reversible renal failure, anemia, leukopenia, thrombocytopenia, abdominal pain, nausea, vomiting, blood disorders and painful injection
Amphotericin B	Deoxycholate: 0.7 mg/kg per day, by infusion, for 25–30 doses Liposomal: 2–3 mg/kg per day, by infusion, up to 20–40 mg/kg total dose	Intravenous Intravenous	*L. braziliensis L. braziliensis*	Fever, nausea, vomiting, anemia, hypokalemia, nephrotoxicity, hepatotoxicity, cardiotoxicity, hypersen-sitivity and anaphylaxis
Miltefosine	2.5 mg/kg per day orally for 28 days	Oral	*L. mexicana L. guyanensis L. panamensis*	Vomiting, diarrhea, toxicity in the gastrointestinal system, toxicity in the hepatic system, toxicity in the renal system, thrombophlebitis and hemolysis
Paromomycin	15% paromomycin/12% methylbenzethonium chloride ointment twice daily for 20 days 15 mg (11 mg base)/ kg per day intramuscularly for 60 days or longer to treat diffuse cutaneous leishmaniasis (together with pentavalent antimonial treatment as above)	Topical Intramuscular	All species *L. aethiopica*	Toxicity in the gastrointestinal system, ototoxicity, hepatotoxicity, vestibular instability and nephrotoxicity
Pentamidine	Pentamidine isethionate: intramuscular injections or brief infusions of 4 mg salt/kg per dose every other day for 3 doses.	Intramuscular injections or brief infusions	*L. guyanensis L. panamensis*	Nephrotoxicity, hypoglycaemia, arrhythmias, ventricular tachycardia, injections-site reactions, dizziness, severe hypotension, syncope, rash, gastrointestinal disturbances and abnormal liver function test

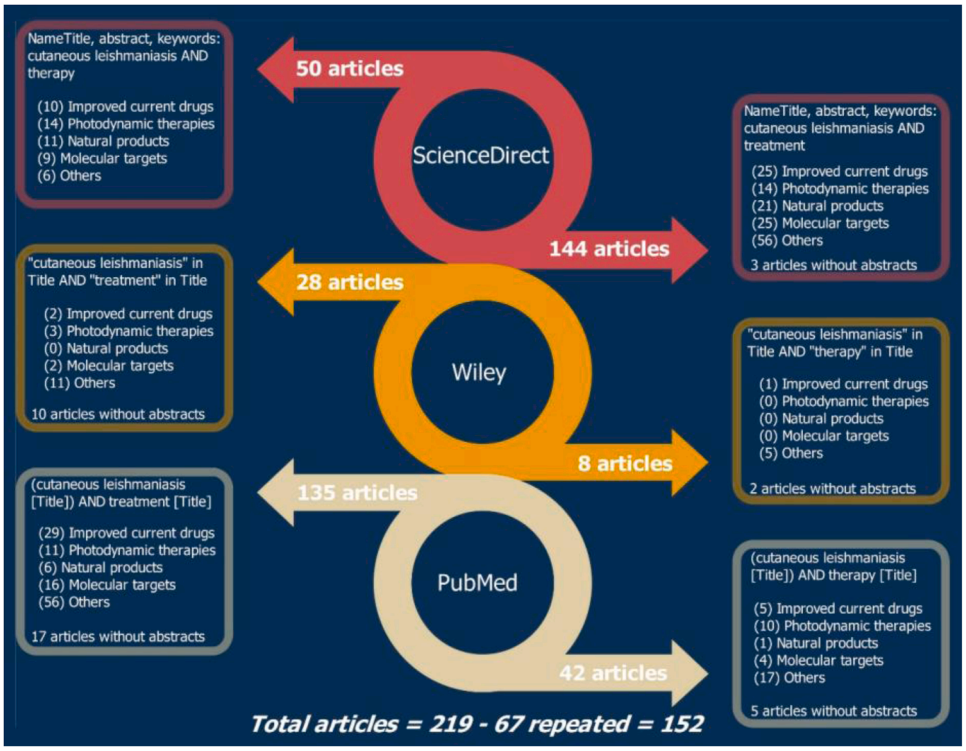

Fig. 4. Process of articles' selection.

administration using different doses and time treatments.

3.1. Pentavalent antimonials

Antimonials are considered the first-line drugs in leishmaniasis treatment and are available as brand-name products, for example Glucantime® (meglumine antimoniate) and Pentostam® (sodium stibogluconate), or in generic forms, like antimony and sodium gluconate. Their mechanism of action is not well understood, but it is probably multifactorial, acting directly on the molecular processes of the parasite, as well as influencing the parasiticidal activity of macrophages (Baiocco et al., 2009).

Glucantime® and Pentostam® are usually used alone in systemic therapy and sometimes in combination with other agents. These drugs require long administration periods (up to 15 days) and are very toxic to human. The half-life of Sb^V in blood after Pentostam® or Glucantime® administration is only 2 hours and most of it (81-97%) is excreted within 6-8 hours. Despite the fast excretion of antimonials, there is a slight accumulation of Sb^V in tissues (Sharma and Anand, 1997).

In recent decades, an impulse to improve therapeutic results, patient compliance, and lower total cost of treatment has put technology at the service of developing new drug carrier systems. Many researchers are working in the development of carriers to improve the way of administration and lower the toxic effects of this drug, for example using colloidal systems (Aragão Horoiwa et al., 2020), gel-based formulations (Berenguer et al., 2019), hydrophobic wound dressing (Pereira et al., 2020) or liposome encapsulation (Moosavian et al., 2019) for topical treatment. In this regard, an interesting study was conducted by

Mostafavi et al., who evaluated the efficacy of Glucantime® and AmpB encapsulated in niosome against CL using *in vitro* and *in vivo* models (Mostafavi et al., 2019). They reported a synergistic effect between both drugs in niosomal form in the inhibition of intracellular and extracellular forms of *L. tropica,* and the in vivo results on *L. major* suggested that topical niosomal formulation could be useful in the treatment of CL.

Another interesting approach includes the use of adjuvants to help the immune system. In this regard, Guzman-Rivero et al. found that zinc supplementation improved the immune response in patients with CL treated with antimony (Guzman-Rivero et al., 2015). Farajzadeh et al. compared the efficacy of intralesional injection of zinc sulphate 2 % solution with intralesional Glucantime® in the treatment of acute CL, concluding that both treatments were equally effective (Farajzadeh et al., 2016a). Two years later, they reported that the use of Glucantime® plus niosomal zinc sulphate had the same efficacy as Glucantime® plus cryotherapy, being this option painless and without risk of skin necrosis (Farajzadeh et al., 2018).

The association of N-methyl glucamine antimoniate with photodynamic therapy with topical liposomal chloroaluminium phthalocyanine was also evaluated, showing the same efficacy as the standard treatment but with a lower Sb^V dose (Ribeiro et al., 2019).

Farajzadeh et al. observed that the use of topical terbinafine in combination with Glucantime® was clinically more effective in the treatment improvement rate, although it depended on the type of lesions (Farajzadeh et al., 2016b). In another study, higher potency and synergistic effect of methotrexate on meglumine antimoniate were reported in inhibiting the growth rate of promastigote and amastigote stages of sensitive and meglumine antimoniate-resistant *L. tropica* (Mahmoudvand et al., 2017).

Other promising results were found when combining antimonials with drugs intended for other diseases, for example, antifungals and antiparasitics, such as amiodarone and itraconazole (Anversa et al., 2017), levamisole (Bamorovat et al., 2019) and oxiranes (epoxy-α-lapachone and epoxymethyl-lawsone) (Gonçalves-Oliveira et al., 2019), as well as the anticancer drug tamoxifen (Machado et al., 2018) (Trinconi et al., 2018). Añez et al. proposed as an alternative treatment the intralesional infiltration of a generic pentavalent antimonial compound combined with lidocaine, based on the successful results in a study including 122 lesions caused by *L. braziliensis* (Añez et al., 2018) Shanehsaz and Ishkhanian found a good response to a treatment based on a lower dose of systemic meglumine antimoniate supplemented with oral cimetidine, although it was less effective than the standard dose (Shanehsaz and Ishkhanian, 2015).

On the other hand, only three articles were found about sodium stibogluconate. Dar et al. evaluated the efficacy of sodium stibogluconate co-loaded with ketoconazole in nano-elastic liposomes, concluding that this system could be a promising approach for the topical treatment of CL (Dar et al., 2020b). An alternative treatment option for pediatric patients consisting of sodium stibogluconate after fractional ablative carbon dioxide laser was proposed by Hilerowicz et al. (Hilerowicz et al., 2018), whereas Thacker et al. reported that CpG ODN D35 improved the response to abbreviated low-dose sodium stibogluconate treatment (Thacker et al., 2020).

3.2. Amphotericin B

AmpB is a naturally occurring antifungal isolated from *Streptomyces nodosus*. Its antileishmanial activity attributed to its selective affinity for ergosterol vis-a-vis cholesterol was discovered in the early 1960s (Ramos et al., 1996).

There are currently different strategies for AmpB administration, which include the conventional AmpB deoxycholate and three lipid formulations: liposomal amphotericin (AmBisome), amphotericin lipid complex (Abelcet) and amphotericin colloidal dispersion (Amphocil) (Cifani et al., 2012). Although the side effects produced by AmpB deoxycholate are also caused by liposomal AmpB, they occur much less frequently for the latter, allowing higher doses (Domingues Passero et al., 2013). In contrast to MLF and PA, AmpB is commercially available in most countries and is approved for use during pregnancy. The high cost and adverse effects of liposomal AmpB are the major limiting factors in its administration, in addition to its poor gastrointestinal absorption and short circulating half-life, rapidly reaching its highest concentrations in liver and spleen (Akbari et al., 2017). Both formulations of the AmpB, the deoxycholate and the liposomal, have been used clinically for leishmaniasis treatment (Barratt and Legrand, 2005).

Although AmpB and its lipid form have effectively served as the therapeutic mainstay against leishmaniasis, recent reports in their limitations have prompted the evaluation of alternative therapeutic modalities. Due to adverse effects, novel and safe dose of AmpB have been tested, ranging from nanoparticles to implants and emulsions.

Most of the research related to AmpB aims to develop effective drug carrier vehicles using different strategies. In this regard, studies were conducted to develop local therapies based on poly(lactic-co-glycolic acid) nanoparticles (Abu Ammar et al., 2019) and microparticles (Sousa-Batista et al., 2019) loaded with AmpB. Casa et al., investigated the antileishmanial activity of bovine serum albumin nanoparticles containing AmpB against *L. amazonensis* (Casa et al., 2018). Although commercial AmpB was more effective than nanoparticles against PM and AM, both formulations showed a significant decrease in the skin lesion, while the nanoparticles containing AmpB did not reveal tissue toxicity, making them a potential candidate for treating CL. Different authors developed and evaluated liposomal or nanoliposomal formulations containing AmpB (Eskandari et al., 2018; Jaafari et al., 2019: Perez et al., 2016; Varikuti et al., 2017; Wijnant et al., 2018) for topical treatment. Pinheiro et al. studied the therapeutic potential *in vivo* of an AmpB + oleic acid emulgel in an experimental model, concluding that it showed good prospects as an alternative therapy for CL (Pinheiro et al., 2016). Two years later, a topical emulsion of AmB was developed using readily available ingredients like canola oil, hydroxypropyl methylcellulose, carbopol and Tween 80 (Ishaq et al., 2018). An *in vitro* anti-leishmanial assay of these emulsions showed 50% killing rate at 0.2 μg/ml of AmB and 100% mortality with emulsions containing 20 μg/ml of AmB, showing its high potential for topical infections. Another interesting approach was made by Nguyen et al., who developed a microneedle based delivery system for AmpB and found promising results of the topical delivery in treating relatively small nodules caused by *L. mexicana*, although the microneedle showed limitations against a disseminated *L. major* infection (Nguyen et al., 2019). Hydrogels were also tested as carriers for AmpB and reported as an efficient new therapeutic approach for the topical treatment of CL (Alexandrino-Junior et al., 2019).

Other studies were focused on testing alternative formulations containing AmpB for local application, such as creams (López et al., 2018), or changing the administration regimen and dose (Goswami et al., 2019), mainly to minimize the toxicity and adverse effects.

Meanwhile, there are also reports on its combination with other compounds, including natural products like bacuri butter (Coêlho et al., 2018), the antileishmanial drug MLF (Dar et al., 2020a) and novel approaches, such as chitosan platelets (Malli et al., 2019). On the other hand, it should be mentioned that despite not being the drug of first choice for the treatment of CL, there are a large number of scientific reports on its use, possibly due to its simple quantification that allows for more complete *in vitro* tests, including release profiles and determination of the pharmacokinetics during the development of new formulations. Moreover, the efficiency of pentavalents for getting rid of the parasites is only around 60%, while it is 85% for AmpB.

3.3. Miltefosine

MLF, an alkyl phospholipid compound that was originally developed as an anticancer drug, is the first effective oral treatment for VL. This drug acts by affecting the phospholipid metabolism of the plasma

membrane of the parasite or by affecting the mitochondrial membrane potential leading to apoptosis-like cell death (Kapil et al., 2018). It is the first non-parenteral drug it does not require hospitalization, and in general, clinical results using oral MLF have been satisfactory.

Misuse of MLF, its long half-life (7 days) and the inactivation of genes responsible for drug uptake are the main three reasons in resistance development against MLF. This compound should be administered IV in the patients with gastrointestinal disorders, but this route of prescription is limited, because of adverse side effects such as thrombophlebitis and hemolysis. Reports of failure in treatment and relapse in some cases treated with this drug have also been observed. Additionally, MLF is teratogenic and should not be administered in pregnant women and people of childbearing age (Akbari et al., 2017). All this can explain the low volume of researches on this drug.

The investigations are mainly oriented to the combination of MLF with other drugs. The interaction of MLF and apigenin was evaluated *in vitro* and *in vivo*, concluding that the combination therapy using low doses of these two drugs resulted in good clinical and parasitological responses (Emiliano and Almeida-Amaral, 2018). Another study on the development and evaluation of novel MLF-polyphenol co-loaded second-generation nano-transfersomes for the topical treatment of CL was carried out (Dar et al., 2020c). A synergistic interaction was observed between MLF and apigenin, among different polyphenols, with an 8.0-fold lower IC_{50} and a 9.5-fold reduced parasitic burden in the *L. mexicana* infected BALB/c mice.

The improved anti-leishmanial efficacy of MLF and ketoconazole loaded on nanoniosomes was reported by Nazari-Vanani et al. (Nazari-Vanani et al., 2018) On the other hand, a study evaluating the use of azithromycin alone or in combination with MLF concluded that this antibiotic can be an alternative oral treatment for CL, but although the combination therapy induced dramatic clinical improvement, relapse rapidly developed after cessation of therapy (Amer et al., 2016), Trinconi et al. found that tamoxifen was able to hinder the emergence of MLF resistance (Trinconi et al., 2016). Finally, one research was aimed at developing liposomes containing the drug for topical application (Kavian et al., 2019), reporting that topical liposomes loaded with MLF showed optimal ex vivo penetration and *in vivo* anti-leishmanial activity against CL caused by *L. major* when compared to MLF cream and other liposomes.

3.4. Paromomycin and pentamidine

PMM is a second-line drug whose antileishmanial activity has been more recently identified. It is a broad-spectrum aminoglycoside isolated from *Streptomyces krestomuceticus*, used to treat intestinal infections, whose effective activity against a wide range of bacteria and protozoa has been demonstrated (Esfandiari et al., 2019). This pharmacologic agent has been used in various topical formulations for the treatment of CL (Laboudi et al., 2018). A possible mechanism of action is based on its ability to bind the 30S subunit of ribosome, leading to inhibition of protein synthesis. Another explanation is that it binds to the disrupted mitochondrial membrane potential that ultimately causes apoptosis-like cell death (Kapil et al., 2018). This drug is not teratogenic or mutagenic and its low cost makes it the most inexpensive available antileishmanial agent (Esfandiari et al., 2019). The main limitations of this drug are associated with its low absorbance (nearly 100% is recovered from feces) and the lack of adequate reports on its use in pregnant women (Weiner and Mason, 2019).

Intending to give an impulse to expand the reach of PMM, One World Health, the Bill and Melinda Gates Foundation, Gland Pharma Limited, International Dispensary Association Solutions and the WHO Special Program for Research and Training in Tropical Diseases partnered to develop a PMM injection as a public health tool to be sold on a not-for-profit basis at a very low price. In phase III clinical trial, 94.6 % of patients treated with its injection were cured of VL. PMM injection was approved on August 31, 2006 for treatment of VL in India (Sundar and Chatterjee, 2006). Despite its remarkable advantage over other drugs targeting leishmaniasis, only two PMM reports on CL were found in the last years. One study evaluated the use of PMM in combination with chloroquine (Wijnant et al., 2017). and although the coadministration of the drugs resulted in a significant reduction in the lesion in murine models, there were no differences in the parasite load compared to PMM alone, and therefore, authors concluded that this combination therapy is unlikely to be a potential candidate for further preclinical development. On the other hand, Schwartz et al. reported that the topical application of human anti-TNF-α antibodies in combination with PMM favored lesion healing without blocking parasite elimination in BALB/c mice with CL lesions (Schwartz et al., 2018), concluding that the administration of formulations with both leishmanicidal and antiinflammatory activities could benefit the process of wound healing, which is a major concern in patients to control the local inflammatory response.

PMD is an aromatic diamidine used as its isethionate salt and can be IV or IM injected for leishmaniasis treatment (Rex and Stevens, 2015). During its mechanism of action, this drug undergoes in a rapid active uptake into the protozoal cell, where it binds avidly to transfer RNA and inhibits the ribosomal synthesis of protein, with additional actions on the synthesis of nucleic acids and phospholipids. PMD is metabolized in the liver and has a very long half-life (10–14 days) (Waller and Sampson, 2018). PMD was abandoned as a second-line treatment for VL due to its toxicity and declining efficacy. Probably for this reason there are only two publications based on this drug. One of the studies is aimed at identifying the main factors associated with the PMD treatment failure in patients with *L. guyanensis* (Christen et al., 2018), while the other one evaluated the efficacy and safety of a single, two or three doses of PMD with intervals of a week between doses (Gadelha et al., 2018). These authors found that the cure rates were significantly higher when the patients received two or three PMD doses.

4. Challenges for new therapies

During the development of new drugs, it is difficult to predict their efficacy in human trials, even if they have promising preclinical activity and low toxicity. In some cases, these new formulations are designed to improve drug administration (including nanoparticles) or decrease the toxicity of compounds used in clinical practice (for example, AmpB and antimonials), which has already been developed in the previous section.

Pharmaceutical R&D difficulties have led the scientific community to propose new ways of addressing classical problems. One of the strategies consists of drugs repositioning, which can be summarized as "old drugs for new therapies". This means that agents that are used clinically for other indications are tested against leishmaniasis.

In the absence of a vaccine and taking into account the increasing resistance to pentavalent antimonial drugs, there is an urgent need for new effective drugs to replace or supplement those currently in use. Therefore, the development of new antileishmanial compounds is imperative. In this sense, one of the most interesting contributions is made by nanomedicine, which investigates therapeutics and prophylaxis of leishmaniasis using three-dimensional nanoobjects metal and oxides nanoparticles [NPs], polymeric and lipid NPs, nanocapsules, dendrimers, micelles, liposomes, and other vesicles (Morilla and Romero, 2015). Different and promising therapeutic strategies will be discussed in this section, including some active agents in the experimental phase found during the research.

4.1. Photodynamic therapy

Treatment of intracellular pathogen infections today represents a medical and economic challenge. Microorganisms that remain within cells are resistant to many mechanisms of the immune response and, because they are less exposed to the action of chemotherapeutic agents, they promote the selection of resistant variants. For this reason, other therapeutic approaches are needed, such as PDT, which appears as a

good option for the management of this type of pathogens. Infections such as CL can represent a valuable model to study the possible application of phototherapy in infectious dermatology due to the location of peripheral lesions (Taylor et al., 2011).

PDT, which is an emerging strategy involving the combination of visible light, a photosensitizer, and oxygen, is used for treating a wide variety of diseases such as cancer and infections, including CL. This therapy consists of exciting a photosensitizer with visible light in the presence of molecular oxygen, inducing the formation of reactive oxygen species, which are highly toxic to the target cells.

One of the main limitations of topical treatments arises from the fact that drug penetration and selectivity depend on its physicochemical properties. In this sense, one of the strategies to improve the performance of a photosensitizer as an antileishmanial drug for topical application is to load it in a suitable carrier. In the last five years many works related to the development of different carriers and photosensitizers against *Leishmania* spp. were published (Table 2).

As it can be seen, most research focuses on photosensitizers such as methylene blue, chloroaluminum phthalocyanine, TiO_2 nanoparticles and aminolevulinate derivatives, and anthraquinones as natural photosensitizers. On the other hand, different types of lasers are being studied, which not only help to eliminate parasites, but also improve the aesthetics of the skin.

4.2. Natural products

Currently, attempts are being made to search for new antiparasitic agents worldwide from plants, animals, and microorganisms. In the development of agents against any particular disease, an important feature is the identification of a possible target molecule, which should be enough to affect the fundamental biological pathway(s) to control the growth of pathogens. It is also important that the putative target should be either absent in the host or structurally and functionally different from the host homologue. Although trypanosomatids are eukaryotes, the organization of their cellular machinery is significantly different from the mammalian cells, and therefore, it is possible to identify targets that are unique to these parasites. For this reason, novel chemotherapeutic interventions against leishmanial diseases based on the screening of natural products are under research and development. Specifically, plants are being extensively explored as a source for the discovery of new drugs (Hazra et al., 2017).

Many native plants of traditional medicine are being used to treat CL, and recent clinical trials have shown the efficacy of some of them. In 2017, Odonne *et al.* reviewed the geographical distribution of the use of Amazonian plants for leishmaniasis (Odonne et al., 2017). In another revision, garlic, shallots, wormwood, yarrow, walnuts, thyme, henna plant, mimosa, aloe, betonia wood, loquat, periwinkle, salty and black beans, among others, are listed as effective agents for CL (Bahmani et al., 2015). Table 3 shows natural products whose effects are scientifically proven to be effective in leishmaniasis treatment.

It can be observed that in the last 5 years many spices were tested *in vitro* and *in vivo* for leishmaniasis treatment, including lapachol, aloe, curcumin, olive oil, copaiba oil and many others, as well as different secretions of larvae, fungi and snakes.

4.3. Molecular targets

Recently, different innovative approaches are being used to discover new drug candidates against vector-borne parasitic diseases. Among them, one interesting strategy consists of new indications for existing drugs, which involves researching existing drugs developed for other indications. Some recognized examples are artemisinin, camptothecin, diospyrin, and MLF that were previously discovered against other diseases but later proved to be effective as antileishmanial agents. On the

Table 2
Latest advances in PDT to improve treatment against the CL from 2015 to 2020.

Strategy based on PDT	Specie of *Leishmania*	λ	Fluency	Ref.
TiO_2 nanoparticles doped with Zn and hypericin	*L. amazonensis*	470 nm and 660 nm	52.8 J/cm^2	(Sepúlveda et al., 2020)
liposomes of chloroaluminum phthalocyanine of egg phosphatidylcholine		660 nm	0–95 J/cm^2	(Lopes et al., 2019)
aluminum phthalocyanine chloride, Aluminum phthalocyanine hydroxide and zinc phthalocyanine		630 nm	10 J/cm^2	(Nesi-Reis et al., 2018)
methylene blue		645±10 nm	21.2, 53.1, 106.2 and 265.4 J/cm^2	(Aureliano et al., 2018)
five natural anthraquinones		410±10 nm	36 J/cm^2	(Dimmer et al., 2019)
Pluronics® P-123 and F-127 as nanocarriers		530 nm and 593 nm	NR	(Oyama et al., 2019)
methylene blue	*L. major*	660±5 nm	10 J/cm^2	(Fagundes et al., 2019)
riboflavin derivatives of O-acyl, N-methyl, N-alkylcarboxyalkyl or N-alkyl(trialkyl)ammonium		470 nm	NR	(Silva et al., 2015)
TiO_2 nanoparticles		200–1100 nm	NR	(Dolat et al., 2020)
methylene blue	*L. major* and *L. braziliensis*	660 nm	10 J/cm^2	(Pinto et al., 2017)
Chlorin e6		660 nm	10 J/cm^2	(Pinto et al., 2016)
5-Aminolevulinic Acid.	*L. braziliensis*	440 nm	50 J/cm^2	(Silva et al., 2019)
ultradeformable liposomes loaded with chlorine aluminum phthalocyanine		672±40 nm band-pass	17 J/cm^2	(Escobar et al., 2018)
methylene blue and light-emitting diode		Light-Emitting Diode 655 nm	NR	(Sbeghen et al., 2015)
novel formulation with hypericin	*L. panamensis*	visible light	5 J/cm^2	(Montoya et al., 2015)
calcium phosphate nanostructures with photodynamic properties and support for hypericin		visible irradiation	9 J/cm^2	(Lopera et al., 2018)
fractioned illumination methylaminolevulinate based PDT	NR	NR	90 J/cm^2 in three fractions	(Khan et al., 2020)
pulsed dye laser therapy		585 nm	7 J/cm^2	(Radmanesh and Omidian, 2017)
non-Ablative Fractional 1540 nm		nonablative fractional 1540 nm Er:glass laser	NR	(Taheri et al., 2020)
Continuous Wave CO_2 Laser and Topical Application of trichloroacetic Acid 50%		CO_2 Laser 3 W	NR	(Iraji et al., 2019)
neodymium-Doped Yttrium aluminum Garnet (Nd:YAG) laser therapy		Nd:YAG laser 1064 nm	200 mJ/cm^2	(Omidian et al., 2019)

λ: wave length, NR: not reported

Table 3
Latest advances in new therapies based on natural products to improve treatment against CL from 2015 to 2020.

Plants derivates	Specie of *Leishmania*	IC50	Ref.
lapachol extracted *Tabebuia, Bignoniaceae*	*L. amazonensis*	191.95 μM^{AM} 79.84±9.10 μM^{PM}	(Araújo et al., 2019)
clarified juice of *Euterpe oleracea Martius*		1:30^{AM} 1:40^{PM}	(Da Silva et al., 2018)
Piper angustifolium essential oil	*L. infantum*	1.43 μg/ml^{AM}	(Bosquiroli et al., 2015)
total phenolic fraction of extra virgin olive oil		213.8±22.7 μg/ml^{AM} 335.4±24.7 μg/ml^{PM}	(Koutsoni et al., 2018)
didecyldimethylammonium bromide β-lapachone	*L. major*	0.3±0.2 μM^{AM} 1.9±0.2 μM^{PM}	(Moreno et al., 2015)
seeds of *C. tinctorius*		23.00±0.59 μg/ml^{PM}	(Maleki et al., 2017)
seeds of *P. anisum*		15.00±0.65 μg/ml^{PM}	(Maleki et al., 2017)
seeds of *C. cyminum*		31.00±0.71 μg/ml^{PM}	(Maleki et al., 2017)
Quercus infectoria Olivier extract		10.31 mg/ml^{AM} 12.65 mg/ml^{PM}	(Kheirandish et al., 2016)
aloe-emodin powder		NR	(Dalimi et al., 2015)
cryotherapy + *Juniperus excelsa M. Bieb* cream		NT	(Parvizi and Handjani, 2017)
Caryocar coriaceum ethyl acetate extracts	*L. amazonensis*	5.25±0.46 μg/ml^{PM}	(Tomiotto-Pellissier et al., 2018)
crude extract of *Guatteria latifolia*		30.5 μg/ml^{AM} 51.7 μg/ml^{PM}	Ferreira et al., 2017)
(−)α-bisabolol sesquiterpene alcohol		4.15 μg/ml^{AM} <4.15 μg/ml^{PM}	(Rottini et al., 2015)
Maytenus guianensis bark encapsulated in microparticles of PLGA		0.71 μg/ml^{PM}	(Aragão Macedo et al., 2019)
nanostructured lipid carriers loaded with curcumin	*L. tropica*	190 μg/ml^{AM} 105 μg/ml^{PM}	(Riaz et al., 2019)
TIO2-AG nanoparticles – *Nigella sativa* oil		NR	(Abamor and Allahverdiyev, 2016)
quercetin in stock solution of phosphate-buffered saline with 2% dimetilsufoxide	*L. braziliensis*	NR	(Cataneo et al., 2019)
Cleoserrata serrata extract	*L. mexicana*	6.11 μg/ml^{AM,LD50} 23.2 μg/ml^{PM,LD50}	(Alamilla-Fonseca et al., 2018)
Artemisia annua L. leaf powder	*L. panamensis*	48.07 μg/ml^{AM,EC50}	(Mesa et al., 2017)
copaiba oil into commercial biopolymeric wound dressings	NT	NT	(Pascoal et al., 2017)
alcoholic extract from *Indian podophyllum*	NR	NT	(Sharquie et al., 2015)
Larval secretions	**Specie of *Leishmania***	**IC50**	**Ref.**
Calliphoridae L. sericata and *Sarconesiopsis magellanica* excretions and secretions	*L. panamensis*	72.57±7.22 μg/ml^{AM,LC50} 41.44±2.87 μg/ml^{PM}	(Laverde-Paz et al., 2018)
therapy from *L. sericata* and *Sarconesiopsis magellanica*		NT	(Cruz-Saavedra et al., 2016)
excretions and secretions *L. sericata*	*L. major*	0.84%^{AM}	(Sanei-Dehkordi et al., 2016)
excretions and secretions *C. vicina*		1.36%^{AM}	
Other natural derivates	**Specie of *Leishmania***	**IC50**	**Ref.**
phospholipase A2(Asp49-PLA2) from *Bothrops jararacussu* venom: liposomes	*L. amazonensis*	14.36 μg/ml^{PM}	(de Barros et al., 2016) (de Barros et al., 2018)
biogenic silver nanoparticles by the nitrate reductase enzyme of *Fusarium oxysporium*		NR	(Fanti et al., 2018)
bacterial cellulose membranes containing diethyldithiocarbamate	*L. braziliensis*	284.9 μg/cm^{2,AM}	(Celes et al., 2016)

IC50: half-maximal inhibitory concentration, EC50: effective concentration 50%, LC50: lethal concentration 50%. LD50: lethal dose 50%, AM: amastigotes, PM: promastigotes, NT: not tested, NR: not reported

other hand, another important approach is de novo discovery, which consists of testing new synthetic molecules against several biological systems to determine their activity. Various classes of compounds have been synthesized, namely aryl S, N-ketene acetals, tetrazole compounds, imidazoline and chalcone, among others. Finally, research is underway to develop drugs that target important metabolic pathways. In this sense, specific antileishmanial agents take advantage of differences in the vital metabolic pathways of the host and pathogens and use parasitic enzymes as targets. For example, several tricyclic molecules have been found to inhibit leishmanial trippanothione (Hazra et al., 2017). Table 4 shows the advances made in molecular targets and new indications for existing drugs against CL since 2015.

It can be clearly seen that the tendency for de novo discovery drugs is based on imidazole compounds, quinolone and chalcone. Furthermore, the marked trend in the design and development of new molecules through bioinformatics, although outside the scope of this review, should not be lost sight of. Developing drugs that target important metabolic pathways focus primarily on different types of cell death depending on their mechanisms of action. For example, the ability of different complex metal compounds to inhibit the activity of DNA topoisomerase was described by several authors. Finally, new indications for existing drugs include a variety of compounds ranging from dewormers, antibiotics and antifungals to antiseptics (Daie Parizi et al., 2015).

5. Analysis of *in vivo* animals' studies

The publications studied in this review include experimental trials conducted in more than 2,125 animals and 1,457 volunteer patients. Fig. 5 shows an analysis of the *in vivo* studies performed in animals, classifying them according to the animal species, the infection site, the animal sex and the specie of *Leishmania*.

It can be observed that the most widely used animal species for experimental testing is BALB/c mice, possibly for reasons already known such as availability, ease of use and standardized laboratory procedures. Remarkably, even today the footpad of the mouse continues to be chosen as the second site of infection after the base of tail, despite the fact that the injections in the footpad cause painful inflammation and swelling, unrelieved distress or progressive weakening of the animals. Rodents use the front feet to handle food and the rear feet are considered the main structures that support the ventral weight. Instead, the base of the tail is a weightless structure that does not generate unnecessary discomfort if used as an injection site.

On the other hand, there is a tendency to choose females over male

Table 4
Latest advances in the development of new molecular targets to improve treatment against the CL from 2015 to 2020.

De novo discovery drugs	Specie of *Leishmania*	IC50	Ref.
novel benzoxaborole DNDI-0690	*L. major*	4.56±1.83 $\mu M^{AM,EC50}$	(Van Bocxlaer et al., 2019)
novel nitroimidazole DNDI-6148		2.10±0.4 $\mu M^{AM, EC50}$	
novel aminopyrazoles DNDI-1047		0.24±0.02 $\mu M^{AM,EC50}$	
28 N-benzyl-1H-benzimidazol-2-amine derivatives: 7	*L. mexicana*	0.28±0.02μM^{AM}	(Nieto-Meneses et al., 2018)
2-aryl-quinazolin-4(3H)-ones: 2h		5.29 $\mu M^{AM,EC50}$	(Romero et al., 2019)
seven synthetic aryl thiosemicarbazones: TS06	*L. amazonensis*	18.3±4.04 μM^{AM} 4.8±0.21 μM^{PM}	(da Silva et al., 2017)
quinoline derivative 4-hydrazinoquinoline analog		7.0 $\mu g/ml^{AM}$	(Antinarelli et al., 2018)
3-nitro-2′-hydroxy-4′,6′-dimethoxychalcone radiolabelled		NT	(Sousa-Batista et al., 2018)
lipid-core nanocapsules 3-nitro-2-hidroxy-4,6-dimethoxy chalcone		2.90±0.15 $\mu g/ml^{AM}$	(Escrivani et al., 2020)
trans-chalcone		10.3 μM^{PM}	(Miranda-Sapla et al., 2019)
hyaluronic acid-coated liposomes with quinoxaline derivative LSPN331		14.79±4.99 μM^{AM} 34.59±0.48 μM^{PM}	(de Oliveira et al., 2020)
synthetic chalcones (1-3)	*L. braziliensis*	NT	(de Mello et al., 2016)
cinnamic acid derivatives: s (E)-3-oxo-1,3-dihydroisobenzofuran-5-yl-(3,4,5-trimethoxy) cinnamate		>8.27 μM^{AM} 7.58 μM^{PM}	(Rodrigues et al., 2019)
niodomethyl-N,N-dimethyl-N-(6,6-diphenylhex-5-en-1-yl) ammonium iodide		NT	(Fernandez et al., 2018)
hydrazones having quinoline cores: 6c	*L. panamensis*	0.8±0.0 mg/ml^{AM}	(Coa et al., 2015)
Drugs targeting important metabolic pathways	**Specie of *Leishmania***	**IC50**	**Ref.**
N-benzyl 1-(4-methoxy) phenyl-9H-beta-carboline-3-carboxamide	*L. amazonensis*	NT	(Mendes et al., 2016)
diethyldithiocarbamate in beeswax - copaiba oil nanoparticles		0.55 μM^{PM}	(Mazur et al., 2019)
cis-[$Ru^{II}(\eta^2$-$O_2CC_7H_7O_2)$ $(dppm)_2]PF_6$		NR	(Costa et al., 2019)
binuclear cyclopalladated complex		10.1±2.2 μM^{AM} 13.2 μM^{PM}	(Velásquez et al., 2017)
nanoassemblies of Sb–N-octanoylN-methylglucamide complex		NT	(Lanza et al., 2016)
nitric oxide-loaded chitosan nanoparticles		31.5 μM^{PM}	(Cabral et al., 2019)
CM11 hybrid peptide	*L. major*	9.015 μM^{AM} 6.92 μM^{PM}	(Khalili et al., 2019)
ru-clotrimazole AM162 and AM160 complexes		NT	(Iniguez et al., 2016)
	L. braziliensis	NR	(Nascimento et al., 2019)
ruthenium nitrosyl complex cis-[Ru(bpy)2 (SO3)(NO)](PF6)			
New indications for existing drugs	**Specie of *Leishmania***	**IC50**	**Ref.**
pills of amiodarone	*L. major*	0.7 μM^{AM} 1 μM^{PM}	(Bemani et al., 2019)
topical simvastatin		NT	(Parihar et al., 2016)
systemic simvastatin		NT	(Parihar et al., 2016)
endoperoxides ascaridole	*L. tarentolae*	14.1±9.8 μM^{PM}	(Geroldinger et al., 2017)
buparvaquone	*L. tropica*	0.53±0.21 μM^{AM} 0.15±0.14 μM^{PM}	(Jamal et al., 2015)
fluconazole	*L. braziliensis*	NT	(Prates et al., 2017)
Tamoxifen	*L. amazonensis* (resistant to MLF)	12.66±1.75 $\mu M^{PM,EC50}$	(Coelho et al., 2015)
intralesional or oral chloroquine	NR	NT	(Hanif et al., 2016)
rifamycin		NT	(Al-Sudany and Ali, 2016)
liposomal azithromycin		NT	(Rajabi et al., 2016)
tincture of thioxolone + benzoxonium chloride (Thio-Ben) + cryotherapy		NT	(Daie Parizi et al., 2015)
pyrazinamide	NT	NT	(Voelkner et al., 2018)

IC50: half-maximal inhibitory concentration, EC50: effective concentration 50%, AM: amastigotes, PM: promastigotes, NT: not tested, NR: not reported

animals, although it is necessary to avoid certain trends since they generate results that are not representative of the entire population. Furthermore, data from infected human patients in the Americas published by SisLeish, report that 70% of cases were male (PAHO, 2019). Finally, the most studied species are *L. amazonensis, L. major, L. braziliensis* and *L. mexicana*, which is half-consistent with the report published in 2009 by WHO / Pan American Health Organization (PAHO) on the distribution of species in the Americas that reveals that the predominant species are *L. braziliensis, L. infantum, L. guyanensis, L. amazonensis* and *L. panamensis* (PAHO, 2009).

6. Conclusions

WHO treatment recommendations for CL are based on the causative species, geographical area, and the clinical features of the disease. It ranges from no treatment, mainly for infections due to *L. mexicana* or *L. major*, to topical or systemic approaches. Current chemotherapeutic treatments produce severe adverse effects and have poor compliance by the patient because in most cases a daily systemic (IV or IM) administration is required for periods ranging from 3 to 5 weeks. For these reasons, nowadays there is a marked trend for research aimed at topical applications, in addition to the fact that this therapy can decrease the risk/benefit ratio, reduce the cost of the treatment and improve patient compliance.

Although drug therapy is the most commonly used treatment for leishmaniasis, its prolonged or inefficient use has resulted, as expected, in widespread drug resistance, and today, several clinical cases do not respond to the first-line drug, the pentavalent antimony. This situation has triggered alarm signals regarding the possibility of the development of resistance to MLF, which is the new oral drug since relapses have been reported among cases treated with this drug. In addition, there are

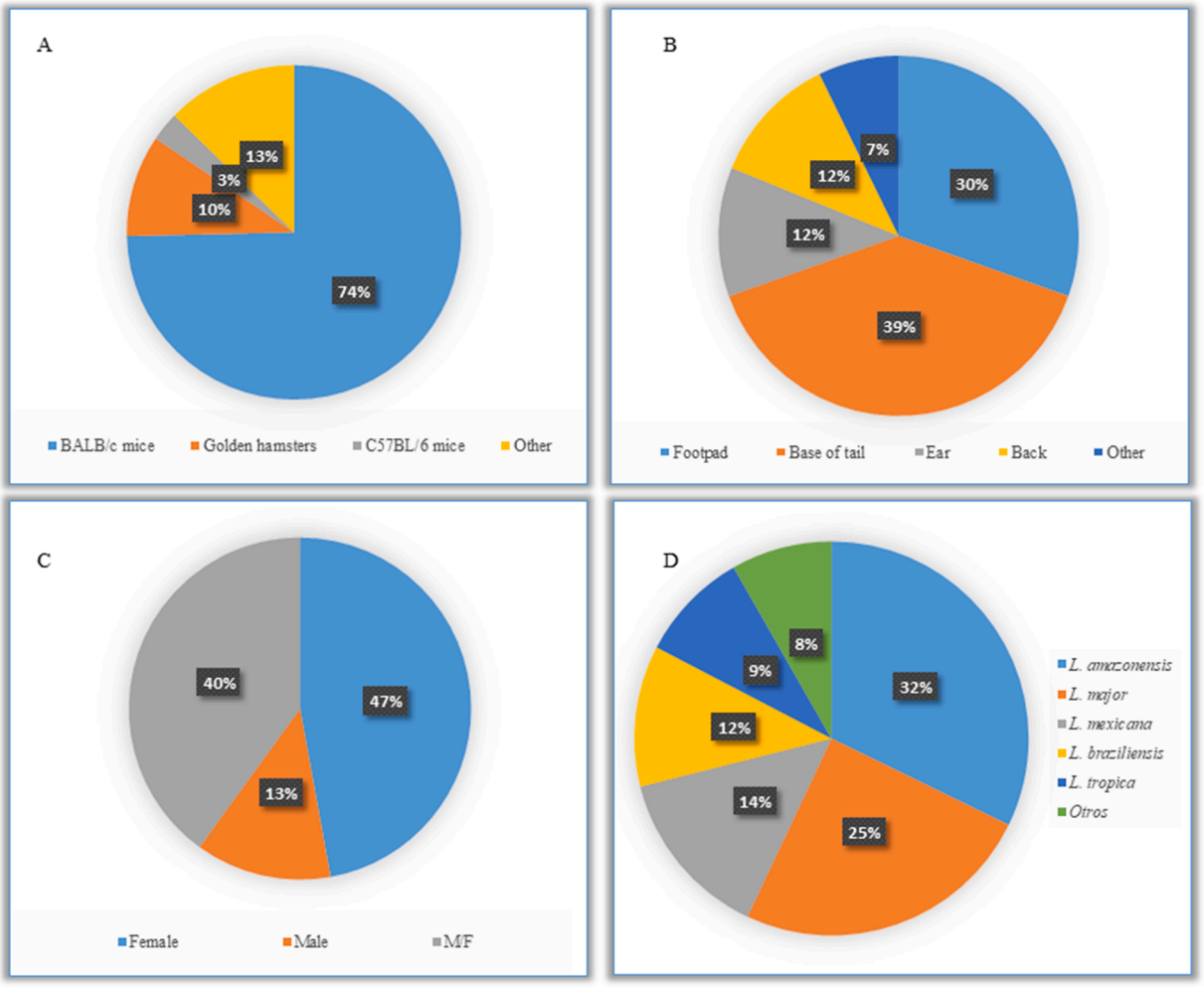

Fig. 5. Classification of articles with *in vivo* tests according to: animal specie (A), infection site (B), animal sex (C), and *Leishmania* sp. (D).

currently no vaccines available against any form of leishmaniasis. The emergence of resistant strains drives the ongoing and urgent search for new drugs against leishmaniasis that are safe and effective in inducing a long-term cure, but this is mainly at the level of individual researchers.

Many researches are focused on evaluating the combination of drugs to achieve a synergistic effect that allows reducing the dose, and therefore, minimizing side effects.

Another strategy widely explored to reduce adverse effects is the use of carriers to deliver currently used drugs, which also allows in some cases to change the administration route. In this regard, nanotechnology provides interesting tools for the development of new drug delivery systems.

The treatment of leishmaniasis will most likely evolve into an approach that uses multiple therapies simultaneously to reduce the possibility of developing drug resistance. An interesting strategy among the possible treatments is drug repositioning, that is, drugs already used for other diseases. This approach is driving many pharmaceutical researches in the last years.

Undoubtedly, more funding is needed in this area, as well as greater participation of the pharmaceutical industry to focus efforts on the development of chemotherapeutic agents and vaccines for this and other neglected tropical diseases.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abamor, E.S., Allahverdiyev, A.M., 2016. A nanotechnology based new approach for chemotherapy of Cutaneous Leishmaniasis: TIO2@AG nanoparticles – Nigella sativa oil combinations. Exp. Parasitol. 166, 150–163.

Abu Ammar, A., Nasereddin, A., Ereqat, S., Dan-Goor, M., Jaffe, C.L., Zussman, E., Abdeen, Z., 2019. Amphotericin B-loaded nanoparticles for local treatment of cutaneous leishmaniasis. Drug Deliv. Transl. Res. 9, 76–84.

Akbari, M., Oryan, A., Hatam, G., 2017. Application of nanotechnology in treatment of leishmaniasis: a review. Acta Trop. 172, 86–90.

Al-Sudany, N.K., Ali, Y.J., 2016. Intralesional 8.33% Rifamycin infiltration; New treatment for cutaneous leishmaniasis. J. Dermatol. Dermatol. Surg. 20, 39–45.

Alamilla-Fonseca, L.N., Delgado-Domínguez, J., Zamora-Chimal, J., Cervantes-Sarabia, R.B., Jiménez-Arellanes, A., Rivero-Cruz, J.F., Becker, I., 2018. Leishmania mexicana cell death achieved by Cleoserrata serrata (Jacq.) Iltis: learning from Maya healers. J. Ethnopharmacol. 211, 180–187.

Alexandrino-Junior, F., Silva, K., Freire, M., 2019. A Functional Wound Dressing as a Potential Treatment for Cutaneous Leishmaniasis. Pharm. 11, 5 200.

Amer, E.I., Eissa, M.M., Mossallam, S.F., 2016. Oral azithromycin versus its combination with miltefosine for the treatment of experimental Old World cutaneous leishmaniasis. J. Parasit. Dis.: Official Organ of the Indian Society for Parasitology 40, 475–484.

Antinarelli, L.M.R., de Oliveira Souza, I., Zabala Capriles, P.V., Gameiro, J., Britta, E.A., Nakamura, C.V., Lima, W.P., da Silva, A.D., Coimbra, E.S., 2018. Antileishmanial activity of a 4-hydrazinoquinoline derivative: Induction of autophagy and apoptosis-related processes and effectiveness in experimental cutaneous leishmaniasis. Exp. Parasitol. 195, 78–86.

Anversa, L., Salles Tiburcio, M.G., Batista, L.R., Cuba, M.B., Nogueira Nascentes, G.A., Martins, T.Y., Richini Pereira, V.B., Ruiz, L.d.S., Dias da Silva, V.J., Ramirez, L.E., 2017. Amiodarone and itraconazole improve the activity of pentavalent antimonial in the treatment of experimental cutaneous leishmaniasis. Int. J. Antimicrob. Agents 50, 159–165.

Añez, N., Rojas, A., Scorza-Dagert, J.V., Morales, C., 2018. Successful treatment against American cutaneous leishmaniasis by intralesional infiltration of a generic antimonial compound-lidocaine combination. A follow up study. Acta Trop. 185, 261–266.
Aragão Horoiwa, T., Cortez, M., Sauter, I.P., Migotto, A., Bandeira, C.L., Cerize, N.N.P., de Oliveira, A.M., 2020. Sugar-based colloidal nanocarriers for topical meglumine antimoniate application to cutaneous leishmaniasis treatment: ex vivo cutaneous retention and in vivo evaluation. Eur. J. Pharm. Sci. 147, 105295.
Aragão Macedo, S.R., Ferreira, A.S., Biguinati de Barros, N., Ulisses de Oliveira Meneguetti, D., Facundo, V.A., Shibayama, T.Y., Nicolete, R., 2019. Evaluation of the antileishmanial activity of biodegradable microparticles containing a hexanic eluate subfraction ofMaytenus guianensis bark. Exp. Parasitol. 205, 107738.
Araújo, I.A.C., de Paula, R.C., Alves, C.L., Faria, K.F., Oliveira, M.M.d., Mendes, G.G., Dias, E.M.F.A., Ribeiro, R.R., Oliveira, A.B.d., Silva, S.M.d., 2019. Efficacy of lapachol on treatment of cutaneous and visceral leishmaniasis. Exp. Parasitol. 199, 67–73.
Aronson, N.E., Magill, A.J., 2020. 104 - Leishmaniasis, in: Ryan, E.T., Hill, D.R., Solomon, T., Aronson, N.E., Endy, T.P. (Eds.), Hunter's Tropical Medicine and Emerging Infectious Diseases (Tenth Edition). Content Repository Only!, London, pp. 776-798.
Aureliano, D.P., Lindoso, J.A.L., de Castro Soares, S.R., Takakura, C.F.H., Pereira, T.M., Ribeiro, M.S., 2018. Cell death mechanisms inLeishmania amazonensis triggered by methylene blue-mediated antiparasitic photodynamic therapy. Photodiagn. Photodyn. Ther. 23, 1–8.
Bahmani, M., Saki, K., Ezatpour, B., Shahsavari, S., Eftekhari, Z., Jelodari, M., Rafieian-Kopaei, M., Sepahvand, R., 2015. Leishmaniosis phytotherapy: review of plants used in Iranian traditional medicine on leishmaniasis. Asian Pac. J. Trop. Biomed. 5, 695–701.
Baiocco, P., Colotti, G., Franceschini, S., Ilari, A., 2009. Molecular basis of antimony treatment in leishmaniasis. J. Med. Chem. 52, 2603–2612.
Bamorovat, M., Sharifi, I., Fekri, A., Keyhani, A., Aflatoonian, M.R., Heshmatkhah, A., Oliaee, R.T., Khosravi, A., Naderi, A., Parizi, M.H., Mostafavi, M., Varma, R.S., 2019. A single-group trial of end-stage patients with anthroponotic cutaneous leishmaniasis: Levamisole in combination with Glucantime in field and laboratory models. Microb. Pathog. 128, 162–170.
Barratt, G., Legrand, P., 2005. Comparison of the efficacy and pharmacology of formulations of amphotericin B used in treatment of leishmaniasis. Curr. Opin. Infect. Dis. 18, 527–530.
Bemani, E., Oryan, A., Bahrami, S., 2019. Effectiveness of amiodarone in treatment of cutaneous leishmaniasis caused by Leishmania major. Exp. Parasitol. 205, 107747.
Berenguer, D., Sosa, L., Alcover, M., 2019. Development and Characterization of a Semi-Solid Dosage Form of Meglumine Antimoniate for Topical Treatment of Cutaneous Leishmaniasis. Curr. Opin. Infect. Dis. 11, 613.
Bosquiroli, L.S.S., Demarque, D.P., Rizk, Y.S., Cunha, M.C., Marques, M.C.S., Matos, M.d. F.C., Kadri, M.C.T., Carollo, C.A., Arruda, C.C.P., 2015. In vitro anti-Leishmania infantum activity of essential oil from Piper angustifolium. Rev. Bras. Farmacog. 25, 124–128.
Cabral, F.V., Pelegrino, M.T., Sauter, I.P., Seabra, A.B., Cortez, M., Ribeiro, M.S., 2019. Nitric oxide-loaded chitosan nanoparticles as an innovative antileishmanial platform. Nitric Oxide 93, 25–33.
Caridha, D., Vesely, B., van Bocxlaer, K., Arana, B., Mowbray, C.E., Rafati, S., Uliana, S., Reguera, R., Kreishman-Deitrick, M., Sciotti, R., Buffet, P., Croft, S.L., 2019. Route map for the discovery and pre-clinical development of new drugs and treatments for cutaneous leishmaniasis. Int. J. Parasitol.: Drugs and Drug Resistance 11, 106–117.
Casa, D.M., Scariot, D.B., Khalil, N.M., Nakamura, C.V., Mainardes, R.M., 2018. Bovine serum albumin nanoparticles containing amphotericin B were effective in treating murine cutaneous leishmaniasis and reduced the drug toxicity. Exp. Parasitol. 192, 12–18.
Cataneo, A.H.D., Tomiotto-Pellissier, F., Miranda-Sapla, M.M., Assolini, J.P., Panis, C., Kian, D., Yamauchi, L.M., Colado Simão, A.N., Casagrande, R., Pinge-Filho, P., Costa, I.N., Verri, W.A., Conchon-Costa, I., Pavanelli, W.R., 2019. Quercetin promotes antipromastigote effect by increasing the ROS production and anti-amastigote by upregulating Nrf2/HO-1 expression, affecting iron availability. Biomed. Pharmacother. 113, 108745.
Celes, F.S., Trovatti, E., Khouri, R., Van Weyenbergh, J., Ribeiro, S.J., Borges, V.M., Barud, H.S., de Oliveira, C.I., 2016. DETC-based bacterial cellulose bio-curatives for topical treatment of cutaneous leishmaniasis. Sci. Rep. 6, 38330.
Chakravarty, J., Sundar, S., 2010. Drug resistance in leishmaniasis. J. Global Infect. Dis. 2 (2), 167–176.
Cifani, C., Costantino, S., Massi, M., Berrino, L., 2012. Commercially available lipid formulations of amphotericin b: are they bioequivalent and therapeutically equivalent? Acta Biomed. 83 (2), 154–163.
Coa, J.C., Castrillón, W., Cardona, W., Carda, M., Ospina, V., Muñoz, J.A., Vélez, I.D., Robledo, S.M., 2015. Synthesis, leishmanicidal, trypanocidal and cytotoxic activity of quinoline-hydrazone hybrids. Eur. J. Med. Chem. 101, 746–753.
Coelho, A.C., Trinconi, C.T., Senra, L., Yokoyama-Yasunaka, J.K.U., Uliana, S.R.B., 2015. Leishmania is not prone to develop resistance to tamoxifen. Int. J. Parasitol. 5, 77–83.
Coêlho, E.S., Lopes, G.L.N., Pinheiro, I.M., Holanda, J.N.P., Alves, M.M.M., Carvalho Nogueira, N., Carvalho, F.A.A., Carvalho, A.L.M., 2018. Emulgel based on amphotericin B and bacuri butter (Platonia insignis Mart.) for the treatment of cutaneous leishmaniasis: characterization andin vitro assays. Drug Dev. Ind. Pharm. 44, 1713–1723.
Costa, M.S., Gonçalves, Y.G., Teixeira, S.C., Nunes, D.C.d.O., Lopes, D.S., da Silva, C.V., da Silva, M.S., Borges, B.C., Silva, M.J.B., Rodrigues, R.S., Rodrigues, V.d.M., Von Poelhsitz, G., Yoneyama, K.A.G., 2019. Increased ROS generation causes apoptosis-like death: mechanistic insights into the anti-Leishmania activity of a potent ruthenium(II) complex. J. Inorg. Biochem. 195, 1–12.
Croft, S.L., Coombs, G.H., 2003. Leishmaniasis–current chemotherapy and recent advances in the search for novel drugs. Trends Parasitol. 19, 502–508.
Cruz-Saavedra, L., Díaz-Roa, A., Gaona, M.A., Cruz, M.L., Ayala, M., Cortés-Vecino, J.A., Patarroyo, M.A., Bello, F.J., 2016. The effect ofLucilia sericata- and Sarconesiopsis magellanica-derived larval therapy on Leishmania panamensis. Acta Trop. 164, 280–289.
Christen, J.-R., Bourreau, E., Demar, M., Lightburn, E., Couppié, P., Ginouvès, M., Prévot, G., Gangneux, J.-P., Savini, H., de Laval, F., Pommier de Santi, V., Briolant, S., 2018. Use of the intramuscular route to administer pentamidine isethionate in Leishmania guyanensis cutaneous leishmaniasis increases the risk of treatment failure. Travel Med. Infect. Dis. 24, 31–36.
da Silva, A.C., dos Santos, T.A.R., da Silva, I.V.B., de Oliveira, M.V.G., Moreira, D.R.M., Leite, A.C.L., Pereira, V.R.A., 2017. Aryl thiosemicarbazones: In vitro and immunomodulatory activities against L. amazonensis. Exp. Parasitol. 177, 57–65.
Da Silva, B.J.M., Souza-Monteiro, J.R., Rogez, H., Crespo-López, M.E., Do Nascimento, J. L.M., Silva, E.O., 2018. Selective effects of Euterpe oleracea (açai) onLeishmania (Leishmania) amazonensis and Leishmania infantum. Biomed. Pharmacother. 97, 1613–1621.
Daie Parizi, M.H., Karvar, M., Sharifi, I., Bahrampour, A., Heshmat Khah, A., Rahnama, Z., Baziar, Z., Amiri, R., 2015. The topical treatment of anthroponotic cutaneous leishmaniasis with the tincture of thioxolone plus benzoxonium chloride (Thio-Ben) along with cryotherapy: a single-blind randomized clinical trial. Dermatol. Ther. 28, 140–146.
Dalimi, A., Delavari, M., Ghaffarifar, F., Sadraei, J., 2015. In vitro andin vivo antileishmanial effects of aloe-emodin onLeishmania major. J. Tradit. Complement. Med. 5, 96–99.
Dar, M.J., Khalid, S., McElroy, C.A., Satoskar, A.R., Khan, G.M., 2020a. Topical treatment of cutaneous leishmaniasis with novel amphotericin B-miltefosine co-incorporated second generation ultra-deformable liposomes. Int. J. Pharm. 573, 118900.
Dar, M.J., Khalid, S., Varikuti, S., Satoskar, A.R., Khan, G.M., 2020b. Nano-elastic liposomes as multidrug carrier of sodium stibogluconate and ketoconazole: a potential new approach for the topical treatment of cutaneous Leishmaniasis. Eur. J. Pharm. Sci. 145, 105256.
Dar, M.J., McElroy, C.A., Khan, M.I., Satoskar, A.R., Khan, G.M., 2020c. Development and evaluation of novel miltefosine-polyphenol co-loaded second generation nano-transfersomes for the topical treatment of cutaneous leishmaniasis. Expert Opin. Drug Deliv. 17, 97–110.
de Barros, N.B., Aragão Macedo, S.R., Ferreira, A.S., Tagliari, M.P., Kayano, A.M., Nicolete, L.D.F., Soares, A.M., Nicolete, R., 2018. ASP49-phospholipase A2-loaded liposomes as experimental therapy in cutaneous leishmaniasis model. Int. Immunopharmacol. 55, 128–132.
de Barros, N.B., Macedo, S.R.A., Ferreira, A.S., Tagliari, M.P., Zanchi, F.B., Kayano, A.M., Soares, A.M., Nicolete, R., 2016. Liposomes containing an ASP49-phospholipase A2 from Bothrops jararacussu snake venom as experimental therapy against cutaneous leishmaniasis. Int. Immunopharmacol. 36, 225–231.
de Mello, T.F.P., Cardoso, B.M., Bitencourt, H.R., Donatti, L., Aristides, S.M.A., Lonardoni, M.V.C., Silveira, T.G.V., 2016. Ultrastructural and morphological changes in Leishmania (Viannia) braziliensis treated with synthetic chalcones. Exp. Parasitol. 160, 23–30.
de Oliveira, J.K., Ueda-Nakamura, T., Corrêa, A.G., Petrilli, R., Lopez, R.F.V., Nakamura, C.V., Auzely-Velty, R., 2020. Liposome-based nanocarrier loaded with a new quinoxaline derivative for the treatment of cutaneous leishmaniasis. Mater. Sci. Eng. C 110, 110720.
Dimmer, J., Cabral, F.V., Sabino, C.P., Silva, C.R., Núñez-Montoya, S.C., Cabrera, J.L., Ribeiro, M.S., 2019. Natural anthraquinones as novel photosentizers for antiparasitic photodynamic inactivation. Phytomed 61, 152894.
Dolat, E., Salarabadi, S.S., Layegh, P., Jaafari, M.R., Sazgarnia, S., Sazgarnia, A., 2020. The effect of UV radiation in the presence of TiO2-NPs on Leishmania major promastigotes. Biochim. Biophys. Acta (BBA) - General Subjects 1864, 129558.
Domingues Passero, L.F., Laurenti, M.D., Santos-Gomes, G., Soares Campos, B.L., Sartorelli, P., Lago, J.H.G., 2013. Chapter 7 - In Vivo Antileishmanial Activity of Plant-Based Secondary Metabolites, in: Rai, M.K., Kon, K.V. (Eds.), Fighting Multidrug Resistance with Herbal Extracts, Essential Oils and Their Components. Academic Press, San Diego, pp. 95-107.
Dujardin, J.-C., Campino, L., Cañavate, C., Dedet, J.-P., Gradoni, L., Soteriadou, K., Mazeris, A., Ozbel, Y., Boelaert, M., 2008. Spread of vector-borne diseases and neglect of Leishmaniasis. Europe. Emerg. Infect. Dis. 14, 1013–1018.
Emiliano, Y.S.S., Almeida-Amaral, E.E., 2018. Efficacy of Apigenin and Miltefosine Combination Therapy against Experimental Cutaneous Leishmaniasis. J. Nat. Prod. 81, 1910–1913.
Escobar, P., Vera, A.M., Neira, L.F., Velásquez, A.O., Carreño, H., 2018. Photodynamic therapy using ultradeformable liposomes loaded with chlorine aluminum phthalocyanine against L. (V.) braziliensis experimental models. Exp. Parasitol. 194, 45–52.
Escrivani, D.O., Lopes, M.V., Poletto, F., Ferrarini, S.R., Sousa-Batista, A.J., Steel, P.G., Guterres, S.S., Pohlmann, A.R., Rossi-Bergmann, B., 2020. Encapsulation in lipid-core nanocapsules improves topical treatment with the potent antileishmanial compound CH8. Nanomed.: Nanotechnol., Biol. Med. 24, 102121.
Esfandiari, F., Motazedian, M.H., Asgari, Q., Morowvat, M.H., Molaei, M., Heli, H., 2019. Paromomycin-loaded mannosylated chitosan nanoparticles: synthesis, characterization and targeted drug delivery against leishmaniasis. Acta Trop 197, 105045.
Eskandari, S.E., Firooz, A., Nassiri-Kashani, M., Jaafari, M.R., Javadi, A., Miramin-Mohammadi, A., Valian-Keshavarz, H., Khamesipour, A., 2018. Safety Evaluation of

Nano-Liposomal Formulation of Amphotericin B (Sina Ampholeish) in Animal Model as a Candidate for Treatment of Cutaneous Leishmaniasis. J. Arthropod Borne Dis. 12, 269–275.
Fagundes, J., Sakane, K.K., Bhattacharjee, T., Pinto, J.G., Ferreira, I., Raniero, L.J., Ferreira-Strixino, J., 2019. Evaluation of photodynamic therapy with methylene blue, by the Fourier Transform Infrared Spectroscopy (FT-IR) in Leishmania major - in vitro. Spectrochimica Acta Part A: Mol. Biomol. Spectrosc. 207, 229–235.
Fanti, J.R., Tomiotto-Pellissier, F., Miranda-Sapla, M.M., Cataneo, A.H.D., Andrade, C.G. T.d.J., Panis, C., Rodrigues, J.H.d.S., Wowk, P.F., Kuczera, D., Costa, I.N., Nakamura, C.V., Nakazato, G., Durán, N., Pavanelli, W.R., Conchon-Costa, I., 2018. Biogenic silver nanoparticles inducingLeishmania amazonensis promastigote and amastigote death in vitro. Acta Trop. 178, 46–54.
Farajzadeh, S., Ahmadi, R., Mohammadi, S., Pardakhty, A., Khalili, M., Aflatoonian, M., 2018. Evaluation of the efficacy of intralesional Glucantime plus niosomal zinc sulphate in comparison with intralesional Glucantime plus cryotherapy in the treatment of acute cutaneous leishmaniasis, a randomized clinical trial. J. Parasit. Dis. 42, 616–620.
Farajzadeh, S., Hakimi Parizi, M., Haghdoost, A.A., Mohebbi, A., Mohammadi, S., Pardakhty, A., Eybpoosh, S., Heshmatkhah, A., Vares, B., Saryazdi, S., Fekri, A.R., Mohebbi, E., 2016a. Comparison between intralesional injection of zinc sulfate 2 % solution and intralesional meglumine antimoniate in the treatment of acute old world dry type cutaneous leishmaniasis: a randomized double-blind clinical trial. J. Parasit. Dis. 40, 935–939.
Farajzadeh, S., Heshmatkhah, A., Vares, B., Mohebbi, E., Mohebbi, A., Aflatoonian, M., Eybpoosh, S., Sharifi, I., Aflatoonian, M.R., Shamsi Meymandi, S., Fekri, A.R., Mostafavi, M., 2016b. Topical terbinafine in the treatment of cutaneous leishmaniasis: triple blind randomized clinical trial. J. Parasit. Dis. 40, 1159–1164.
Fernandez, M., Murillo, J., Ríos-Vásquez, L.A., Ocampo-Cardona, R., Cedeño, D.L., Jones, M.A., Velez, I.D., Robledo, S.M., 2018. In vivo studies of the effectiveness of novel N-halomethylated and non-halomethylated quaternary ammonium salts in the topical treatment of cutaneous leishmaniasis. Parasitol. Res. 117, 273–286.
Ferreira, C., Passos, C.L.A., Soares, D.C., Costa, K.P., Rezende, M.J.C., Lobão, A.Q., Pinto, A.C., Hamerski, L., Saraiva, E.M., 2017. Leishmanicidal activity of the alkaloid-rich fraction from Guatteria latifolia. Exp. Parasitol. 172, 51–60.
Fraga, J., Montalvo, A.M., Van der Auwera, G., Maes, I., Dujardin, J.C., Requena, J.M., 2013. Evolution and species discrimination according to the Leishmania heat-shock protein 20 gene. Infect. Genet. Evol. 18, 229–237.
Gadelha, E.P.N., Ramasawmy, R., da Costa Oliveira, B., Morais Rocha, N., de Oliveira Guerra, J.A., Allan Villa Rouco da Silva, G., Gabrielle Ramos de Mesquita, T., Chrusciak Talhari Cortez, C., Chrusciak Talhari, A., 2018. An open label randomized clinical trial comparing the safety and effectiveness of one, two or three weekly pentamidine isethionate doses (seven milligrams per kilogram) in the treatment of cutaneous leishmaniasis in the Amazon Region. PLoS Negl. Trop. Dis. 12, e0006850.
Geroldinger, G., Tonner, M., Hettegger, H., Bacher, M., Monzote, L., Walter, M., Staniek, K., Rosenau, T., Gille, L., 2017. Mechanism of ascaridole activation in Leishmania. Biochem. Pharmacol. 132, 48–62.
Gonçalves-Oliveira, L.F., Souza-Silva, F., de Castro Côrtes, L.M., Veloso, L.B., Santini Pereira, B.A., Cysne-Finkelstein, L., Lechuga, G.C., Bourguignon, S.C., Almeida-Souza, F., da Silva Calabrese, K., Ferreira, V.F., Alves, C.R., 2019. The combination therapy of meglumine antimoniate and oxiranes (epoxy-α-lapachone and epoxymethyl-lawsone) enhance the leishmanicidal effect in mice infected by Leishmania (Leishmania) amazonensis. Int. J. Parasitol. 10, 101–108.
Goswami, P., Ghiya, B.C., Kumar, V., Rekha, S., Mehta, R.D., 2019. Comparison of Efficacy of Two Different Concentrations of Intralesional Amphotericin B in the Treatment of Cutaneous Leishmaniasis; A Randomized Controlled Trial. Indian Dermatol. Online J. 10, 627–631.
Guzman-Rivero, M., Verduguez-Orellana, A., Montaño, K., Cloetens, L., Rojas, E., Åkesson, B., Sejas, E., 2015. The immune response in patients with cutaneous leishmaniasis and the influence of zinc supplementation. Biomed. Pharmacother. 69, 56–62.
Hanif, M.M., Akram, K., Mustafa, G., 2016. Intralesional Versus Oral Chloroquine in Cutaneous Leishmaniasis: Comparison of Outcome, Duration of Treatment and Total Dose of Drug. J. College Phys. Surg.–Pak. 26, 260–262.
Hazra, S., Ghosh, S., Hazra, B., 2017. Chapter 8 - Phytochemicals With Antileishmanial Activity: Prospective Drug Targets, in: Atta ur, R. (Ed.), Stud. Nat. Prod. Chem.. Elsevier, pp. 303-336.
Hilerowicz, Y., Koren, A., Mashiah, J., Katz, O., Sprecher, E., Artzi, O., 2018. Fractional ablative carbon dioxide laser followed by topical sodium stibogluconate application: a treatment option for pediatric cutaneous leishmaniasis. Pediatr. Dermatol. 35, 366–369.
Iniguez, E., Varela-Ramirez, A., Martínez, A., Torres, C.L., Sánchez-Delgado, R.A., Maldonado, R.A., 2016. Ruthenium-Clotrimazole complex has significant efficacy in the murine model of cutaneous leishmaniasis. Acta Trop. 164, 402–410.
Iraji, F., Asilian, A., Heidari, A., Shariat, S., Bokaie Jazi, S., Siadat, A.H., 2019. Combination of continuous wave CO(2) laser and topical application of trichloroacetic acid 50% vs CO(2) laser alone the treatment of cutaneous leishmaniasis (A case series of 6 patients). J. Cosmet. Dermatol. 19, 1367–1370.
Ishaq, Z.-A., Ahmed, N., Anwar, M.N., ul-Haq, I., ur-Rehman, T., Ahmad, N.M., Elaissari, A., 2018. Development and in vitro evaluation of cost effective amphotericin B polymeric emulsion. J. Drug Deliv. Sci. Technol. 46, 66–73.
Jaafari, M.R., Hatamipour, M., Alavizadeh, S.H., Abbasi, A., Saberi, Z., Rafati, S., Taslimi, Y., Mohammadi, A.M., Khamesipour, A., 2019. Development of a topical liposomal formulation of Amphotericin B for the treatment of cutaneous leishmaniasis. Int. J. Parasitol. 11, 156–165.
Jamal, Q., Khan, N.H., Wahid, S., Awan, M.M., Sutherland, C., Shah, A., 2015. In-vitro sensitivity of Pakistani Leishmania tropica field isolate against buparvaquone in comparison to standard anti-leishmanial drugs. Exp. Parasitol. 154, 93–97.
Kapil, S., Singh, P.K., Silakari, O., 2018. An update on small molecule strategies targeting leishmaniasis. Eur. J. Med. Chem. 157, 339–367.
Kavian, Z., Alavizadeh, S.H., Golmohamadzadeh, S., Badiee, A., Khamesipour, A., Jaafari, M.R., 2019. Development of topical liposomes containing miltefosine for the treatment of Leishmania major infection in susceptible BALB/c mice. Acta Trop. 196, 142–149.
Kevric, I., Cappel, M.A., Keeling, J.H., 2015. New World and Old World Leishmania Infections: a Practical Review. Dermatol. Clin. 33, 579–593.
Khalili, S., Ebrahimzade, E., Mohebali, M., Shayan, P., Mohammadi-Yeganeh, S., Moosazadeh Moghaddam, M., Elikaee, S., Akhoundi, B., Sharifi-Yazdi, M.K., 2019. Investigation of the antimicrobial activity of a short cationic peptide against promastigote and amastigote forms ofLeishmania major (MHRO/IR/75/ER): Anin vitro study. Exp. Parasitol. 196, 48–54.
Khan, K., Khan, A.U., Ghufran, Khan, A., Khan, M., Ahmad, I., 2020. Fractionated illumination improves the treatment outcomes of photodynamic therapy for high grade cutaneous leishmaniasis. Photodiagn. Photodyn. Ther. 29, 101622.
Kheirandish, F., Delfan, B., Mahmoudvand, H., Moradi, N., Ezatpour, B., Ebrahimzadeh, F., Rashidipour, M., 2016. Antileishmanial, antioxidant, and cytotoxic activities of Quercus infectoria Olivier extract. Biomed. Pharmacother.y 82, 208–215.
Koutsoni, O.S., Karampetsou, K., Kyriazis, I.D., Stathopoulos, P., Aligiannis, N., Halabalaki, M., Skaltsounis, L.A., Dotsika, E., 2018. Evaluation of total phenolic fraction derived from extra virgin olive oil for its antileishmanial activity. Phytomed 47, 143–150.
Laboudi, M., Sahibi, H., Elabandouni, M., Nhammi, H., Ait Hamou, S., Sadak, A., 2018. A review of cutaneous leishmaniasis in Morocco: a vertical analysisto determine appropriate interventions for control and prevention. Acta Trop. 187, 275–283.
Lanza, J.S., Fernandes, F.R., Correa-Junior, J.D., Vilela, J.M., Magalhaes-Paniago, R., Ferreira, L.A., Andrade, M.S., Demicheli, C., Melo, M.N., Frezard, F., 2016. Polarity-sensitive nanocarrier for oral delivery of Sb(V) and treatment of cutaneous leishmaniasis. Int. J. Nanomed. 11, 2305–2318.
Laverde-Paz, M.J., Echeverry, M.C., Patarroyo, M.A., Bello, F.J., 2018. Evaluating the anti-leishmania activity ofLucilia sericata andSarconesiopsis magellanica blowfly larval excretions/secretions in an in vitro model. Acta Trop. 177, 44–50.
Leishmaniases, W.E.C.o.tT.C.oO.tT., World Health, O., 1990. In: Control of the leishmaniases: report of a WHO expert committee [meeting held in Geneva from 6 to 10 February 1989]. World Health Organization, Geneva.
Lopera, A.A., Montoya, A., Vélez, I.D., Robledo, S.M., Garcia, C.P., 2018. Synthesis of calcium phosphate nanostructures by combustion in solution as a potential encapsulant system of drugs with photodynamic properties for the treatment of cutaneous leishmaniasis. Photodiagn. Photodyn. Ther. 21, 138–146.
Lopes, S.C., Silva, R.A., Novais, M.V., Coelho, L.D., Ferreira, L.A., Souza, P.E., Tedesco, A., Azevedo, R.B., Aguiar, M.G., Oliveira, M.C., 2019. Topical photodynamic therapy with chloroaluminum phthalocyanine liposomes is as effective as systemic pentavalent antimony in the treatment of experimental cutaneous leishmaniasis. Photodiagn. Photodyn. Ther. 28, 210–215.
López, L., Vélez, I., Asela, C., Cruz, C., Alves, F., Robledo, S., Arana, B., 2018. A phase II study to evaluate the safety and efficacy of topical 3% amphotericin B cream (Anfoleish) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia. PLoS Neg. Trop. Dis. 12, e0006653.
Machado, P.R.L., Ribeiro, C.S., França-Costa, J., Dourado, M.E.F., Trinconi, C.T., Yokoyama-Yasunaka, J.K.U., Malta-Santos, H., Borges, V.M., Carvalho, E.M., Uliana, S.R.B., 2018. Tamoxifen and meglumine antimoniate combined therapy in cutaneous leishmaniasis patients: a randomised trial. Trop. Med. Int. Health 23, 936–942.
Mahmoudvand, H., Kheirandish, F., Mirbadie, S.R., Kayedi, M.H., Rezaei Riabi, T., Ghasemi, A.A., Bamorovat, M., Sharifi, I., 2017. The Potential Use of Methotrexate in the Treatment of Cutaneous Leishmaniasis:In Vitro Assays against Sensitive and Meglumine Antimoniate-resistant Strains of Leishmania tropica. Iran. J. Parasitol. 12, 339–347.
Maleki, F., Zarebavani, M., Mohebali, M., Dayer, M.S., Hajialiani, F., Tabatabaie, F., 2017. In vitro and in vivo susceptibility of Leishmania major to some medicinal plants. Asian Pac. J. Trop. Biomed. 7, 37–42.
Malli, S., Pomel, S., Dennemont, I., Loiseau, P.M., Bouchemal, K., 2019. Combination of amphotericin B and chitosan platelets for the treatment of experimental cutaneous leishmaniasis: histological and immunohistochemical examinations. J. Drug Deliv. Sci. Technol. 50, 34–41.
Mazur, K.L., Feuser, P.E., Valério, A., Poester Cordeiro, A., de Oliveira, C.I., Assolini, J.P., Pavanelli, W.R., Sayer, C., Araújo, P.H.H., 2019. Diethyldithiocarbamate loaded in beeswax-copaiba oil nanoparticles obtained by solventless double emulsion technique promote promastigote death in vitro. Colloid. Surf. B 176, 507–512.
Mendes, E.A., Desoti, V.C., Silva, S.d.O., Ueda-Nakamura, T., Dias Filho, B.P., Yamada-Ogatta, S.F., Sarragiotto, M.H., Nakamura, C.V., 2016. C5 induces different cell death pathways in promastigotes of Leishmania amazonensis. Chem. Biol. Interact. 256, 16–24.
Mesa, L.E., Vasquez, D., Lutgen, P., Vélez, I.D., Restrepo, A.M., Ortiz, I., Robledo, S.M., 2017. In vitro and in vivo antileishmanial activity of Artemisia annua L. leaf powder and its potential usefulness in the treatment of uncomplicated cutaneous leishmaniasis in humans. Rev. Soc. Bras. Med. Trop. 50, 52–60.
Miranda-Sapla, M.M., Tomiotto-Pellissier, F., Assolini, J.P., Carloto, A.C.M., Bortoleti, B. T.d.S., Gonçalves, M.D., Tavares, E.R., Rodrigues, J.H.dD.S., Simão, A.N.C., Yamauchi, L.M., Nakamura, C.V., Verri, W.A., Costa, I.N., Conchon-Costa, I., Pavanelli, W.R., 2019. trans-Chalcone modulates Leishmania amazonensis infection

in vitro by Nrf2 overexpression affecting iron availability. Eur. J. Pharmacol. 853, 275–288.
Montoya, A., Daza, A., Muñoz, D., Ríos, K., Taylor, V., Cedeño, D., Vélez, I.D., Echeverri, F., Robledo, S.M., 2015. Development of a novel formulation with hypericin to treat cutaneous leishmaniasis based on photodynamic therapy in in vitro andin vivo studies. Antimicrob. Agents Chemother. 59, 5804–5813.
Moosavian, S.A., Fallah, M., Jaafari, M.R., 2019. The activity of encapsulated meglumine antimoniate in stearylamine-bearing liposomes against cutaneous leishmaniasis in BALB/c mice. Exp. Parasitol. 200, 30–35.
Moreno, E., Schwartz, J., Larrea, E., Conde, I., Font, M., Sanmartín, C., Irache, J.M., Espuelas, S., 2015. Assessment of β-lapachone loaded in lecithin-chitosan nanoparticles for the topical treatment of cutaneous leishmaniasis in L. major infected BALB/c mice. Nanomedicine 11, 2003–2012.
Morilla, M.J., Romero, E.L., 2015. Chapter 18 - Nanomedical Therapeutic and Prophylaxis Strategies Against Intracellular Protozoa in the Americas, in: Rai, M., Kon, K. (Eds.), Nanotechnology in Diagnosis, Treatment and Prophylaxis of Infectious Diseases. Academic Press, Boston, pp. 297-317.
Mostafavi, M., Sharifi, I., Farajzadeh, S., Khazaeli, P., Sharifi, H., Pourseyedi, E., Kakooei, S., Bamorovat, M., Keyhani, A., Parizi, M.H., Khosravi, A., Khamesipour, A., 2019. Niosomal formulation of amphotericin B alone and in combination with glucantime:In vitro and in vivo leishmanicidal effects. Biomed. Pharmacother. 116, 108942.
Nascimento, N.R.F.dD., Aguiar, F.L.N.dD., Santos, C.F., Costa, A.M.L., Hardoim, D.dD.J., Calabrese, K.dD.S., Almeida-Souza, F., Sousa, E.H.S.dD., Lopes, L.G.dD.F., Teixeira, M.J., Pereira, V.S., Brilhante, R.S.N., Rocha, M.F.G., 2019. In vitro and in vivo leishmanicidal activity of a ruthenium nitrosyl complex against Leishmania (Viannia) braziliensis. Acta Trop. 192, 61–65.
Nazari-Vanani, R., Vais, R.D., Sharifi, F., Sattarahmady, N., Karimian, K., Motazedian, M. H., Heli, H., 2018. Investigation of anti-leishmanial efficacy of miltefosine and ketoconazole loaded on nanoniosomes. Acta Trop. 185, 69–76.
Nesi-Reis, V., Navasconi, T.R., Lera-Nosone, D.S.S.L., Oliveira, E.L., Barbosa, P.M., Caetano, W., Silveira, T.G.V., Aristides, S.M.A., Hioka, N., Lonardoni, M.V.C., 2018. Phototoxic effect of aluminium-chlorine and aluminium-hydroxide phthalocyanines on Leishmania (l.) amazonensis. Photodiagn. Photodyn. Ther. 21, 239–245.
Nguyen, A.K., Yang, K.H., Bryant, K., Li, J., Joice, A.C., Werbovetz, K.A., Narayan, R.J., 2019. Microneedle-Based Delivery of Amphotericin B for Treatment of Cutaneous Leishmaniasis. Biomed. Microdevices 21, 8.
Nieto-Meneses, R., Castillo, R., Hernández-Campos, A., Maldonado-Rangel, A., Matius-Ruiz, J.B., Trejo-Soto, P.J., Nogueda-Torres, B., Dea-Ayuela, M.A., Bolás-Fernández, F., Méndez-Cuesta, C., Yépez-Mulia, L., 2018. In vitro activity of new N-benzyl-1H-benzimidazol-2-amine derivatives against cutaneous, mucocutaneous and visceral Leishmania species. Exp. Parasitol. 184, 82–89.
Odonne, G., Houël, E., Bourdy, G., Stien, D., 2017. Treating leishmaniasis in Amazonia: a review of ethnomedicinal concepts and pharmaco-chemical analysis of traditional treatments to inspire modern phytotherapies. J. Ethnopharmacol. 199, 211–230.
Omidian, M., Jadbabaei, M., Omidian, E., Omidian, Z., 2019. The effect of Nd:YAG laser therapy on cutaneous leishmaniasis compared to intralesional meglumine antimoniate. Postepy dermatologii i alergologii 36, 227–231.
Oyama, J., Lera-Nonose, D.S.S.L., Ramos-Milaré, Á.C.F.H., Padilha Ferreira, F.B., de Freitas, C.F., Caetano, W., Hioka, N., Silveira, T.G.V., Lonardoni, M.V.C., 2019. Potential of Pluronics® P-123 and F-127 as nanocarriers of anti-Leishmania chemotherapy. Acta Trop. 192, 11–21.
PAHO, W.a., 2009. Especies de Leishmanias en las Americas, https://www.paho.org/es/documentos/especies-leishmanias-americas-2009.
PAHO, W.a., 2019. LEISHMANIASIS Informe Epidemiológico de las Américas, https://iris.paho.org/handle/10665.2/51739.
Parihar, S.P., Hartley, M.A., Hurdayal, R., Guler, R., Brombacher, F., 2016. Topical Simvastatin as Host-Directed Therapy against Severity of Cutaneous Leishmaniasis in Mice. Sci. Rep. 6, 33458.
Parvizi, M.M., Handjani, F., 2017. Efficacy of cryotherapy plus topicalJuniperus excelsa M. Bieb cream versus cryotherapy plus placebo in the treatment of Old World cutaneous leishmaniasis: a triple-blind randomized controlled clinical trial. PLoS Negl. Trop. Dis. 11 (10), e0005957.
Pascoal, D.R.C., Cabral-Albuquerque, E.C.M., Velozo, E.S., de Sousa, H.C., de Melo, S.A. B.V., Braga, M.E.M., 2017. Copaiba oil-loaded commercial wound dressings using supercritical CO2: a potential alternative topical antileishmanial treatment. J. Supercrit. Fluids 129, 106–115.
Pelczar Jr, M.J.C., E.C. S.; Krieg, N.R., 1993. Microbiology.
Pereira, V., de Barros, N.B., Macedo, S.R.A., Dos Santos Ferreira, A., Kanis, L.A., Nicolete, R., 2020. Drug-containing hydrophobic dressings as a topical experimental therapy for cutaneous leishmaniasis. J. Parasit. Dis. 44, 79–87.
Perez, A.P., Altube, M.J., Schilrreff, P., Apezteguia, G., Celes, F.S., Zacchino, S., de Oliveira, C.I., Romero, E.L., Morilla, M.J., 2016. Topical amphotericin B in ultradeformable liposomes: formulation, skin penetration study, antifungal and antileishmanial activity in vitro. Colloid. Surf. B 139, 190–198.
Pinheiro, I.M., Carvalho, I.P., de Carvalho, C.E.S., Brito, L.M., da Silva, A.B.S., Conde Júnior, A.M., de Carvalho, F.A.A., Carvalho, A.L.M., 2016. Evaluation of the in vivo leishmanicidal activity of amphotericin B emulgel: an alternative for the treatment of skin leishmaniasis. Exp. Parasitol. 164, 49–55.
Pinto, J.G., Martins, J.F.d.S., Pereira, A.H.C., Mittmann, J., Raniero, L.J., Ferreira-Strixino, J., 2017. Evaluation of methylene blue as photosensitizer in promastigotes of Leishmania major and Leishmania braziliensis. Photodiagn. Photodyn. Ther. 18, 325–330.
Pinto, J.G., Pereira, A.H.C., de Oliveira, M.A., Kurachi, C., Raniero, L.J., Ferreira-Strixino, J., 2016. Chlorin E6 phototoxicity in L. major and L. braziliensis promastigotes—in vitro study. Photodiagn. Photodyn. Ther. 15, 19–24.
Prates, F.V., Dourado, M.E., Silva, S.C., Schriefer, A., Guimarães, L.H., Brito, M.D., Almeida, J., Carvalho, E.M., Machado, P.R., 2017. Fluconazole in the Treatment of Cutaneous Leishmaniasis Caused by Leishmania braziliensis: a Randomized Controlled Trial. Clin. Infect. Dis. 64, 67–71.
Radmanesh, M., Omidian, E., 2017. The pulsed dye laser is more effective and rapidly acting than intralesional meglumine antimoniate therapy for cutaneous leishmaniasis. J. Dermatol. Treat. 28, 422–425.
Rajabi, O., Layegh, P., Hashemzadeh, S., Khoddami, M., 2016. Topical liposomal azithromycin in the treatment of acute cutaneous leishmaniasis. Dermatol. Ther. 29, 358–363.
Ramos, H., Valdivieso, E., Gamargo, M., Dagger, F., Cohen, B.E., 1996. Amphotericin B kills unicellular leishmanias by forming aqueous pores permeable to small cations and anions. J. Membr. Biol. 152, 65–75.
Reithinger, R., Dujardin, J.-C., Louzir, H., Pirmez, C., Alexander, B., Brooker, S., 2007a. Cutaneous leishmaniasis. Lancet Infect. Dis. 7, 581–596.
Reithinger, R., Dujardin, J.C., Louzir, H., Pirmez, C., Alexander, B., Brooker, S., 2007b. Cutaneous leishmaniasis. Lancet. Infect. Dis. 7, 581–596.
Rex, J.H., Stevens, D.A., 2015. 39 - Drugs Active against Fungi, Pneumocystis, and Microsporidia, in: Bennett, J.E., Dolin, R., Blaser, M.J. (Eds.), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition). Content Repository Only!, Philadelphia, pp. 479-494.e474.
Riaz, A., Ahmed, N., Khan, M.I., Haq, I.-uU., Rehman, A.uU., Khan, G.M., 2019. Formulation of topical NLCs to target macrophages for cutaneous leishmaniasis. J. Drug Deliv. Sci. Technol. 54, 101232.
Ribeiro, J.B.P., Miranda-Vilela, A.L., Amorim, A.A.S., Garcia, R.D., Moreira, J.R., Gomes, C.M., Takano, G.H.S., de Oliveira, G.M.F., Lima, A.V., da Silva, I.C.R., Sampaio, R.N.R., 2019. Study of the efficacy of N-methyl glucamine antimoniate (SbV) associated with photodynamic therapy using liposomal chloroaluminium phthalocyanine in the treatment of cutaneous leishmaniasis caused by Leishmania (L.) amazonensis in C57BL6 mice. Photodiagn. Photodyn. Ther. 26, 261–269.
Rodrigues, M.P., Tomaz, D.C., Ângelo de Souza, L., Onofre, T.S., Aquiles de Menezes, W., Almeida-Silva, J., Suarez-Fontes, A.M., Rogéria de Almeida, M., Manoel da Silva, A., Bressan, G.C., Vannier-Santos, M.A., Rangel Fietto, J.L., Teixeira, R.R., 2019. Synthesis of cinnamic acid derivatives and leishmanicidal activity against Leishmania braziliensis. Eur. J. Med. Chem. 183, 111688.
Romero, A.H., Rodríguez, N., Oviedo, H., 2019. 2-Aryl-quinazolin-4(3H)-ones as an inhibitor of leishmania folate pathway:In vitro biological evaluation, mechanism studies and molecular docking. Bioorg. Chem. 83, 145–153.
Rottini, M.M., Amaral, A.C.F., Ferreira, J.L.P., Silva, J.R.dD.A., Taniwaki, N.N., Souza, C. d.S.F.dD., d'Escoffier, L.N., Almeida-Souza, F., Hardoim, D.dD.J., Gonçalves da Costa, S.C., Calabrese, K.dD.S., 2015. In vitro evaluation of (−)α-bisabolol as a promising agent against Leishmania amazonensis. Exp. Parasitol. 148, 66–72.
Sanei-Dehkordi, A., Khamesipour, A., Akbarzadeh, K., Akhavan, A.A., Mir Amin Mohammadi, A., Mohammadi, Y., Rassi, Y., Oshaghi, M.A., Alebrahim, Z., Eskandari, S.E., Rafinejad, J., 2016. Anti Leishmania activity of Lucilia sericata and Calliphora vicina maggots in laboratory models. Exp. Parasitol. 170, 59–65.
Sbeghen, M.R., Voltarelli, E.M., Campois, T.G., Kimura, E., Aristides, S.M., Hernandes, L., Caetano, W., Hioka, N., Lonardoni, M.V., Silveira, T.G., 2015. Topical and Intradermal Efficacy of Photodynamic Therapy with Methylene Blue and Light-Emitting Diode in the Treatment of Cutaneous Leishmaniasis Caused by Leishmania braziliensis. J. Laser. Med. Sci. 6, 106–111.
Schwartz, J., Moreno, E., Calvo, A., Blanco, L., Fernández-Rubio, C., Sanmartín, C., Nguewa, P., Irache, J.M., Larrea, E., Espuelas, S., 2018. Combination of paromomycin plus human anti-TNF-α antibodies to control the local inflammatory response in BALB/mice with cutaneous leishmaniasis lesions. J. Dermatol. Sci. 92, 78–88.
Sepúlveda, A.A.L., Arenas Velásquez, A.M., Patiño Linares, I.A., de Almeida, L., Fontana, C.R., Garcia, C., Graminha, M.A.S., 2020. Efficacy of photodynamic therapy using TiO2 nanoparticles doped with Zn and hypericin in the treatment of cutaneous Leishmaniasis caused byLeishmania amazonensis. Photodiagn. Photodyn. Ther. 30, 101676.
Shanehsaz, S.M., Ishkhanian, S., 2015. A comparative study between the efficacy of oral cimetidine and low-dose systemic meglumine antimoniate (MA) with a standard dose of systemic MA in the treatment of cutaneous leishmaniasis. Int. J. Dermatol. 54, 834–838.
Sharma, S., Anand, N., 1997. Chapter 15 - Organometallics, in: Sharma, S., Anand, N. (Eds.), Pharmacochem. Lib.. Elsevier, pp. 384-392.
Sharquie, K.E., Noaimi, A.A., Al-Ghazzi, A.G., 2015. Treatment of cutaneous leishmaniasis by topical 25% podophyllin solution (single, blinded, therapeutic, controlled study). J. Dermatol. Dermatol. Surg. 19, 108–113.
Silva, A.V., López-Sánchez, A., Junqueira, H.C., Rivas, L., Baptista, M.S., Orellana, G., 2015. Riboflavin derivatives for enhanced photodynamic activity against Leishmania parasites. Tetrahedron 71, 457–462.
Silva, M.L.F., Alves, P.M., Souza, D.M., Silva, M.V., Dos Santos, J.P., Paulino, T.P., Rodrigues, D.B., Rodrigues Jr., V., 2019. Analysis of Macrophage Activation Markers in an Experimental Model of Cutaneous Leishmaniasis Treated with Photodynamic Therapy Mediated by 5-Aminolevulinic Acid. Photobiomodul. Photomed. Laser Surg. 37, 298–304.
Sousa-Batista, A.d.J., Philipon, C.I.M.S., de Souza Albernaz, M., Pinto, S.R., Rossi-Bergmann, B., Santos-Oliveira, R., 2018. New chalcone compound as a promising antileishmanial drug for an old neglected disease: biological evaluation using radiolabelled biodistribution. J. Glob. Antimicrob. Resist. 13, 139–142.
Sousa-Batista, A.J., Pacienza-Lima, W., Ré, M.I., Rossi-Bergmann, B., 2019. Novel and safe single-dose treatment of cutaneous leishmaniasis with implantable amphotericin B-loaded microparticles. Int. J. Parasitol. 11, 148–155.

Sundar, S., Chatterjee, M., 2006. Visceral leishmaniasis - current therapeutic modalities. Indian J. Med. Res. 123, 345–352.
Taheri, A.R., Mashayekhi-Goyonlo, V., Salehi, M., Mohammadzadeh, H., 2020. Non-Ablative Fractional 1,540-nm Er:Glass Laser in the Treatment of Atrophic Cutaneous Leishmaniasis Scars. Lasers Surg. Med. 52, 182–187.
Taylor, V.M., Cedeño, D.L., Robledo, S.M., 2011. Fototerapia para el tratamiento de la leishmaniasis cutánea. Infectio 15, 277–288.
Thacker, S.G., McWilliams, I.L., Bonnet, B., Halie, L., Beaucage, S., Rachuri, S., Dey, R., Duncan, R., Modabber, F., Robinson, S., Bilbe, G., Arana, B., Verthelyi, D., 2020. CpG ODN D35 improves the response to abbreviated low-dose pentavalent antimonial treatment in non-human primate model of cutaneous leishmaniasis. PLoS Negl. Trop. Dis. 14, e0008050.
Tiwari, N., Kumar, A., Singh, A.K., Bajpai, S., Agrahari, A.K., Kishore, D., Tiwari, V.K., Singh, R.K., 2019. 8 - Leishmaniasis control: limitations of current drugs and prospects of natural products, in: Brahmachari, G. (Ed.), Discovery and Development of Therapeutics from Nat. Prod. Against Neg. Trop. Dis. Elsevier, pp. 293-350.
Tomiotto-Pellissier, F., Alves, D.R., Miranda-Sapla, M.M., de Morais, S.M., Assolini, J.P., da Silva Bortoleti, B.T., Gonçalves, M.D., Cataneo, A.H.D., Kian, D., Madeira, T.B., Yamauchi, L.M., Nixdorf, S.L., Costa, I.N., Conchon-Costa, I., Pavanelli, W.R., 2018. Caryocar coriaceum extracts exert leishmanicidal effect acting in promastigote forms by apoptosis-like mechanism and intracellular amastigotes by Nrf2/HO-1/ferritin dependent response and iron depletion: Leishmanicidal effect of Caryocar coriaceum leaf exracts. Biomed. Pharmacother. 98, 662–672.
Torres-Guerrero, E., Quintanilla-Cedillo, M.R., Ruiz-Esmenjaud, J., Arenas, R., 2017. Leishmaniasis: a review. F1000Res 6, 750-750.
Trinconi, C.T., Reimão, J.Q., Bonano, V.I., Espada, C.R., Miguel, D.C., Yokoyama-Yasunaka, J.K.U., Uliana, S.R.B., 2018. Topical tamoxifen in the therapy of cutaneous leishmaniasis. Parasitol 145, 490–496.
Trinconi, C.T., Reimão, J.Q., Coelho, A.C., Uliana, S.R., 2016. Efficacy of tamoxifen and miltefosine combined therapy for cutaneous leishmaniasis in the murine model of infection withLeishmania amazonensis. J. Antimicrob. Chemother. 71, 1314–1322.
Van Bocxlaer, K., Caridha, D., Black, C., Vesely, B., Leed, S., Sciotti, R.J., Wijnant, G.-J., Yardley, V., Braillard, S., Mowbray, C.E., Ioset, J.-R., Croft, S.L., 2019. Novel benzoxaborole, nitroimidazole and aminopyrazoles with activity against experimental cutaneous leishmaniasis. Int. J. Parasitol. 11, 129–138.
Varikuti, S., Oghumu, S., Saljoughian, N., Pioso, M.S., Sedmak, B.E., Khamesipour, A., Satoskar, A.R., 2017. Topical treatment with nanoliposomal Amphotericin B reduces early lesion growth but fails to induce cure in an experimental model of cutaneous leishmaniasis caused by Leishmania mexicana. Acta Trop 173, 102–108.
Velásquez, A.M.A., Ribeiro, W.C., Venn, V., Castelli, S., Camargo, M.S., de Assis, R.P., de Souza, R.A., Ribeiro, A.R., Passalacqua, T.G., da Rosa, J.A., Baviera, A.M., Mauro, A. E., Desideri, A., Almeida-Amaral, E.E., Graminha, M.A.S., 2017. Efficacy of a Binuclear Cyclopalladated Compound Therapy for Cutaneous Leishmaniasis in the Murine Model of Infection with Leishmania amazonensis and Its Inhibitory Effect on Topoisomerase 1B. Antimicrob. Agents Chemother. 61 (8) e00688-17.
Voelkner, N.M.F., Voelkner, A., Costa, J., Sy, S.K.B., Hermes, J., Weitzel, J., Morales, S., Derendorf, H., 2018. Dermal pharmacokinetics of pyrazinamide determined by microdialysis sampling in rats. Int. J. Antimicrob. Agents 51, 190–196.
Waller, D.G., Sampson, A.P., 2018. 51 - Chemotherapy of infections, in: Waller, D.G., Sampson, A.P. (Eds.), Med. Pharmacol. Therap. (Fifth Edition). Elsevier, pp. 581-629.
Weiner, C.P., Mason, C., 2019. P, in: Weiner, C.P., Mason, C. (Eds.), Drugs for Pregnant and Lactating Women (Third Edition). Elsevier, Philadelphia, pp. 651-750.
WHO, 1975. Tropical Diseases Today the Challenge and the Opportunity. World Health Organization, Geneva.
WHO, 2010. In: Control of the leishmaniasis: report of a meeting of the WHO committee on the control of the Leishmaniasis. WHO technical report series.
Wijnant, G.-J., Van Bocxlaer, K., Yardley, V., Harris, A., Alavijeh, M., Silva-Pedrosa, R., Antunes, S., Mauricio, I., Murdan, S., Croft, S.L., 2018. Comparative efficacy, toxicity and biodistribution of the liposomal amphotericin B formulations Fungisome® and AmBisome® in murine cutaneous leishmaniasis. Int. J. Parasitol. 8, 223–228.
Wijnant, G.J., Van Bocxlaer, K., Yardley, V., Murdan, S., Croft, S.L., 2017. Efficacy of Paromomycin-Chloroquine Combination Therapy in Experimental Cutaneous Leishmaniasis. Antimicrob. Agents Chemother. 61 (8) e00358-17.
https://www3.paho.org/hq/index.php?option=com_content&view=article&id=9417:2014-informacion-general-leishmaniasis&Itemid=40370&lang=es#:~:text=La%20leishmaniasis%20es%20una%20enfermedad,variedad%20de%20especies%20de%20fleb%C3%B3tomos (Accessed 15 July 2020).