Leishmaniasis in the contemporary clinical context and its therapeutics interventions: A review

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ABSTRACT

Leishmaniasis is a tropical disease categorized as neglected due to its impact on populations with limited access to resources. It is caused by various species of the parasite Leishmania, belonging to the Trypanosomatidae family within the order Kinetoplastida, and transmitted by sandflies (Phlebotomine sandflies) during the female's blood meal. Several mammal species, which often coexist closely with humans, serve as biological reservoirs. Leishmaniasis manifests in different forms, including cutaneous (CL), diffuse (DCL), mucocutaneous (MCL), visceral (VL), post-kala-azar dermal (PKDL), and mucosal (ML). In this context, our objective is to provide updated information to facilitate access to data for various specialists dealing with this parasitic disease. Simultaneously, we aim to contribute to public education, particularly among populations facing precarious living conditions and challenges in accessing healthcare services in endemic areas. A total of 135 articles on Leishmania were reviewed, sourced from 95 journals. This endeavor serves as a means to identify potential risks and formulate strategies for preventing and mitigating the consequences of leishmaniasis.

Keywords: *Leishmania*, Cutaneous, Diffuse, Mucocutaneous and visceral.

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INTRODUCTION

The genus *Leishmania* is a parasite of vertabrates and belongs to the Trypanomasomatidae family (order *Kinetoplastida*) (Melby *et al*., 2014; Li_evin-Le Moal *et al*., 2015; WHO, 2018; Taylor, 2016), responsible for causing leishmaniasis, a disease transmitted through the bite of sandflies (Melby *et al*., 2019). Classified as a neglected tropical disease, leishmaniasis stands as one of the most significant neglected infectious diseases (Rosário, *et al*., 2017; Azevedo and Marcili, 2020).

Indeed, parasitic diseases caused by protozoa represent a significant challenge for public health worldwide (Stuart *et al*., 2008; Alvar *et al*., 2012; Comandolli-Wyrepkowski *et al*., 2020), due to their high morbidity and mortality (Stuart *et al*., 2008; Alvar *et al*., 2012), among them leishmaniasis, a neglected tropical disease that affects more than 12 million people (WHO, 2015; Alvar *et al*., 2012; Rocha and Petroni, 2017 ; Amaral *et al*., 2019), being endemic in a total of 98 countries spanning five continents (WHO, 2015; Alvar *et al*., 2012; Akhoundi *et al*., 2016; Lara-Silva *et al*., 2017). Only in New Zealand and the South Pacific, there are no records of this disease (Alvar *et al*., 2012).

According to its clinical manifestations, this disease has different forms: cutaneous (LC), diffuse (LCD), mucocutaneous (LCM) and visceral (LV), these interact with the membrane receptors of neutrophils and macrophages (Alvar et al., 2012; Li_evin-Le *et al*., 2015; WHO, 2018), post-kalasar dermal (LDPK) and mucosa (LM) (Alvar *et al*., 2012). Leishmaniasis is regarded as a complex system involving interactions between the parasite and host cell. It features a multifaceted life cycle comprising two distinct forms: the amastigote stage within mammalian hosts and the promastigote stage within the invertebrate vector (promastigote) (Melby *et al*., 2019).

The disease cycle initiates when female Phlebotomus sandflies ingest infected tissue macrophages from mammalian hosts. Within the insect's gut, the membrane of these macrophages ruptures, releasing amastigote forms (lacking flagella) into the mosquito's digestive tract. Despite the presence of digestive enzymes and immune system responses, which could be lethal to the parasite, it is within this environment that the amastigote forms proliferate, transitioning into promastigote metacyclic (flagellated) forms. (Shital, *et al*., 2024). These flagellated forms migrate to the proboscis region, and when the mosquito is about to feed on blood again, the promastigote forms residing in the proboscis are injected into the host. Subsequently, these flagellated forms are phagocytosed by macrophages. Within the acidic environment of lysosomes, they lose their flagellum, transforming into amastigotes. This environment provides favorable conditions for parasite proliferation. The amastigotes then rupture the membrane of these cells, spreading parasites to be phagocytosed by other cells (Figure 1) (Podinovskaia and Descoteaux, 2015). In this process, the parasites interact with immune system cells residing in the epithelial tissue, remodeling the environment of the host's

phagolysosomes. They release molecular patterns associated with tissue damage, thereby establishing the infection (Kupani, *et al*., 2021).

Leishmaniasis can manifest as a zoonotic, anthropozoonotic, or anthroponotic disease, with only a few species being exclusively anthroponotic. Typically, female sandflies infect hosts such as dogs, rodents, marsupials, mongooses, bats, and hyraxes. This illustrates the involvement of various animals as non-human reservoir hosts, along with multiple vectors in the transmission process (Stauch *et al*., 2014). It's worth noting that only a small proportion of infected humans actually develop the disease (Singh *et al*., 2002). The establishment of leishmaniasis in a particular region and the subsequent clinical manifestation of the disease in patients result from a complex interplay of environmental, social, and economic factors, with environmental changes playing a pivotal role in this process. The encroachment of marginalized human communities into unsanitary conditions contributes significantly to this issue (Alemayehu & Alemayehu, 2017; Ellwanger *et al*., 2020), compounded by healthcare challenges across different regions (WHO, 2018; 2019). Human displacement and the loss of biodiversity further exacerbate the problem by promoting the proliferation and spread of blood-sucking insects that serve as vectors for various diseases, thus intensifying human interaction with these organisms (Rosário *et al*., 2017). The issue is compounded by the introduction of domestic animals into areas originally occupied by forests (Oliveira *et al*., 2020). Studies have indicated that vector insects tend to adapt to urban environments due to significant alterations in their natural habitats (Amorin *et al*., 2021), leading to a close interconnection between land use, occupation, and the advancement of the disease. This intricate relationship poses a challenge for the control and mitigation of leishmaniasis, particularly in hot and humid regions.

These factors may indeed impact the socioeconomic conditions of the population, underscoring the importance of maintaining vigilance in rural or endemic areas to identify potential risks. This facilitates efforts to prevent and mitigate the consequences of leishmaniasis. In this context, our objective is to update information variables, streamlining data retrieval for various specialists involved in managing this parasitic disease. Simultaneously, we aim to contribute to public education initiatives.

Figure 1. 1-Leishmaniasis is transmitted through the bite of infected sandflies (females). When feeding on blood, the sandflies inject metacyclic promastigotes (the infective stage) from their proboscis. 2- Promastigotes are phagocytized by macrophages and other phagocytic mononuclear cells. 3- Within these cells, promastigotes transform into amastigotes (the tissue stage without flagella). 4- Amastigotes multiply by simple division and infect other mononuclear phagocytic cells. 5-6 When feeding on the blood of an infected host, female mosquitoes ingest macrophages infected with amastigotes. 7- In the midgut of the sandflies, amastigotes transform into promastigotes. 8- From this point onward, promastigotes multiply, develop, and migrate to the proboscis. *Image of the Centers for Disease Control and Prevention, Global Health, Division of Parasitic Diseases and Malaria.*

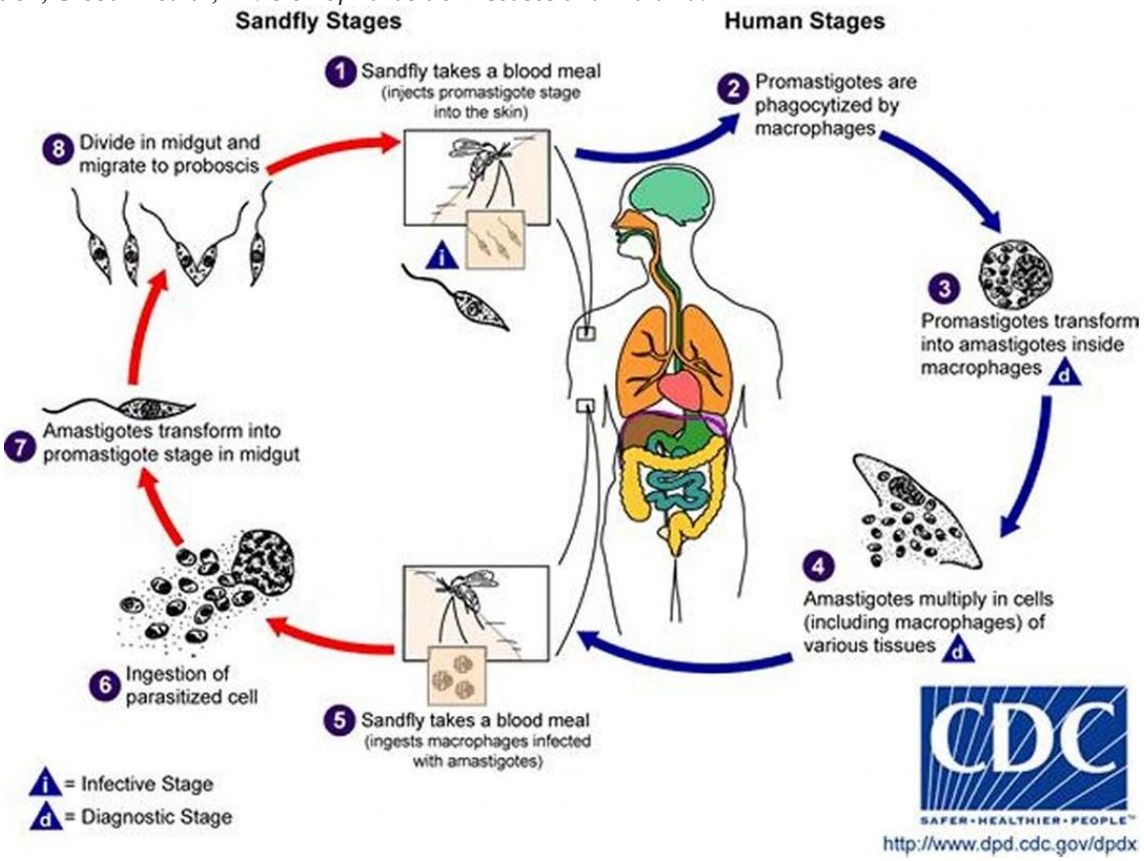
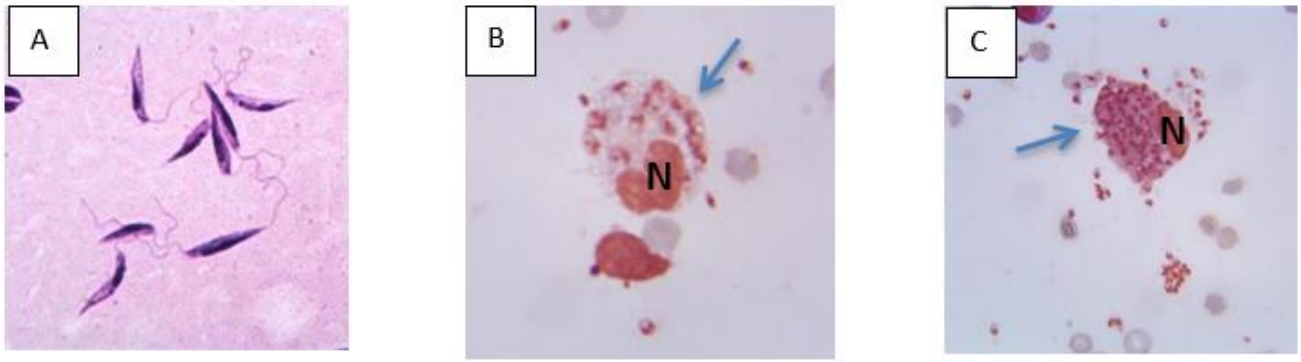


Figure 2. A: Metacyclic flagellated forms; B: Macrophage containing amastigote forms in its cytoplasmic interior (arrow), Nucleous (N); C: Macrophage saturated with amastigotes (arrow), which are released into the extracellular environment, Nucleous (N). 1,250x magnification



MATERIALS AND METHODS

We reviewed 135 articles related to the genre Leishmania, available in 95 different magazines. This also review facilitates the historical compression of the disease.

RESULTS

GENDER *LEISHMANIA*

The causing agent of the disease was discovered in 1898 and 1901 by P. Borovsky, W. B. Leishman and C. Donovan, and the gender Leishmania was first described by R. Ross in 1903 (Weyers, 2016).

HISTORY AND EVOLUTION

Through the study of samples of insects preserved in amber, *Paleoleishmania* proterus was identified, one of the first fossils of *Kinetoplastida* similar to the leishmania studied, demonstrating the protozoan-vector association that was already established in the Lower Cretaceous period (Poinar and Poinar, 2004), around 140 and 100 million years ago. Another study with an insect preserved in amber, identified a progenitor of at least one of the several existing Neotropical Leishmania clades, Paleoleishmania neotropicum, belonging to the Tertiary period, around 65 to 2.6 million years ago (Poinar, 2008).

A hypothesis for the distribution of Leishmanias throughout the world is based on the theory of the supercontinent Gondwana, in the Mesozoic era, that through the separation movement, the subgender Leishmania and Sauroleishmania would be involved in the region of Africa while the subgender Viannia would have developed in the region of the South America (Steverding, 2017).

In human history, in ancient times, through studies that analyze samples by sequencing DNA fragments, they suggest that the visceral variant of leishmaniasis, caused by *L. donovani*, was present in mummies of ancient Egypt (Steverding, 2017).

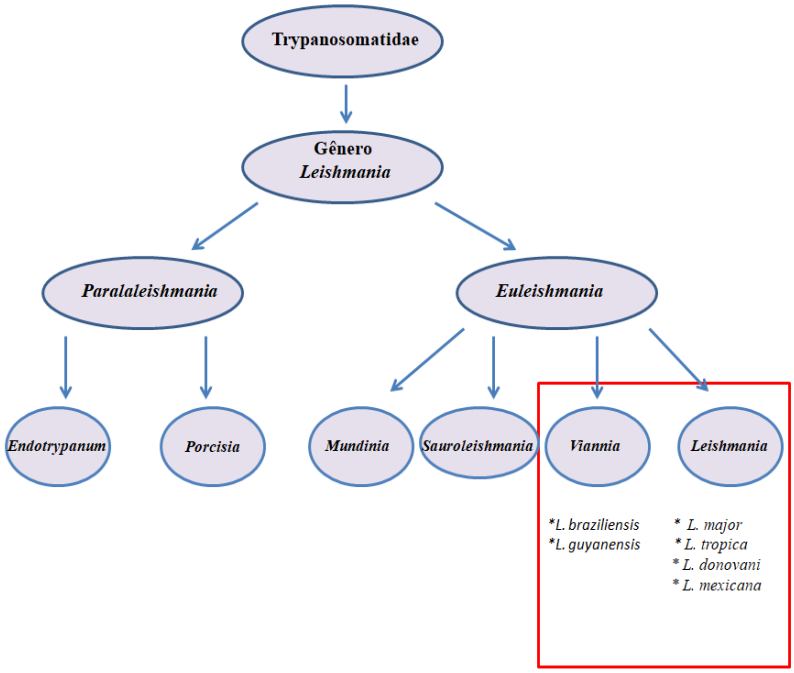
In the Middle Ages, records indicate that the variant of CL was present in the Baghdad region (Steverding, 2017). Other studies through molecular analyzis, indicate that there was the presence of the MCL variant for millennials, in altitude regions, at 2400 meters, more specifically, in San Pedro de Atacama, launching the hypothesis of population migration from endemic regions to areas of altitude (Costa et al. 2009).

A study with a 300-year-old naturally mummified body, in the Itacambira region, a small village in Minas Gerais, Brazil, which at the time was a mining region with a migration of people between Portuguese people and the local population. The experiment demonstrated through molecular techniques of DNA fragments analysis by PCR, that the analyzed sequence showed 100% similarity with *L. tarentolae*. The original host of this species is the lizard *Tarentolae mauritanica*. Even though there is no evidence that L. tarentolae causes disease in humans, the study in question managed to identify through the samples collected in the analyzed body, so that is to say there was enough material to generate a result, showing that the parasite has achieved some success in replication in a human being (Novo, *et al*., 2015).

Geographic distribution, Leishmania behavior, clinical manifestations, among others, were taken into account to separate Leishmania species, with the gender being divided into two subgenders; Leishmania and Viannia (Safjanova, 1982; Lainson and Shaw, 1987). In the beginning of 1970, immunology, biochemistry and molecular typing were taken into account for the identification of Leishmania, however at the end of the same year, the MON zymodeme system used in 1990 was considered (Akhoundi *et al*., 2016). Different concepts and methods were used for the classification of species of this genders, those that evolved later (Weyers, 2016).

There are 21 known species of Leishmania pathogenic to man (Akhoundi *et al*., 2016; 2017), of which we will only take into account in this work the ones represented in Graph 1.

Graph 1. Taxonomic classification of the genus *Leishmania*



Adapted from Akhoundi et al., 2016; 2017. * Each forms a complex of species

FORMS OF LEISHMANIA

Visceral leishmania (LV)

Among leishmaniasis, the visceral variant is the most severe clinical form of manifestation of the disease (Daoudi, *et al*. 2020), transmitted by the etiologic agent *Leishmania chagasi = infantum* to men and dogs as the main reservoir of the parasite, through the sting of the female flobotominium, in the urban environment (Cortes, 2012; Daoudi, *et al*., 2020), however, in the wild environment the following are part: *Dusicyon vetulus; Cerdocyon thous; Didelphis albiventris* (Lara-Silva, *et al*., 2015).

The incidence of VL is produced by the adaptation of the vector in anthropically modified areas (Teles *et al*., 2015), configuring one of the biggest public health problems. When left untreated,

it is responsible for 95% of mortality (Oliveira, *et al*., 2020). Actions to control the VL by government actions have shown low effectiveness, in addition to exposing the fragility of the situation, especially with regard to the processes of assessment and quantification of the disease scenario (Graepp-Fontoura, *et al*., 2020).

As this disease affects organs and viscera of the lymphohematopoietic system, such as the liver, spleen, ganglia and bone marrow, it can also be present in other organs such as kidney (Meneses, *et al*., 2020), and lung (Bispo, *et al*., 2020), with reports of transmission through infected blood in HIV patients at the time of syringe exchange during the use of illicit drugs. In this situation coinfection facilitates the evolution of HIV, through the process of immune exhaustion (Lindoso *et al*., 2012). On the other hand, the death produced by leishmaniasis, can be avoided with an early diagnosis (Sundar and Chakravarty, 2013).

Cutaneous leishmania (LC)

The manifestation of this variant occurs through a local dysfunction producing an erythematous pustule that progresses to ulcers with permanent scarring; in America it is caused primarily by *Leishmania peruviana, L. guyanensis, L. panamensis, L. braziliensis, L. amazonensis* and *L. mexicana*, whereas in Africa, Europe and Asia by *L. major, L. tropica* and *L. aethiopica* (Who, 2015). The parasite infects a variety of host cells, through a complex interaction, however, macrophages and dendritic cells are the main ones in this process. Faced with macrophages residing in the skin, promastigote forms are phagocytized. Inside the phagosomes, after fusion with lysosomes, the promastigote forms become amastigotes in the acidic environment of these organelles, the latter being the infective form of the parasite (Liu and Uzonna, 2012), inducing cell death in the epidermis, in the area parasitized (Martins *et al*., 2014).

Mucosa (LM)

Generally, it fundamentally covers the tissue areas of the nasal, oral, pharynx, larynx and genitalia mucosa, caused mainly by parasites of the *Leishmania viannia* group. The manifestation of this variant has a difficult diagnosis in the initial cases, hampered by the possibility of confusion with other diseases that affect mucous membranes, and must be confirmed with the IgG and IgM serological test (Sbroglio *et al*., 2020).

MECHANISM OF ACTION

The course of the infection is defined by a series of factors of the parasite (species, strain, evolutionary form, initial number) and host (cells of the innate and adaptive immune system, complement system, chemokines, etc.). The location of the parasite in the SFM cells, associated with

the immune response, stimulated by the presence of the parasitic antigen, produces an inflammatory reaction with cellular predominance (chronic inflammatory process of the granulomatous type). The interaction between parasitic multiplication and the host's immune response may produce a more or less severe infection and, depending on the species of parasite involved, tissue damage may occur affecting the cutaneous and / or mucous membrane (LT), or visceral organs (LV) (Conceição-Silva and Alves, 2014).

HOST

Among the hosts, dogs and cats have great importance as reservoirs of leishmaniasis, whether or not they develop the disease. Other mammals such as horses, have shown seropositivity for leishmaniasis (Gazzonis, *et al*., 2020). Cattle also appears as reservoirs (Alam, *et al*., 2018; Paixão-Marques, *et al*., 2019) and this variety in terms of hosts, increases the complexity in combating and controlling the disease, as the methodology currently used is the euthanasia of infected animals (Lopes, *et al*., 2017). However, the euthanasia of domestic animals such as horses, as well as dogs, entails ethical and even legal issues. Some studies reveal that the euthanasia of seropositive dogs demonstrates low efficacy in disease control, necessitating more effective solutions in controlling the spread of leishmaniasis (Passantino; Russo & Coluccio, 2010). Some types of reptiles appear as hosts. A study analyzed the blood of 13 species of lizards in China and managed to identify potentially pathogenic parasites in the animals analyzed, demonstrating that the lizards contribute to the dispersion of the parasites, conferring epidemiological importance (Zhang, *et al*., 2019), this host range reveals the complexity of the disease cycle, therefore the euthanasia procedure must be reevaluated.

DOGS: THE MAIN RESERVOIR IN LEISHMANIASIS

Despite the wide variety of animals classified as hosts, dogs serve as the primary reservoir for leishmaniasis, facilitating transmission of the infection to humans due to their close proximity and interaction with humans, particularly in the more severe cases of the disease, visceral leishmaniasis (VL). Other wild animals such as wolves, coyotes, foxes, opossums, as well as felines can affect this function for the parasite (Costa, 2011), and equines (Costa, 2011; Vieira *et al*., 2020).

Different authors question euthanasia as a treatment for the control of visceral leishmaniasis in seropositive infected dogs, since there is no evidence of efficincy with an increase in cases (Machado, 2016; Nery *et al*., 2017). In addition, other drugs have been used such as Milteforan (Greene and Vandevelde, 2015; Ribeiro *et al*., 2016.)

Allopurinol is a medicine for human use, used to control excess of uric acid (Tonhati, 2018), but when combined with other antimicrobial, antiparasitic and antifungal drugs, they acquire the

leishmaniostatic, leishmanicidal and immunomodulatory functions together (WSPA, 2011). It was also used: Domperidone (Gomez-ochoa et al., 2009); Miltefosine (Miró *et al*., 2009; Manna et. Al., 2009; Brazil, 2016; Nogueira, 2019); Meglumine antimoniate (Ikeda-Garcia *et al*., 2007; Manna *et. al*., 2008; Miró *et al*., 2009; Miró *et al*., 2011; Travi *et al*., 2018); Allopurinol (Miró *et al*., 2011; Greene and Vandevelde, 2015; Jericó *et al*., 2015); Pentamidine (Noli, 2005).

TREATMENTS FOR LEISHMANIASIS

An inconvenient reality is that these neglected diseases, such as Leishmaniasis, end up presenting few treatment alternatives due to the cost-benefit ratio. On the one hand, the cost of the research and development process for companies in the sector makes certain processes unfeasible due to the high costs involved in this process, a period of high investments and uncertain returns, on the other hand, more vulnerable sections of the population suffer from these neglected diseases, in this sense, the public sector such as universities, research institutes, has contributed greatly to the development of new therapeutic processes.

An exemple of this public sector interaction in the search for new treatments, a practically recent study, worked with lipid nanoparticles as carriers of an active ingredient, lupeol, a phenolic triterpenoid found and extracted from vegetables such as *Bauhinia variegata*; *Ehphorbia resinifera* and *Sterculea villosa*, researchers demonstrated positive effects against amastigote forms of visceral leishmania, effectively eliminating them from the spleen and liver of experimental hamsters (Jesus J.A., *et al*., 2023).). Another tratment more focused on natural bioactives uses the free propolis extract is commonly used in experimental models of leishmaniasis, the development of pharmaceuticals offering greater stability and preparations permitting controlled release, or even increased compound bioavailability, constitutes a substantial therapeutic advantage.(Silva R. J., *et al*., 2023).

Another possibility would be the development of vaccines against disease variants; however, currently, commercially effective vaccines against leishmaniasis in humans are not available (Singh & Sundar, 2012). In the interim, some research is advancing toward the development of vaccines, demonstrating efficacy for certain parasite species (Avendaño-Rangel, *et al*., 2024). While these advancements are not yet available in the market, the most commonly used treatment remains pentavalent antimony, which is the most accepted treatment for all forms of leishmaniasis (Meirelas, *et al*., 2017).

According to Table 1, Pentostam and Glucantime are medications for the treatment of leishmaniasis based on pentavalent antimonial compounds, and were introduced as chemotherapeutics in the 1940s, remaining the main drugs used in the treatment of leishmaniasis. They are associated with severe side effects, such as loss of appetite, nausea, muscular dysfunctions,

feelings of fatigue, among others. The principle of action of this class of drugs is based on the susceptibility of amastigotes to the medication in the process of inhibiting glycolytic enzymes and beta-oxidation of fatty acids (FIOCRUZ).

In most cases, treatment is often interrupted due to the severe side effects of antimonials, necessitating the application of a second-line treatment such as Amphotericin B (Carvalho, *et al*., 2019). Amphotericin B was developed for the treatment of systemic fungal infections through a mechanism of action involving binding and interaction with the lipid structures of the parasites' membrane, which are rich in ergosterol in contrast to mammalian cell membranes rich in cholesterol. This interaction increases the permeability of the parasites' cell membrane, leading to the loss of cations such as K+ and ultimately causing cell death. However, Amphotericin B is also associated with severe side effects, which may be minimized by its interaction with liposomal nanoparticles (Cháves-Fumagalli, *et al*., 2015).

Others drugs such as verapamil and nifedipine are calcium channel blockers, both producing similar effects and indicated for the treatment of hypertension, with Nifedipine being a sustained-release medication and Verapamil indicated for reducing high blood pressure crises. Their application in the treatment against leishmaniasis is based on the principle of inhibiting Ca2+ channels, interfering with the binding and interaction of parasites with macrophages, as this process of adhesion to macrophages is dependent on Ca2+ channels. However, no antiparasitic effect was observed (Misra, *et al*., 1991).

The compound 1,4-dihydropyridines, like those previously described, is also a Ca2+ channel blocker known as an antihypertensive agent. It has shown promising effects against visceral leishmaniasis, being able to reverse antimony resistance (Tempone, *et al*., 2009).

Miltefosine is an alkylphospholipid developed for the treatment of cutaneous tumors, which has also demonstrated activity against both cutaneous and visceral leishmaniasis. It was approved in India in 2002, however, it showed teratogenic effects, leading to its prohibition for use in pregnant women (Tiuman, *et al*., 2011). Miltefosine is not capable of causing direct cytotoxicity to the parasite, but it modulates the immune system to stimulate T-helper cells through the induction of Th1 cytokines. This mechanism is essential for treatment success (Palic, *et al*., 2019).

Amphotericin B has demonstrated activity against Leishmania parasites *in vitro* experiments; however, its clinical application is associated with severe side effects such as hypokalemia, renal dysfunction, and decreased hemoglobin levels. The liposomal formulation of amphotericin B could represent a better alternative for tissue absorption, consequently allowing for dose reduction and toxicity reduction. Clinical application in patients infected with visceral leishmaniasis treated with amphotericin B, both in its conventional and liposomal forms, has shown similar results, with around 96% cure rates (Moore and Lockwood, 2010).

Compounds such as ketoconazole, fluconazole, and itraconazole are azole derivatives, which are aromatic heterocyclic organic compounds containing a cyclic chain of five atoms, one of which is nitrogen. These compounds act on the ergosterol synthesis process by inhibiting the demethylation step, hindering lanosterol's development into ergosterol. Statistically, treatments with this class of drugs are similar to treatments with pentavalent antimonials; however, they have not shown satisfactory results against *L. braziliensis*, the species causing mucocutaneous leishmaniasis. The toxicity of these treatments presents certain characteristics that must be taken into account regarding individual patient profiles. It is safe to say that they cannot be used in pregnant women or in patients with hepatic, renal, cardiac, or pancreatic issues (López-Carvajal, *et al*., 2016).

Table 1. Treatments performed on different types of Leishmania. (HUMANS)

TREATMENTS				
VL	**CL**	**MCL**	**Used Drugs**	**References**
x			Nifedipina	Misra *et al*., 1991
x			Verapamil	Misra *et al*., 1991
x	x		1,4-dihidropiridinas	Núñez-Vergara *et al*., 1998; Palit e Ali, 2008; Tempone et al., 2009; Reimão et al., 2010
			Pentostam	Torres *et al*., 2010
		x	N-metilgucamina (Glucantime®)	Yan *et al*., 2003 ; Rath , *et al*., 2003 ; Berman , 2005; Torres *et al*., 2010; Tluman, TS *et al*., 2011; Vera *et al*., 2018; Cataldo , *et al*., 2018;
	x			Viana *et al*., 2013; Navarro *et al*., 2014; Chávez-Fumagalli *et al*., 2015; Miranda *et al*., 2015; Soares *et al*., 2017; Gelvez *et al*., 2018; Regli *et al*., 2018; Vasconcelos *et al*., 2018; Cardona-Arias *et al*., 2018; Da Silva *et al*., 2018; Uribe-Restrepo *et al*., 2018; Sousa-Batista *et al*., 2019; Brito *et al*., 2019; Gonçalves-Oliveira *et al*., 2019; Carvalho *et al*., 2019; Arboleda *et al*., 2019; Ribeiroa *et al*., 2019; Moosaviana *et al*., 2019.
x				Sundar e Chakravarty. 2014; Navarro *et al*., 2014; Chávez-Fumagalli *et al*., 2015; Ministerio da Saude, 2016; Sousa-Batista *et al*., 2019; Alborzi *et al*., 2017; Vieira-Araújo *et al*., 2018; Cardona-Arias, *et al*., 2018; Kasabalis *et al*., 2019; Camara *et al*., 2019;
		x		Alborzi *et al*.,2017; Vasconcelos *et al*., 2018; Cardona-Arias *et al*., 2018; Goyonlo *et al*., 2019; Brito *et al*., 2019; Akhtaria *et al*., 2019;
x	x	x	Amphotericin B	Furtado *et al*., 1960; Tluman *et al*., 2011; Chavez Fumagalli, *et al*., 2015; Cunha *et al*., 2015; Txwari *et al*., 2017; Vera *et al*., 2018; Carvalho *et al*., 2019.
x	x		Miltefosine	Tluman TS *et al*., 2011; Singh e Sundar, 2012; Sundar e Chakravarty, 2015; Twari *et al*., 2017; Vera *et al*., 2018; Soto *et al*., 2018; Carvalho *et al*., 2019; Bamorovat *et al*., 2019; Alonso *et al*., 2019; Palic *et al*., 2019;
TREATMENTS				
VL	**CL**	**MCL**	**Used Drugs**	**References**
x			Anfo b desoxicolato	Hiramoto *et al*., 2019
x			Antimonial Pentavalente	Hiramoto *et al*., 2019
x	x		Estibogloconato de sodio	Moore e Lockwood, 2010; Tluman TS *et al*., 2011
x	x		Paramomicina	Sundar e Chakravarty, 2015
x	x	x	Anfotericina B lipossomal	Wijanant *et al*., 2018; Vera *et al*., 2018; Carvalho *et al*., 2019; Hiramoto *et al*., 2019
	x		ketoconazol	McCall *et al*., 2015; López-Carvajal *et al*., 2016; Vera *et al*., 2018
	x		Fluconazol	López-Carvajal *et al*., 2016
	x		Itraconazol	López-Carvajal *et al*., 2016
			Azitromicina	Toledo-Junior , *et al*., 2014

x	x		Pentamidine	Basselin , *et al*. 2002 ; Croft e Coombs, 2003; Coelho , *et al*.,2003; TlumanTS *et al*., 2011; Singh , *et al*.,2012; Carvalho *et al*., 2019; Vera *et al*., 2018

Leishmania : cutaneous (CL), diffuse (DCL), mucocutaneous (MCL), visceral (VL).

DISCUSSION

Although the contemporary world is in an era of advanced technological development, neglected diseases such as leishmaniasis still plague populations, especially the poorest layers of society. The challenges to control and combat the disease are compounded by the issue of climate change, leading to consequences across various countries. Currently, there is still debate about whether the effects of deforestation and wildfires impact the global thermal cycle. Studies indicate an occurrence of temperature rise in certain regions of the planet; thus, the temperature increase affects the rainfall cycle and promotes uncontrolled cycles of vectors and parasites.

With the increase in concentrated rainfall in certain regions, floods and the spreading of water bodies are likely to occur. Subsequently, as water levels recede, areas that were previously submerged become muddy, forming suitable breeding grounds for sandflies and other vectors of various diseases. This proliferation of vectors is directly proportional or at least systemically interconnected with the loss of biodiversity and consequently, the loss of mosquito predators, leading to a massive increase in certain populations, namely disease vectors.

Thus, the scenario of leishmaniasis tends to become more complex with the advancement of populations into deforested areas, which is directly proportional to economic factors. In pursuit of opportunities, people leave their cities and migrate to these regions to establish themselves or simply generate resources through extractive activities, creating a complex interplay between economic and humanistic factors within a systemic situation.

Another issue to be considered is that protozoal diseases present certain peculiarities and challenges in treatments, and the challenges are greater for vaccine production. In light of this, the treatments currently available in the public health system include meglumine antimoniate, which is associated with heavy side effects and low efficacy. However, this low efficacy cannot be confirmed as a definitive statement, as it depends on many interdependent factors such as the stage of the disease, characteristics of the patient's immune system, adherence to treatment, quality of rest, environmental factors in which the patient is situated, among others.

Other drugs such as azole derivatives have demonstrated similar effectiveness to antimonials, yet for some Leishmania species, they have not yielded satisfactory results. The medication amphotericin B showed satisfactory results in in vitro experiments, but in clinical applications, it produced severe side effects in patients. Another medication, miltefosine, demonstrated teratogenic activities, leading to its prohibition for use in pregnant women. In Brazil, miltefosine is only

marketed for veterinary use, with a high cost for acquisition, thus restricting its widespread use in treating hosts such as domestic dogs.

In the face of all these issues, a tool that tends to yield results as a prevention strategy is information and education about the topic, aimed at raising awareness of the reality and involving concepts that should be addressed with a certain depth. This educational approach should be didactic and explanatory about the risks and characteristics of the disease. Issues such as cleaning households and their surroundings, observing the behavior of domestic animals, and especially the importance of seeking help at health centers when the first symptoms arise should be addressed.

To implement these actions, public policies aimed at these goals must be widely established, as well as combating deforestation. The latter is considered an important action to minimize the spread of the disease and mitigate the effects of climate change by modifying microclimatic factors relative to microregions. These microregions could be subdivided by hydrographic micro-basins, which would contribute to a more global scale in some way.

In addition to these educational activities, it is of utmost importance to incentivize new research in the development of new drugs as well as in the search for more effective active principles against leishmaniasis. This effort aims to improve the future prospects of the disease scenario by providing more effective medications with fewer side effects, thereby enhancing the quality of life and life expectancy of patients. While professionals in the scientific field work with numbers, statistics, and other metrics, the individual suffering caused by the disease is immeasurable.

REFERENCES

1. Akhoundi, M., Kuhls, K., Cannet, A., Votýpka, J., Marty, P., Delaunay, P., & Sereno, D. (2016). A historical overview of the classification, evolution, and dispersión of Leishmania parasites and sandflies. *PLOS Neglected Tropical Diseases, 10*(6), e0004770.

2. Akhoundi, M., Downing, T., Votýpka, J., Kuhls, K., Luke, J., Cannet, A., Ravel, C., Marty, P., Delaunay, P., Kasbari, M., Granouillac, B., Gradoni, L., & Sereno, D. (2017). Leishmania infections: Molecular targets and diagnosis. *Molecular Aspects of Medicine, 57*, 1-29.

3. Akhtaria, J., Faridniab, R., Kalanic, H., Bastanid, R., Fakhard, M., Rezvane, H., & Beydokhtif, A. K. (2019). Potent in vitro antileishmanial activity of a nanoformulation of cisplatin with carbon nanotubes against Leishmania major. *Journal of Global Antimicrobial Resistance, 16*, 11-16.

4. Alam, M. Z., Rahman, M. M., Akter, S., Talukder, H., & Dey, A. R. (2018). An investigation about the possible role of cattle and goats as reservoir hosts for Leishmania donovani in Bangladesh. *Journal of Vector Borne Diseases, 55*(3), 242-244.

5. Alborzi, A. V., Pouladfar, G., Attar, A., Falahi, F., Jafarpour, F., Karimi, A., & Kadivar, R. M. (2017). Effectiveness of short-course meglumine antimoniate (Glucantime®) for treatment of visceral leishmaniasis: A 13-year, multistage, non-inferiority study in Iran. *The American Journal of Tropical Medicine and Hygiene, 96*(1), 182-189.

6. Alemayehu, B., & Alemayehu, M. (2017). Leishmaniasis: A review on parasite, vector and reservoir host. *Health Science Journal, 11*(4), 519.

7. Alonso, L., Cardoso, E. J. S., Gomes, R. S., Mendanha, S. A., Dorta, M. L., & Alonso, A. (2019). Antileishmanial and cytotoxic activities of ionic surfactants compared to those of miltefosine. *Colloids and Surfaces B: Biointerfaces, 183*(1), 110421.

8. Alvar, J., Velez, I. D., Bern, C., Herrero, M., Desjeux, P., Cano, J., Jannin, J., den Boer, M., & Team WHOLC. (2012). Leishmaniasis worldwide and global estimates of its incidence. *PLoS One, 7*(5), e35671.

9. Amaral, M., de Sousa, F. S., Silva, T. A. C., Jimenez, A. J. G., Taniwaki, N. N., Johns, D. M., Lago, J. H. G., Anderson, A. A., & Tempone, A. G. (2019). A semi-synthetic neolignan derivative from dihydrodieugenol B selectively affects the bioenergetic system of Leishmania infantum and inhibits cell division. *Scientific Reports, 9*, 6114.

10. Amorim, R. D. F., de Lima, M. A. P., Souza, R. O. S., Silva, U. M., Santos, A. P., Tavares, A. P., Gadelha, M. S. V., & da Silva, C. G. (2021). Characterization of the sand fly fauna in Barbalha, one of the municipalities with the highest leishmaniasis rates in Brazil. *Parasitology International, 80*(102245), 1-5.

11. Arboleda, M., Barrantes, S., Úsuga, L. Y., & Robledo, S. M. (2019). Successful treatment of cutaneous leishmaniasis with intralesional meglumine antimoniate: A case series. *Revista da Sociedade Brasileira de Medicina Tropical, 52*, e20180211.

12. Azevedo, R. C. F., & Marcili, A. (2020). Skin disturbs caused by Leishmania sp. infection: Review. *Brazilian Journal of Development, 6*(4), 19328-19346.

13. Avendaño-Rangel, F., Agra-Duarte, G., Borba, P. B., Moitinho, V., Avila, L. T., da Silva, L. O., Viana, S. M., Sharma, R., Gannavaram, S., Nakhasi, H. L., & Oliveira, C. I. (2024).

Immunization with centrin-deficient Leishmania braziliensis does not protect against homologous challenge. *Vaccines, 12*, 310.

14. 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. *Microbial Pathogenesis, 128*, 162-170.

15. Basselin, M., Denise, H., Coombs, G. H., & Barrett, M. P. (2002). Resistance to Pentamidine in Leishmania mexicana involves exclusion of the drug from the mitochondrion. *Antimicrobial Agents and Chemotherapy, 46*(2), 3731-3738.

16. Berman, J. (2005). Recent developments in leishmaniasis: Epidemiology, diagnosis, and treatment. *Clinical Infectious Diseases, 7*, 33-38.

17. Bispo, A. J. B., Dória, A. M. L., Roque Pacheco de, A., Neto, J. B., Brito, Valadão de Oliveira, B. A., & Mendonça, F. C. (2020). Pulmonary involvement in human visceral leishmaniasis: Clinical and tomographic evaluation. *PLOS ONE Journal Pone*, e0228176.

18. Brasil. Ministério da Agricultura Pecuária e Abastecimento. (2016). Nota Técnica Nº 11/2016/CPV/DFIP/SDA/GM/MAPA.

19. Brito, C. N., Machado De Assis, T. S., Rabello, A., & Cota, G. (2019). Intralesional infiltration versus parenteral use of meglumine antimoniate for treatment of cutaneous leishmaniasis: A cost-effectiveness analysis. *PLOS Neglected Tropical Diseases, 13*(12), e0007856.

20. Camara, C., Queirós, J., Ribeiro, R., & Teófilo, E. (2019). Meglumine antimoniate combination treatment for relapsing Kala-azar after treatment and secondary prophylaxis failure with liposomal amphotericin B in two HIV-coinfected patients. *Diabetes Case Reports, 12*, e231929.

21. Cardona-Arias, J. A., López-Carvajal, L., Tamayo-Plata, M. P., & Vélez, I. D. (2018). Comprehensive economic evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Colombia. *Public Health, 185*, 1-11.

22. Carvalho, S. H., Frezard, S., Pereira, N. P., Moura, A. S., Ramos, L. M. Q. C., Carvalho, G. B., Rocha, M. O. C. (2019). American tegumentary leishmaniasis in Brazil: A critical review of the current therapeutic approach with systemic meglumine antimoniate and short-term possibilities for an alternative treatment. *Tropical Medicine and International Health, 24*(4), 380-391.

23. Carvalho de Freitas, R., & Marcili, A. A. (2020). Alterações cutâneas secundárias à infecção por Leishmania sp.: revisão de literatura. *The Journal of Infection in Developing Countries, 6*(4), 19328-19346.

24. Cataldo, J. I., Conceição-Silva, F., Antônio, L. F., Schubach, A. O., Marzochi, M. C. A., Valete-Rosalino, C. M., Pimentel, M. I. F., Lyra, M. R., de Oliveira, R. V. C., Barros, J. H. S., Pacheco, R. S., & Madeira, M. F. (2018). Favorable responses to treatment with 5 mg Sbv/kg/day meglumine antimoniate in patients with American tegumentary leishmaniasis acquired in different Brazilian regions. *Sociedade Brasileira de Medicina Tropical, 51*(6), 769-780.

25. Chávez-Fumagalli, M. G., Ribeiro, T. G., Castilho, R. O., Fernandes, S. O. A., Cardoso, V. N., Coelho, C. S. P., Mendonça, D. V. C., Soto, M., Tavares, C. P. T., Faraco, A. A. G., & Coelho, E.

A. F. (2015). New delivery systems for amphotericin B applied to the improvement of leishmaniasis treatment. *Revista da Sociedade Brasileira de Medicina Tropical, 48*, 235-242.

26. Coelho, A. C., Stephen, M., Beverley, B., & Cotrim, P. C. (2003). Functional genetic identification of PRP1, an ABC transporter superfamily member conferring pentamidine resistance in Leishmania major. *Molecular & Biochemical Parasitology, 130*(11), 83-91.

27. Comandolli-Wyrepkowski, C. D., da Costa Paz, A. P., Bezerra Jensen, B. B., & Franco, A. M. R. (2020). Aspectos farmacológicos da terapia medicamentosa utilizada para a leishmaniose cutânea: uma revisão de literatura. *Revista Eletrônica Acervo Saúde, 12*(8), e3352.

28. Conceição-Silva, F., & Alves, C. R. (2014). Leishmanioses do continente americano [online]. Rio de Janeiro: Editora FIOCRUZ. ISBN 978-85-7541-568-9. SciELO Books / SciELO Livros / SciELO Libros.

29. Cortes, S., Vaz, Y., Neves, R., Maia, C., Cardoso, L., & Campino, L. (2012). Risk factors for canine leishmaniasis in an endemic Mediterranean region. *Veterinary Parasitology, 189*(2–4), 189-196.

30. Costa, M. A., Matheson, C., Lachetta, L., Llagostera, A., & Appenzeller, O. (2009). Ancient Leishmaniasis in a Highland Desert of Northern Chile. *PLoS ONE, 4*(9), e6983.

31. Costa, C. H. N. (2011). How effective is dog culling in controlling zoonotic visceral leishmaniasis? A critical evaluation of the science, politics and ethics behind this public health policy. *Revista Da Sociedade Brasileira de Medicina Tropical, 44*(2), 232-242.

32. Croft, S. L., & Coombs, G. H. (2003). Leishmaniasis- current chemotherapy and recent advances in the search for novel drugs. *Trends Parasitology, 19*(11), 502-508.

33. Cunha, M. A., Leao, A. C., De Cassi Soler, R., & Lindoso, J. Á. (2015). Efficacy and Safety of Liposomal Amphotericin B for the Treatment of Mucosal Leishmaniasis from the New World: A Retrospective Study. *The American Journal of Tropical Medicine and Hygiene, 93*(6), 1214-1218.

34. Da Silva, R. S., Carvalho, J. P., Ramalho, D. B., De Senna, M. C. R., Moreira, H. S. A., Rabello, A., Cota, E., & Cota, C. (2018). Towards a standard protocol for antimony intralesional infiltration technique for cutaneous leishmaniasis treatment. *Memórias do Instituto Oswaldo Cruz, 113*, 71-79.

35. Daoudi, M., Boussaa, S., & Hafidi, M. (2020). Potential distributions of phlebotomine sandfly vectors of human visceral leishmaniasis caused by Leishmania infantum in Morocco. *Medical and Veterinary Entomology, 34*, 385-393.

36. Ellwanger, J. H., Kulmann-Leal, B., Kaminski, V. L., Valverde-Villegas, J. M., Da Veiga, A. B. G., Spilki, F. R., Fearnside, P. M., Caesar, L., Giatti, L. L., Wallau, G. L., Almeida, S. E. M., Borba, M. R., Da Hora, V. P., Artur, J., & Chies, B. (2020). Beyond diversity loss and climate change: Impacts of Amazon deforestation on infectious diseases and public health. *Anais da Academia Brasileira de Ciências, 92*(1), e20191375.

37. FIOCRUZ - As Leishmanioses – Laboratório de Imunomodulação - Dpto. de Protozoologia/IOC – FIOCRUZ.

38. Furtado, T. A., Cisalpino, E. O., & Santos, U. M. (1960). In vitro studies of the effect of amphotericin B on Leishmania Brasiliensis. *Antibiotic Chemotherapy, 10*(11), 692-693.

39. Gazzonis, A. L., Bertero, F., Moretta, I., Morganti, G., Mortarino, M., Villa, L., Zanzani, S. A., Morandi, B., Rinnovati, R., Vitale, F., Manfredi, M. T., Cardoso, L., & Veronesi, F. (2020). Detecting antibodies to Leishmania infantum in horses from areas with different epizooticity levels of canine leishmaniosis and a retrospective revision of Italian data. *Parasites Vectors, 13*, 530.

40. Gelvez, A. P. C., Farias, L. H. S., Pereira, V. S., Da Silva, I. C. M., Costa, A. C., Tavares Dias, C. G. B., Costa, R. M. R., Da Silva, S. H. M., & Rodrigues, A. P. D. (2018). Biosynthesis, characterization and leishmanicidal activity of a biocomposite containing AgNPs-PVP-glucantime. *Nanomedicine, 13*(4), 1-18.

41. Gomes-Ochoa, P., Castilho, J. A., Gascón, M., Zarate, J. J., Alvarez, F., & Couto, C. G. (2009). Uso da domperidona no tratamento da leishmaniose visceral canina: um ensaio clínico. *Revista Veterinária, 179*(2), 259-263.

42. Gonçalves-Oliveira, L. F., Souza-Silva, F., Côrtes, L. M. C., Veloso, L. B., Pereira, A. S. B., Cysne-Finkelstein, L., Lechuga, C. G., Bourguignon, C. S., Almeida-Souza, F., Calabrese, S. K., Ferreira, F. V., & Alves, R. C. (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. *Drugs and Drug Resistance, 10*, 101-108.

43. Goyonlo, V. M., Vahabi-Amlashia, B. A., & Taghavia, F. (2019). Successful treatment by adding thalidomide to meglumine antimoniate in a case of refractory anthroponotic mucocutaneous leishmaniasis. *Drugs and Drug Resistance, 11*, 177-179.

44. Graepp-Fontoura, I., Barbosa, D. S., Nascimento, L. F. C., Fontoura, V. M., Ferreira, A. G. N., Santos, F. A. A. S., Sousa, B. S., Santos, F. S., Santos-Neto, M., dos Santos, L. H., & Abreu-Silva, A. L. (2020). Epidemiological aspects and spatial patterns of human visceral leishmaniasis in Brazil. *Parasitology, 147*(14), 1665-1677.

45. Greene, C. E., & Vandevelde, M. C. (Eds.). (2015). Doenças infecciosas em cães e gatos. Guanabara Koogan.

46. Hiramoto, R. M., Oliveira, S. S., Rangel, O., Henriques, L. F., Taniguchi, H. H., Barbosa, J. E. R., Casanoca, C., Affonso, J. V., Sampaio, S. M. P., Spinola, R., Rehder, S., Lindoso, J. A. L., & Tolezano, J. E. (2019). Classificação epidemiológica dos municípios do Estado de São Paulo segundo o Programa de Vigilância e Controle da Leishmaniose Visceral, 2017 / Epidemiological classification of the municipalities of the State of São Paulo according to the Visceral Leishmaniasis Control and Surveillance Program, 2017. *Boletim Epidemiológico Paulista, 16*(181-182), 11-35.

47. Ikeda-Garcia, F. A., Lopes, R. S., Marques, F. J., Lima, V. M., Morinishi, C. K., Bonello, F. L., Zanette, M. F., Perri, S. H., & Feitosa, M. M. (2007). Avaliação clínica e parasitológica de cães naturalmente infectados por Leishmania (Leishmania) chagasi submetidos ao tratamento com antimoniato de meglumina. *Veterinary Parasitology, 143*(3-4), 254-259.

48. Jericó, M. M., Kogika, M. M., & Andrade Neto, J. P. (Eds.). (2015). Tratado de medicina interna de cães e gatos. Guanabara Koogan.

49. Jesus, J. A., Silva, T. N. F., Sousa, I. M. O., Ferreira, A. F., Laurenti, M. D., Costa, P. C., Ferreira, D. C., & Passero, L. F. D. (2023). Nanostructured lipid carriers as robust systems for lupeol delivery in the treatment of experimental visceral leishmaniasis. *Pharmaceuticals, 16*, 1646.

50. Kasabalis, A. D., Chatzis, M. K., Apostolidis, K., Xenoulis, P. G., Buono, A., Petanides, T., Leontides, L. S., Polizopoulou, Z. S., Steiner, J. M., Suchodolski, L. S., & Saridomichelakis, M. N. (2019). Evaluation of nephrotoxicity and ototoxicity of aminosidine (paromomycin)-allopurinol combination in dogs with leishmaniosis due to Leishmania infantum: A randomized, blinded, controlled study. *Experimental Parasitology, 206*.

51. Kupani, M., Pandey, R. K., & Mehrotra, S. (2021). Neutrophils and Visceral Leishmaniasis: Impact on innate immune response and cross-talks with macrophages and dendritic cells. *Journal of Cellular Physiology, 236*(3), 2255-2267.

52. Laison, R., & Shaw, J. J. (1987). Evolution, classification and geographical distribution. In Peters, W., & Lillick-Kendrick, R. (Eds.), *The Leishmaniasis in Biology and Medicine* (Vol. 1, pp. 1-120). Academic Press.

53. Lara-Silva, F. O., Michalsky, E. M., Fortes-Dias, C. L., Fiuza, V. de O., Pessanha, J. E. M., Regina-Silva, S., Avelar, D. M., Silva, M. A., Lima, A. C. V. M. da R., Machado-Coelho, G. L. L., & Dias, E. S. (2015). Epidemiological aspects of vector, parasite, and domestic reservoir in areas of recent transmission and no reported human cases of visceral leishmaniasis in Brazil. *Acta Tropica, 148*, 128-136.

54. Lara-Silva, F. O., Monteiro, E. M., Fortes-Dias, C. L., Fiuza, V. O., & Dias, E. S. (2017). Evaluation of chemical spraying and environmental management efficacy in areas with minor previous application of integrated control actions for visceral leishmaniasis in Brazil. *Acta Tropica, 176*, 109-113.

55. Liesen, V. M., & Loiseau, P. M. (2016). Leishmania hijacking of the macrophage intracellular compartments. *The FEBS Journal, 283*(4), 598-607.

56. Lindoso, J. A. L., Moreira, C. H. V., Cunha, M. A., & Queiroz, I. T. (2018). Visceral leishmaniasis and HIV coinfection: current perspectives. *HIV/AIDS - Research and Palliative Care, 10*, 1-8.

57. Liu, D., & Uzonna, J. E. (2012). The interaction of Leishmania with macrophages and dendritic cells and its influence on the host immune response. *Frontiers in Cellular and Infection Microbiology, 2*(83), 1-8.

58. López-Carvajal, L., Palacio-Barco, M. A., & Cardona-Arias, J. A. (2016). Eficacia de Los Azoles en el Tratamiento de la Leishmaniasis Cutánea. *Archivos De Medicina, 12*(2), 4.

59. Lopes, E. G., Sevá, A. P., Ferreira, F., Nunes, C. M., Keid, L. B., Hiramoto, R. M., Ferreira, H. L., Oliveira, T. M. F. S., Bigotto, M. F. D., Galvis-Ovallos, F., Galati, E. A. B., & Soares, R. M. (2017). Serological and molecular diagnostic tests for canine visceral leishmaniasis in Brazilian endemic area: one out of five seronegative dogs are infected. *Epidemiology and Infection, 145*(12), 2436-2444.

60. Machado, C. P. S., Silva, E. G., & Vilani, R. M. (2016). O uso de um instrumento de política de saúde pública controverso: a eutanásia de cães contaminados por leishmaniose no Brasil. *Saúde e Sociedade, 25*(1), 247-258.

61. Manna, L., Reale, S., Vitale, F., Picillo, E., Pavone, L. M., & Gravino, A. E. (2008). Ensaio de PCR em tempo real em cães infectados por Leishmania, tratados com antimoniato de meglumina e alopurinol. *The Veterinary Journal, 177*(2), 279-282.

62. Manna, L., Vitale, F., Reale, S., Picillo, E., Neglia, G., Vescio, F., & Gravino, A. E. (2009). Estudo da eficácia de miltefosina e alopurinol em cães com leishmaniose. *The Veterinary Journal, 182*(3), 441-445.

63. Martins, A. L. G. P., Barreto, J. Á., Lauris, J. R. P., & Martins, A. C. G. (2014). American tegumentary leishmaniasis: correlations among immunological, histopathological and clinical parameters. *Anais Brasileiros de Dermatologia, 89*(1), 52-58.

64. Melby, P. C., Travi, B. L., & Yaneth Osorio, E. (2014). Leishmania☆, University of Texas Medical Branch, Galveston, Texas, USA ã 2014 Elsevier Inc. All rights reserved. *Reference Module in Biomedical Research*.

65. Melby, P. C., Travi, B. L., & Yaneth-Osorio, E. (2019). Leishmania. In *Reference Module in Biomedical Sciences - Encyclopedia of Microbiology* (4th ed., pp. 769-779). https://doi.org/10.1016/B978-0-12-801238-3.02473-9

66. Meireles, C. B., Maia, L. C., Soares, G. C., Teodoro, I. P. P., Gradelha, M. S. V., Silva, C. L. G., & Lima, M. A. P. (2017). Atypical presentations of cutaneous leishmaniasis: A systematic review. *Acta Tropica, 172*, 240-254.

67. Meneses, G. C., Junior, G. B. S., Tôrres, P. P. B. F., Castro, V. Q., Lopes, R. L., Martins, A. M. C., & Daher, E. F. (2020). Novel kidney injury biomarkers in tropical infections: a review of the literature. *Revista do Instituto de Medicina Tropical de São Paulo, 62*, e14.

68. McCall, L. I., El Aroussi, A., Choi, J. Y., Vieira, D. F., De Muylder, G., Johnston, J. B., Chen, S., Kellar, D., Siqueira-Neto, J. L., Roush, W. R., Podust, L. M., & McKerrow, J. H. (2015). Targeting ergosterol biosynthesis in Leishmania donovani: essentiality of sterol 14 alpha-demethylase. *PLoS Neglected Tropical Diseases, 9*(3), e0003588.

69. Ministério Da Saúde (MS). Secretaria De Vigilância Em Saúde. (2016). *Guia de Vigilância em Saúde*. Brasília: MS.

70. Miranda, M. M., Panis, C., Silva, S. S., Macri, A. J., Kawakami, Y. N., Hayashida, H. T., Madeira, B. T., Acquaro, J. R., Nixdorf, L. S., Pizzatti, L., Ambrósio, R. S., Cecchini, R., Arakawa, S. N., Verri Jr., A. W., Costa, C. I., & Pavanelli, R. W. (2015). Kaurenoic Acid Possesses Leishmanicidal Activity by Triggering a NLRP12/IL-1β/cNOS/NO Pathway. *Mediators of Inflammation, 2015*, 1-10.

71. Miro, G., Oliva, G., Cruz, I., Canavate, C., Mortarino, M., Vischer, C., & BIanciardi, P. (2009). Estudo clínico multicêntrico controlado para avaliar a eficácia e segurança de miltefosina e alopurinol para leishmaniose canina. *Veterinary Dermatology, 20*(5-6), 397-404.

72. Miró, G., Gálvez, R., Fraile, C., et al. (2011). Infectividade para Phlebotomus perniciosus de cães parasitados naturalmente com Leishmania infantum após diferentes tratamentos. *Parasites & Vectors, 4*, 52.

73. Misra, S., Naskar, K., Sarkar, D., & Ghosh, D. K. (1991). Role of Ca2+ ion on Leishmania–macrophage attachment. *Molecular and Cellular Biochemistry, 102*(1-2), 13-18.

74. Moore, E. M., & Lockwood, D. N. (2010). Treatment of visceral leishmaniasis. *Journal of Global Infectious Diseases, 2*(2), 151-158.

75. Moosaviana, 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. *Experimental Parasitology, 200*, 30-35.

76. Nogueira, F. S., Avino, V. C., Galvis-Ovallos, F., Pereira-Chioccola, V. L., Batistella Moreira, M. A., Romariz, A. P. P. L., Molla, L. M., & Menz, I. (2019). Uso de miltefosina no tratamento da leishmaniose visceral canina causada por Leishmania infantum no Brasil. *Parasites & Vectors, 12*, 79.

77. Navarro, P., Sánchez-Moreno, M., Marín, C., García-España, E., Ramírez-Macías, I., Olmo, F., Rosales, J. M., Gómez-Contreras, F., Yunta, J. M. R., & Gutiérrez-Sánchez, R. (2014). In vitro leishmanicidal activity of pyrazole-containing polyamine macrocycles which inhibit the Fe-SOD enzyme of Leishmania infantum and Leishmania braziliensis species. *Parasitology, 141*(13), 1742-1752.

78. Nery, G., Becerra, D. R. D., Borja, L. S., Magalhães-Junior, J. T., Souza, B. M. P. S., Franke, C. R., Veras, P. S. T., Larangeira, D. F., & Barroun-Melo, S. M. (2017). Avaliação da infectividade parasitária a Lutzomyia longipalpis por xenodiagnóstico em cães tratados para leishmaniose visceral naturalmente adquirida. *Pesquisa Veterinária Brasileira, 37*(7), 701-707.

79. Noli, C., & Auxilia, S. T. (2005). Tratamento da Leishmaniose visceral canina do Velho Mundo: uma revisão sistemática. *Veterinária Dermatologia, 16*(4), 213-232.

80. Novo, S. P. C., Leles, D., Bianucci, R., & Araujo, A. (2015). Leishmania tarentolae molecular signatures in a 300 hundred-years-old human Brazilian mummy. *Parasites & Vectors, 8*, 72.

81. Núñez-Vergara, L. J., Squella, J. A., Bollo-Dragnic, S., Marín-Catalán, R., Pino, L., Díaz-Araya, G., & Letelier, M. E. (1998). Isradipine and lacidipine: effects in vivo and in vitro on Trypanosoma cruzi epimastigotes. *General Pharmacology, 30*, 85-87.

82. Oliveira, G. G., Castilho, M. O., & Souza, A. I. (2020). Calcium, phosphorus, urinary fractional excretion of phosphorus and parathormone in dogs with visceral leishmaniasis. *Acta Veterinaria Brasilica, 14*(3), 180-184.

83. Organização Mundial da Saúde (OMS). (2015). *Leishmaniasis. Nota descriptiva N°375*.

84. Organização Mundial da Saúde (OMS). (2019). *Leishmaniasis*. 14 mar. 2019. Disponível em: http://www.who.int/mediacentre/factsheets/fs375/.

85. Organização Pan-Americana da Saúde (OPAS). (2013). *United, Washington (DC): OPAS* (Official Document 345).

86. Paixão-Marques, M. S., Alves-Martin, M. F., Guiraldi, L. M., Wesley José dos Santos, W. J., Lemos, F. A., Sánchez, G. P., Richini-Pereira, V. B., & Lucheis, S. B. (2019). First isolation of Leishmania infantum by blood culture in bovines from endemic area for canine visceral leishmaniasis. *Parasitology, 146*(7), 911-913.

87. Palit, P., & Ali, N. (2008). Oral therapy with amlodipine and lacidipine, 1,4-dihydropyridine derivatives showing activity against experimental visceral Leishmaniasis. *Antimicrobial Agents and Chemotherapy, 52*, 374-377.

88. Palic, S., Bhairosing, P., Beijnen, J. H., & Dorlo, T. P. C. (2019). Systematic Review of Host-Mediated Activity of Miltefosine in Leishmaniasis through Immunomodulation. *Antimicrobial Agents and Chemotherapy, 63*(7), e02507-18.

89. Passantino, A., Russo, M., & Coluccio, P. (2010). Canine leishmaniosis and euthanasia in Italy: a critical legal-ethical analysis. *Revista de ciência e técnica da Officina Internacional de Epizootias, 29*(3), 537-548.

90. Podinovskala, M., & Descoteaux, A. (2015). Leishmania and the macrophage: a multifaceted interaction. *Future Microbiology, 10*(1), 111-129.

91. Poinar Jr., G. (2008). Lutzomyia adiketis sp. n. (Diptera: Phlebotomidae), a vector of Paleoleishmania neotropicum sp. n. (Kinetoplastida: Trypanosomatidae) in Dominican amber. *Parasites & Vectors, 1*, 22.

92. Poinar Jr., G., & Poinar, R. (2004). Paleoleishmania proterus n. gen., n. sp., (Trypanosomatidae: Kinetoplastida) from Cretaceous Burmese Amber. *Protist, 155*, 305-310.

93. Rath, S., Trivelin, L. A., Imbrunito, T. R., Tomazela, D. M., Nunes de Jesús, M., & Marzal, P. C. (2003). Antimoniais empregados no tratamento da leishmaniose: estado da arte. *Química Nova, 26*(4), 550-555.

94. Reimão, J. Q., Scotti, M. T., & Tempone, A. G. (2010). Anti-leishmanial and antitrypanosomal activities of 1,4-dihydropyridines: in vitro evaluation and structure–activity relationship study. *Bioorganic and Medicinal Chemistry, 18*, 8044-8053.

95. Regli, I. B., Fernández, O. L., Martínez-Salazar, B., Gómez, M. D., Saravia, N. G., & Tacchini-Cottier, B. (2018). Resistance of Leishmania (Viannia) Panamensis to Meglumine Antimoniate or Miltefosine Modulates Neutrophil Effector Functions. *Frontiers in Immunology, 9*, 1-11.

96. Ribeiro, J.B.P., Miranda-Vilela, A.L., Graziani, D., Gomes, M.R.A., Amorim, A.A.R., Garcia, R.D., Souza Filho, J., Tedesco, A.C., Lucas Primo, F., Moreira, J.R., Lima, A.V., & Sampaio, R.N.R. (2016). Evaluation of the efficacy of systemic miltefosine associated with photodynamic therapy with liposomal chloroaluminium phthalocyanine in the treatment of cutaneous leishmaniasis caused by *Leishmania (L.) amazonensis* in C57BL/6 mice. *Photodiagnosis and Photodynamic Therapy, 13*, 282-290.

97. 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., Farias De Oliveira, G.M., 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. *Photodiagnosis and Photodynamic Therapy, 26*, 261-269.

98. Rocha, G.P., & Petroni, T.F. (2017). Leishmaniose visceral e tegumentar americana. *Revista Saúde Uni Toledo, 1*(02), 40-55.

99. Rosário, M.S., Oliveira, M.L., Lima, C.L., Vieira, M.V., Carneiro, J.A., & Marques da Costa, F. (2017). Doenças tropicais negligenciadas: caracterização dos indivíduos afetados e sua distribuição espacial. *Revista Brasileira de Pesquisa em Ciências da Saúde, 19*(3), 118-127.

100. Safjanova, V.M. (1982). Classification of the genus *Leishmanis* Ross. In: *The leishmaniasis. Protozoology, Academy of Sciences, USSR. All Union Society of Protozoologists* (Chapter 11, pp. 95-101). Lennigrad.

101. Sbroglio, L.L., Maiolini, V.M., Rabelo, I.M.M.A., Giraldelli, G.A., Tuccori, L.P., & Cunha, R.G. (2020). Mucocutaneous leishmaniasis in a cocaine user: diagnostic and therapeutic knowledge. *Revista da Sociedade Brasileira de Medicina Tropical, 53*, e40.

102. Shital, Gupta, C., Krishnan, A., & Selvapandiyan, A. (2024). Factors affecting *Leismania* infection in sand fly. In *Springer Nature* (pp. 63-79).

103. Silva, R.J., Amorim, A.A., Santos, J.H.F., Lima, A.J., Lima, B.J., Beretta, A.A., & Borges, M.V. (2023). Leishmanicidal and immunomodulatory properties of Brazilian green propolis extract (EPP-AF) and a gel formulation in a pre-clinical model. *Frontiers in Pharmacology, 14*. https://doi.org/10.3389/fphar.2023.1013376

104. Singh, S., Kumari, V., & Singh, N. (2002). Predicting kala-azar disease manifestations in asymptomatic patients with latent *Leishmania donovani* infection by detection of antibody against recombinant K39 antigen. *Clinical and Diagnostic Laboratory Immunology, 9*, 568e572.

105. Singh, B., & Sundar, S. (2012). Leishmaniosis: vaccine candidates and perspectives. *Vaccine, 30*(26), 3834-3842.

106. Soto, J., Soto, P., Ajata, A., Rivero, D., Luque, C., Tintaya, C., & Bermanm, J. (2018). Miltefosine combined with intralesional pentamidine for *Leishmania braziliensis* cutaneous leishmaniasis in Bolivia. *The American Journal of Tropical Medicine and Hygiene, 99*(5), 1153–1155.

107. Steverding, D. (2017). The history of Leishmaniasis. *Parasites & Vectors, 10*, 82.

108. Soares, V.B., De Almeida, A.S., Sabroza, P.C., & Vargas, W.P. (2017). Vigilância epidemiológica da leishmaniose tegumentar: análise territorial local. *Revista de Saúde Pública, 51*, 1-11.

109. Sousa-Batista, A.J., Coutinho, C.C., Do Carmo, F.S., Albernaz, M.Z., & Santos-Oliveira, R. (2019). Polycaprolactone antimony nanoparticles as drug delivery system for leishmaniasis. *American Journal of Therapeutics, 26*, e12–e17.

110. Sundar, S., & Chakravarty, J. (2013). Leishmaniasis: An update of current pharmacotherapy. *Expert Opinion on Pharmacotherapy, 14*(1), 53-63.

111. Sundar, S., & Chakravarty, J. (2014). An update on pharmacotherapy for leishmaniasis. *Expert Opinion on Pharmacotherapy, 16*, 1-16.

112. Sundar, S., & Chakravarty, J. (2015). Investigational drugs for visceral leishmaniasis. *Expert Opinion on Investigational Drugs, 24*(1), 43-59.

113. Stuart, K., Brun, R., Croft, S., Fairlamb, A., Gurtler, R.E., McKerrow, J., Reed, S., & Tarleton, R. (2008). Kinetoplastids: Related protozoan pathogens, different diseases. *The Journal of Clinical Investigation, 118*, 1301–1310.

114. Stauch, A., Duerr, H.P., Picado, A., Ostyn, B., Sundar, S., Rijal, S., Boelaert, M., Dujardin, J.C., & Eichner, M. (2014). Model-based investigations of different vector-related intervention strategies to eliminate visceral leishmaniasis on the Indian subcontinent. *PLoS Neglected Tropical Diseases, 8*(11), e2810.

115. Taylor, M.A., Coop, R.L., & Wall, R.L. (2016). *Veterinary Parasitology* (4th ed.). Wiley Blackwell.

116. Teles, A.P.S., Herrera, H.M., Ayres, F.M., Brazuna, J.C.M., & de Abreu, U.G.P. (2015). Fatores de risco associados à ocorrência da leishmaniose visceral na área urbana do Município de Campo Grande/MS. *Hygeia, 11*(21), 35-48.

117. Tempone, A.G., Taniwaki, N.N., & Reimão, J.Q. (2009). Antileishmanial activity and ultrastructural alterations of *Leishmania (L.) chagasi* treated with the calcium channel blocker nimodipine. *Parasitology Research, 105*, 499–505.

118. Tluman, T.S., Santos, A.O., Ueda-Nakamura, T., Filho, B.P., & Nakamura, C.V. (2011). Recent advances in leishmaniasis treatment. *International Journal of Infectious Diseases, 15*, e525–e532.

119. Tiwari, N., Gedda, M.R., Tiwari, V.K., Singh, S.P., & Singh, R.K. (2017). Limitations of current therapeutic options, possible drug targets and scope of natural products in control of leishmaniasis. *Mini-Reviews in Medicinal Chemistry, 18*, 26–41.

120. Toledo Junior, A., Daher, A.B., Amaral, T.A., Carvalho, S.F.G., Romero, G.A.S., & Rabello, A. (2014). Poor response to azithromycin in cutaneous leishmaniasis leading to a premature interruption of a multicentric phase III clinical trial in Brazil. *Revista da Sociedade Brasileira de Medicina Tropical, 47*(6), 756-762.

121. Tonhati, W. (2018, July 10). Tratamento para leishmaniose é eficiente, mas ainda é caro para a maioria. *Jornal Midiamax*. https://www.midiamax.com.br/cotidiano/2018/tratamento-paraleishmaniose-e-eficiente-mas-ainda-e-caro-para-maioria.

122. Torres, D.C., Adaui, V., Ribeiro-Alves, M., Romero, G.A., Arévalo, J., Cupolillo, E., & Dujardin, J.C. (2010). Targeted gene expression profiling in *Leishmania braziliensis* and *Leishmania guyanensis* parasites isolated from Brazilian patients with different antimonial treatment outcomes. *Infection, Genetics and Evolution, 10*, 727–733.

123. Travi, B.L., Cordeiro-Da-Silva, A., Dantas-Torres, F., & Miró, G. (2018). Leishmaniose visceral canina: diagnóstico e manejo do reservatório que vive entre nós. https://doi.org/10.1371/journal.pntd.0006082.

124. Uribe-Restrepo, A., Cossio, A., Desa, M.M., Davalos, D., & Del Mar Castro, M.I. (2018). Interventions to treat cutaneous leishmaniasis in children: A systematic review. *PLOS Neglected Tropical Diseases, 12*(7), 1-16.

125. Vasconcelos, J.M., Gomes, C.G., Sousa, A., Teixeira, A.B., & Lima, J.M. (2018). Leishmaniose tegumentar americana: perfil epidemiológico, diagnóstico e tratamento. *RBAC, 50*, 221-227.

126. Vera, A.M., Casadiego, O.A., Mantilla, J.C., & Escobar, P. (2018). Evaluación De Formulaciones De Ketoconazol Para Uso Tópico En Leishmaniasis Cutánea Por *Leishmania (Viannia)*. *Revista Peruana de Medicina Experimental y Salud Pública, 35*(3), 476-482.

127. Viana, A.G., Mayrink, W., Fraga, C.A.C., Silva, L.M., Domingos, P.L.B., Bonan, P.R.F., De Paula, A.M.B., & Botelho, A.C.C. (2013). Histopathological and immunohistochemical aspects of American cutaneous leishmaniasis before and after different treatments. *Anais Brasileiro de Dermatologia, 88*, 32-40..

128. Vieira-Araújo, M.F., Rondon, M.C.F., Vieira, P.G.I., Mendes, P.N.F., Freitasa, C.C.J., & Morais, M.S. (2018). Sinergism between Alkaloids Piperine and Capsaicin with Meglumine Antimoniate against *Leishmania infantum*. *Experimental Parasitology, 188*, 79-82.

129. Vieira, A.F., Alvarenga, T.F.F., Oliveira, S.F.C., Coelho, E.G., Teixeira, M.C., Moscon, L.A., Rondon, D.A., & Pereira, C.M. (2020). *14*(8): 163.

130. Yan, S.C., Li, F., Ding, K., & Sun, H. (2003). Reduction of pentavalent antimony by trypanothione and formation of a binary and ternary complex of antimony (III) and trypanothione. *Journal of Biological Inorganic Chemistry, 8*, 689-697.

131. WSPA. (2011). *Leishmaniose visceral canina: um manual para o clínico veterinário*. Sociedade Mundial de Proteção Animal.

132. Weywers, W.B. (2016). Leishmania brief remainder of this life and work on the occasion of his 150th birthday. *The American Journal of Dermatopathology, 38*, 436-444.

133. Wijnant, G.J., Bocxlaer, K.V., 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. *Drugs and Drug Resistance, 8*, 223–228.

134. World Health Organization. (2015). Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected diseases. Geneva: WHO.

135. World Health Organization. (2018). Leishmaniasis. http://www.who.int/topics/leishmaniasis/en/

136. Zhang, J.R., Guo, X.G., Chen, H., Liu, J.L., Gong, X., Chen, D.L., & Chen, J.P. (2019). Pathogenic *Leishmania* spp. detected in lizards from Northwest China using molecular methods. *BMC Veterinary Research, 15*:446.