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Tropical Medicine and Leishmaniasis: Unraveling the Complexities of a Neglected Tropical Disease

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Abstract

Protozoan parasites of the genus Leishmania are the cause of the vector-borne disease leishmaniasis, which poses a serious threat to global public health in tropical and subtropical areas. Despite being common and having a significant effect on human health, leishmaniasis is still a neglected tropical disease, with little funding available for investigation and prevention. This article examines the relationship between leishmaniasis and tropical medicine, emphasizing the particular difficulties this intricate illness presents and the continuous efforts to treat it. With its emphasis on illnesses common in tropical areas, tropical medicine offers an essential foundation for comprehending the pathophysiology, epidemiology, and treatment of leishmaniasis. Even with these developments, leishmaniasis detection and treatment still face difficulties, especially in areas with low resources where the illness is most prevalent. Disease control is still hampered by a lack of access to reliable diagnostic instruments and efficient therapies, which emphasizes the necessity of ongoing funding for research and development. In conclusion, there is a rare chance to address the intricacies of this neglected tropical illness thanks to the convergence of research on leishmaniasis and tropical medicine. Through the utilization of interdisciplinary techniques and cooperative endeavours, we can progress our comprehension of leishmaniasis and formulate inventive approaches for managing and eradicating the disease, consequently enhancing the welfare and health of impacted communities.

Keywords: Protozoan , leishmania, tropical medicine, epidemiology, neglected tropical illness, vector-borne diseases

INTRODUCTION

Leishmaniasis is a poorly treated tropical disease that affects millions of people globally. It is carried by sandflies and is brought on by a protozoan parasite belonging to the genus Leishmania[1,2]. Leishmaniasis continues to be underreported and underfunded despite having a substantial negative impact on public health, especially in areas where it is endemic[2,3]. In this piece, we examine the intricacies of leishmaniasis from the standpoint of tropical medicine, emphasizing the various obstacles and continuous endeavors to tackle this underappreciated illness [1].

A protozoa parasite from more than 20 Leishmania species is the cause of leishmaniasis. More than 90 species of sandflies are known to transmit leishmania parasites (Figure 1).

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TYPES OF LEISHMANIA DISEASE

Visceral Leishmaniasis

In more than 95% of cases, kala-azar, another name for visceral leishmaniasis (VL), is fatal if treatment is not received. Its characteristic symptoms include anemia, enlarged spleen and liver, weight loss, and intermittent fever episodes [2, 3]. Most incidences happen in India, Brazil, and East Africa. Only 25–45% of the estimated 50 000–

90 000 new cases of VL that occur annually are reported to the WHO [3]. It has the capacity to spread and kill. In more than 95% of cases, kala-azar, another name for visceral leishmaniasis (VL), is fatal if treatment is not received [4, 5].

Cutaneous Leishmaniasis

The most prevalent type, cutaneous leishmaniasis (CL), results in skin lesions, primarily ulcers, on exposed body areas. These may result in severe disabilities or stigma, as well as lifelong scars [4, 5]. Approximately 95% of CL cases are found in the Americas, the Mediterranean basin, the Middle East, and central Asia. Between 600,000 and 1 million new cases are thought to arise globally each year, however only about 200 000 of those cases are reported to the WHO [3, 4].

Mucocutaneous leishmaniasis

The mucocutaneous leishmaniasis causes the throat, mouth, and nose mucous membranes to completely or partially degrade. In Bolivia, Brazil, Ethiopia, and Peru, mucocutaneous leishmaniasis accounts for over 90% of cases. Mucosal leishmaniasis typically presents with uncommon and persistent nasal symptoms (e.g., stuffiness, bleeding), though oral or pharyngeal symptoms can also occur initially [5].

Post-kala-azar dermal leishmaniasis (PKDL)

This condition, which appears as a macular, papular, or nodular rash on the face, upper arms, and trunk, usually develops after visceral leishmaniasis. Even though it's rare, reports of it from Brazil and HIV-coinfected VL cases brought on by infantum have been made[5,6]. Though it can happen sooner, it typically manifests six months to a year or more after kala-azar appears to have been cured. Individuals who have PKDL are thought to be possible carriers of Leishmania infection [6] (Figure 2).

UNDERSTANDING THE EPIDEMIOLOGY AND TRANSMISSION DYNAMICS

Understanding the dynamics of leishmaniasis transmission and epidemiology is critical to the field of tropical medicine. To shed light on the intricate cycles of Leishmania parasite transmission, researchers in this field examine the ecological factors controlling the distribution of sandfly vectors and their interactions with reservoir hosts [6, 7]. Furthermore, research on the effects of environmental changes, like urbanization and deforestation, sheds light on the consequences of leishmaniasis's expanding geographic range for disease control measures [7, 8].

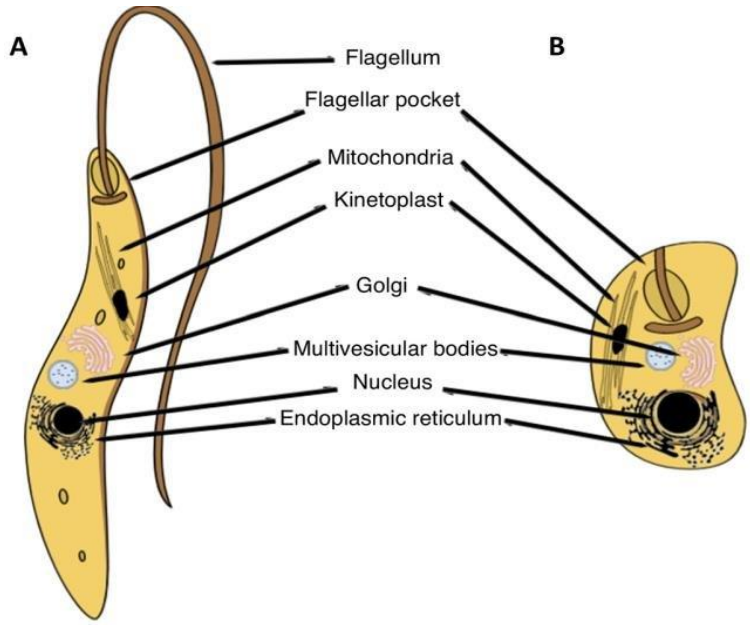


Figure 1. Anatomy of leishmania parasite cell.

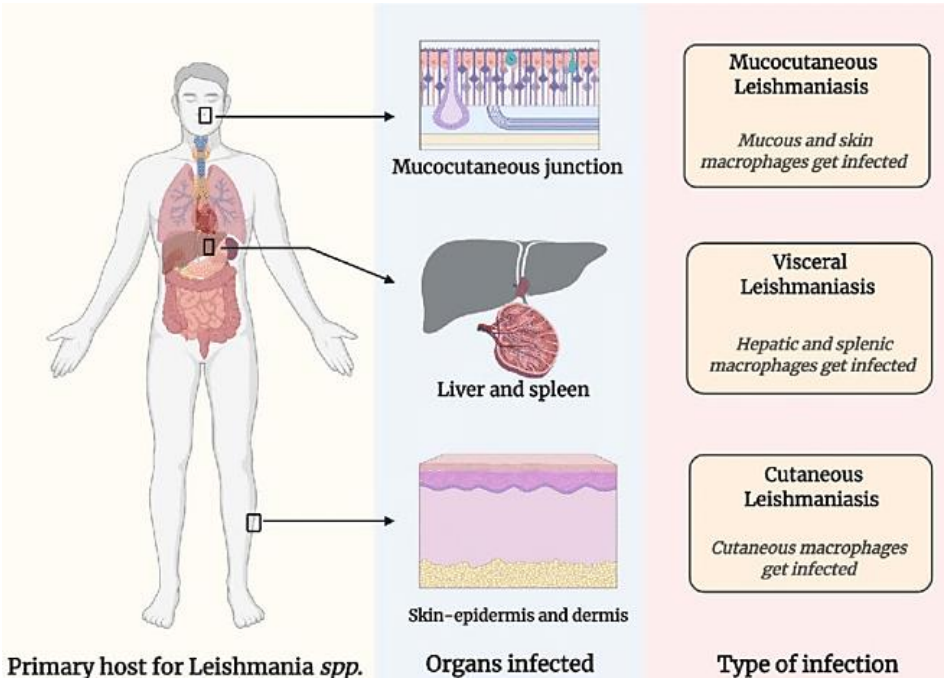


Figure 2. Types of Leishmaniasis.

Epidemiology

People in focal regions of about 90 nations in the tropics, subtropics, and southern Europe are infected with leishmaniasis. Rain forests and deserts are among the several ecological situations[6]. Leishmaniasis is typically more prevalent in rural than in urban regions, while it can occur in some urban fringe areas. The geographic range of sand fly vectors and the regions of the world where leishmaniasis is present may increase due to changes in the climate and other environmental factors [7, 8].

Everyone on every continent, with the exception of Australia and Antarctica, has leishmaniasis

- Many parts of Asia, the Middle East, Africa (mostly in the tropical regions and North Africa, with a few cases elsewhere), and southern Europe in the Old World (the Eastern Hemisphere) are affected by leishmaniasis. It is absent from both Australia and the Pacific islands[9].
- It can be found in several parts of the New World (the Western Hemisphere), specifically in Mexico, Central America, and South America. Chile and Uruguay don't have it. There have been sporadic cases of cutaneous leishmaniasis in Texas and Oklahoma[8,9].

It is challenging to determine the number of new instances because it can fluctuate or alter over time. Estimates of the number of new cases of cutaneous leishmaniasis each year have varied from roughly 700,000 to 1.2 million or more[8,9]. The annual projected number of new cases of visceral leishmaniasis may have dropped to less than 100,000, however earlier estimates varied as high as 400,000 cases or more. The leishmaniasis cases under evaluation in the US are representative of immigration and travel trends[8,9]. For instance, a large number of cutaneous leishmaniasis cases among civilian travelers from the United States have been contracted in popular Latin American tourist destinations like Costa Rica[10]. Overall, human infection is caused by more than 20 species (types) of Leishmania parasites, which are spread by about 30 species of phlebotomine sand flies. Specific sand flies are responsible for the dissemination of specific parasite species. Twilight, evening, and nighttime are often the busiest times for sand fly vectors (from dusk to morning)[10].

Transmission of Disease

The most significant process is the formation of a "blocked fly" as a result of the parasites in the anterior midgut secreting **Promastigote Secretory Gel (PSG).** This prevents the sand fly from feeding

on blood, forcing it to regurgitate PSG, which ends up deposited in the epidermis of a mammalian host together with infectious metacyclic promastigotes[9,10]. Other possible mechanisms of transmission include damage to the stomodeal valve, the presence of parasites in the salivary glands, and the discharge of parasites from the anus of infected sand flies [9]. There is also discussion of the variations in the methods of transmission used by parasites belonging to the three subgenera, Sauroleishmania, Viannia, and Leishmania [10].

The **Female Phlebotomine Sand Fly Bite** is the sole known method of infection. About 700 species of phlebotomine sand flies have been reported to far. They are dipteran insects that belong to the **Psychodidae** family. Roughly 10% of these have been implicated as leishmaniasis vectors with varied degrees of certainty; for roughly 30 species, strong evidence of vectorial potential has been shown [11] (Figure 3).

PATHOPHYSIOLOGY

Leishmaniasis Spread Through Blood Feeding.

- *Step 1:* Female Phlebotomines inject metacyclic prosmastigotes into the skin of mammals during bloodstream
- *Step 2:* In the skin after getting centralized by Dendritic & macrophages, prosmastigotes differentiate into amastigotes & multiply in the cells with the parasitophorous vacuoles.
- *Step 3:* Cutaneous & Mucocutaneous leishmaniasis are the consequences of an intense proinflammatory Th1 response.

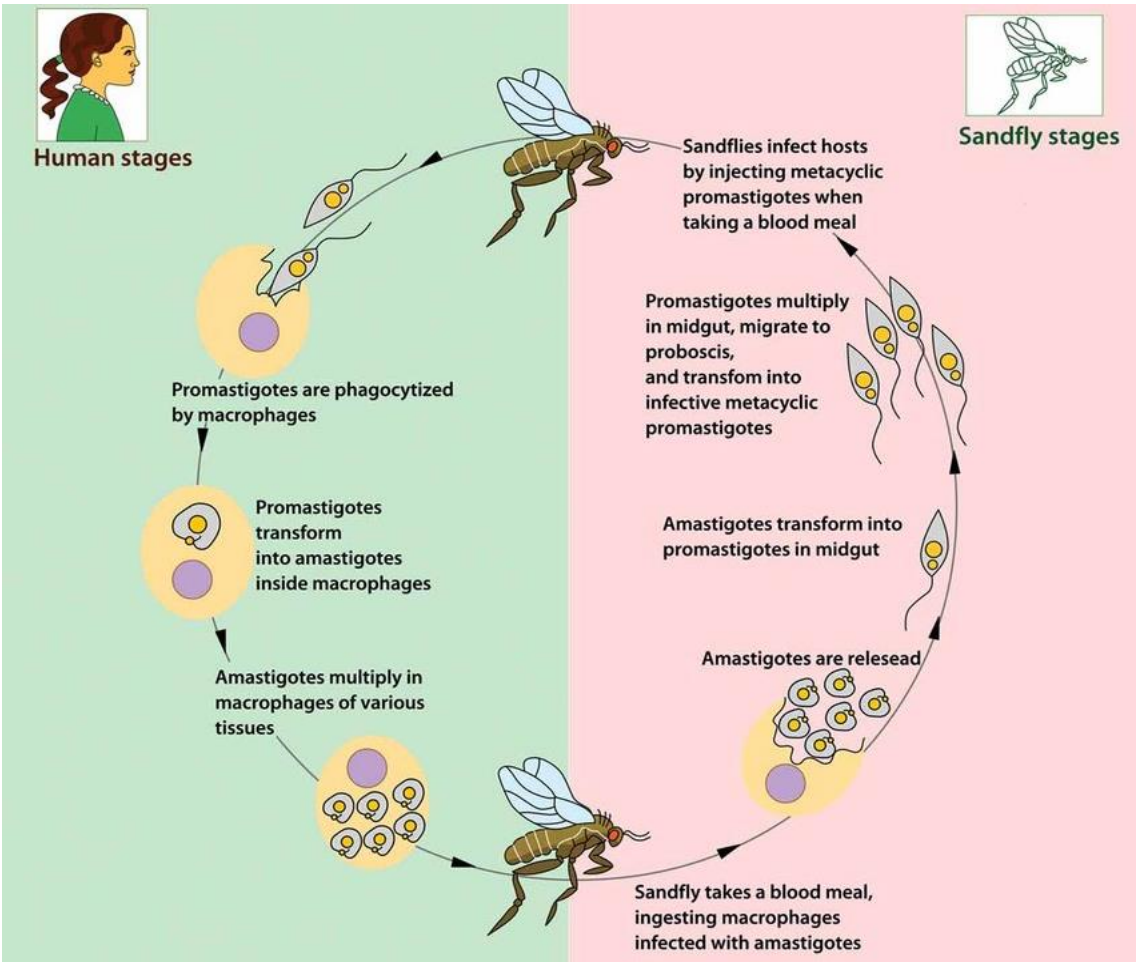


Figure 3. Pathophysiology of Leishmaniasis.

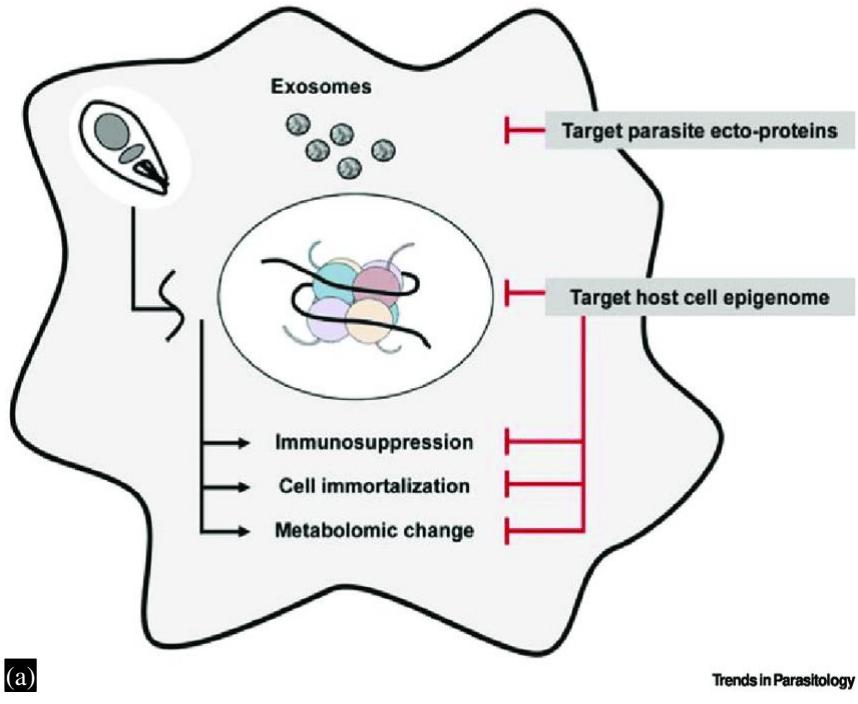
- *Step 4:* Infected phagocytes disseminate the infection to spleen, liver, bone marrow & lymph nodes, via bloodstream causing the sequelae of visceral leishmaniasis such as hepatosplenomaegaly.
- *Step 5:* Female phlebetomites inject infected cells while feeding on infected human blood
- *Step 6:* And the cycle continues from person to person causing infectious leishmaniasis disease

EXPLORING HOST-PARASITE INTERACTIONS

Research on leishmaniasis in tropical medicine revolves around the study of host-parasite interactions. The intricate interaction between host defence mechanisms and parasite evasion mechanisms is shown by investigations into the immunological response of the human host to Leishmania infection[11,12]. Moreover, genetic research clarifies the host variables affecting susceptibility to infection and the course of the disease, opening the door for the creation of individualized treatment plans. Designing leishmaniasis vaccines and immunotherapies that work requires an understanding of these interactions[11,12].

A number of signaling pathways that lead to macrophage functions, such as phagocytosis, chemokine secretion, and prostaglandin secretion, are rapidly activated and deactivated as a result of the receptor-mediated internalization of leishmania within the macrophage[12]. In many regions where leishmaniasis is prevalent in humans, sand flies and animal reservoir hosts—such as dogs or rodents—maintain the parasite's cycle of transmission without the requirement for afflicted humans. Although neutrophils and macrophages are thought to be the primary immune cells that respond to Leishmania infection, there are a number of other immune cells as well, including monocytes, dendritic cells (DCs), natural killer (NK) cells, CD4+ and CD8+ T cells, and effector molecules like cytokines like interferon (IFN)-γ and interleukin (IL)-12 [13].

The fitness of hosts can be negatively impacted by parasites in a variety of ways, from decreased rates of reproduction and survival to death and sterilization. Even though there are only a few ectoparasites present, a microparasitic disease has the potential to kill a host or render it vulnerable to predators [12, 13] (Figure 4).



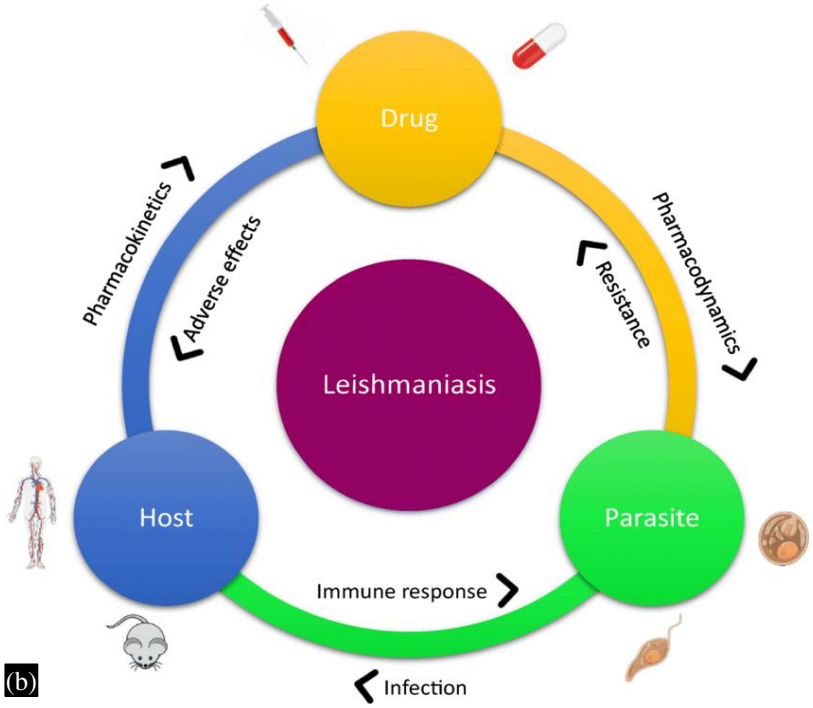


Figure 4. (a, b) Host – parasite interactions between leishmaniatic cell & hunman body.

CHALLENGES IN DIAGNOSIS

Leishmaniasis diagnosis is still debatable, nevertheless, as none of the current tests have 100% specificity and sensitivity. Additionally, the symptoms might differ from one kind to another and sometimes they can resemble those of other illnesses[11, 12].

The simplest way to diagnose leishmaniasis is to identify the parasite's amastigote form under a microscope using stained smears of samples taken from lymph nodes, skin lesions, liver, spleen, or bone marrow[12,13].

- Microscopically observable methods are less sensitive than sophisticated, expensive methods like Polymerase Chain Reaction (PCR) [12,13].
- Parasites in blood can also be found using immunological techniques, which are commonly employed [14].
- Anti-leishmanial antibodies are primarily found using the Indirect Fluorescent Antibody (IFA) test [15].
- For the purpose of identifying visceral leishmaniasis, another more effective serological test is the Enzyme Linked Immunosorbent Assay (ELISA). Leishmaniasis detection also involves immunochromatographic assays, such as the rK39 test, which uses recombinant K39 antigen as its basis[15].
- The Leishmanin Skin Test (LST), which measures the delayed hypersensitivity brought on by CL, can be used to diagnose Cutaneous Leishmania .Compared to the other immunological tests previously discussed, the Direct Agglutination Test (DAT) is comparatively less expensive. Nevertheless, because of its decreased sensitivity, this approach is inappropriate[14,15].

The microscopic identification of parasites in VL necessitates the use of several extremely challenging procedures. For instance, spleen aspiration, which has a comparatively higher sensitivity, may be quite harmful since it might harm the spleen fatally and thus needs to be performed by professionals with the necessary training . Other readily acquired samples with limited sensitivity come from peripheral blood and bone marrow [16, 17]. While it is significantly simpler to get samples from skin lesions in CL, the quality of the prepared slides and the observers' experience will determine the outcome [16,17].

Leishmaniasis can be diagnosed by a variety of laboratory techniques, which can also be used to determine the Leishmania species (type) and detect the parasite. A few of the techniques are exclusive to reference labs[17]. Samples of tissue, such as those from bone marrow for visceral leishmaniasis or from skin sores for cutaneous leishmaniasis, can be tested for the parasite using molecular assays, specific cultures, and a microscope[17]. In situations with visceral leishmaniasis, blood tests that identify antibodies, or an immune response to the parasite, can be beneficial; tests to find the parasite (or its DNA) itself are typically conducted as well [17,18].

In situations with visceral leishmaniasis, blood tests that identify antibodies, or an immune response to the parasite, can be beneficial; tests to find the parasite (or its DNA) itself are typically conducted as well. Because PCR offers the best reported sensitivities and specificities of all the diagnostic procedures, it has been suggested as the gold standard for Leishmania detection in the future [18,19]. Up to 100% specificities and up to 100% sensitivities were observed in one systematic review and meta-analysis (Figure 5).

TREATMENT FOR LEISHMANIASIS

To treat leishmaniasis, a number of anti-parasitic drugs are available. The exact drug a doctor recommends for you will depend on the kind of leishmaniasis you have [19]. Medication can take several forms, such as:

- Tablets that you ingest.
- Lotion or cream that you put on your skin.
- Liquids administered by your doctor through an IV catheter inserted into a vein.
- Your healthcare provider might be able to treat your wounds immediately with thermotherapy, cryotherapy, or laser therapy if you have cutaneous leishmaniasis. These can help your wound heal and eradicate the parasite.

Avoiding sand fly bites is the best defence against all forms of leishmaniasis, particularly in regions where the disease is prevalent [19] (Figure 6).

TROPICAL MEDICINE IN THE TREATMENT OF LEISHMANIASIS

Amphotericin – Antifungal Antibiotic

A 20-day course of sodium antimony gluconate is effective in treating mucocutaneous illness; patients that are more advanced or resistant to treatment may require amphotericin B. Additionally, pentavalent antimony for a duration of four weeks has been suggested [20].

Amphotericin B appears to primarily act on membrane sterols in L. donovani promastigote cells, causing the permeability barrier to be breached by tiny metabolites. Thus, a fascinating metabolic parallel between fungus and flagellated protozoa is shown [19,20]. Amphotericin B appears to primarily act through membrane sterols on L. donovani promastigote cells, resulting in a breakdown of the permeability barrier to tiny metabolites. Thus, there is an intriguing biochemical parallel between fungi and flagellated protozoa. When amphotericin B binds to ergosterol in the fungal cell membrane, pores form, ions seep out, and the fungal cell dies[20, 21].

For more than ten years, India has been treating visceral leishmaniasis (kala-azar) using amphotericin B deoxycholate. Large-scale resistance to traditional pentavalent antimony therapy in Bihar State led to its rediscovery as an efficacious treatment for Leishmania donovani infection [20, 21].

Miltefosin – Phospholipids

It is a phospholipid and a member of the phosphocholine family. Originally created as an anti-cancer medication in the 1980s, miltefosine is a phospholipid with broad range antibacterial and anti-leishmanial properties [21, 22].

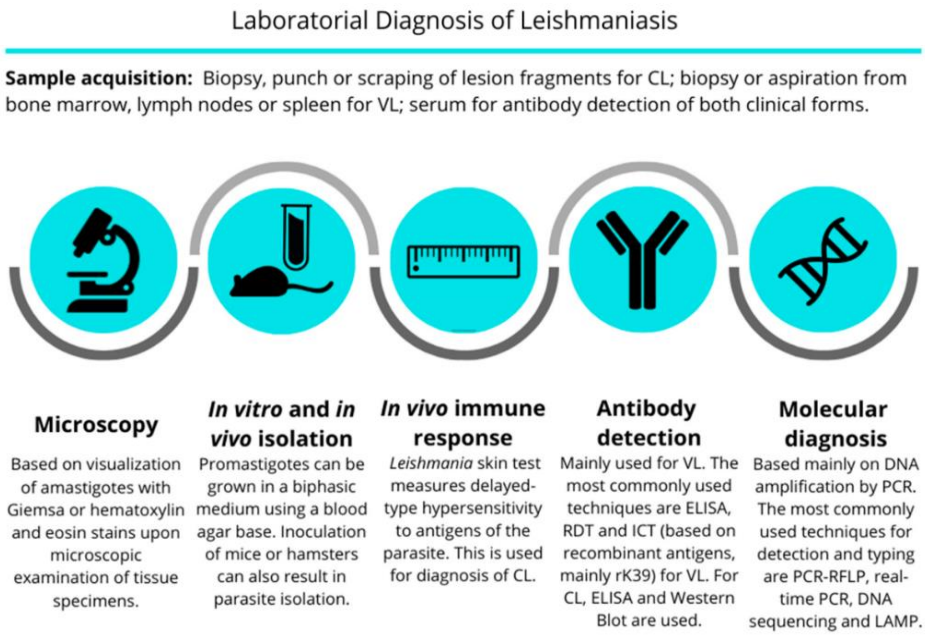


Figure 5. Diagnostic tests for leishmaniasis & hunman body.

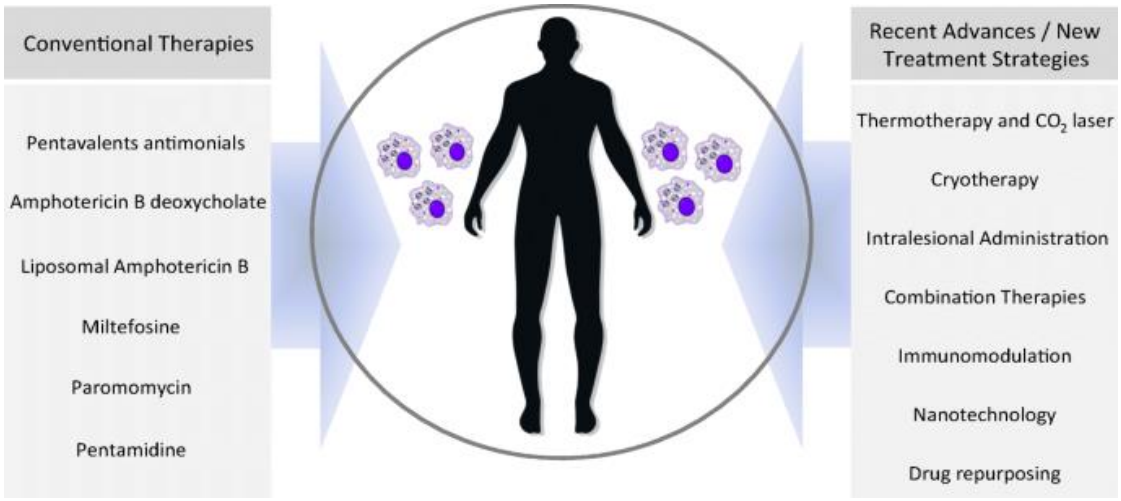


Figure 6. Treatments for leishmaniasis & hunman body.

Miltefosine acts by causing intracellular, extracellular, and promastigotes of Lactobacillus donovani to die in a manner similar to that of apoptosis. The same mechanism of action (MOA) that causes leishmaniasis also causes disruptions in lipid-dependent cell signaling pathways in cancer cells [22]. In resistant leishmaniasis, antifungal and antiparasitic drugs are used in conjunction with other treatments. The modes of action could be changes in the metabolism of RNA and DNA or an intracellular build-up of peroxide that is harmful to the fungal cell [21,22].

An antileishmanial medication called miltefosine is used to treat leishmaniasis, a group of diseases brought on by Leishmania type parasites. Originally created as an anti-cancer medication in the 1980s, miltefosine is a phospholipid with broad range antibacterial and anti-leishmanial properties [22,23].

Pentavalent Antimonials

In Leishmania amastigotes, these substances seem to block bioenergetic processes like glycolysis and fatty acid oxidation. Treatment failures and the need for substitute agents have resulted from the rise in

leishmania strains resistant to pentavalent antimony compounds, particularly in India [23,24]. **A derivative of organic antimony is sodium stibogluconate**. Although its exact mode of action is unknown, it might work by attaching to the parasite's thiol groups and preventing the synthesis of ATP and guanosine triphosphate [GTP], two high-energy phosphates. Treating visceral leishmaniasis is one of its uses [22]. A class of drugs known as pentavalent antimonials (abbreviated pentavalent Sb or SbV) is used to treat leishmaniasis. They go by the name pentavalent antimony compounds as well [24].

Leishmaniasis is treated with sodium stibogluconate, which may only be administered intravenously. It is a member of the pentavalent antimonials class of medications. In the UK, sodium stibogluconate is sold under the brand name Pentostam, which is manufactured by GlaxoSmithKline [24,25]. For over fifty years, antimony–carbohydrate compounds such as sodium stibogluconate, meglumine antimoniate, and pentavalent antimonials were utilized in the management of leishmaniasis. In 1920, urea stibamine—a less hazardous and more potent antimonial—was employed to treat Indian kala-azar.

Paromomycin – Aminoglycoside Antibiotic

Paromomycin is a member of the antibiotic class called aminoglycosides. It works by either getting rid of microorganisms or preventing them from growing. It is not possible to treat viral infections such as the flu or colds with this drug. When papomycin binds to 16S ribosomal RNA, it prevents the creation of proteins. Bacterial proteins are produced by ribosomal RNA complexes, which consist of two subunits: a small (30s) subunit and a large (50s) subunit that together make up the 70s ribosomal subunit [25].

This medication can be used topically, intravenously, and/or intramuscularly. Ototoxicity, local discomfort (from injectable paromomycin), erythema, vesicles, and skin irritation are the most common adverse effects of this medication [24,25]. It functions as an anthelminthic, antibacterial, antiprotozoal, and antiparasitic medication. It is both an amino cyclitol glycoside and an aminoglycoside antibiotic. It shares functional similarities with streptamines. One type of antiprotozoal is pacomycin [25, 26].

Thermotherapy

It's easy to treat cutaneous leishmaniasis with thermotherapy, just apply the appropriate amount of heat to the lesion to eradicate the parasite and heal the patient. Radiofrequency thermotherapy may be a viable substitute for pentavalent antimonials, particularly in cases where there is a formal contraindication to traditional treatment or where there is only one lesion. More randomized controlled trials with a bigger patient population and a longer follow-up period are required before this treatment option can be regarded as a primary alternative to traditional treatment [26].

Cryotherapy

Cryotherapy is being examined as a local therapeutic option for cutaneous leishmaniasis (CL), as an alternative to the current pentavalent antimonials. Cryotherapy for CL typically uses liquid nitrogen (N2) at a temperature of -196 °C, yet results are inconsistent. Lesions produced by leishmaniasis infection were healed, especially smaller lesions, with weekly to biweekly intervals of one to four cryotherapy sessions. Unlike other first-line therapies, liquid nitrogen cryotherapy provides a safe, efficient, affordable, and accessible therapeutic technique for cutaneous leishmaniasis [26] . These factors suggest that cryotherapy should be investigated more and used as the first line of treatment for cutaneous leishmaniasis, particularly in underdeveloped nations with limited resources where the disease is endemic [27].

Laser Therapy

While antiparasitic drugs are usually used in conventional leishmaniasis treatments, research into complementary therapies, such as laser therapy, has continued. The possibility of laser therapy to target

parasites directly, decrease inflammation, and promote wound healing has been studied [26,27]. However, depending on the leishmaniasis kind, infection stage, and laser therapy parameters, its effectiveness may differ when treating leishmaniasis particularly. A few research have looked into combining traditional leishmaniasis therapies with laser therapy, specifically low-level laser therapy (LLLT). Low-power lasers (LLLT) or light-emitting diodes (LEDs) are used to promote tissue repair and lessen inflammation. Numerous medicinal uses, such as pain relief and wound healing, have made use of it [26,27].

Studies on the efficacy of laser therapy for leishmaniasis are still being conducted, and the findings are inconsistent. More investigation is required to ascertain whether this treatment is effective when used alone or in conjunction with traditional therapy, even though some trials have demonstrated encouraging findings in terms of quickening wound healing and lowering inflammation linked to cutaneous leishmaniasis lesions [27].

A triple therapy involving oral zinc sulfate, oral ketoconazole, and topical podophyllin is utilized to treat both acute and chronic cases of cutaneous leishmaniasis [28, 29]. Pentamidine (ketoconazole 600 mg PO qd for 28 d) is the first-line treatment for cutaneous leishmaniasis, with the exception of L mexicana. It is a different approach to treating visceral leishmaniasis [28].

CONCLUSION

In summary, leishmaniasis is a neglected tropical disease with significant health and socioeconomic effects. Tropical medicine is essential to understanding the complexity of this illness. Through the use of interdisciplinary methods and the application of recent developments in immunology, epidemiology, and treatments, scientists hope to create all-encompassing plans to manage and eradicate disease [29]. Nonetheless, to guarantee that impacted communities receive the attention and care they merit on the global health agenda, tackling the problems associated with leishmaniasis necessitates persistent investment, cooperation, and advocacy [29,30].

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