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Nanotechnology-Augmented Herbal Remedies and Synthetic Substances for Leishmaniasis: An In-Depth Review of Promising Solutions

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Abstract:

Background: Visceral leishmaniasis (VL), the deadliest form of leishmaniasis, remains endemic in tropical/subtropical regions. Conventional treatments are limited by toxicity, high cost, and emerging drug resistance. **Objective:** This review synthesizes recent advances in herbal and synthetic therapeutics, with an emphasis on nanotechnology-based drug delivery systems. **Methods:** Studies published between 2000–2024 on the antileishmanial efficacy of herbal extracts, synthetic drugs, and nanoformulations (liposomes, polymeric nanoparticles, metallic nanocarriers) were analyzed using databases including PubMed, Scopus, and Web of Science, following PRISMA guidelines. **Results:** Gold-standard therapies like liposomal amphotericin-B (AmBisome®) remain vital but require improved targeting and reduced toxicity. Phytocompounds from *Azadirachta indica, Curcuma longa, and Withania somnifera* exhibit significant in vitro/in vivo antileishmanial activity. Nanocarriers—liposomes, solid-lipid NPs, polymeric dendrimers, metallic nanoparticles—enhance bioavailability, reduce off-target effects, and support targeted macrophage uptake. Patents focus on curcumin-PLGA systems, dendrimer-mediated combination therapies, and ligand-targeted delivery. **Conclusion:** Integrating low-toxicity phytochemicals with nanotechnology platforms offers a promising, next-generation approach to treat VL. Future preclinical standardization and clinical trials are urgently needed.

Keywords: Nanotechnology, Leishmaniasis, Phytochemicals, Synthetic Drugs, Herbal drugs, Nano-composition.

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1. Introduction

Leishmaniasis is a serious neglected tropical disease caused by protozoan parasites of the Leishmania genus and spread via the bite of infected female phlebotomine sandflies. The disease appears in three clinical forms: (1) cutaneous leishmaniasis (CL), which is the most common and causes skin ulcers; (2) mucocutaneous leishmaniasis, which affects mucous membranes; and (3) visceral leishmaniasis (VL), also known as kala-azar, which is the most severe and fatal form. Untreated, VL causes fever, weight loss, anemia, and enlargement of the liver and spleen, with a death rate exceeding 95% [1,2]

Leishmaniasis is a protozoan parasitic illness transmitted through the bites of female sandflies, often presenting with lesions that can be cutaneous, mucosal, or visceral. Leishmania parasites mainly target mononuclear phagocytes located near the bite site made by the sandflies, with the potential for opportunistic spread throughout the body[2–4]. Leishmaniasis, caused by over 20 species of Leishmania, is endemic in 70+ countries, primarily affecting India, Brazil, Ethiopia, Kenya, Somalia, Sudan, and South Sudan. It consists of Old World leishmaniasis in the Eastern Hemisphere and New World leishmaniasis in the Americas [4–6].

Since 2016, global cases of visceral leishmaniasis have decreased by over 30%. The WHO aims to eradicate neglected tropical diseases by 2030, targeting less than 1% mortality in 64 endemic countries. In 2018, East Africa reported 45% of all cases worldwide [7–9].

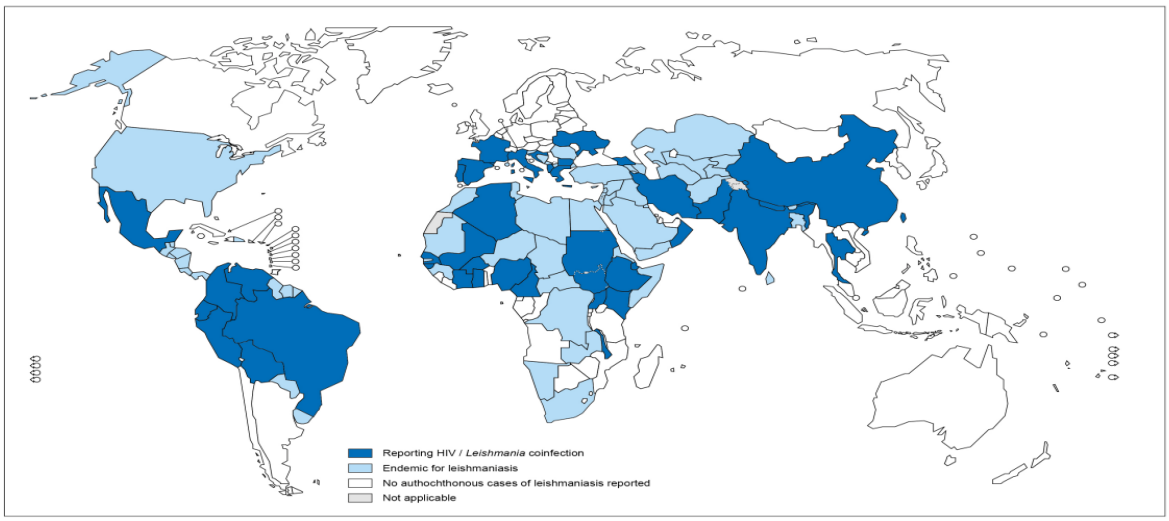

Fig. 1 - Global distribution of leishmaniasis and countries reporting HIV/Leishmaniasis coinfection which is given by the World Health Organization (WHO)

Over 89 countries face leishmaniasis, affecting 350 million people, with 12 million reported cases and an estimated 2 to 2.5 million underreported annually. The main types are cutaneous and visceral leishmaniasis [8,10,11].

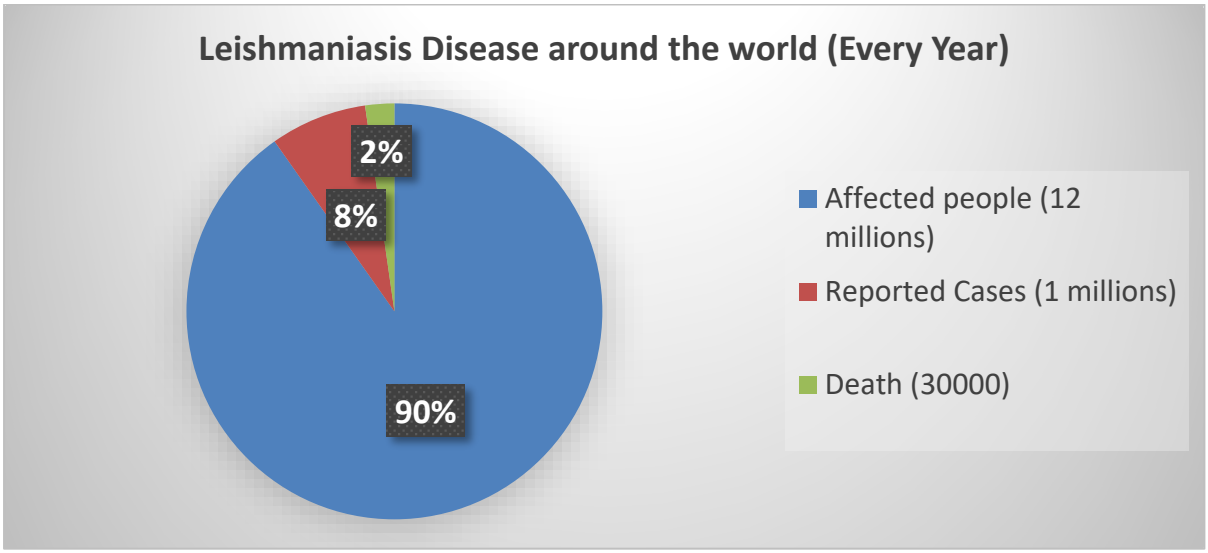

Fig. 2 – Leishmaniasis disease around the world including affected people, reported cases and death caused by leishmaniasis

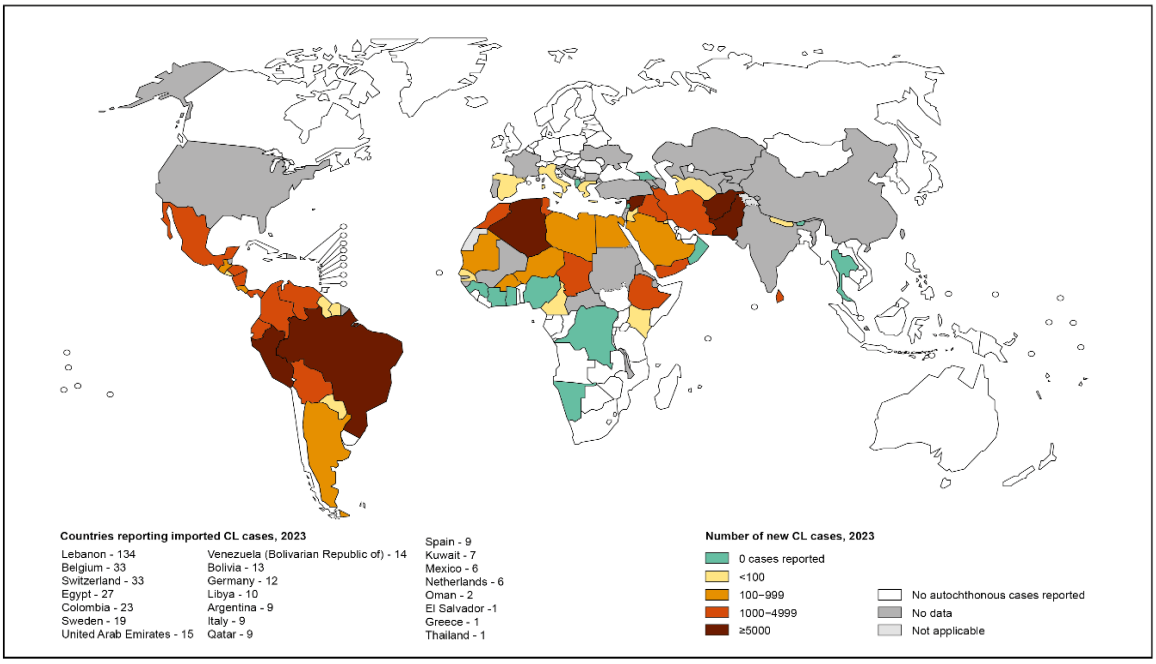

Fig. 3 - Global distribution of cutaneous leishmaniasis (CL) which is given by the World Health Organization (WHO)

Leishmaniasis, a neglected tropical disease, affects around 12 million people in nearly 100 countries, with 1.5 to 2 million new cases each year. It leads to 20,000 to 30,000 deaths annually and is caused by various Leishmania protozoan species. Symptoms range from self-healing skin lesions to severe visceral diseases, with mucosal tissue damage also occurring [1,10–14].

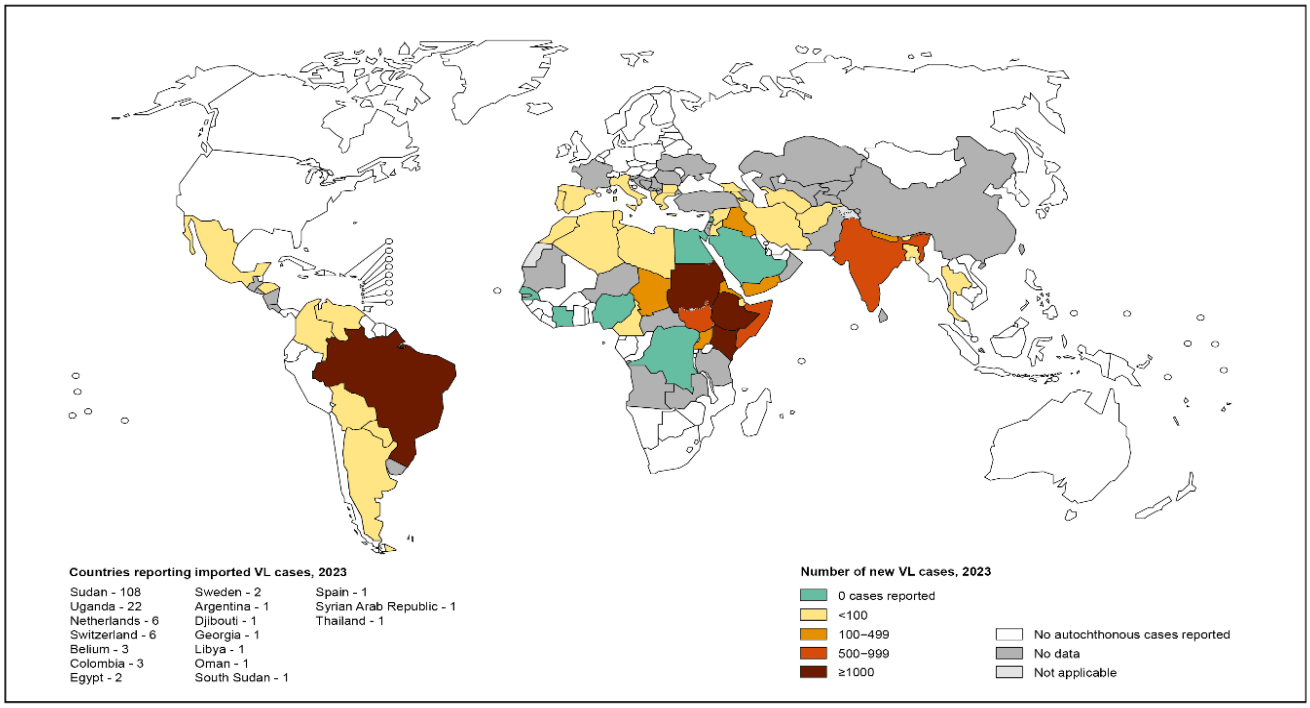

Fig. 4 - The World Health Organization (WHO) reports the global distribution of visceral leishmaniasis (VL)

1.1 Types & Causes

At least 20 different species of the genus Leishmania include the protozoan parasites that cause visceral leishmaniasis (VL) and tegumentary leishmaniasis (TL), with new species being discovered every ten years. Female phlebotomine sandflies are the vectors via which these parasites spread among mammalian hosts [1,15,16].

Leishmaniasis is a long-lasting infectious disease caused by various protozoan species belonging to the Leishmania genus. In Brazil, the most common species responsible for cutaneous infections are L. (V.) braziliensis and L. (L.) amazonensis. The next most frequently encountered species include Guyanensis, Lainsoni, Shawi, Naiffi, and Lindberg, with the latter being the least common [13,17].

Table No. 1 Difference between CL, MCL and VL

Characteristic / Feature	Cutaneous Leishmaniasis (CL)	Visceral Leishmaniasis (VL) or Kala-azar	Mucocutaneous Leishmaniasis (MCL)	References
Definition	Affects the skin, causing localized sores or ulcers.	Impacts internal organs such as the bone marrow, spleen, and liver.	Impacts the throat, mouth, and nose mucous membranes.	1,5,13,18
Cause/ Causative Species	Leishmania tropica, L. major, L. mexicana, etc.	Leishmania donovani, L. infantum (L.	Related species and Leishmania braziliensis	19–21

		chagasi)		
Transmission Vector	Sandflies (Phlebotomus or Lutzomyia).	Sandflies (Phlebotomus or Lutzomyia).	Sandflies (Phlebotomus or Lutzomyia).	22–24
Target Organs/ Affected Area	Skin only/ Skin (localized to bite site).	Internal organs: spleen, liver, bone marrow	throat, mouth, and nose mucous membranes	1,25–27
Primary Symptoms	Skin ulcers or sores, often painless	Fever, weight loss, hepatosplenomegaly, anemia, and fatigue	Nasal congestion, nosebleeds, ulcers, and destruction of mucosal tissue	1,2,28
Onset/ Incubation Period	Weeks to months after infection	Months to years after infection	Months to years after initial cutaneous lesion	29–31
Severity	Generally mild, may self-heal	Severe, potentially fatal if untreated	Deforming and disabling but rarely fatal	19,20,31
Geographic Distribution	Worldwide: Mediterranean, Middle East, Americas, Central Asia	Endemic to India, East Africa, Brazil, and Mediterranean	Central and South America	1,10,15,32
Immune Response	Localized immune reaction	Systemic immune suppression	Hyperactive immune response with localized tissue destruction	12,13,33
Diagnosis	Skin biopsy, culture, PCR	Bone marrow or spleen aspirate, serological tests, PCR	Biopsy of affected mucosal tissue	1,34–36
Treatment	Topical or systemic antimonials, miltefosine	Liposomal amphotericin B, miltefosine, antimonials	Systemic treatment with antimonials or amphotericin B	1,19,35,37
Complications	Scarring from healed lesions	Fatal if untreated due to organ damage and immune suppression	Significant facial and respiratory deformities	23,30,31,38
Spread from Initial Site	Localized to the skin	Disseminates through the bloodstream	Spreads from skin to mucosal tissues	23,25,39,40

Prognosis	Good, with minimal medical intervention	Poor if untreated, high mortality rate	Disfiguring but treatable; early intervention crucial	1,41–44

1.2 Symptoms

The symptoms of all forms of leishmaniasis are marked by the appearance of lesions on the skin (which can occur as one or multiple, dispersed or scattered) and/or on mucous membranes (including areas such as the mouth, throat, or nose). These lesions appear as ulcers with raised borders and a granular base, typically painless, and are often found in exposed areas of the skin, ranging in shape from oval to rounded and measuring a few millimeters to even several centimeters [1,3,4,9,36,45,46].

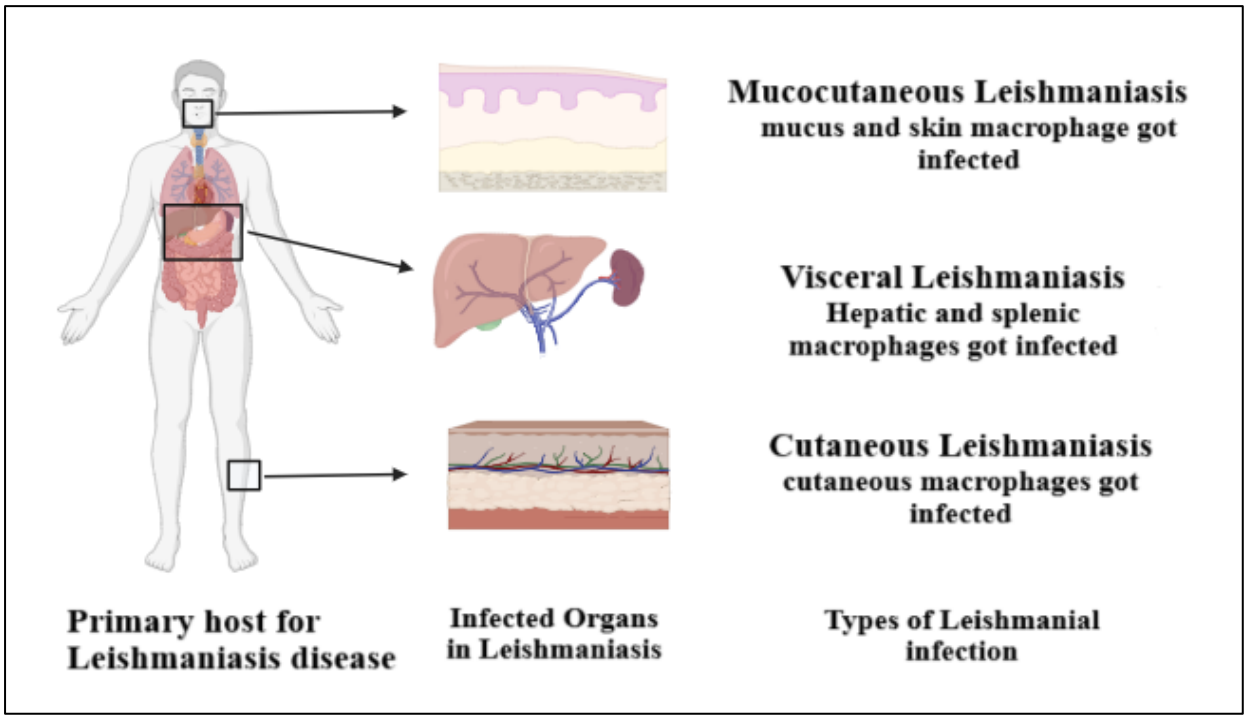

Fig. 5 – Symptoms of Leishmaniasis

Current leishmaniasis treatments, such as miltefosine and amphotericin B, face challenges like drug resistance and high costs. Herbal remedies like neem and turmeric show potential but have limitations due to poor solubility. Nanotechnology may enhance their effectiveness [6,12,17,31,35,38,41,45,47]

Nanotechnology-based drug delivery systems, such as liposomes and nanoparticles, have been developed to enhance drug delivery to infected macrophages, improve pharmacokinetics, and reduce toxicity. These systems, including mannosylated nanoparticles and phyto-nano formulations, show promise in targeting Leishmania-infected macrophages and overcoming drug resistance.

In summary, the integration of Phytotherapeutics and synthetic drugs with nanotechnological carriers offers a strategic multidisciplinary approach for more effective visceral leishmaniasis

treatment. The following sections explore the detailed biology and immunopathogenesis of VL, diagnostic challenges, and current therapeutic developments—highlighting the evolving role of nano-enabled drug delivery in advancing both treatment and drug discovery [48–52].

2. Pathogenesis & Immunology

Leishmania spp. employs intricate strategies to survive and proliferate within the host, subverting both innate and adaptive immune defenses.

The Leishmania parasite has two lifecycle stages: motile promastigotes in the sandfly vector and immotile amastigotes in host macrophages. It's transmitted via sandfly bites, multiplying in the female's digestive system and infecting vertebrates during blood meals. [3,49,52–55]

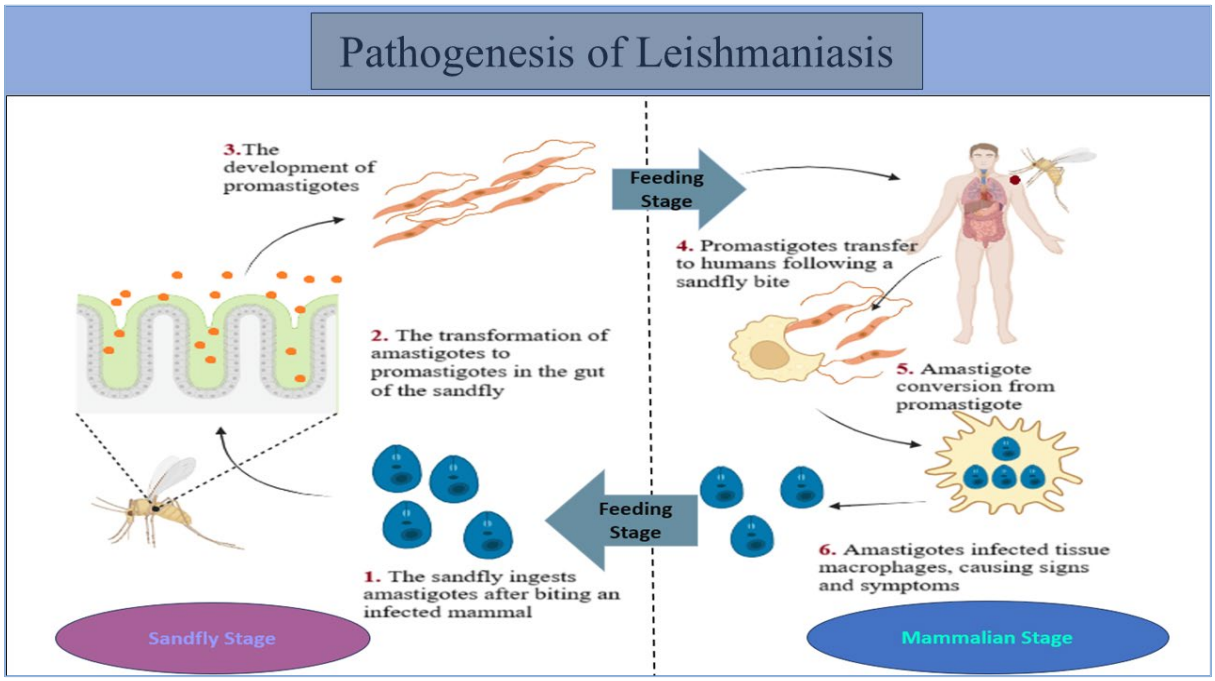

Fig. 6 - Leishmaniasis pathogenesis consists of two phases.

2.1 Early Infection and Phagocyte Hijacking

Promastigotes enter host neutrophils and monocytes via sandfly bites, where neutrophils delay apoptosis and recruit more phagocytes to aid in parasite persistence. The promastigotes then transform into amastigotes in macrophages, using surface molecules to disrupt phagosome maturation and neutralize host oxidative defenses. [26,46,49,53,56,57]

2.2 Cytokine Modulation & Chemokine Dysregulation

Leishmania suppresses pro-inflammatory cytokines (IL-12, TNF-α, IFN-γ) and up-regulates anti-inflammatory ones (IL-10, IL-4, IL-13), promoting its growth. It hinders Th1 differentiation by lowering IL-12 in macrophages and reduces CCL2, impacting macrophage chemotaxis while enhancing Th2-recruiting chemokines (e.g., CCL7) for immune evasion [2,11,31,44,47]

2.3 Macrophage Polarization (M1 vs. M2)

Macrophages in VL polarize into M1 or M2 states. M1 polarization (driven by IFN-γ, IL-12) promotes parasite control through NO and ROS production, relying on glycolytic metabolism. In contrast, M2 polarization (driven by IL-4, IL-10, TGF-β) supports parasite survival via arginase pathways and reduced microbicidal activity [31,38,58–60]

Leishmania also exploits host lipid metabolism, inducing the formation of lipid bodies near parasitophorous vacuoles. Through Rab18 and Rab5a activation, the parasite commandeers fatty acids and glycerol for replication and enhances macrophage longevity [31,58,61]

2.4 Adaptive Immune Responses

T Lymphocytes

Successful anti-Leishmania immunity relies on a Th1 response, driven by IFN-γ from $CD4^+$ and $CD8^+$ T cells, activating macrophages to produce leishmanicidal NO. In contrast, Th2 responses, marked by IL-4, IL-5, and IL-13, promote disease progression. Leishmania can also activate the NLRP3 inflammasome, leading to IL-18 production and worsening outcomes [56,57,62,63]

Regulatory Cells

Regulatory T and B cells (Tr1, Treg, Breg) secrete IL-10 and other immunosuppressive cytokines to control inflammation. However, excessive regulatory activity is linked to T-cell anergy, persistent infection, and relapse [2,9,64]

2.5 Dendritic Cells and NK Cells

Dendritic cells (DCs) are critical in antigen presentation and Th1 induction. Leishmania impairs DC maturation by disrupting MHC-II loading and antigen presentation via lipid raft disruption. NK cells contribute early IFN-γ but can be directly targeted and neutralized by promastigotes through gp63-mediated mechanisms [39,65]

3. Diagnostic Techniques

Serum and biochemical profiles aren't effective for diagnosing leishmaniasis but are important for monitoring infected animals and identifying its causes [1,66]

Leishmaniasis can be diagnosed using lateral flow biosensors, immunological tests (like ELISA), parasitological exams, and molecular methods (such as PCR). Antigen detection assays are crucial for monitoring persistent infections [39,46,67]

Leishmaniasis is typically diagnosed through bone marrow aspirates, but low protozoa densities may be overlooked. Clinical detection is common in endemic areas, though symptoms can be unclear and resemble other diseases [49,50]

Serological techniques like the Enzyme-Linked Immunosorbent Assay (ELISA) and the indirect immunofluorescence assay (IFA) require the identification of specific antibodies in serum samples [53,65,68,69]

A rapid test based on the rK39 antigen is used in East Africa to diagnose visceral leishmaniasis in cases that are clinically suspected. Due to the mediocre sensitivity of this test (around 85%), additional diagnostic testing is often necessary. Amastigotes are found by the direct agglutination

test, bone marrow or spleen aspirates, and stained smears from lymph node punctures under a microscope [21,70–72]

The most reliable and precise methods for diagnosing ACL depend on molecular testing (real-time PCR), which is currently accessible only in specialized laboratories that require costly equipment and trained professionals. This study showcases the accuracy of an affordable DNA extraction method that facilitates the direct amplification of Leishmania using portable PCR devices (miniPCR™) [21,67]

For the condition to be effectively treated and managed, a timely and accurate diagnosis is essential. Clinical signs of CL might be confused with eczema, leprosy, bacterial and fungal infections, cutaneous tuberculosis, and other skin conditions [1,46,56,64,71]. In the parasite cultures, bacterial and fungal contamination is also a possibility. Most significantly, these conventional techniques are unpleasant and intrusive, which may increase the chance of co-infection, especially in young patients [42,46,48]

4. Current Therapeutics

Effective management of leishmaniasis requires attention to the clinical presentation, Leishmania species, and patient health. Traditional treatments like sodium stibogluconate are being replaced by safer options such as liposomal amphotericin B and miltefosine for visceral leishmaniasis. Cutaneous leishmaniasis treatment varies from localized approaches (cryotherapy, topical paromomycin) to systemic options for severe cases. Personalized strategies are vital to address drug resistance and individual factors like age and co-infections, ensuring effective treatment and minimizing public health impacts [7,52,55,64,73–75]

4.1 Synthetic Drugs

Therapeutic medications for visceral leishmaniasis, such as antimonials and Amphotericin B, have become less effective due to toxicity and drug resistance. Sodium antimony gluconate (SAG) has been the main treatment since the 1940s, but its cure rate is only 60%, and clinical resistance has been a concern in India since the late 1990s [76–78]

Table No. 2. Available drugs for the treatment of leishmaniasis

S. No.	Drug	Disease	References
01	Paromomycin	CL	1,4,75,78
02	Pentavalent antimonial (Sodium stibogluconate)	VL, CL	1,2,7,14,17,20,39
03	Miltefosine	VL, CL, MCL	6,52,64,68,79–81
04	Amphotericin B	VL	1,55,59,64,73,76,77,82–84
05	Pentamidine	VL	40,52,55,56,85,86
06	imiquimod	CL	33,73,87
07	Nitazoxanide	CL	5,9
08	Quercetin	CL	5,88
09	Amodiaquine	VL	1,64,68,89
10	d,l-glyceraldehyde	CL	64,68
11	Isopentyl caffeate	CL, VL, MCL	4,68,90,91

12	Phthalocianato silicon	CL	1,4,68
13	2 – substituted quinolines	CL, VL	92,93
14	Magnesium oxide	CL & VL	1,58,68,94
15	Rifampicin	VL	4,68,95
16	Meglumine Antimoniate	VL	35,41,96
17	Oleanolic acid	VL	35,45,97
18	Buparvaquone	CL	4,68,98
19	Maghemite	CL	1,35,68
20	Vorinostat	VL	35,68,99

4.2 Phyto-therapeutics

Recent studies have found that certain herbal remedies, like extracts from Croton pullei, Lippia sidoides, and Valeriana wallichii, can effectively inhibit the growth of leishmaniasis-causing parasites in experimental models[1,30,100,101]. Essential oils from plants like Artemisia show leishmanicidal properties, but more research is needed to evaluate their efficacy and safety in clinical use [100–103]

Table No. 3. Available herbal drugs for the treatment of leishmaniasis

S. No.	Herbal plant	Family	Disease	References
01.	*Foeniculum vulgare*	*Apiaceae*	CL	104
02.	*Linum usitatissimum*	*Linaceae*	CL	105
03.	*Curcuma longa*	*Zingiberaceae*	CL, VL	75,88,106
04.	*Thymus vulgaris*	*Lamiaceae*	CL	107
05.	*Berberis vulgaris* (macrophage target)	*Berberidaceae*	CL	61
06.	*Galipea longiflora* (macrophage target)	*Rutaceae*	CL	61,108,109
07.	*Artemisia Annua,dracunculus*	*Asteraceae*	VL	102,103,110
08.	*Cinnamomum zeylanicum*	*Lauraceae*	CL	111,112
09.	*Zingiber officinale*	*Zingiberaceae*	CL	52,113
10.	*Zataria multiflora*	*Lamiaceae*	CL	1,7
11.	*Mentha piperita, arvensis*	*Lamiaceae*	CL	64,100,114
12.	*Anethum graveolens*	*Apiacceae*	CL	7,68,109
13.	*Citrus limon*	*Rutaceae*	CL	7,115
14.	*Mangifera indica (pulp)*	*Anacardiaceae*	CL	16,116,117
15.	*Duguetia furfuracea*	*Annonaceae*	CL, MCL, VL	4,7,52

5. Nanotechnology-Based Delivery

The utilization of Nano formulations with antileishmanial medications for enhanced delivery began in 1992[55]. Since that time, numerous novel formulations, including both pharmaceuticals and vaccines, have been developed and evaluated in preclinical studies for leishmaniasis[14,55,68,116] .

Nanotechnology is important due to its ability to modify materials at the nanoscale (1 to 1000 nm). Natural materials like plants and microbes are increasingly used to create nanoparticles, such as gold and silver, which exhibit enhanced antimicrobial properties and lower toxicity compared to chemically produced ones. Additionally, nanoparticles can be embedded in textiles, creating self-cleaning antimicrobial fabrics[4,103,115,116] .

Nanocarrier systems offer transformative advantages for antileishmanial therapies—they enable specific targeting of infected macrophages in organs like the liver and spleen, improve pharmacokinetics, reduce systemic toxicity, and overcome issues like poor solubility and drug resistance [14,52,118–120].

5.1 Lipid-Based Systems

• Liposomes

These are spherical vesicles made from natural/synthetic phospholipids and cholesterol that encapsulate either hydrophilic or hydrophobic drugs [16,85]. Liposomes tend to gather in areas with a lot of macrophages, which are the main cells that host the Leishmania parasite [17,59,94]. By applying surface modifications like PEGylation, we can significantly enhance the half-life of compounds. Imagine adding mannose or sugar moieties to facilitate targeted uptake through receptors, boosting both precision and circulation time. It's all about tailoring solutions for optimal performance. Clinical Application of Liposomal amphotericin B (AmBisome®) represents a gold standard, significantly reducing nephrotoxicity and demonstrating high efficacy. Yet, liposomes can face stability issues and drug leakage in circulation [16,17,85]

• Nanostructured Lipid Carriers (NLCs) & Solid Lipid Nanoparticles (SLNs)

NLCs improve on SLNs by mixing solid and liquid lipids, preventing drug expulsion and increasing loading[107,121–123] . Having Preclinical Evidence like SLN-loaded amphotericin B outperforming AmBisome® in efficacy and safety, and paromomycin-loaded SLNs that suppressed *L. tropica* more effectively and promoted Th1 immune responses in mice[107,122,124,125]. SLNs are lipid-core particles (<1000 nm) stabilized with surfactants, offering controlled release and biodegradability. Advantages include protecting payloads from degradation, scalable production, and good biocompatibility. It has Limited drug loading and risk of burst release due to crystalline matrix [122,123,125–127].

5.2 Polymeric Carriers

• Polymeric Nanoparticles

Constructed from biodegradable polymers like PLGA, chitosan, PCL, PEG, and PLA. It has High stability, tuneable size and surface properties, controlled payload release, low immunogenicity, and biodegradability[81,108] . Also having Macrophage Targeting as Surface modifications (e.g., mannose-conjugated or chitosan-coated) enhance uptake by macrophages[81,106,108,128] . Consisting the Efficacy that Studies show amphotericin B–PLGA and berberine-PLGA nanoparticles outperform free drug and AmBisome® with lower cytotoxicity[129–132] . Applications of Paromomycin and pentamidine encapsulated in PLGA nanoparticles improved oral bioavailability and antileishmanial activity [129,131]

• Dendrimers

Branching macromolecules with high drug-loading capacity and functionalization potential. Enable enhanced solubility, stability, and potential for targeted delivery, though their use in leishmaniasis is still exploratory[14,75,95]

5.3 Metallic Nanoparticles

• Gold (AuNPs), Silver (AgNPs), Zinc Oxide, Titanium Dioxide

Metallic NPs are synthesized using chemical or green methods, offering easy surface modifications and dual therapeutic/diagnostic ("theranostic") functions[57,133] . Mechanisms of activities of Metallic nanoparticles are Produce reactive oxygen species (ROS), disrupt parasite membranes, release metal ions, and activate immune pathways [4,64,68,83,132]. Silver NPs are the most studied class in cutaneous leishmaniasis; show strong in vitro and in vivo efficacy. Gold NPs are demonstrated oxidative stress–mediated *Leishmania* killing and used in conjugation with amphotericin B or drug-silencers for improved efficacy [3,57,134–136]. Metallic Strategies: Manganese NPs show apoptotic effects in promastigotes; while antimony sulfide and gold–AmB conjugates are emerging as innovative therapies [3,57,106,134,136]

Table No. 4. Summary of Various Nano Formulation

System	Key Benefits	Limitations
Liposomes	Dual drug loading, modifiable surface, proven clinical success	Stability issues, potential drug leakage
SLNs/NLCs	Biocompatible, scalable, protect payloads, improved loading (NLCs)	Lower drug load (SLNs), potential burst release
Polymeric NPs	Biodegradable, customizable release, stable, targeted	Synthesis complexity, regulatory hurdles
Dendrimers	High payload capacity, targeted delivery potential	Still early-stage in leishmaniasis
Metallic NPs	Multi-modal activity, surface	Toxicity concerns, limited in

	functionalization, theramostics potential	vivo testing

In essence, nanotechnology platforms are unlocking new therapeutic avenues for leishmaniasis by enhancing drug delivery precision, efficacy, and safety. Lipid-based systems are clinically validated, polymeric carriers offer sustained and targeted release, and metallic systems introduce novel mechanisms of action. Continued optimization and clinical validation will pave the way for more effective, patient-friendly treatments—especially when combining these platforms with herbal or synthetic antileishmanial compounds[4,20,68,98,103,137].

Table No. 5. Available Nano formulations of some synthetic drugs

S. No.	Drug	Formulation	Disease	References
01	Paromomycin	Nanoparticles	CL	40,73,78,138
02	Pentavalent antimonial (Sodium stibogluconate)	cationic nanovesicles, nano-elastic liposomes, Intramuscular, intravenous, intralesional	VL, CL	16,17,39,139
03	Miltefosine	Polymeric micelles & hydrogels, cationic nanovesicles, Nano transferosomes, Nanocochleates, NLC,	VL, CL, MCL	6,79–81,140
04	Amphotericin B	Liposomal, NPs encapsulated, nanofibers, micelles, SLNs, Transferosome, Carbon nanotubes, nanocochletes, mannosylated Gelatin NPs, Gold NPs,	VL	59,76,77,82,83
05	Pentamidine	Liposomes	VL	16,85
06	imiquimod	cationic nanovesicles	CL	33,139
07	Nitazoxanide	Nano-transfersomal gel	CL	5
08	Quercetin	Nano-transfersomal gel	CL	5
09	Amodiaquine	Microparticles	VL	89
10	d,l-glyceraldehyde	Intranasal	CL	7,100
11	Isopentyl caffeate		CL, VL, MCL	90,141
12	Phthalocianato silicon	Polyelectrolyte Gelatine NPs	CL	142

13	2 – substituted quinolines	Oral (synthesis)	CL, VL	92,93
14	Magnesium oxide	Metal NPs	CL & VL	20,58
15	Rifampicin	Nanoparticles, Nanotransferosomal gel.	VL	95,128
16	Meglumine Antimoniate	Nanoparticles (suspension)	VL	96
17	Oleanolic acid	NPs	VL	97
18	Buparvaquone	Nano-enabled Hydrogels	CL	98
19	Maghemite	Nano-Leish-IL	CL	99
20	Vorinostat	Gold NPs	VL	99

6. In – Silico Approaches

The molecular docking method simulates interactions between proteins and ligands, revealing intermolecular forces like hydrogen bonds and electrostatic attractions that influence binding stability and biological functions [90,100,143]

Molecular docking is a computational technique used in drug development to predict how well a ligand binds to a receptor by exploring various interactions and conformations [144,145]

Proteins essential to the parasite's development, survival, or virulence are the main targets of leishmaniasis treatments. These crucial proteins include transporters, surface receptors, signaling proteins, and enzymes involved in metabolic pathways [30,128,146,147]

Mannose receptors bind fructose and mannose on pathogens to promote endocytosis. Mannose-binding proteins aid in cytoskeleton reshaping during this process. Scavenger receptors, which can bind various ligands like phosphatidylserine and LDL, are classified as SR-A and SR-B [145–148]

Table no. 6. Some receptors/targets for treating leishmaniasis disease

S. No.	Name of receptors/ targets	Targeting For	Functions	References
01.	Toll-like receptor (TLR)	CL, MCL, VL,	I. Recognition of PAMPs / DAMPs. II. Recruitment of adaptor proteins. III. Activation of a signalling pathway. IV. Immune response.	146,149,150
02.	Fc gamma receptor	CL, MCL, VL,	I. Phagocytosis by macrophage. II. Cytokine production. III. Regulation of adaptive immunity. IV. Influence on disease outcome.	46,143–145,151

03.	Mannose	CL, MCL, VL,	I. Leishmanial adhesion - The mannose residues on the leishmaniasis parasite's surface bind to the mannose receptor on the host macrophage. II. Drug targeting - By blocking the parasite from attaching itself to host cells, the medications hope to avoid infection and possibly enhance the effectiveness of treatment.	30,31,38,106,128,152
04.	Mitogen-activated protein kinase (MAPKs)	CL, MCL, VL,	I. Host immune response - MAPKs are activated in response to leishmanial infection playing a role in both innate & adaptive immune response. II. Leishmanial survival – Leishmanial parasite may inhibit the activation of certain MAPKs that They may activate MAPKs that promote their growth and survival. III. Potential therapeutic targets – The importance of MAPKs in both host immunity & leishmaniasis survival targeting these enzymes has been explored as a potential therapeutic strategy for leishmaniasis.	62,65,71,153
05.	Pannexin	CL, VL, MCL	I. The pathophysiology of parasite diseases is significantly influenced by pannexins. II. These facilitate the release of ATP which acts as a danger signal & recruits immune cells to the site of infections. III. These might also be involved in the development of cell membrane holes that permit the flow of ions and chemicals.	23,31,44,78,130,154

06.	Dihydrofolate reductase (DHFR)	CL, VL, MCL	I. Essential for growth & proliferation – a. Most of living organisms requires a constant supply of DHF for its growth & development. b. DHFR catalyzes the reduction of dihydrofolate to trihydrofolate, ensuring a steady supply of this essential cofactor. II. Target for antiparasitic drugs – DHFR is now a popular target for anti-parasitic drugs. drug development, compounds that inhibit DHFR can disrupt the parasite's metabolic pathways, leading to death or impaired growth.	51,78,94,130,143–145
07.	Pteridine Reductase (PTR)	CL, VL, MCL	I. PTR is essential for leishmaniasis to produce folate, which is vital for their growth and replication. II. Toxicity – Ensuring the selectively of the PTR inhibitors is crucial to minimize potential side effects. III. Unique to parasite – This difference offer a potential therapeutic window, as drugs targeting. the parasite's PTR could selectively kill the parasite without harming human cells.	20,31,33,51,59,78,87,130,155–157

7. Patents & Innovation

Patents on leishmaniasis reflect ongoing research to combat this serious parasitic infection from the Leishmania genus, which affects millions in tropical areas. Studies are evaluating new therapeutics, while counting parasites with a hemacytometer remains a laborious method for assessing anti-leishmanial drug efficacy.

7.1 Patents

Leishmaniasis research focuses on new therapies for this parasitic infection affecting millions, but counting parasites with a hemacytometer is a time-consuming process.

Table No. 7. Some International patents on leishmaniasis which help treat leishmaniasis -

S. No.	Patent	Patent No.	Date of Patent	Title of Patent
01	Brazil	BR102020009366B1	2024-01-02	Kit and ELISA method for immunodiagnosis of human visceral and cutaneous leishmaniasis and canine visceral leishmaniasis using new synthetic peptide antigen psli409
02	European	EP3902788B1	2024-02-21	Naphthalimide derivatives as anti-parasitic agents for the treatment of leishmaniasis as well as viral, bacterial and neoplastic diseases
03	Russia	RU2816109C1	2024-03-26	Fluorine-containing triaryl antimony (v) dicarboxylates, having antileishmanial activity
04	Russia	RU2816240C2	2024-03-27	Nanostructured lipid carriers and stable emulsions and applications thereof
05	France	FR3081870B1	2024-04-19	Epitopes, mono-or multiepitopic peptide compounds and vaccines against leishmania
06	Brazil	BR132017028144E8	2023-03-07	Recombinant protein, kit for diagnosis of human and canine visceral leishmaniasis, vaccination composition against leishmaniasis and uses
07	United State	US11833197B2	2023-12-05	Immunotherapy of leishmaniasis
08	China	CN110368384B	2023-05-12	Use of dihydroartemisinin and quinolone conjugates in preparation of anti-leishmania drugs
09	United state	US11219677B2	2022-01-11	Immunotherapy of canine leishmaniasis
10	Brazil	BR102020015591A2	2022-03-08	Recombinant chimeric protein, kit, and method for diagnosis of tegumentary leishmaniasis and uses
11	Brazil	BR102012030066B1	2022-07-19	Process for production of recombinant leishmania peroxiredoxin and use in the diagnosis of leishmaniasis
12	Brazil	BR102021000794A2	2022-07-26	Chimeric protein, kit, method for diagnosing leishmaniasis, use of a chimeric protein, vaccine composition against visceral leishmaniasis, and, use of a vaccine

				composition
13	Brazil	BR102020021166A2	2022-05-10	Pharmaceutical and/or immunogenic compositions against visceral leishmaniasis and use
14	Spain	ES2795149B2	2022-07-04	Synthetic multiepitopic chimera as a vaccine and treatment against leishmaniosis in mammals
15	Brazil	BR102018016046A2	2021-11-16	Vaccine compositions against tegumentary and visceral leishmaniasis and use
16	Brazil	BR102018070807A2	2021-11-16	Recombinant chimeric protein, vaccine against tegumentary and visceral leishmaniasis and uses
17	China	CN113337542A	2021-09-03	Human replication-defective recombinant adenovirus vector for efficiently expressing Leishmania PEPCK
18	United State	US10898460B1	2021-01-26	Leishmania inhibitors
19	Spain	ES2875862T3	2021-11-11	Monovalent and polyvalent vaccines against Leishmania
20	European	EP2637687B1	2021-01-06	Vaccines comprising non-specific nucleoside hydrolase and sterol 24-c-methyltransferase (smt) polypeptides for the treatment and diagnosis of leishmaniasis
21	World Intellectual Property Organisation (WIPO)	WO2020168402A1	2020-08-27	Chimeric protein, method of production and use thereof, and also a nucleic acid molecule, expression cassette, expression vector, host cell, composition for the diagnosis of leishmaniasis, kit for the diagnosis of leishmaniasis and method of diagnosis of leishmaniasis in vitro
22	United State	US20200261558A1	2020-08-20	Vaccines against leishmania infection
23	World Intellectual Property Organisation (WIPO)	WO2019043212	2019-04-25	Topical compositions for the treatment of cutaneous leishmaniasis
24	Japan	JP2019517	2019-06-24	Animal and human anti-trypanosoma and anti-

		500A		leishmania drugs
25	United State	US10111854B2	2018-10-30	Synthesis and use of amine-containing flavonoids as potent anti-leishmanial agents
26	China	CN103890004B	2018-02-02	The chimeric molecule being made up of the Leishmania infantum PFR1 protein fragments with specific immunodominant epitopes can be used for the immunotherapy of leishmaniasis
27	United State	US9872849B2	2018-01-23	Diterpenoid membranolide compounds having anti-leishmania activity and uses thereof
28	Spain	ES2566228B1	2017-02-08	Use of proton-ionizable pyrazole-derived esters and their corresponding salts for the treatment of Chagas disease and leishmaniasis
29	United state	US 9562037	2017-02-07	Synthesis and use of amine-containing flavonoids as potent anti-leishmanial agents
30	World Intellectual Property Organisation (WIPO)	WO2016116550	2016-07-28	An immunotoxin for use in the treatment of leishmaniasis
31	World Intellectual Property Organisation (WIPO)	WO2016116563	2016-07-28	Pyrazolo[3,4-d] pyrimidine derivative and its use for the treatment of leishmaniasis
32	China	CN102811992B	2015-06-17	Anti-leishmania compound and anti-leishmania drug
33	Spain	ES2528928T3	2015-02-13	Recombinant polyprotein vaccines for the treatment and diagnosis of leishmaniasis
34	United state	US20150306035	2015-10-29	Pharmaceutical composition containing conventional liposomes and prolonged-circulation liposomes for the treatment of visceral leishmaniasis
35	World Intellectu	WO2015177820	2015-11-26	Nanoparticulate systems for vehiculating drugs for the treatment of leishmania infection-related

	al Property Organisation (WIPO)			pathologies

7.2 Clinical Trials

In India, liposomal amphotericin B is the primary medication used for treating VL. Nevertheless, anti-leishmanial vaccines have failed repeatedly in clinical trials.

Table No. 8. Clinical Trials of some antileishmanial drugs (At: http://clinicaltrials.gov/ (accessed 03.07.13))

S. No.	Phases	Objectives	Drugs	Reference
01.	Phase 3	1. to determine a combination that is both safe and successful for treating visceral leishmaniasis in a short amount of time while lowering the likelihood of parasite resistance.	• Miltefosine + AmBiosome • Paromomycin sulfate with AmBiosome • Paromomycin sulfate with miltefosine • Deoxycholate of Amphotericin B	[158]
		2. To evaluate the safety and effectiveness of treating patients with visceral leishmaniasis with sodium stibogluconate alone for 30 days, paromomycin sulfate alone for 21 days, and sodium stibogluconate and paromomycin sulfate together for 17 days.	• Stibogluconate of sodium • Sulfate of paromomycin • Paromomycin sulfate with sodium stibogluconate	
		3. The purpose is to evaluate the standard treatment utilizing a total dosage of 15 mg/kg of AmBisome to determine the safety and efficacy of various combinations of the three drugs—AmBisome, paromomycin, and	• - AmBisome • - AmBisome in combination with Miltefosine • - AmBisome in combination with Paromomycin • - Miltefosine in combination with Paromomycin	

		miltefosine—at a reduced overall dosage.		
02.	Phase 2	1.In Eastern Africa, to evaluate the efficacy of miltefosine with single dose AmBisomeW, sodium stibogluconate plus single dosage AmBisomeW, and miltefosine alone in treating visceral leishmaniasis	• Both sodium stibogluconate and amBisome • Miltefosine + AmBisome. • Miltefosin	[158]
		2. Miltefosine and AmBisome are combined in varying doses using a sequential strategy.	Both AmBisome and Miltefosine	
		3. After six months of consecutively administering both medications, the final cure is evaluated. Miltefosine will be administered for 14 days after AmBisome on day 1.	Miltefosine with AmBisome	
		4. To describe the safety and acceptability of oral sitamaquine as well as its pharmacokinetic profile	Sitamaquine	

8. Challenges in Treatment and Future Directions for Disease Control

The protozoan parasite's transmission cycle in humans, as well as its vectors, reservoirs, and different social and environmental elements, provide substantial obstacles to disease control [159–161]

The main challenge in treating Leishmania is the limited therapies targeting the parasites' intracellular locations. Activated macrophages initiate an oxidative burst during phagocytosis, but Leishmania uses redox signaling pathways to resist oxidative stress and conventional treatments[38,42,58–60,152].

Leishmania parasites evade macrophage destruction and grow in hosts by neutralizing reactive oxygen species. Their treatment resistance stems from drug removal and reduced cellular uptake. Targeting macrophages with surface-modified nanocarriers can enhance drug delivery and improve treatment outcomes [91,103,115].

Managing leishmaniasis is challenging due to the diversity of Leishmania species, drug resistance, and adverse effects of current treatments like pentavalent antimonials and

amphotericin B. High treatment costs also limit accessibility in endemic regions, highlighting the need for safer, more effective alternatives [59,95,99,162]

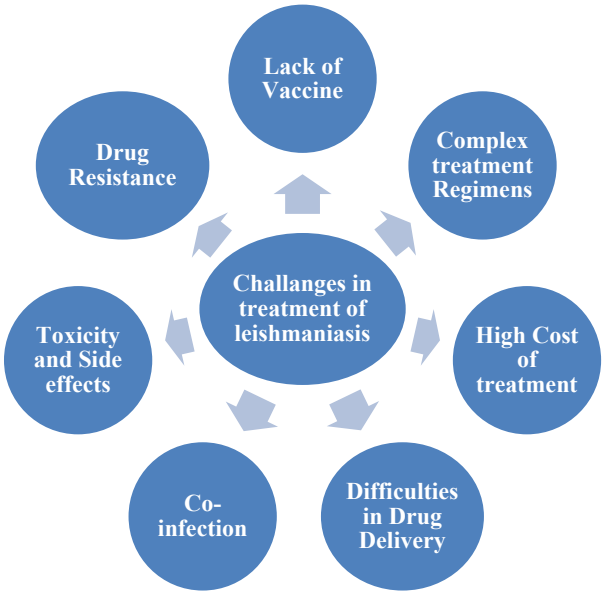

Fig. 7 - Challenge ratio during leishmaniasis therapy

The treatment of leishmaniasis faces several significant challenges, including:

1. **Drug Resistance**: Recent studies highlight increasing resistance of Leishmania parasites to standard treatments, complicating leishmaniasis management and leading to longer recovery times and higher mortality rates. There is a pressing need for innovative treatments and deeper insight into the resistance mechanisms [96,163]
2. **Toxicity and Side Effects**: Treatment options for fungal infections include amphotericin B and its liposomal formulations, but they often come with significant side effects and toxicity. This is especially challenging for patients in rural areas with limited healthcare access. Adverse effects can lead to poor adherence to treatment, complicating health outcomes [7,103,164,165]
3. **Complex Treatment Regimens**: Current treatment recommendations often require long-term medication use, posing challenges for patient adherence. This is particularly evident in under-resourced settings, where limited access to medications, financial constraints, and inadequate healthcare resources impede effective treatment compliance [7,100,165]
4. **High Cost of Treatment**: The high cost of leishmaniasis treatments limits access for patients in endemic regions, where healthcare resources are scarce. This economic barrier impacts health outcomes and disease transmission, making affordable treatments essential for effective care [20,35,68,134,166]
5. **Co-infections**: Co-infections like HIV complicate leishmaniasis management, leading to altered immune responses and more severe cases. Standard treatments may be less effective, requiring tailored approaches and careful attention from healthcare professionals for optimal care [54,167,168]
6. **Lack of Vaccines**: At present, there is no effective vaccine to stop leishmaniasis, a disease transmitted by sandflies. Therefore, the battle against this condition should focus mainly on

controlling the vectors that spread it and implementing robust public health measures. These strategies are essential for reducing the risk of infection and protecting at-risk populations in impacted regions [4,35,36,41,45,169]

7. **Difficulties in Drug Delivery**: Leishmania parasites reside within macrophages, presenting a significant barrier to the effective administration of therapeutic medications to these immune cells. To tackle this issue, scientists are currently investigating novel nanoparticle-based drug delivery systems with the goal of greatly improving the bioavailability and overall effectiveness of leishmaniasis treatments [7,40,129,138,170]
8. **High Toxicity of Existing Treatments**: Many treatments today are associated with higher toxicity levels, posing significant risks of side effects, particularly for vulnerable groups such as the elderly, children, or those with pre-existing health conditions. These risks can limit treatment options, making careful selection of therapy essential [68,83,106,116,164,165]
9. **Low Investment in Drug Development**: Insufficient investment in the exploration and development of new pharmaceutical treatments for leishmaniasis greatly hampers progress in discovering more effective and safer therapeutic alternatives for this condition. This deficiency not only restricts the possibility of innovative solutions but also obstructs the overall advancement in meeting the medical needs of individuals impacted by leishmaniasis [77,161,171]

9. Conclusion

Available literature and ethnomedical surveys have highlighted the use of various plants in traditional medicine as effective and safe anti-leishmanial agents. This review is a summary of the research that shows how important natural herbal remedies are for treating leishmaniasis. Nowadays, the significance of herbal medicines has increased significantly due to their fewer side effects compared to conventional drugs. As a result, the demand for herbal formulations is growing daily. It will be crucial in the future to identify lead compounds and comprehend the molecular mechanisms underlying these plant-based medications. This will help meet the demand for high-potency options and facilitate the development of superior herbal formulations that can replace or complement currently available synthetic medications. The research provides a platform for exploring innovative targeting techniques aimed at reducing the morbidity and mortality rates associated with the leishmanial parasite in the lymphatic system. The development of novel lead molecules may potentially improve the safety and effectiveness of treatments for various types of leishmaniasis.

10. References

1. Mann S, Frasca K, Scherrer S, et al. A Review of Leishmaniasis: Current Knowledge and Future Directions. *Curr Trop Med Rep*. 2021;8(2):121-132. doi:10.1007/s40475-021-00232-7

2. Divenuto F, Pavia G, Marascio N, Barreca GS, Quirino A, Matera G. Role of Treg, Breg and other cytokine sets in host protection and immunopathology during human leishmaniasis: Are they potential valuable markers in clinical settings and vaccine evaluation? *Acta Trop*. 2023;240:106849. doi:10.1016/j.actatropica.2023.106849

3. Kumar P, Shivam P, Mandal S, et al. <p>Synthesis, characterization, and mechanistic studies of a gold nanoparticle–amphotericin B covalent conjugate with enhanced antileishmanial efficacy

and reduced cytotoxicity</p>. *Int J Nanomedicine*. 2019;Volume 14:6073-6101. doi:10.2147/IJN.S196421

4. Prasanna P, Kumar P, Kumar S, et al. Current status of nanoscale drug delivery and the future of nano-vaccine development for leishmaniasis – A review. *Biomedicine & Pharmacotherapy*. 2021;141:111920. doi:10.1016/j.biopha.2021.111920

5. Bashir S, Shabbir K, Din F ud, et al. Nitazoxanide and quercetin co-loaded nanotransfersomal gel for topical treatment of cutaneous leishmaniasis with macrophage targeting and enhanced anti-leishmanial effect. *Heliyon*. 2023;9(11):e21939. doi:10.1016/j.heliyon.2023.e21939

6. Dar MJ, McElroy CA, Khan MI, Satoskar AR, Khan GM. Development and evaluation of novel miltefosine-polyphenol co-loaded second generation nano-transfersomes for the topical treatment of cutaneous leishmaniasis. *Expert Opin Drug Deliv*. 2020;17(1):97-110. doi:10.1080/17425247.2020.1700227

7. dos Santos DB, Lemos JA, Miranda SEM, et al. Current Applications of Plant-Based Drug Delivery Nano Systems for Leishmaniasis Treatment. *Pharmaceutics*. 2022;14(11):2339. doi:10.3390/pharmaceutics14112339

8. Mohamed AH, Bashir AM. Acute kidney injury as initial presentation of visceral leishmaniasis in a young patient- A case report. *Annals of Medicine & Surgery*. 2022;78:103821. doi:10.1016/j.amsu.2022.103821

9. Tsai PH, Chen YT, Liau JY, et al. Molecular diagnosis and therapy for cutaneous leishmaniasis of a returned traveler from Mexico. *Journal of Microbiology, Immunology and Infection*. 2021;54(6):1154-1158. doi:10.1016/j.jmii.2020.07.007

10. Faccini-Martínez ÁA, Katime Zuñiga A, Orozco Sebá BE, Herrera-Bedoya MJ. Photo timeline of localized cutaneous leishmaniasis, Colombia. *Infectious Medicine*. *Elsevier B.V.* 2023;2(1):63-65. doi:10.1016/j.imj.2023.01.001

11. Medeiros RMTE, Carvalho AMRS, Ferraz I de A, et al. Mapping linear B-cell epitopes of the Tryparedoxin Peroxidase and its implications in the serological diagnosis of tegumentary leishmaniasis. *Acta Trop*. 2022;232. doi:10.1016/j.actatropica.2022.106521

12. Khattak FA, Akbar N ul, Riaz M, et al. Novel IL-12Rβ1 deficiency-mediates recurrent cutaneous leishmaniasis. *International Journal of Infectious Diseases*. 2021;112:338-345. doi:10.1016/j.ijid.2021.08.049

13. Khattak FA, Khan TA, Hussain M, et al. Analysis of associated risk factors among recurrent cutaneous leishmaniasis patients: A cross-sectional study in Khyber Pakhtunkhwa, Pakistan. *J Infect Public Health*. 2022;15(11):1175-1179. doi:10.1016/j.jiph.2022.09.010

14. Jamshaid H, Din F ud, Khan GM. Nanotechnology based solutions for anti-leishmanial impediments: a detailed insight. *J Nanobiotechnology*. 2021;19(1):106. doi:10.1186/s12951-021-00853-0

15. Khan M, Ghayyur S, yasmin S. Distribution, clinical features, and epidemiology of cutaneous leishmaniasis: A case study of District Haripur, KPK, Pakistan. *Medical Reports*. 2023;2:100025. doi:10.1016/j.hmedic.2023.100025

16. Alving CR, Steck EA, Chapman WL, et al. Therapy of leishmaniasis: Superior efficacies of liposome-encapsulated drugs. *Proceedings of the National Academy of Sciences*. 1978;75(6):2959-2963. doi:10.1073/pnas.75.6.2959

17. Dar MJ, Khalid S, Varikuti S, Satoskar AR, Khan GM. Nano-elastic liposomes as multidrug carrier of sodium stibogluconate and ketoconazole: A potential new approach for the topical treatment of cutaneous Leishmaniasis. *European Journal of Pharmaceutical Sciences*. 2020;145:105256. doi:10.1016/j.ejps.2020.105256

18. Moraes CS, Seabra SH, Castro DP, et al. Leishmania (Leishmania) chagasi interactions with Serratia marcescens: Ultrastructural studies, lysis and carbohydrate effects. *Exp Parasitol*. 2008;118(4):561-568. doi:10.1016/j.exppara.2007.11.015

19. Seifert K, Matu S, Javier Pérez-Victoria F, Castanys S, Gamarro F, Croft SL. Characterisation of Leishmania donovani promastigotes resistant to hexadecylphosphocholine (miltefosine). *Int J Antimicrob Agents*. 2003;22(4):380-387. doi:10.1016/S0924-8579(03)00125-0

20. Ahmad A, Ullah S, Syed F, Tahir K, Khan AU, Yuan Q. Biogenic Metal Nanoparticles as A Potential Class of Antileishmanial Agents: Mechanisms and Molecular Targets. *Nanomedicine*. 2020;15(8):809-828. doi:10.2217/nnm-2019-0413

21. Veasey JV, Zampieri RA, Lellis RF, Freitas THP de, Winter LMF. Identification of Leishmania species by high-resolution DNA dissociation in cases of American cutaneous leishmaniasis. *An Bras Dermatol*. 2020;95(4):459-468. doi:10.1016/j.abd.2020.02.003

22. Borghi SM, Fattori V, Conchon-Costa I, Pinge-Filho P, Pavanelli WR, Verri WA. Leishmania infection: painful or painless? *Parasitol Res*. 2017;116(2):465-475. doi:10.1007/s00436-016-5340-7

23. Séguin O, Descoteaux A. Leishmania, the phagosome, and host responses: The journey of a parasite. *Cell Immunol*. 2016;309:1-6. doi:10.1016/j.cellimm.2016.08.004

24. Andrade BB, De Oliveira CI, Brodskyn CI, Barral A, Barral-Netto M. Role of Sand Fly Saliva in Human and Experimental Leishmaniasis: Current Insights. *Scand J Immunol*. 2007;66(2-3):122-127. doi:10.1111/j.1365-3083.2007.01964.x

25. Olivier M, Zamboni DS. Leishmania Viannia guyanensis, LRV1 virus and extracellular vesicles: a dangerous trio influencing the faith of immune response during muco-cutaneous leishmaniasis. *Curr Opin Immunol*. 2020;66:108-113. doi:10.1016/j.coi.2020.08.004

26. Uwishema O, Sapkota S, Wellington J, Onyeaka CVP, Onyeaka H. Leishmaniasis control in the light of the COVID-19 pandemic in Africa. *Annals of Medicine & Surgery*. 2022;80. doi:10.1016/j.amsu.2022.104263

27. Trópia de Abreu R, Carvalho M das G, Carneiro CM, et al. Influence of Clinical Status and Parasite Load on Erythropoiesis and Leucopoiesis in Dogs Naturally Infected with Leishmania (Leishmania) chagasi. Davis T, ed. *PLoS One*. 2011;6(5):e18873. doi:10.1371/journal.pone.0018873

28. Alvar J, den Boer M, Dagne DA. Towards the elimination of visceral leishmaniasis as a public health problem in east Africa: reflections on an enhanced control strategy and a call for action. *Lancet Glob Health*. 2021;9(12):e1763-e1769. doi:10.1016/S2214-109X(21)00392-2

29. Almeida JR, Gomes A, Mendes B, et al. Unlocking the potential of snake venom-based molecules against the malaria, Chagas disease, and leishmaniasis triad. *Int J Biol Macromol*. 2023;242:124745. doi:10.1016/j.ijbiomac.2023.124745

30. Vital W de S, Santos FJ de A, Gonçalves MLF, Wyrepkowski CDC, Ramasawmy R, Furtado S da C. Influence of the presence of mannose-binding lectin polymorphisms on the occurrence of leishmaniasis: a systematic review and meta-analysis. *An Bras Dermatol*. 2022;97(3):298-306. doi:10.1016/j.abd.2021.08.004

31. Sarwar HS, Akhtar S, Sohail MF, et al. Redox Biology of *Leishmania* and Macrophage Targeted Nanoparticles for Therapy. *Nanomedicine*. 2017;12(14):1713-1725. doi:10.2217/nnm-2017-0049

32. Souza LWF, Souza SVT, Botelho ACC. Comparative analysis of the geographic distribution of the histopathological spectrum and Leishmania species of American cutaneous leishmaniasis in Brazil. *An Bras Dermatol*. 2012;87(3):369-374. doi:10.1590/S0365-05962012000300003

33. Melo MGN de, Reino IB da SM, Vaitkevicius-Antão V, et al. Chlorella vulgaris extract and Imiquimod as new therapeutic targets for leishmaniasis: An immunological approach. *Immunobiology*. 2024;229(1):152779. doi:10.1016/j.imbio.2023.152779

34. Aramayo L V., Copa GN, Hoyos CL, et al. Leishmaniasis tegumentaria y flebótomos en la localidad de Colonia Santa Rosa del norte de Argentina. *Rev Argent Microbiol*. 2022;54(2):143-151. doi:10.1016/j.ram.2021.06.002

35. Kaye PM, Cruz I, Picado A, Van Bocxlaer K, Croft SL. Leishmaniasis immunopathology—impact on design and use of vaccines, diagnostics and drugs. *Semin Immunopathol*. 2020;42(3):247-264. doi:10.1007/s00281-020-00788-y

36. Kaye PM, Matlashewski G, Mohan S, et al. Vaccine value profile for leishmaniasis. *Vaccine*. 2023;41:S153-S175. doi:10.1016/j.vaccine.2023.01.057

37. Raimundo VD, Carvalho RPR, Machado-Neves M, Marques-da-Silva E de A. Effects of terpenes in the treatment of visceral leishmaniasis: A systematic review of preclinical evidence. *Pharmacol Res*. 2022;177:106117. doi:10.1016/j.phrs.2022.106117

38. Shoaib Sarwar H, Varikuti S, Farhan Sohail M, et al. Oral delivery and enhanced efficacy of antimonal drug through macrophage-guided multifunctional nanocargoes against visceral

Leishmaniasis. *European Journal of Pharmaceutics and Biopharmaceutics*. 2020;152:307-317. doi:10.1016/j.ejpb.2020.05.029

39. Franca M, Guimarães LH, Nascimento MT, Rocha PN, Carvalho LP. The Leishmania antigen-specific pro-inflammatory response in cutaneous leishmaniasis is linked to disease progression but not to the therapeutic failure of pentavalent antimonials. *Microbes Infect*. 2021;23(9-10):104866. doi:10.1016/j.micinf.2021.104866

40. Coelho E, Ribeiro T, Chávez-Fumagalli M, et al. Novel targeting using nanoparticles: an approach to the development of an effective anti-leishmanial drug-delivery system. *Int J Nanomedicine*. 2014;9(1):877. doi:10.2147/IJN.S55678

41. Hotez PJ, Bottazzi ME, Kaye PM, Lee BY, Puchner KP. Neglected tropical disease vaccines: hookworm, leishmaniasis, and schistosomiasis. *Vaccine*. 2023;41:S176-S179. doi:10.1016/j.vaccine.2023.04.025

42. Mouhoub B, Bensalah M, Berhili A, et al. Visceral leishmaniasis associated with macrophage activation syndrome: Case report and literature review. *IDCases*. 2021;26:e01247. doi:10.1016/j.idcr.2021.e01247

43. Sinan M, Ansari KJ, Kanwal A, et al. Analysis of the mathematical model of cutaneous Leishmaniasis disease. *Alexandria Engineering Journal*. 2023;72:117-134. doi:10.1016/j.aej.2023.03.065

44. Abass E, Kang C, Martinkovic F, et al. Heterogeneity of Leishmania donovani Parasites Complicates Diagnosis of Visceral Leishmaniasis: Comparison of Different Serological Tests in Three Endemic Regions. Afrin F, ed. *PLoS One*. 2015;10(3):e0116408. doi:10.1371/journal.pone.0116408

45. Younis BM, Osman M, Khalil EAG, et al. Safety and immunogenicity of ChAd63-KH vaccine in post-kala-azar dermal leishmaniasis patients in Sudan. *Molecular Therapy*. 2021;29(7):2366-2377. doi:10.1016/j.ymthe.2021.03.020

46. Thakur S, Joshi J, Kaur S. Leishmaniasis diagnosis: an update on the use of parasitological, immunological and molecular methods. *Journal of Parasitic Diseases*. 2020;44(2):253-272. doi:10.1007/s12639-020-01212-w

47. Chaves M, Savio LE, Coutinho-Silva R. Purinergic signaling: A new front-line determinant of resistance and susceptibility in leishmaniasis. *Biomed J*. 2022;45(1):109-117. doi:10.1016/j.bj.2021.06.003

48. Taslimi Y, Sadeghipour P, Habibzadeh S, et al. A novel non-invasive diagnostic sampling technique for cutaneous leishmaniasis. Louzir H, ed. *PLoS Negl Trop Dis*. 2017;11(7):e0005750. doi:10.1371/journal.pntd.0005750

49. Bahrami F, Masoudzadeh N, Van Veen S, et al. Blood transcriptional profiles distinguish different clinical stages of cutaneous leishmaniasis in humans. *Mol Immunol*. 2022;149:165-173. doi:10.1016/j.molimm.2022.07.008

50. Taslimi Y, Habibzadeh S, Goyonlo VM, et al. Tape-disc-loop-mediated isothermal amplification (TD-LAMP) method as noninvasive approach for diagnosis of cutaneous leishmaniasis caused by L. tropica. *Heliyon*. 2023;9(11):e21397. doi:10.1016/j.heliyon.2023.e21397

51. Singh K, Garg G, Ali V. Current Therapeutics, Their Problems and Thiol Metabolism as Potential Drug Targets in Leishmaniasis. *Curr Drug Metab*. 2016;17(9):897-919. doi:10.2174/1389200217666160819161444

52. Singh OP, Gedda MR, Mudavath SL, Srivastava ON, Sundar S. Envisioning the Innovations in Nanomedicine to Combat Visceral Leishmaniasis: For Future Theranostic Application. *Nanomedicine*. 2019;14(14):1911-1927. doi:10.2217/nnm-2018-0448

53. Bañuls AL, Bastien P, Pomares C, Arevalo J, Fisa R, Hide M. Clinical pleiomorphism in human leishmaniases, with special mention of asymptomatic infection. *Clinical Microbiology and Infection*. 2011;17(10):1451-1461. doi:10.1111/j.1469-0691.2011.03640.x

54. Kaur R, Kumar R, Chaudhary V, et al. Prevalence of HIV infection among visceral leishmaniasis patients in India: A systematic review and meta-analysis. *Clin Epidemiol Glob Health*. 2024;25:101504. doi:10.1016/j.cegh.2023.101504

55. Akbari M, Oryan A, Hatam G. Application of nanotechnology in treatment of leishmaniasis: A Review. *Acta Trop*. 2017;172:86-90. doi:10.1016/j.actatropica.2017.04.029

56. Poloni A, Giacomelli A, Corbellino M, et al. Delayed diagnosis among patients with cutaneous and mucocutaneous leishmaniasis. *Travel Med Infect Dis*. 2023;55:102637. doi:10.1016/j.tmaid.2023.102637

57. Want MY, Yadav P, Khan R, et al. Critical antileishmanial in vitro effects of highly examined gold nanoparticles. *Int J Nanomedicine*. 2021;16:7285-7295. doi:10.2147/IJN.S268548

58. Karimipour-Saryazdi A, Jafari MM, Omidi R, Ghaffarifar F, Sadeghi SH. Anti-leishmania Effect of Magnesium Oxide Nanoparticles on *Leishmania tropica/infantum* and *Leishmania* -Infected Macrophages. *Int J Enteric Pathog*. 2022;10(4):144-154. doi:10.34172/ijep.2022.5546

59. Kumar Singh P, Gorain B, Choudhury H, et al. Macrophage targeted amphotericin B nanodelivery systems against visceral leishmaniasis. *Materials Science and Engineering: B*. 2020;258:114571. doi:10.1016/j.mseb.2020.114571

60. Shilakari Asthana G, Asthana A, Kohli DV, Vyas SP. Mannosylated Chitosan Nanoparticles for Delivery of Antisense Oligonucleotides for Macrophage Targeting. *Biomed Res Int*. 2014;2014:1-17. doi:10.1155/2014/526391

61. Nahar M, Dubey V, Mishra D, Mishra PK, Dube A, Jain NK. *In vitro* evaluation of surface functionalized gelatin nanoparticles for macrophage targeting in the therapy of visceral leishmaniasis. *J Drug Target*. 2010;18(2):93-105. doi:10.3109/10611860903115290

62. Durán-Galea A, Cristóbal-Verdejo JI, Barrera-Chacón R, et al. Clinical importance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index in dogs with leishmaniasis. *Comp Immunol Microbiol Infect Dis*. 2024;107:102148. doi:10.1016/j.cimid.2024.102148

63. Rogerio LA, Takahashi TY, Cardoso L, et al. Co-infection of Leishmania infantum and a Crithidia-related species in a case of refractory relapsed visceral leishmaniasis with non-ulcerated cutaneous manifestation in Brazil. *International Journal of Infectious Diseases*. 2023;133:85-88. doi:10.1016/j.ijid.2023.05.012

64. Roatt BM, de Oliveira Cardoso JM, De Brito RCF, Coura-Vital W, de Oliveira Aguiar-Soares RD, Reis AB. Recent advances and new strategies on leishmaniasis treatment. *Appl Microbiol Biotechnol*. 2020;104(21):8965-8977. doi:10.1007/s00253-020-10856-w

65. Valadares DG, Clay OS, Chen Y, et al. NLRP12-expressing dendritic cells mediate both dissemination of infection and adaptive immune responses in visceral leishmaniasis. *iScience*. 2023;26(3):106163. doi:10.1016/j.isci.2023.106163

66. Srividya G, Kulshrestha A, Singh R, Salotra P. Diagnosis of visceral leishmaniasis: developments over the last decade. *Parasitol Res*. 2012;110(3):1065-1078. doi:10.1007/s00436-011-2680-1

67. Ramírez JD, Cao L, Castillo-Castañeda AC, et al. Clinical performance of a quantitative pan-genus Leishmania Real-time PCR assay for diagnosis of cutaneous and visceral leishmaniasis. *Pract Lab Med*. 2023;37:e00341. doi:10.1016/j.plabm.2023.e00341

68. Kammona O, Tsanaktsidou E. Nanotechnology-aided diagnosis, treatment and prevention of leishmaniasis. *Int J Pharm*. 2021;605:120761. doi:10.1016/j.ijpharm.2021.120761

69. Lopes LC, Trindade GV de M, Bezerra JMT, et al. Epidemiological profile, spatial patterns and priority areas for surveillance and control of leishmaniasis in Brazilian border strip, 2009–2017. *Acta Trop*. 2023;237:106704. doi:10.1016/j.actatropica.2022.106704

70. Lestinova T, Rohousova I, Sima M, de Oliveira CI, Volf P. Insights into the sand fly saliva: Blood-feeding and immune interactions between sand flies, hosts, and Leishmania. Milon G, ed. *PLoS Negl Trop Dis*. 2017;11(7):e0005600. doi:10.1371/journal.pntd.0005600

71. Elmahallawy EK, Alkhaldi AAM, Saleh AA. Host immune response against leishmaniasis and parasite persistence strategies: A review and assessment of recent research. *Biomedicine & Pharmacotherapy*. 2021;139:111671. doi:10.1016/j.biopha.2021.111671

72. Lata S, Kumari S, Das R, Pasi S, Dhiman RC. Typical and atypical cutaneous leishmaniasis in Himachal Pradesh (India). *Heliyon*. 2021;7(6):e07282. doi:10.1016/j.heliyon.2021.e07282

73. Nafari A, Cheraghipour K, Sepahvand M, Shahrokhi G, Gabal E, Mahmoudvand H. Nanoparticles: New agents toward treatment of leishmaniasis. *Parasite Epidemiol Control*. 2020;10:e00156. doi:10.1016/j.parepi.2020.e00156

74. Maruf S, Sagar SK, Rashid MU, et al. Assessment of treatment outcomes of visceral leishmaniasis (VL) treated cases and impact of COVID-19 on VL management and control services in Bangladesh. *J Infect Public Health*. 2023;16(11):1716-1721. doi:10.1016/j.jiph.2023.09.003

75. Fattahi Bafghi A, Haghirosadat BF, Yazdian F, et al. A novel delivery of curcumin by the efficient nanoliposomal approach against *Leishmania major*. *Prep Biochem Biotechnol*. 2021;51(10):990-997. doi:10.1080/10826068.2021.1885045

76. Bansal R, Sen SS, Muthuswami R, Madhubala R. Stigmasterol as a potential biomarker for amphotericin B resistance in Leishmania donovani. *Journal of Antimicrobial Chemotherapy*. 2020;75(4):942-950. doi:10.1093/jac/dkz515

77. Kumar R, Pandey K, Sahoo GC, et al. Development of high efficacy peptide coated iron oxide nanoparticles encapsulated amphotericin B drug delivery system against visceral leishmaniasis. *Materials Science and Engineering: C*. 2017;75:1465-1471. doi:10.1016/j.msec.2017.02.145

78. Esfandiari F, Motazedian MH, Asgari Q, Morowvat MH, Molaei M, Heli H. Paromomycin-loaded mannosylated chitosan nanoparticles: Synthesis, characterization and targeted drug delivery against leishmaniasis. *Acta Trop*. 2019;197:105072. doi:10.1016/j.actatropica.2019.105072

79. Barba PJ, Morgado-Carrasco D, Quera A. Miltefosine to Treat Childhood Cutaneous Leishmaniasis. *Actas Dermosifiliogr*. 2022;113(8):827-831. doi:10.1016/j.ad.2020.11.033

80. Dirany Z, El-Dirany R, Smith GN, Nguewa P, González-Gaitano G. Mixed micelles and gels of a hydrophilic poloxamine (Tetronic 1307) and miltefosine: Structural characterization by small-angle neutron scattering and in vitro evaluation for the treatment of leishmaniasis. *J Mol Liq*. 2023;379:121654. doi:10.1016/j.molliq.2023.121654

81. Dirany Z, Smith GN, Aydillo C, Nguewa P, González-Gaitano G. Structure and activity of amphiphilic PEO-PPO-based polymeric micelles and gels incorporating host–guest complexes of miltefosine as novel formulations for the treatment of leishmaniasis. *J Mol Liq*. 2024;400:124455. doi:10.1016/j.molliq.2024.124455

82. Lipa Castro A, Pomel S, Cailleau C, et al. Pharmacokinetics, biodistribution, and activity of Amphotericin B-loaded nanocochleates on the Leishmania donovani murine visceral leishmaniasis model. *Int J Pharm*. 2022;624:121985. doi:10.1016/J.IJPHARM.2022.121985

83. Jamal F, Altaf I, Ahmed G, et al. Amphotericin B Nano-Assemblies Circumvent Intrinsic Toxicity and Ensure Superior Protection in Experimental Visceral Leishmaniasis with Feeble Toxic Manifestation. *Vaccines (Basel)*. 2023;11(1):100. doi:10.3390/vaccines11010100

84. Swaminathan S, Mai LT, Meli AP, et al. LAG-3- and CXCR5-expressing CD4 T cells display progenitor-like properties during chronic visceral leishmaniasis. *Cell Rep*. 2024;43(3):113879. doi:10.1016/j.celrep.2024.113879

85. Román-Álamo L, Allaw M, Avalos-Padilla Y, et al. In Vitro Evaluation of Aerosol Therapy with Pentamidine-Loaded Liposomes Coated with Chondroitin Sulfate or Heparin for the Treatment of Leishmaniasis. *Pharmaceutics*. 2023;15(4). doi:10.3390/pharmaceutics15041163

86. karmaoui A, Ben Salem A, Sereno D, El Jaafari S, Hajji L. Geographic distribution of Meriones shawi,Psammomys obesus, and Phlebotomus papatasi the main reservoirs and principal vector of zoonotic cutaneous leishmaniasis in the Middle East and North Africa. *Parasite Epidemiol Control*. 2022;17:e00247. doi:10.1016/j.parepi.2022.e00247

87. Wilson ME, Lewis TS, Miller MA, McCormick ML, Britigan BE. Leishmania chagasi: uptake of iron bound to lactoferrin or transferrin requires an iron reductase. *Exp Parasitol*. 2002;100(3):196-207. doi:10.1016/S0014-4894(02)00018-8

88. Clemente CM, Murillo J, Garro AG, et al. Piperine, quercetin, and curcumin identified as promising natural products for topical treatment of cutaneous leishmaniasis. *Parasitol Res*. 2024;123(4). doi:10.1007/s00436-024-08199-w

89. Nettey H, Erskine IJ, Antwi Mensah A, et al. Oral amodiaquine microparticles repurposed for the treatment of visceral leishmaniasis. *Sci Afr*. 2022;17. doi:10.1016/j.sciaf.2022.e01285

90. Mota WS, Oliveira SSC, Pereira MM, et al. Isopentyl caffeate as a promising drug for the treatment of leishmaniasis: An in silico and in vivo study. *Curr Res Biotechnol*. 2024;7:100209. doi:10.1016/j.crbiot.2024.100209

91. Kannan S, Harel Y, Levy E, et al. Nano-Leish-IL: A novel iron oxide-based nanocomposite drug platform for effective treatment of cutaneous leishmaniasis. *Journal of Controlled Release*. 2021;335:203-215. doi:10.1016/j.jconrel.2021.05.019

92. Fakhfakh MA, Fournet A, Prina E, et al. Synthesis and biological evaluation of substituted quinolines: Potential treatment of protozoal and retroviral co-infections. *Bioorg Med Chem*. 2003;11(23):5013-5023. doi:10.1016/j.bmc.2003.09.007

93. Nakayama H, Loiseau PM, Bories C, et al. Efficacy of Orally Administered 2-Substituted Quinolines in Experimental Murine Cutaneous and Visceral Leishmaniases. *Antimicrob Agents Chemother*. 2005;49(12):4950-4956. doi:10.1128/AAC.49.12.4950-4956.2005

94. Sundar S, Singh B. Emerging therapeutic targets for treatment of leishmaniasis. *Expert Opin Ther Targets*. 2018;22(6):467-486. doi:10.1080/14728222.2018.1472241

95. Rabia S, Khaleeq N, Batool S, et al. Rifampicin-Loaded Nanotransferosomal Gel for Treatment of Cutaneous Leishmaniasis: Passive Targeting Via Topical Route. *Nanomedicine*. 2020;15(2):183-203. doi:10.2217/nnm-2019-0320

96. Goyonlo VM, Vahabi-Amlashi S, Taghavi F. Successful treatment by adding thalidomide to meglumine antimoniate in a case of refractory anthroponotic mucocutaneous leishmaniasis. *Int J Parasitol Drugs Drug Resist*. 2019;11:177-179. doi:10.1016/j.ijpddr.2019.08.007

97. Ghosh S, Kar N, Bera T. Oleanolic acid loaded poly lactic co- glycolic acid- vitamin E TPGS nanoparticles for the treatment of Leishmania donovani infected visceral leishmaniasis. *Int J Biol Macromol*. 2016;93:961-970. doi:10.1016/j.ijbiomac.2016.09.014

98. Lalatsa A, Statts L, Adriana de Jesus J, et al. Topical buparvaquone nano-enabled hydrogels for cutaneous leishmaniasis. *Int J Pharm*. 2020;588:119734. doi:10.1016/j.ijpharm.2020.119734

99. Corpas-López V, Díaz-Gavilán M, Franco-Montalbán F, et al. A nanodelivered Vorinostat derivative is a promising oral compound for the treatment of visceral leishmaniasis. *Pharmacol Res*. 2019;139:375-383. doi:10.1016/j.phrs.2018.11.039

100. Pyne N, Paul S. Screening of medicinal plants unraveled the leishmanicidal credibility of Garcinia cowa; highlighting Norcowanin, a novel anti-leishmanial phytochemical through in-silico study. *Journal of Parasitic Diseases*. 2022;46(1):202-214. doi:10.1007/s12639-021-01441-7

101. Pereira IO, Marques MJ, Pavan ALR, et al. Leishmanicidal activity of benzophenones and extracts from Garcinia brasiliensis Mart. fruits. *Phytomedicine*. 2010;17(5):339-345. doi:10.1016/j.phymed.2009.07.020

102. Islamuddin M, Chouhan G, Tyagi M, Abdin MZ, Sahal D, Afrin F. Leishmanicidal activities of Artemisia annua leaf essential oil against Visceral Leishmaniasis. *Front Microbiol*. 2014;5(NOV):1-15. doi:10.3389/fmicb.2014.00626

103. Ghanbariasad A, Azadi S, Agholi M, Osanloo M. The nanoemulsion-based nanogel of Artemisia dracunculus essential oil with proper activity against Leishmania tropica and Leishmania major. *Nanomedicine Research Journal*. 2021;6(1):89-95. doi:10.22034/nmrj.2021.01.010

104. Gholamrezaei Mostafa, Jalallou Nahid, Seyyedtabaei Seyyed javad, Dadashi Alireza, Salimi Sabour Ebrahim. Effect of Foeniculum Vulgare Aqueous and Alcoholic Seed Extract against Zoonotic Cutaneous Leishmaniasis. *Ethiop J Health Sci*. 2021;31(2):401-408. doi:10.4314/ejhs.v31i2.23

105. Khan BA, Faiz S, Khan MK, et al. Fabrication and Evaluation of W/O Emulsion Loaded with Linum usitatissimum Seeds Extract for Anti-Leishmaniasis Efficacy. *Antibiotics*. 2022;11(4). doi:10.3390/antibiotics11040432

106. Chaubey P, Mishra B, Mudavath SL, et al. Mannose-conjugated curcumin-chitosan nanoparticles: Efficacy and toxicity assessments against Leishmania donovani. *Int J Biol Macromol*. 2018;111:109-120. doi:10.1016/j.ijbiomac.2017.12.143

107. Zabihi M, Shafaei M, Ramezani V, Dara T, Mirzaie F. Preparation of Thymol Nanoliposome and Solid Lipid Nanoparticle and Evaluation of their Inhibitory Effects on Leishmania Major

Promastigotes. *Advances in Pharmacology and Therapeutics Journal*. Published online April 17, 2023. doi:10.18502/aptj.v3i1.12501

108. Asthana S, Gupta PK, Chaurasia M, Dube A, Chourasia MK. Polymeric colloidal particulate systems: intelligent tools for intracellular targeting of antileishmanial cargos. *Expert Opin Drug Deliv*. 2013;10(12):1633-1651. doi:10.1517/17425247.2013.838216

109. Shrivastava S, Gupta A, Kaur CD. The Epitome of Novel Techniques and Targeting Approaches in Drug Delivery for Treating Lymphatic Filariasis. *Curr Drug Targets*. 2020;21(12):1250-1263. doi:10.2174/1389450121666200630111250

110. Want MY, Islamuddin M, Chouhan G, et al. Therapeutic efficacy of artemisinin-loaded nanoparticles in experimental visceral leishmaniasis. *Colloids Surf B Biointerfaces*. 2015;130:215-221. doi:10.1016/j.colsurfb.2015.04.013

111. Peterson DW, George RC, Scaramozzino F, et al. Cinnamon extract inhibits tau aggregation associated with alzheimer's disease in vitro. *Journal of Alzheimer's Disease*. 2009;17(3):585-597. doi:10.3233/JAD-2009-1083

112. Ghanbariasad A, Valizadeh A, Ghadimi SN, Fereidouni Z, Osanloo M. Nanoformulating Cinnamomum zeylanicum essential oil with an extreme effect on Leishmania tropica and Leishmania major. *J Drug Deliv Sci Technol*. 2021;63:102436. doi:10.1016/j.jddst.2021.102436

113. Huang B, Mo S, He C, et al. Investigation of the anti-inflammatory mechanisms of fermented Chinese herbal residue solution in an APEC-Infected HD11 cell model through the PI3K/AKT and NF-κB pathways. *Poult Sci*. 2025;104(9). doi:10.1016/j.psj.2025.105383

114. van Griensven J, Diro E. Visceral Leishmaniasis. *Infect Dis Clin North Am*. 2019;33(1):79-99. doi:10.1016/j.idc.2018.10.005

115. Zarenezhad E, Agholi M, Ghanbariasad A, Ranjbar A, Osanloo M. A nanoemulsion-based nanogel of Citrus limon essential oil with leishmanicidal activity against Leishmania tropica and Leishmania major. *Journal of Parasitic Diseases*. 2021;45(2):441-448. doi:10.1007/s12639-020-01318-1

116. De Almeida L, Fujimura AT, Cistia ML Del, et al. Nanotechnological Strategies for Treatment of Leishmaniasis—A Review. *J Biomed Nanotechnol*. 2017;13(2):117-133. doi:10.1166/jbn.2017.2349

117. Lozano YY, Giraldo SE, Zapata AC, Escobar JE, Sánchez RM. Medicinal plants with antileishmanial activity on parasites responsible for new-world cutaneous leishmaniasis. A systematic review 2018-2022. *J Pharm Pharmacogn Res*. 2023;11(6):975-1001. doi:10.56499/jppres23.1697_11.6.975

118. Pund S, Borade G, Rasve G. Improvement of anti-inflammatory and anti-angiogenic activity of berberine by novel rapid dissolving nanoemulsifying technique. *Phytomedicine*. 2014;21(3):307-314. doi:10.1016/j.phymed.2013.09.013

119. Chaudhary S, Garg T, Murthy RSR, Rath G, Goyal AK. Development, optimization and evaluation of long chain nanolipid carrier for hepatic delivery of silymarin through lymphatic transport pathway. *Int J Pharm*. 2015;485(1-2):108-121. doi:10.1016/j.ijpharm.2015.02.070

120. Bahraminegad S, Pardakhty A, Sharifi I, Ranjbar M. Therapeutic effects of the as-synthesized polylactic acid/chitosan nanofibers decorated with amphotricin B for in vitro treatment of Leishmaniasis. *Journal of Saudi Chemical Society*. 2021;25(11):101362. doi:10.1016/j.jscs.2021.101362

121. Aji Alex MR, Chacko AJ, Jose S, Souto EB. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. *European Journal of Pharmaceutical Sciences*. 2011;42(1-2):11-18. doi:10.1016/j.ejps.2010.10.002

122. Moghddam SMM, Ahad A, Aqil M, Imam SS, Sultana Y. Optimization of nanostructured lipid carriers for topical delivery of nimesulide using Box–Behnken design approach. *Artif Cells Nanomed Biotechnol*. 2017;45(3):617-624. doi:10.3109/21691401.2016.1167699

123. Chaurasia R, Jain N. CURRENT STRATEGIES AND RECENT ADVANCES IN NANOSTRUCTURED DELIVERY SYSTEMS FOR MANAGING LEISHMANIASIS-A REVIEW. *J Adv Sci Res*. 2022;13(01):43-55. doi:10.55218/jasr.202213104

124. Gidwani B, Vyas A. Preparation, characterization, and optimization of altretamine-loaded solid lipid nanoparticles using Box-Behnken design and response surface methodology. *Artif Cells Nanomed Biotechnol*. 2016;44(2):571-580. doi:10.3109/21691401.2014.971462

125. Shrivastava S, Gidwani B, Kaur CD. Development of mebendazole loaded nanostructured lipid carriers for lymphatic targeting: Optimization, characterization, in-vitro and in-vivo evaluation. *Particulate Science and Technology*. 2021;39(3):380-390. doi:10.1080/02726351.2020.1750515

126. Gurumukhi VC, Bari SB. Quality by design (QbD)–based fabrication of atazanavir-loaded nanostructured lipid carriers for lymph targeting: bioavailability enhancement using chylomicron flow block model and toxicity studies. *Drug Deliv Transl Res*. 2022;12(5):1230-1252. doi:10.1007/s13346-021-01014-4

127. Soleimanian Y, Goli SAH, Varshosaz J, et al. β-Sitosterol loaded nanostructured lipid carrier: Physical and oxidative stability, in vitro simulated digestion and hypocholesterolemic activity. *Pharmaceutics*. 2020;12(4). doi:10.3390/pharmaceutics12040386

128. Chaubey P, Mishra B. Mannose-conjugated chitosan nanoparticles loaded with rifampicin for the treatment of visceral leishmaniasis. *Carbohydr Polym*. 2014;101(1):1101-1108. doi:10.1016/j.carbpol.2013.10.044

129. Kumara R, Sahoo GC, Pandeya K, et al. PLGA-PEG Encapsulated sitamaquine nanoparticles drug delivery system against Leishmania donovani. *Journal of Scientific and Innovative Research*. 2014;3(1):85-90. www.jsirjournal.com

130. Singh Y, Srinivas A, Gangwar M, Meher JG, Misra-Bhattacharya S, Chourasia MK. Subcutaneously Administered Ultrafine PLGA Nanoparticles Containing Doxycycline Hydrochloride Target Lymphatic Filarial Parasites. *Mol Pharm*. 2016;13(6):2084-2094. doi:10.1021/acs.molpharmaceut.6b00206

131. Andima M, Costabile G, Isert L, Ndakala AJ, Derese S, Merkel OM. Evaluation of β-sitosterol loaded PLGA and PEG-PLA nanoparticles for effective treatment of breast cancer: Preparation, physicochemical characterization, and antitumor activity. *Pharmaceutics*. 2018;10(4). doi:10.3390/pharmaceutics10040232

132. Tosyali OA, Allahverdiyev A, Bagirova M, et al. Nano-co-delivery of lipophosphoglycan with soluble and autoclaved leishmania antigens into PLGA nanoparticles: Evaluation of in vitro and in vivo immunostimulatory effects against visceral leishmaniasis. *Materials Science and Engineering: C*. 2021;120:111684. doi:10.1016/j.msec.2020.111684

133. Visbal G, Justo RMS, dos Santos da Silva e Miranda G, et al. Zinc(II)-Sterol Hydrazone Complex as a Potent Anti-Leishmania Agent: Synthesis, Characterization, and Insight into Its Mechanism of Antiparasitic Action. *Pharmaceutics*. 2023;15(4). doi:10.3390/pharmaceutics15041113

134. Singh A, Maheshwari S. Formulation, development and evaluation of Woodfordia fruticosa and β-sitosterol mediated silver nanoparticles gel for synergistic effect. *Intelligent Pharmacy*. 2024;2(1):94-101. doi:10.1016/j.ipha.2023.10.012

135. Javed B, Raja NI, Nadhman A, Mashwani Z ur R. Understanding the potential of bio-fabricated non-oxidative silver nanoparticles to eradicate Leishmania and plant bacterial pathogens. *Appl Nanosci*. 2020;10(6):2057-2067. doi:10.1007/s13204-020-01355-5

136. Raj R K, Ezhilarasan D, Rajeshkumar S. β-Sitosterol-assisted silver nanoparticles activates Nrf2 and triggers mitochondrial apoptosis via oxidative stress in human hepatocellular cancer cell line. *J Biomed Mater Res A*. 2020;108(9):1899-1908. doi:10.1002/jbm.a.36953

137. Pham TTH, Gueutin C, Cheron M, et al. Development of antileishmanial lipid nanocomplexes. *Biochimie*. 2014;107(Part A):143-153. doi:10.1016/j.biochi.2014.06.007

138. Sousa-Batista A de J, Cerqueira-Coutinho C, do Carmo FS, Albernaz M de S, Santos-Oliveira R. Polycaprolactone Antimony Nanoparticles as Drug Delivery System for Leishmaniasis. *Am J Ther*. 2019;26(1):e12-e17. doi:10.1097/MJT.0000000000000539

139. Khalid S, Salman S, Iqbal K, et al. Surfactant free synthesis of cationic nano-vesicles: A safe triple drug loaded vehicle for the topical treatment of cutaneous leishmaniasis. *Nanomedicine*. 2022;40:102490. doi:10.1016/j.nano.2021.102490

140. Tripathi P, Jaiswal AK, Dube A, Mishra PR. Hexadecylphosphocholine (Miltefosine) stabilized chitosan modified Ampholiposphere as prototype co-delivery vehicle for enhanced killing of L. donovani. *Int J Biol Macromol*. 2017;105:625-637. doi:10.1016/j.ijbiomac.2017.07.076

141. Khanna VG, Kannabiran K, Getti G. Leishmanicidal activity of saponins isolated from the leaves of Eclipta prostrata and Gymnema sylvestre. *Indian J Pharmacol*. 2009;41(1):32-35. doi:10.4103/0253-7613.48891

142. de Souza C, Carvalho JA, Abreu AS, et al. Polyelectrolytic gelatin nanoparticles as a drug delivery system for the promastigote form of *Leishmania amazonensis* treatment. *J Biomater Sci Polym Ed*. 2021;32(1):1-21. doi:10.1080/09205063.2020.1815495

143. Baltaci N, Aydogdu N, Sarikurkcu C, Tepe B. Onosma gracilis (Trautv.) and O. oreodoxa (Boiss. & Heldr.): Phytochemistry, in silico docking, antioxidant and enzyme inhibitory activities. *South African Journal of Botany*. 2021;143:410-417. doi:10.1016/j.sajb.2021.03.022

144. Hemeg HA, Rauf A, Rashid U, et al. In-Vitro Leishmanicidal Activity and Molecular Docking Simulations of a Flavonoid Isolated from Pistacia integerrima Stew ex Brandis. Sadiq B, ed. *J Food Qual*. 2022;2022:1-5. doi:10.1155/2022/6003869

145. Majid Shah S, Ullah F, Ayaz M, et al. β-Sitosterol from Ifloga spicata (Forssk.) Sch. Bip. as potential anti-leishmanial agent against leishmania tropica: Docking and molecular insights. *Steroids*. 2019;148:56-62. doi:10.1016/j.steroids.2019.05.001

146. Kropf P, Freudenberg MA, Modolell M, et al. Toll-Like Receptor 4 Contributes to Efficient Control of Infection with the Protozoan Parasite *Leishmania major*. *Infect Immun*. 2004;72(4):1920-1928. doi:10.1128/IAI.72.4.1920-1928.2004

147. de Veer MJ, Curtis JM, Baldwin TM, et al. MyD88 is essential for clearance of *Leishmania major* : possible role for lipophosphoglycan and Toll-like receptor 2 signaling. *Eur J Immunol*. 2003;33(10):2822-2831. doi:10.1002/eji.200324128

148. Kaisho T, Akira S. Toll-like receptor function and signaling. *Journal of Allergy and Clinical Immunology*. 2006;117(5):979-987. doi:10.1016/j.jaci.2006.02.023

149. Schleicher U, Liese J, Knippertz I, et al. NK cell activation in visceral leishmaniasis requires TLR9, myeloid DCs, and IL-12, but is independent of plasmacytoid DCs. *Journal of Experimental Medicine*. 2007;204(4):893-906. doi:10.1084/jem.20061293

150. Gianchecchi E, Fierabracci A. Gene/environment interactions in the pathogenesis of autoimmunity: New insights on the role of Toll-like receptors. *Autoimmun Rev. Elsevier B.V.* 2015;14(11):971-983. doi:10.1016/j.autrev.2015.07.006

151. Tavares CAP, Fernandes AP, Melo MN. Molecular diagnosis of leishmaniasis. *Expert Rev Mol Diagn*. 2003;3(5):657-667. doi:10.1586/14737159.3.5.657

152. Bogdan C. Macrophages as host, effector and immunoregulatory cells in leishmaniasis: Impact of tissue micro-environment and metabolism. *Cytokine X*. 2020;2(4). doi:10.1016/j.cytox.2020.100041

153. Dehghani A, Mamizadeh M, Karimi A, et al. Multi-epitope vaccine design against leishmaniasis using IFN-γ inducing epitopes from immunodominant gp46 and gp63 proteins. *Journal of Genetic Engineering and Biotechnology*. 2024;22(1):100355. doi:10.1016/j.jgeb.2024.100355

154. Goncalves R, Christensen SM, Mosser DM. Humoral immunity in leishmaniasis – Prevention or promotion of parasite growth? *Cytokine X*. 2020;2(4):100046. doi:10.1016/j.cytox.2020.100046

155. Pramanik PK, Chakraborti S, Bagchi A, Chakraborti T. Bioassay-based Corchorus capsularis L. leaf-derived β-sitosterol exerts antileishmanial effects against Leishmania donovani by targeting trypanothione reductase. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-77066-2

156. Russell CN, Carter JL, Borgia JM, et al. Bromodomain Factor 5 as a Target for Antileishmanial Drug Discovery. *ACS Infect Dis*. 2023;9(11):2340-2357. doi:10.1021/acsinfecdis.3c00431

157. Harush-Frenkel O, Debotton N, Benita S, Altschuler Y. Targeting of nanoparticles to the clathrin-mediated endocytic pathway. *Biochem Biophys Res Commun*. 2007;353(1):26-32. doi:10.1016/j.bbrc.2006.11.135

158. Jain K, Jain NK. Novel therapeutic strategies for treatment of visceral leishmaniasis. *Drug Discov Today*. 2013;18(23-24):1272-1281. doi:10.1016/j.drudis.2013.08.005

159. Mengeot L, Yombi JC, Baeck M. Cutaneous leishmaniasis due to Leishmania aethiopica: A therapeutic challenge. *JAAD Case Rep*. 2022;20:72-75. doi:10.1016/j.jdcr.2021.12.028

160. Ponte-Sucre A, Gamarro F, Dujardin JC, et al. Drug resistance and treatment failure in leishmaniasis: A 21st century challenge. Maes L, ed. *PLoS Negl Trop Dis*. 2017;11(12):e0006052. doi:10.1371/journal.pntd.0006052

161. Gupta D, Singh PK, Yadav PK, et al. Emerging strategies and challenges of molecular therapeutics in antileishmanial drug development. *Int Immunopharmacol*. 2023;115:109649. doi:10.1016/J.INTIMP.2022.109649

162. Kannan S, Harel Y, Israel LL, et al. Novel Nanocarrier Platform for Effective Treatment of Visceral Leishmaniasis. *Bioconjug Chem*. 2021;32(11):2327-2341. doi:10.1021/ACS.BIOCONJCHEM.1C00381

163. Bamorovat M, Sharifi I, Agha Kuchak Afshari S, et al. Poor adherence is a major barrier to the proper treatment of cutaneous leishmaniasis: A case-control field assessment in Iran. *Int J Parasitol Drugs Drug Resist*. 2023;21:21-27. doi:10.1016/j.ijpddr.2022.11.006

164. Ahmad I, Mehmood Z, Mohammad F. *Screening of Some Indian Medicinal Plants for Their Antimicrobial Properties*. Vol 62. 1998.

165. Sidana A, Farooq U. Evaluation of antileishmanial activity of plants used in Indian traditional medicine. *Bangladesh J Pharmacol*. 2015;10(2):423-426. doi:10.3329/bjp.v10i2.22674

166. Chhajed R, Dahal P, Singh-Phulgenda S, et al. Estimating the proportion of relapse following treatment of Visceral Leishmaniasis: meta-analysis using Infectious Diseases Data Observatory

(IDDO) systematic review. *The Lancet Regional Health - Southeast Asia*. 2024;22:100317. doi:10.1016/j.lansea.2023.100317

167. Takele Y, Mulaw T, Adem E, et al. Immunological factors, but not clinical features, predict visceral leishmaniasis relapse in patients co-infected with HIV. *Cell Rep Med*. 2022;3(1). doi:10.1016/j.xcrm.2021.100487

168. Singh OP, Chaubey R, Kushwaha AK, Fay M, Sacks D, Sundar S. VISCERAL LEISHMANIASIS -HIV COINFECTED PATIENTS ARE HIGHLY INFECTIOUS TO SAND FLIES IN ENDEMIC AREA OF BIHAR, INDIA. *International Journal of Infectious Diseases*. 2023;130:S23. doi:10.1016/j.ijid.2023.04.054

169. Kupani M, Pandey RK, Vashisht S, Singh S, Prajapati VK, Mehrotra S. Prediction of an immunogenic peptide ensemble and multi-subunit vaccine for Visceral leishmaniasis using bioinformatics approaches. *Heliyon*. 2023;9(12):e22121. doi:10.1016/j.heliyon.2023.e22121

170. Kushwaha SK, Kumar Rai A. *Novel Drug Delivery System for Anticancer Drug: A Review*. 2012. https://www.researchgate.net/publication/287478414

171. Chemak F, Nouiri I, Bellali H, Chahed MK. Irrigation practices, prevalence of leishmaniasis and sustainable development: Evidence from the Sidi Bouzid region in central Tunisia. *Sci Afr*. 2022;15. doi:10.1016/j.sciaf.2022.e01094