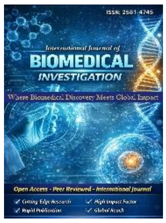
International Journal of Biomedical Investigation

journal homepage: https://ijbi.edwiserinternational.com



Review Article

Visceral Leishmaniasis (Kala-azar): Epidemiology, Pathogenesis, Diagnosis, and Emerging Therapeutic Strategies

Shammy Kishor Deepak[1], Basit Fazal[1,*] Md. Javed Karim[2], Debankini Dasgupta[3] and Shwetlana Bandyopadhyay[3]

[1]Department of Pharmacology, Nibha Institute of Pharmaceutical Sciences, Rajgir, India
[2]Department of Pharmacy, Bhabha University, Bhopal, India
[3]Department of Pharmacy, MGM College of Pharmacy, Patna, India

ARTICLE INFO

Received 27 May 2026
Revised 21 July 2026
Available Online 30 July 2026

Keywords:
Epidemiology
Pathogenesis
Macrophage infection
Visceral leishmaniasis
Sandfly transmission

ABSTRACT

Visceral leishmaniasis (VL), commonly known as Kala-azar, is one of the most severe neglected tropical diseases caused primarily by intracellular protozoan parasites belonging to the Leishmania donovani complex. Despite significant advances in disease control, VL continues to pose a major public health challenge, particularly in tropical and subtropical regions of South Asia, East Africa, and South America. The disease is transmitted through the bite of infected female phlebotomine sandflies and is characterized by persistent fever, hepatosplenomegaly, pancytopenia, weight loss, and progressive immune dysfunction. The pathogenesis of VL involves complex interactions between Leishmania parasites and host immune responses, including parasite survival within macrophages, modulation of cytokine networks, oxidative stress regulation, and immune evasion mechanisms. This review provides a comprehensive overview of the epidemiology, transmission dynamics, and global burden of visceral leishmaniasis, while highlighting recent advances in understanding its molecular and cellular pathogenesis. Current diagnostic approaches, including parasitological examination, serological assays, antigen detection methods, and molecular techniques such as polymerase chain reaction (PCR), are critically discussed with emphasis on their sensitivity, specificity, and clinical applicability. Furthermore, conventional therapeutic strategies, including amphotericin B formulations, miltefosine, paromomycin, and combination regimens, are evaluated alongside emerging approaches such as nanotechnology-based drug delivery systems, immunomodulatory therapies, vaccine development, host-directed therapies, and novel antileishmanial compounds. An improved understanding of parasite biology, host–pathogen interactions, and mechanisms of therapeutic resistance is essential for developing safer, more effective, and sustainable interventions. This review emphasizes the need for integrated approaches combining early diagnosis, optimized treatment strategies, surveillance programs, and innovative therapeutic platforms to achieve effective control and eventual elimination of visceral leishmaniasis.

Introduction

Skin Visceral leishmaniasis (VL), commonly known as kala-azar, is one of the most devastating neglected tropical diseases (NTDs) caused by obligate intracellular protozoan parasites of the genus Leishmania. The disease is transmitted to humans through the bite of infected female phlebotomine sandflies and remains a major public health concern in tropical and subtropical regions of Asia, Africa, South America, and the Mediterranean basin. Among the different clinical manifestations of leishmaniasis—cutaneous, mucocutaneous, and visceral—visceral leishmaniasis is the most severe form because of its systemic dissemination to the spleen, liver, bone marrow, and lymphoid tissues, resulting in progressive immunosuppression and, if left untreated, a mortality rate approaching 95–100%. The disease is predominantly caused by Leishmania donovani in the Indian subcontinent and East Africa, whereas Leishmania infantum is the principal causative species in the Mediterranean region and Latin America [1-3].

Despite significant advances in infectious disease control, visceral leishmaniasis continues to impose a substantial socioeconomic and healthcare burden on low- and middle-income countries. It primarily affects impoverished populations living under conditions characterized by malnutrition, inadequate housing, poor sanitation, limited access to healthcare, and close proximity to sandfly breeding habitats. Environmental changes such as deforestation, irrigation projects, rapid urbanization, climate change, and population displacement have further expanded the geographical distribution of vector populations, increasing disease transmission in previously non-endemic regions. Consequently, visceral leishmaniasis has become not only a parasitic disease but also a disease of poverty, social inequality, and environmental vulnerability.

Globally, leishmaniasis is endemic in more than 90 countries, placing over one billion people at risk of infection. Although the global burden of visceral leishmaniasis has declined considerably over the past three decades owing to improved surveillance, vector control, and elimination programs, the disease remains highly endemic in parts of South Asia, East Africa, and South America [4-6].

*Corresponding author: Basit Fazal, Department of Pharmacology, Nibha Institute of Pharmaceutical Sciences, Rajgir, India.

https://doi.org/10.31531/2581-4745.1000178

India has historically contributed one of the largest proportions of global visceral leishmaniasis cases, with Bihar accounting for the majority of reported infections. Significant progress has been achieved through the National Kala-azar Elimination Programme, integrated vector management, improved diagnostic facilities, and widespread availability of liposomal amphotericin B; however, sporadic outbreaks continue to occur, and sustained surveillance remains essential to prevent disease resurgence.

The pathogenesis of visceral leishmaniasis represents a complex interplay between parasite virulence factors and host immune responses. Following inoculation into the skin by an infected sandfly, promastigotes are rapidly phagocytosed by macrophages, where they transform into intracellular amastigotes capable of surviving within phagolysosomes. The parasite has evolved multiple immune evasion strategies, including inhibition of oxidative burst, modulation of antigen presentation, suppression of pro-inflammatory cytokines, and alteration of macrophage signaling pathways. These mechanisms facilitate uncontrolled parasite replication within the reticuloendothelial system, leading to hepatosplenomegaly, pancytopenia, anemia, hypergammaglobulinemia, and progressive immune dysfunction. The outcome of infection is largely determined by the balance between protective Th1-mediated cellular immunity and disease-promoting Th2 or regulatory immune responses. Furthermore, host genetic susceptibility, nutritional status, age, and HIV co-infection substantially influence disease severity, treatment response, and prognosis [7-10].

Clinically, visceral leishmaniasis presents with prolonged irregular fever, progressive weight loss, severe anemia, fatigue, splenomegaly, hepatomegaly, and generalized weakness. Because these manifestations overlap with those of several other febrile illnesses such as malaria, tuberculosis, typhoid fever, lymphoma, and hematological malignancies, early diagnosis remains challenging, particularly in resource-limited settings. Conventional diagnostic methods include microscopic demonstration of amastigotes in splenic, bone marrow, or lymph node aspirates, which remain the reference standard but are invasive and require specialized expertise. Over the past two decades, several serological assays, including the rK39 immunochromatographic rapid diagnostic test, direct agglutination test (DAT), enzyme-linked immunosorbent assay (ELISA), and molecular techniques such as polymerase chain reaction (PCR), have substantially improved diagnostic sensitivity and specificity. Nevertheless, limitations persist in distinguishing active infection from previous exposure, detecting asymptomatic carriers, and monitoring therapeutic response, highlighting the need for more sensitive, affordable, and field-deployable diagnostic technologies [11-13].

Although several antileishmanial drugs are currently available, therapeutic management of visceral leishmaniasis remains far from ideal. Pentavalent antimonials, once regarded as first-line therapy, have lost effectiveness in many endemic regions because of widespread drug resistance. Amphotericin B and its liposomal formulation have demonstrated remarkable efficacy but remain expensive and require intravenous administration. Oral miltefosine represented a major therapeutic breakthrough; however, concerns regarding gastrointestinal toxicity, teratogenicity, prolonged treatment duration, and emerging resistance have restricted its long-term utility. Paromomycin has also shown favorable efficacy but is limited by parenteral administration and variable regional effectiveness. Consequently, multidrug combination therapy has become increasingly important for improving treatment outcomes, reducing treatment duration, minimizing toxicity, and delaying resistance development. Simultaneously, considerable research efforts are focused on discovering novel therapeutic targets, host-directed therapies, immunomodulatory agents, nanoparticle-based drug delivery systems, vaccines, and natural product-derived antileishmanial compounds.

An additional challenge to visceral leishmaniasis elimination is post-kala-azar dermal leishmaniasis (PKDL), a dermatological complication that develops months to years after apparent clinical cure. Although PKDL is not usually life-threatening, affected individuals may serve as long-term parasite reservoirs, thereby sustaining community transmission even in areas approaching elimination. Moreover, increasing reports of HIV–Leishmania co-infection have complicated disease management because immunocompromised patients experience higher parasite burdens, increased relapse rates, reduced treatment efficacy, and greater mortality. These emerging challenges underscore the necessity for integrated disease control strategies encompassing early diagnosis, effective treatment, vector surveillance, reservoir control, socioeconomic interventions, and continued investment in translational research [14].

Given the persistent public health significance of visceral leishmaniasis despite notable reductions in disease incidence, a comprehensive synthesis of recent advances is warranted. This review aims to provide an updated and critical overview of the epidemiology, parasite biology, immunopathogenesis, clinical manifestations, diagnostic approaches, current therapeutic interventions, drug resistance mechanisms, emerging treatment strategies, vaccine development, and future prospects for visceral leishmaniasis control. By integrating recent scientific evidence with ongoing elimination initiatives, this review seeks to facilitate a deeper understanding of disease biology while highlighting research priorities necessary for achieving sustainable control and eventual elimination of kala-azar as a public health problem [15,16].

History and Global Distribution of Visceral Leishmaniasis

Visceral leishmaniasis (VL), commonly known as kala-azar, is one of the oldest documented vector-borne parasitic diseases affecting humans. Historical evidence suggests that leishmaniasis has existed for several millennia, with descriptions of skin lesions resembling leishmaniasis found in ancient Mesopotamian and Egyptian records dating back to 1500–2500 BCE. Molecular studies have further confirmed the presence of Leishmania donovani DNA in Egyptian mummies from the Middle Kingdom period, indicating that visceral leishmaniasis was present in ancient civilizations. Historical accounts from the Middle East and Central Asia also describe chronic skin lesions compatible with leishmaniasis, while archaeological findings from South America demonstrate that the disease affected indigenous populations long before European colonization. These observations collectively indicate that leishmaniasis has accompanied human populations throughout history and has evolved alongside environmental and demographic changes.

The modern understanding of visceral leishmaniasis began during the nineteenth century when recurrent epidemics of prolonged fever associated with splenomegaly, cachexia, and high mortality were reported in the Indian subcontinent. One of the earliest clinical descriptions was provided by William Twining in Bengal in the early 1800s, who documented patients suffering from chronic fever, severe anemia, emaciation, and enlarged spleens. The first recognized epidemic occurred in the Jessore region of present-day Bangladesh during 1824–1825 and subsequently spread throughout Bengal, Bihar, and Assam, causing devastating mortality. Historical records indicate that tens of thousands of individuals died during these outbreaks, leading to severe depopulation in several endemic districts. In Bihar, the disease became known locally as "Kala Dukh," while in Assam it caused repeated epidemics during the late nineteenth century, with mortality rates exceeding 90% in some affected communities before effective treatment became available [17-20].

The term kala-azar, meaning "black disease" or "black fever," originated in India during the late nineteenth century. The name refers to the dark pigmentation observed in some patients with advanced disease, although it has also been interpreted as describing the fatal nature of the illness. Visceral leishmaniasis is caused by protozoan parasites belonging to the genus Leishmania, which invade macrophages of the reticuloendothelial system, particularly those located in the spleen, liver, bone marrow, and lymph nodes. Unlike cutaneous leishmaniasis, which primarily affects the skin, visceral leishmaniasis is characterized by systemic dissemination and progressive immune dysfunction, making it the most severe clinical manifestation of leishmanial infection [21-23].

The etiological agent of kala-azar was identified at the beginning of the twentieth century through the pioneering work of William Boog Leishman and Charles Donovan. In 1903, Leishman observed intracellular protozoan bodies in splenic smears obtained from a soldier who had died from chronic fever and splenomegaly in India. Shortly thereafter, Donovan independently reported similar organisms in Indian patients with the same clinical syndrome. Ronald Ross subsequently recognized these organisms as a new protozoan parasite and proposed the name Leishmania donovani in honor of its discoverers. This landmark discovery established the parasitic etiology of kala-azar and marked the beginning of modern leishmaniasis research. Subsequent investigations identified Leishmania infantum as the principal cause of zoonotic visceral leishmaniasis in the Mediterranean region and Latin America, while numerous additional Leishmania species responsible for cutaneous and mucocutaneous disease were characterized during the twentieth century.

Another milestone in the history of visceral leishmaniasis was the identification of phlebotomine sandflies as biological vectors. Although sandflies had long been suspected of transmitting the disease, experimental evidence confirming vector transmission emerged during the early twentieth century. Studies conducted by Edmond and Étienne Sergent demonstrated that infected sandflies were capable of transmitting Leishmania parasites, while later investigations conclusively established transmission through sandfly bites. Subsequent entomological research identified numerous vector species belonging to the genus Phlebotomus in the Old World and Lutzomyia in the New World, explaining the extensive geographical distribution of the disease [24,25].

Today, visceral leishmaniasis remains one of the most important neglected tropical diseases worldwide. The disease is endemic in approximately 75–90 countries across Asia, Africa, Europe, and the Americas, placing more than one billion people at risk of infection. Although over 20 Leishmania species are capable of infecting humans, visceral disease is primarily caused by L. donovani and L. infantum. The epidemiology differs considerably between regions. In the Indian subcontinent and East Africa, transmission is predominantly anthroponotic, with humans serving as the principal reservoir of infection. Conversely, zoonotic transmission predominates in the Mediterranean basin and Latin America, where domestic dogs constitute the primary reservoir host. These epidemiological differences have important implications for disease surveillance, vector control, and elimination strategies.

The global burden of visceral leishmaniasis is unevenly distributed, with the highest incidence occurring in South Asia, East Africa, and parts of South America. Historically, more than 90% of reported cases originated from India, Bangladesh, Nepal, Sudan, South Sudan, Ethiopia, and Brazil. India has carried one of the largest disease burdens worldwide, with Bihar contributing the majority of reported cases. However, sustained implementation of national elimination programs, indoor residual insecticide spraying, improved surveillance, rapid diagnostic testing, and effective treatment with liposomal amphotericin B have dramatically reduced disease incidence during the past two decades. According to recent elimination reports, the majority of endemic districts in India have achieved the World Health Organization target of fewer than one case per 10,000 population annually, although sporadic outbreaks continue to occur and ongoing surveillance remains essential [26-28].

Despite encouraging progress, visceral leishmaniasis continues to present major public health challenges in several endemic regions. Civil conflicts, forced migration, urbanization, deforestation, agricultural expansion, and climate change have altered vector ecology and facilitated the emergence of new transmission foci. Outbreaks associated with refugee populations in the Middle East and East Africa illustrate the strong relationship between humanitarian crises and disease transmission. Furthermore, globalization and international travel have increased the likelihood of imported cases in previously non-endemic countries. Climate-driven expansion of sandfly habitats into temperate regions has also raised concerns regarding future changes in disease distribution, emphasizing the importance of integrated surveillance and vector monitoring programs.

Socioeconomic determinants remain central to the global distribution of visceral leishmaniasis. The disease disproportionately affects marginalized populations living in poverty, where poor housing, malnutrition, inadequate sanitation, limited healthcare access, and close proximity to vector breeding sites create ideal conditions for sustained transmission. Children, immunocompromised individuals, and people living with HIV are particularly vulnerable to severe disease and adverse outcomes. The emergence of HIV–Leishmania coinfection has further complicated disease management by increasing parasite burden, treatment failure, relapse rates, and mortality. Consequently, successful elimination requires not only effective chemotherapy and vector control but also improvements in socioeconomic conditions, strengthened healthcare infrastructure, and sustained political commitment [29,30].

Although the global burden of visceral leishmaniasis has declined considerably over recent decades, the disease remains a significant neglected tropical disease requiring continued international collaboration. Advances in molecular epidemiology, genomic surveillance, vector biology, immunology, and vaccine research have substantially improved understanding of disease transmission and pathogenesis. Nevertheless, persistent challenges, including asymptomatic infections, post-kala-azar dermal leishmaniasis, drug resistance, climate change, and emerging transmission zones, continue to threaten elimination efforts. Strengthening integrated disease surveillance, expanding access to rapid diagnostics and effective treatment, and investing in innovative preventive strategies will be critical for achieving the World Health Organization's long-term goal of sustainable control and eventual elimination of visceral leishmaniasis as a public health problem.

Epidemiology of Visceral Leishmaniasis

Visceral leishmaniasis (VL), also known as kala-azar, is one of the most significant neglected tropical diseases (NTDs), posing a persistent public health challenge in many low- and middle-income countries. The disease is caused predominantly by Leishmania donovani and Leishmania infantum, which are transmitted through the bites of infected female phlebotomine sandflies. Despite remarkable progress in disease control over the past two decades, VL continues to affect millions of people living in endemic areas, particularly in regions characterized by poverty, inadequate healthcare infrastructure, malnutrition, and environmental conditions favorable for vector survival. The epidemiology of visceral leishmaniasis is dynamic and influenced by complex interactions among the parasite, vector, reservoir hosts, environmental conditions, and socioeconomic factors. Understanding these epidemiological characteristics is essential for developing effective surveillance systems, improving disease prevention, and achieving the World Health Organization (WHO) targets for elimination [31-33].

Global Incidence and Prevalence

Visceral leishmaniasis remains endemic in approximately 75–90 countries across Asia, Africa, Europe, and Latin America, with more than one billion people living in areas at risk of infection. According to the World Health Organization (WHO), an estimated 30,000–50,000 new VL cases occur annually worldwide, although the actual burden is believed to be considerably higher because of underreporting, limited diagnostic capacity, and weak surveillance systems in endemic regions. Approximately 90% of reported cases originate from a limited number of countries, including India, Bangladesh, Nepal, Brazil, Ethiopia, Sudan, South Sudan, Kenya, Somalia, and Uganda [35].

The global incidence of VL has declined substantially during the past three decades owing to improved vector control measures, early diagnosis, enhanced case detection, and effective treatment programs. Nevertheless, localized outbreaks continue to occur in regions affected by armed conflict, migration, political instability, and natural disasters. Furthermore, asymptomatic infections remain several times more common than clinically apparent disease, creating hidden reservoirs that sustain transmission within endemic communities. The prevalence of asymptomatic infection varies considerably between geographical regions, reflecting differences in parasite species, host immunity, nutritional status, and transmission intensity.

Mortality and Disability-Adjusted Life Years (DALYs)

Visceral leishmaniasis is the deadliest form of leishmaniasis and one of the leading causes of mortality among neglected tropical diseases. Untreated VL is associated with a case fatality rate exceeding 95%, primarily due to severe anemia, secondary bacterial infections, hemorrhage, malnutrition, and progressive immunosuppression. Although prompt diagnosis and appropriate chemotherapy have dramatically improved survival rates, delayed diagnosis continues to contribute to preventable deaths in resource-poor settings.

Global Burden of Disease (GBD) analyses demonstrate a marked decline in age-standardized mortality and disability-adjusted life years (DALYs) since 1990. Nevertheless, VL continues to account for a substantial proportion of infectious disease-related disability in endemic countries. Children younger than five years of age experience the highest mortality rates because of immature immune responses and poor nutritional status. Likewise, HIV-positive individuals exhibit increased parasite burdens, higher relapse rates, and significantly greater mortality than immunocompetent patients. Recent GBD estimates indicate that although the overall burden of VL has decreased, East Africa and South Asia continue to contribute disproportionately to global mortality, emphasizing the need for sustained control measures [36-38].

Geographic Distribution

The geographical distribution of visceral leishmaniasis closely reflects the distribution of competent sandfly vectors and suitable environmental conditions. The disease occurs predominantly in tropical, subtropical, and Mediterranean climatic zones where temperature, humidity, vegetation, and soil characteristics support sandfly breeding.

The epidemiology of VL differs between the Old World and the New World. In the Old World, the disease is endemic throughout the Indian subcontinent, East Africa, the Mediterranean basin, and parts of the Middle East and Central Asia. Leishmania donovani predominates in South Asia and East Africa, where transmission is mainly anthroponotic. Conversely, Leishmania infantum is responsible for zoonotic visceral leishmaniasis in Southern Europe, North Africa, the Middle East, and Latin America, with domestic dogs serving as the principal reservoir hosts [39-40].

Although global incidence has declined, emerging foci have been reported in previously non-endemic regions owing to climate change, ecological alterations, deforestation, urban expansion, and increased human migration. Expansion of sandfly habitats into higher altitudes and temperate regions has raised concerns regarding the future geographical spread of the disease.

Epidemiology in India and South Asia

South Asia has historically represented the largest global focus of visceral leishmaniasis, with India contributing the majority of reported cases. Within India, Bihar remains the most severely affected state, accounting for nearly 90% of the country's disease burden, followed by Jharkhand, West Bengal, and eastern Uttar Pradesh. Sporadic cases have also been documented in Assam, Gujarat, Himachal Pradesh, Kerala, Madhya Pradesh, Tamil Nadu, and Jammu and Kashmir.

The epidemiology of kala-azar in India is characterized by periodic epidemics occurring every 10–20 years, influenced by vector density, environmental changes, population immunity, and public health interventions. Following the implementation of the National Kala-azar Elimination Programme, widespread indoor residual spraying, improved surveillance, rapid diagnostic testing using rK39 antigen assays, and single-dose liposomal amphotericin B therapy have dramatically reduced disease incidence. Bangladesh and Nepal have similarly achieved substantial reductions through coordinated regional elimination initiatives under the WHO South-East Asia Regional Office framework [41-43].

Despite these achievements, isolated outbreaks continue to occur, particularly in remote rural communities where healthcare access remains limited. Persistent transmission in highly endemic villages and the presence of asymptomatic carriers continue to challenge elimination efforts.

Transmission Dynamics

The transmission of visceral leishmaniasis primarily occurs through the bite of infected female phlebotomine sandflies. During blood feeding, promastigote forms of Leishmania are inoculated into human skin, where they are rapidly phagocytosed by macrophages and differentiate into intracellular amastigotes. These multiply within macrophages and disseminate through the reticuloendothelial system.

Transmission patterns differ geographically. In the Indian subcontinent and East Africa, humans serve as the principal reservoir (anthroponotic transmission), whereas in Mediterranean countries and Latin America, zoonotic transmission predominates through infected domestic dogs. Rare modes of transmission include congenital infection, blood transfusion, organ transplantation, needle sharing, and laboratory exposure.

Post-kala-azar dermal leishmaniasis (PKDL) has emerged as an important contributor to sustained transmission because affected individuals harbor viable parasites within skin lesions, enabling infection of sandflies long after apparent cure of visceral disease [44-46].

Reservoirs and Vectors

Female phlebotomine sandflies constitute the only proven biological vectors of visceral leishmaniasis. Species of the genus Phlebotomus transmit the disease throughout the Old World, whereas Lutzomyia species are responsible in the Americas. These tiny nocturnal insects breed in warm, humid environments rich in organic matter, including animal shelters, cracks in walls, termite mounds, and vegetation.

Reservoir hosts vary according to geographical location. Humans represent the principal reservoir in areas where L. donovani predominates, particularly in South Asia. In contrast, domestic dogs are the major reservoir for L. infantum in Mediterranean countries and Latin America. Wild canids, rodents, foxes, jackals, and other mammals may also contribute to parasite maintenance in certain ecological settings [47-49].

Risk Factors

The occurrence of visceral leishmaniasis is influenced by multiple host, environmental, and behavioral risk factors. Malnutrition remains one of the strongest predictors of disease progression because impaired cellular immunity increases susceptibility to symptomatic infection. Young children, elderly individuals, pregnant women, and immunocompromised patients are particularly vulnerable.

Additional risk factors include HIV infection, diabetes mellitus, organ transplantation, corticosteroid therapy, poor housing conditions, sleeping outdoors, inadequate vector control, proximity to livestock shelters, migration into endemic areas, and occupational exposure among agricultural workers. Population displacement resulting from war, famine, and natural disasters frequently precipitates epidemics by introducing susceptible populations into highly endemic regions [50].

Socioeconomic and Environmental Determinants

Visceral leishmaniasis is widely recognized as a disease of poverty. Poor-quality housing, overcrowding, inadequate sanitation, limited access to healthcare, and low educational status collectively increase exposure to infected sandflies and delay diagnosis. Nutritional deficiencies, particularly protein-energy malnutrition and deficiencies of iron, zinc, and vitamin A, further compromise immune function and increase disease severity.

Environmental changes have significantly influenced disease epidemiology during recent decades. Deforestation, irrigation projects, urbanization, agricultural expansion, mining activities, and climate change have altered sandfly habitats and increased human-vector contact. Rising global temperatures and changing rainfall patterns have facilitated the expansion of vector populations into previously unaffected regions. These environmental changes, combined with increased international travel and migration, have contributed to the emergence of visceral leishmaniasis in new geographical areas [51].

Current WHO Elimination Status

The World Health Organization has designated visceral leishmaniasis as a priority neglected tropical disease targeted for elimination as a public health problem. Through coordinated regional initiatives, remarkable progress has been achieved in reducing disease incidence across South Asia. India, Bangladesh, and Nepal have implemented integrated elimination strategies comprising active case detection, prompt treatment, vector control through indoor residual spraying, community awareness programs, strengthened surveillance systems, and continuous monitoring of endemic districts.

The WHO elimination target is defined as maintaining fewer than one new VL case per 10,000 population annually at the sub-district or block level. Most endemic districts in India have achieved this milestone, demonstrating the effectiveness of integrated control programs. Nevertheless, maintaining elimination remains challenging because of asymptomatic infections, post-kala-azar dermal leishmaniasis, imported cases, vector persistence, climate change, and emerging drug resistance. Sustained surveillance, operational research, improved diagnostics, and continued investment in healthcare infrastructure remain essential to prevent disease resurgence.

Overall, the epidemiology of visceral leishmaniasis continues to evolve in response to ecological,

 e-ISSN: 2581-4745

biological, and socioeconomic changes. Although significant reductions in global incidence and mortality have been achieved, the disease remains a major public health concern in several endemic regions. Comprehensive epidemiological surveillance, integrated vector management, early diagnosis, effective chemotherapy, and international collaboration will remain indispensable for achieving sustainable elimination and ultimately interrupting transmission worldwide [52].

Pathogenesis and Immunopathogenesis of Visceral Leishmaniasis

Visceral leishmaniasis (VL) is a complex systemic parasitic disease resulting from intricate interactions between Leishmania parasites and the host immune system. The clinical outcome of infection depends not only on parasite virulence but also on the host's innate and adaptive immune responses. Following transmission by infected female phlebotomine sandflies, Leishmania donovani or Leishmania infantum establishes intracellular infection within macrophages and other cells of the mononuclear phagocyte system, enabling long-term survival despite robust host immune defenses. The parasite has evolved sophisticated mechanisms to evade immune surveillance, suppress microbicidal responses, and manipulate host signaling pathways, ultimately leading to chronic infection and systemic dissemination. Understanding the molecular and cellular mechanisms underlying pathogenesis and immunopathogenesis is essential for developing improved diagnostics, vaccines, and immunotherapeutic strategies.

Parasite Entry and Early Establishment of Infection

Transmission begins when an infected female sandfly injects metacyclic promastigotes into the dermis during blood feeding. Along with parasites, the vector introduces salivary proteins and parasite-secreted promastigote secretory gel (PSG), which facilitate parasite establishment by modulating the local inflammatory response and enhancing parasite survival. Immediately after inoculation, promastigotes encounter neutrophils, dendritic cells, macrophages, and complement proteins that constitute the first line of innate immune defense.

Although complement activation destroys many parasites, metacyclic promastigotes possess surface molecules, including lipophosphoglycan (LPG) and the metalloprotease glycoprotein-63 (GP63), that confer resistance to complement-mediated lysis. These molecules inhibit membrane attack complex formation, promote complement receptor-mediated uptake, and facilitate parasite entry into macrophages without triggering effective microbicidal responses. Neutrophils are among the earliest immune cells recruited to the bite site and transiently internalize parasites. Rather than eliminating the infection, apoptotic neutrophils may act as "Trojan horses," transferring viable parasites to macrophages while minimizing inflammatory activation.

Intracellular Survival Within Macrophages

Macrophages represent the principal host cells for Leishmania replication. Following phagocytosis, promastigotes transform into non-flagellated amastigotes within acidic phagolysosomes. Unlike most intracellular pathogens, Leishmania thrives in this hostile environment by adapting its metabolism and modifying phagolysosomal maturation.

The parasite suppresses macrophage antimicrobial mechanisms through multiple strategies. LPG interferes with phagosome maturation, while GP63 cleaves host signaling proteins involved in cytokine production and antigen presentation. In addition, Leishmania inhibits the assembly of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby reducing reactive oxygen species (ROS) production. Simultaneously, suppression of inducible nitric oxide synthase (iNOS) decreases nitric oxide (NO) generation, one of the most effective leishmanicidal molecules produced by activated macrophages.

The parasite also manipulates intracellular signaling pathways such as mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/Akt, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and nuclear factor-kappa B (NF-κB). These alterations suppress macrophage activation while promoting an intracellular environment favorable for parasite replication and persistence [53].

Innate Immune Responses

The innate immune system plays a critical role in determining the initial outcome of infection. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), recognize parasite-derived pathogen-associated molecular patterns and initiate inflammatory responses. Activation of TLR2, TLR4, and TLR9 stimulates production of interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-α), interferon-alpha (IFNα), and other pro-inflammatory mediators that promote parasite killing.

Dendritic cells function as professional antigen-presenting cells by processing Leishmania antigens and activating naïve T lymphocytes within regional lymph nodes. Natural killer (NK) cells contribute to early protection by secreting interferon-gamma (IFN-γ), which enhances macrophage microbicidal activity. However, Leishmania interferes with dendritic cell maturation, decreases IL-12 production, and impairs antigen presentation, thereby weakening the development of effective adaptive immunity. Complement activation initially contributes to parasite elimination; nevertheless, surviving parasites exploit complement receptors CR1 and CR3 to facilitate silent macrophage entry without inducing robust inflammatory responses. Consequently, the parasite converts several components of innate immunity into mechanisms that enhance its intracellular survival [54].

Adaptive Immune Responses

Protective immunity against visceral leishmaniasis depends primarily on a strong cell-mediated immune response. $CD4^+$ T-helper (Th) lymphocytes differentiate into distinct functional subsets that determine disease outcome. A dominant Th1 immune response is associated with resistance to infection. Cytokines such as IL-12, IFN-γ, and TNF-α activate infected macrophages, leading to increased nitric oxide production and intracellular parasite destruction. IFN-γ remains the principal cytokine responsible for macrophage activation, while TNF-α acts synergistically to enhance leishmanicidal activity. Conversely, disease progression is characterized by predominance of Th2 and regulatory immune responses. Increased production of IL-4, IL-5, IL-10, IL-13, and transforming growth factor-beta (TGF-β) suppresses macrophage activation and inhibits Th1-mediated immunity. IL-10 is particularly important because it inhibits antigen presentation, reduces IL-12 synthesis, suppresses IFN-γ production, and directly impairs macrophage microbicidal mechanisms. Elevated IL-10 concentrations correlate strongly with high parasite burdens, disease severity, and therapeutic failure. Regulatory T cells (Tregs) further suppress protective immunity by secreting IL-10 and TGF-β, promoting parasite persistence while limiting excessive tissue inflammation. Although this regulatory response prevents immunopathology, it simultaneously favors chronic infection [55].

Cytokine Network in Disease Progression

The immunopathogenesis of visceral leishmaniasis is governed by a complex cytokine network that determines the balance between parasite clearance and disease progression. Pro-inflammatory cytokines, including IFN-γ, IL-12, TNF-α, IL-1β, and IL-18, promote macrophage activation and intracellular parasite killing. IL-12 serves as the central cytokine driving Th1 differentiation, whereas IFN-γ activates nitric oxide synthesis through induction of iNOS. TNF-α enhances macrophage antimicrobial activity and contributes to granuloma formation within infected organs. In contrast, anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and TGF-β inhibit macrophage activation, suppress antigen presentation, and facilitate parasite survival. High circulating concentrations of IL-10 are consistently associated with active disease, while declining IL-10 levels following treatment correlate with clinical recovery. The relative balance between these opposing cytokine profiles ultimately determines whether infection remains asymptomatic, resolves spontaneously, or progresses to severe visceral disease [56].

Organ-Specific Pathogenesis

Following intracellular multiplication, infected macrophages disseminate parasites through the bloodstream and lymphatic system to the spleen, liver, bone marrow, and lymph nodes. Progressive accumulation of infected macrophages within these organs produces the characteristic pathological features of visceral leishmaniasis.

The spleen undergoes marked enlargement due to hyperplasia of the reticuloendothelial system, disruption of normal splenic architecture, and chronic inflammatory cell infiltration. Loss of organized lymphoid follicles impairs adaptive immune responses and contributes to persistent immunosuppression.

Within the liver, granulomatous inflammation develops around infected Kupffer cells. Effective granuloma formation facilitates parasite clearance and is generally associated with favorable clinical outcomes. Conversely, defective granuloma maturation permits continued parasite replication and disease progression. Bone marrow infiltration suppresses hematopoiesis, leading to pancytopenia manifested by anemia, leukopenia, and thrombocytopenia. These hematological abnormalities increase susceptibility to opportunistic infections, fatigue, bleeding complications, and poor clinical prognosis.

Mechanisms of Immune Evasion

Leishmania employs numerous immune evasion mechanisms that enable long-term persistence within the host. These include inhibition of complement activation, interference with phagosome maturation, suppression of oxidative burst, downregulation of major histocompatibility complex (MHC) class II expression, inhibition of antigen presentation, induction of regulatory cytokines, modulation of apoptosis, and metabolic adaptation to intracellular stress. The parasite also alters host gene expression through epigenetic modifications and microRNA regulation, affecting inflammatory signaling, macrophage polarization, and immune cell differentiation. Emerging evidence suggests that parasite-derived extracellular vesicles further manipulate host immune responses by delivering virulence factors directly into infected cells.

Immunopathological Consequences

Persistent infection results in chronic immune activation accompanied by progressive immune dysfunction. Patients frequently develop polyclonal B-cell activation, hypergammaglobulinemia, circulating immune complexes, and impaired antigen-specific cellular immunity. Despite elevated antibody concentrations, humoral immunity alone provides little protection because Leishmania resides intracellularly. Chronic immune dysregulation contributes to severe clinical manifestations including prolonged fever, cachexia, hepatosplenomegaly, anemia, pancytopenia, and increased susceptibility to secondary bacterial infections. HIV coinfection further exacerbates immunosuppression by reducing $CD4^+$ T-cell numbers and impairing macrophage activation, leading to higher parasite burdens, frequent relapses, and increased mortality [57].

Implications for Therapeutic Development

A comprehensive understanding of the immunopathogenesis of visceral leishmaniasis has significant therapeutic implications. Current research focuses on host-directed therapies that restore protective Th1 immunity while limiting excessive immunosuppression. Immunomodulatory agents targeting IL-10, PD-1/PD-L1 signaling, TGF-β pathways, and macrophage activation are under investigation as adjuncts to conventional chemotherapy. Advances in vaccine development emphasize induction of durable Th1-mediated cellular immunity using recombinant proteins, DNA vaccines, viral vectors, and nanoparticle-based delivery systems. Moreover, identification of parasite virulence factors such as LPG, GP63, and extracellular vesicles has provided promising molecular targets for novel drug discovery.

In summary, the pathogenesis of visceral leishmaniasis reflects a dynamic interaction between parasite virulence mechanisms and host immune responses. Successful infection depends on the parasite's ability to evade innate immunity, establish intracellular survival within macrophages, and manipulate adaptive immune responses toward an anti-inflammatory phenotype. The balance between protective Th1 immunity and disease-promoting regulatory responses ultimately determines disease outcome. Continued advances in understanding host–parasite interactions will facilitate the development of more effective diagnostics, immunotherapies, vaccines, and targeted antileishmanial interventions [58].

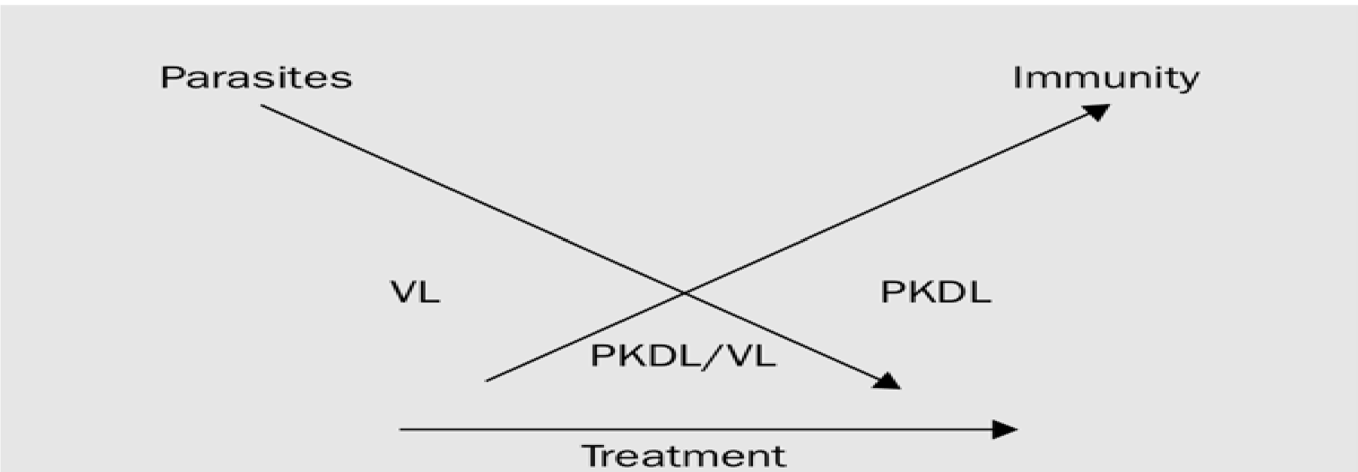


Figure 1: The hypothetical relationship between decreasing parasite load, increasing immunity, and ensuring clinical presentation during treatment of visceral leishmaniasis.

Clinical Manifestations and Complications of Visceral Leishmaniasis

Visceral leishmaniasis (VL), or kala-azar, is a chronic systemic protozoan infection characterized by progressive involvement of the reticuloendothelial system. Following an incubation period that typically ranges from 2 to 8 months, although it may extend up to one year depending on host immunity and parasite burden, infected individuals may remain asymptomatic or develop overt clinical disease. The clinical spectrum varies considerably according to the infecting Leishmania species, parasite load, nutritional status, age, immune competence, and the presence of coexisting illnesses such as HIV infection. While many infected individuals remain asymptomatic throughout life, symptomatic VL is associated with significant morbidity and, if left untreated, a fatality rate approaching 95% [59].

Clinical Manifestations

The hallmark presentation of visceral leishmaniasis is prolonged or intermittent fever, which often persists for several weeks or months. Fever is usually accompanied by progressive constitutional symptoms, including generalized weakness, malaise, fatigue, anorexia, and marked weight loss. Patients frequently develop cachexia due to chronic inflammation, poor nutritional intake, and increased metabolic demands associated with persistent infection.

One of the most characteristic clinical findings is massive splenomegaly, resulting from infiltration of infected macrophages and hyperplasia of the reticuloendothelial system. Splenic enlargement is often painless but progressive and may occupy a large portion of the abdominal cavity in advanced disease. Hepatomegaly is also common, although it is generally less pronounced than splenomegaly. Generalized lymphadenopathy may occur, particularly in East African patients, whereas it is relatively uncommon in the Indian subcontinent.

Hematological abnormalities constitute another major feature of VL. Bone marrow infiltration by infected macrophages suppresses normal hematopoiesis, leading to pancytopenia, including normocytic normochromic anemia, leukopenia, and thrombocytopenia. Anemia contributes to pallor, fatigue, dyspnea, and reduced physical activity. Leukopenia predisposes patients to recurrent bacterial infections, whereas thrombocytopenia increases the risk of spontaneous bleeding, petechiae, epistaxis, and gastrointestinal hemorrhage.

Laboratory investigations typically reveal elevated erythrocyte sedimentation rate (ESR), hypoalbuminemia, hypergammaglobulinemia, and abnormal liver function tests. Increased immunoglobulin production results from polyclonal B-cell activation despite impaired cell-mediated immunity, producing a characteristic paradox of elevated antibody levels with ineffective parasite clearance.

Children often present with severe malnutrition, growth retardation, recurrent infections, and developmental delay. In immunocompromised individuals, particularly those with HIV/AIDS, clinical manifestations may be atypical, involving unusual organs such as the gastrointestinal tract, lungs, skin, or central nervous system. These patients usually exhibit higher parasite burdens, more frequent relapses, and poorer treatment outcomes [60].

Major Complications

If untreated, visceral leishmaniasis progresses relentlessly and produces multiple life-threatening complications. Progressive pancytopenia significantly increases susceptibility to opportunistic bacterial, fungal, and viral infections, which remain among the leading causes of mortality. Septicemia, pneumonia, urinary tract infections, and tuberculosis frequently complicate advanced disease.

Severe anemia contributes to cardiovascular stress and heart failure in vulnerable individuals, while thrombocytopenia may result in life-threatening hemorrhage. Splenic rupture, although uncommon, represents a surgical emergency associated with massive splenomegaly.

Persistent inflammation and hepatic dysfunction may lead to coagulation abnormalities, hypoalbuminemia, peripheral edema, and ascites. Chronic nutritional deficiencies further impair immune function and delay recovery.

An important late complication is Post-Kala-Azar Dermal Leishmaniasis (PKDL), which develops months to several years after successful treatment, particularly in patients infected with Leishmania donovani. PKDL is characterized by hypopigmented macules, papules, plaques, or nodules involving the face, trunk, and extremities. Although generally not life-threatening, affected individuals harbor viable parasites within skin lesions and may serve as long-term reservoirs for continued transmission [13].

Another major challenge is HIV–Leishmania coinfection, which has emerged as a significant public health concern in several endemic regions. HIV-induced depletion of CD4^{+} T lymphocytes markedly impairs macrophage activation, resulting in uncontrolled parasite multiplication, recurrent relapses, atypical clinical presentations, reduced responsiveness to therapy, and substantially increased mortality.

Rare complications include acute kidney injury, myocarditis, pancreatitis, disseminated intravascular coagulation, hemophagocytic lymphohistiocytosis (HLH), and multi-organ failure. Without prompt diagnosis and effective treatment, these complications frequently culminate in death.

Diagnostic Approaches

Accurate and timely diagnosis of visceral leishmaniasis is essential for reducing disease-related morbidity and mortality. Since the clinical manifestations overlap considerably with malaria, tuberculosis, typhoid fever, lymphoma, leukemia, and other chronic febrile illnesses, laboratory confirmation is indispensable. Current diagnostic approaches integrate clinical assessment with parasitological, serological, molecular, and emerging biomarker-based techniques. Selection of diagnostic methods depends on disease prevalence, available laboratory infrastructure, technical expertise, and healthcare resources.

Clinical Diagnosis

Clinical suspicion remains the initial step in diagnosis, particularly in endemic regions. Patients presenting with prolonged fever, significant splenomegaly, hepatomegaly, weight loss, anemia, and residence in or travel to endemic areas should be evaluated for visceral leishmaniasis. However, clinical diagnosis alone lacks specificity because these manifestations occur in numerous infectious and hematological disorders.

Parasitological Diagnosis

Direct demonstration of Leishmania amastigotes remains the reference standard for definitive diagnosis. Microscopic examination of splenic aspirates provides the highest sensitivity (approximately 90–98%) because of the high parasite burden within splenic tissue. Nevertheless, splenic aspiration carries a risk of severe hemorrhage and should only be performed by experienced clinicians.

Bone marrow aspiration offers lower sensitivity (60–85%) but is considered safer and is widely employed in routine clinical practice. Lymph node aspiration may be useful in selected patients, particularly in East Africa where lymphadenopathy is common.

Parasite isolation using specialized culture media such as Novy–MacNeal–Nicolle (NNN) medium or Schneider's medium permits species identification and drug susceptibility testing. However, culture methods are labor-intensive, technically demanding, and unsuitable for routine diagnosis in endemic settings [17].

Serological Diagnosis

Serological tests detect anti-Leishmania antibodies and have become indispensable tools for field diagnosis because they are minimally invasive and relatively inexpensive.

The rK39 immunochromatographic rapid diagnostic test (RDT) is currently the most widely used point-of-care diagnostic assay in South Asia. It demonstrates excellent sensitivity and specificity in the Indian subcontinent and has greatly improved community-based case detection. However, reduced diagnostic accuracy has been reported in East Africa, where genetic diversity among parasite strains affects antigen recognition.

Other commonly employed serological assays include the Direct Agglutination Test (DAT), enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test (IFAT), and Western blot analysis. DAT exhibits high diagnostic accuracy but requires standardized reagents and prolonged incubation, whereas ELISA offers excellent sensitivity for laboratory diagnosis.

One limitation of antibody-based assays is their inability to distinguish active disease from previous infection because antibodies may persist for months or years following successful treatment. Consequently, serological tests are less useful for monitoring treatment response or detecting relapse [27].

Molecular Diagnosis

Molecular techniques have significantly improved the diagnosis of visceral leishmaniasis by enabling highly sensitive and specific detection of parasite DNA.

Polymerase chain reaction (PCR) assays targeting kinetoplast DNA (kDNA), small subunit ribosomal RNA (SSU-rRNA), internal transcribed spacer (ITS), and heat shock protein genes provide excellent diagnostic performance, even in patients with low parasite burdens. Quantitative real-time PCR (qPCR) further enables estimation of parasite load and assessment of therapeutic response [29].

Loop-mediated isothermal amplification (LAMP) has emerged as a promising molecular alternative for resource-limited settings because it provides rapid amplification without requiring sophisticated thermal cyclers. Portable molecular platforms suitable for field diagnosis are currently under active development.

Despite their excellent sensitivity, molecular assays remain expensive and require specialized laboratory infrastructure, limiting their routine implementation in many endemic countries.

Antigen Detection and Biomarkers

Recent research has focused on antigen detection assays capable of identifying active infection. Urinary antigen detection tests, latex agglutination assays, and recombinant antigen-based immunoassays have demonstrated encouraging results for diagnosis and post-treatment monitoring.

Several host biomarkers, including IL-10, IFN-γ, soluble CD163, neopterin, C-reactive protein, and circulating microRNAs, are being investigated as indicators of disease severity, therapeutic response, and relapse risk. Although promising, these biomarkers require further validation before widespread clinical application.

Imaging and Laboratory Evaluation

Although imaging studies are not diagnostic, ultrasonography frequently demonstrates hepatosplenomegaly and enlarged abdominal lymph nodes. Computed tomography (CT) and magnetic resonance imaging (MRI) may assist in evaluating complicated cases or excluding alternative diagnoses.

Routine laboratory investigations commonly reveal pancytopenia, elevated ESR, hypergammaglobulinemia, hypoalbuminemia, elevated liver enzymes, and increased inflammatory markers. These findings support clinical suspicion but are not disease-specific.

Emerging Diagnostic Technologies

Advances in genomics, proteomics, metabolomics, nanotechnology, and artificial intelligence have accelerated the development of next-generation diagnostic platforms. CRISPR-based nucleic acid detection systems, microfluidic biosensors, smartphone-assisted point-of-care devices, nanoparticle-enhanced immunoassays, and machine learning-assisted diagnostic algorithms are currently under investigation. These technologies aim to provide rapid, highly sensitive, affordable, and field-deployable diagnostic solutions suitable for endemic resource-limited settings [22].

Current Therapeutic Strategies

The therapeutic management of visceral leishmaniasis (VL) has evolved considerably over the past several decades owing to improved understanding of parasite biology, drug pharmacology, and emerging patterns of antimicrobial resistance. The primary objectives of treatment are complete parasite eradication, rapid clinical recovery, prevention of relapse, interruption of disease transmission, and reduction of mortality.

The selection of an appropriate therapeutic regimen depends on several factors, including the infecting Leishmania species, geographical region, drug susceptibility patterns, disease severity, patient age, pregnancy status, HIV coinfection, and the availability of healthcare resources. Although several antileishmanial agents are currently available, none fulfills the characteristics of an ideal drug because limitations such as toxicity, prolonged treatment duration, high cost, parenteral administration, and emerging drug resistance continue to compromise treatment success.

Table 1. Currently Available Therapeutic Agents for Visceral Leishmaniasis

Drug	Mechanism of Action	Route of Administration	Advantages	Limitations / Adverse Effects	Current Clinical Status
Sodium Stibogluconate (SSG)	Inhibits parasite energy metabolism and thiol-dependent pathways	Intravenous/Intramuscular	Historically effective; inexpensive	Drug resistance, cardiotoxicity, pancreatitis, hepatotoxicity, prolonged treatment	Limited use due to resistance; recommended only in selected endemic regions
Meglumine Antimoniate	Similar to SSG; interferes with ATP synthesis and parasite metabolism	Intramuscular	Effective in some endemic regions	Cardiotoxicity, nephrotoxicity, pancreatitis, emerging resistance	Used mainly in Latin America and Mediterranean countries
Amphotericin B Deoxycholate	Binds parasite membrane ergosterol causing membrane disruption	Intravenous	High cure rate (>95%)	Nephrotoxicity, infusion reactions, electrolyte imbalance, hospitalization required	Alternative treatment where liposomal formulation is unavailable
Liposomal Amphotericin B (L-AmB)	Targeted delivery of amphotericin B to macrophages	Intravenous	High efficacy, reduced toxicity, short treatment duration	High acquisition cost	WHO-recommended first-line therapy in many endemic regions
Miltefosine	Disrupts phospholipid metabolism, mitochondrial function, and apoptosis pathways	Oral	First effective oral drug; outpatient therapy	Gastrointestinal toxicity, teratogenicity, emerging resistance	Widely used in combination therapy
Paromomycin	Aminoglycoside inhibiting protein synthesis	Intramuscular	Cost-effective, good efficacy	Injection-site pain, nephrotoxicity, ototoxicity	Used alone or in combination regimens
Combination Therapy (L-AmB + Miltefosine / L-AmB + Paromomycin / Miltefosine + Paromomycin)	Multiple mechanisms reducing parasite survival	Oral + Injectable	Improved efficacy, reduced resistance, shorter treatment duration	Regimen-specific adverse effects and logistical challenges	Increasingly recommended by WHO and national treatment guidelines

Pentavalent Antimonials

Pentavalent antimonials, including sodium stibogluconate (SSG) and meglumine antimoniate, were the first effective chemotherapeutic agents introduced for VL and remained the standard of care for several decades. These drugs are believed to interfere with parasite energy metabolism, inhibit ATP synthesis, and disrupt thiol-dependent redox homeostasis, ultimately inducing parasite death [34].

Clinical cure rates exceeding 90% were historically achieved in many endemic regions. However, extensive and prolonged use has resulted in widespread resistance, particularly in the Indian state of Bihar, where therapeutic failure rates exceeded 60%. Additionally, antimonials are associated with significant adverse effects, including cardiotoxicity, pancreatitis, hepatotoxicity, nephrotoxicity, myalgia, arthralgia, and electrocardiographic abnormalities. Consequently, pentavalent antimonials are no longer recommended as first-line therapy in regions with documented resistance but continue to be used selectively in parts of East Africa and Latin America.

Amphotericin B

Amphotericin B is one of the most effective drugs against visceral leishmaniasis owing to its potent leishmanicidal activity. It binds to ergosterol-like sterols present in the parasite membrane, creating pores that increase membrane permeability and cause intracellular ion leakage, leading to parasite death.

Conventional amphotericin B deoxycholate achieves cure rates exceeding 95%; however, its clinical use is limited by infusion-related reactions, nephrotoxicity, electrolyte disturbances, anemia, and prolonged hospitalization due to intravenous administration.

To overcome these limitations, lipid-based formulations, particularly liposomal amphotericin B (L-AmB), have become the preferred treatment in many countries. Liposomal encapsulation enhances selective drug delivery to macrophages of the reticuloendothelial system while substantially reducing renal toxicity and infusion-related adverse events. Single-dose liposomal amphotericin B has demonstrated excellent efficacy in the Indian subcontinent and forms the cornerstone of the National Kala-azar Elimination Programme. Nevertheless, the relatively high cost limits widespread implementation in many resource-constrained settings despite negotiated price reductions through international health initiatives [39].

Miltefosine

Miltefosine was the first orally administered antileishmanial drug approved for the treatment of visceral leishmaniasis and represented a major breakthrough in disease management. Originally developed as an anticancer agent, miltefosine disrupts parasite membrane phospholipid metabolism, mitochondrial function, and apoptosis-related pathways.

Clinical studies have demonstrated cure rates of approximately 90–95% in immunocompetent patients. The oral route of administration significantly improves treatment compliance and facilitates outpatient management. However, prolonged treatment duration, gastrointestinal adverse effects such as nausea, vomiting, and diarrhea, and the emergence of drug resistance have reduced its long-term effectiveness. Furthermore, miltefosine is teratogenic and contraindicated during pregnancy, necessitating reliable contraception for women of reproductive age during treatment and for several months thereafter.

Paromomycin

Paromomycin is an aminoglycoside antibiotic with proven efficacy against visceral leishmaniasis. It inhibits parasite protein synthesis through irreversible binding to ribosomal RNA, resulting in impaired cellular metabolism and parasite death.

Intramuscular paromomycin has demonstrated cure rates exceeding 90% in several endemic regions while exhibiting relatively low systemic toxicity. The most commonly reported adverse effects include injection-site pain, reversible nephrotoxicity, and transient ototoxicity. Although paromomycin is considerably less expensive than liposomal amphotericin B, the requirement for daily intramuscular injections limits patient acceptance and accessibility in remote endemic areas [43].

Combination Therapy

Combination chemotherapy has become an increasingly important strategy for improving therapeutic efficacy while minimizing treatment-related toxicity and delaying the emergence of drug resistance. Simultaneous administration of two or more drugs with different mechanisms of action reduces parasite exposure to individual agents, shortens treatment duration, and improves patient adherence.

Several combination regimens have demonstrated excellent clinical outcomes, including:

- Liposomal amphotericin B plus miltefosine
- Liposomal amphotericin B plus paromomycin
- Miltefosine plus paromomycin

These regimens have achieved cure rates exceeding 95% in several multicenter clinical trials while reducing cumulative drug toxicity and healthcare costs. Consequently, combination therapy is increasingly recommended in national treatment guidelines and WHO recommendations for selected endemic regions.

Treatment of Special Populations

Management of visceral leishmaniasis requires individualized therapeutic approaches for vulnerable populations.

Patients with HIV coinfection exhibit high parasite burdens, frequent relapses, and reduced treatment responsiveness. Liposomal amphotericin B remains the preferred therapy owing to its superior efficacy and safety profile, although repeated treatment courses and secondary prophylaxis are frequently necessary.

During pregnancy, liposomal amphotericin B is considered the safest available treatment because pentavalent antimonials and miltefosine are associated with fetal toxicity. Pediatric treatment generally follows adult therapeutic principles, with dosage adjustments according to body weight [9].

Treatment of post-kala-azar dermal leishmaniasis (PKDL) often requires prolonged administration of liposomal amphotericin B or miltefosine because dermal lesions may persist for months despite successful treatment of visceral disease.

Limitations of Current Therapeutics

Despite considerable advances in chemotherapy, several limitations continue to hinder effective disease control. These include increasing antimicrobial resistance, high treatment costs, prolonged hospitalization for injectable therapies, drug toxicity, poor patient compliance, inadequate availability in remote endemic regions, and the absence of effective vaccines. Furthermore, current drugs exhibit limited efficacy against asymptomatic infection and cannot completely prevent relapse in immunocompromised patients.

Emerging Therapeutic Strategies

Growing concerns regarding drug resistance, toxicity, and therapeutic failure have accelerated research into innovative treatment approaches for visceral leishmaniasis. Modern therapeutic strategies aim to improve drug efficacy, reduce adverse effects, enhance targeted delivery, overcome parasite resistance mechanisms, and stimulate protective host immune responses.

Novel Drug Discovery

Recent advances in parasite genomics, proteomics, metabolomics, and structural biology have facilitated identification of several promising molecular targets for antileishmanial drug development. Enzymes involved in trypanothione metabolism, sterol biosynthesis, folate metabolism, protein kinases, DNA topoisomerases, cysteine proteases, and mitochondrial respiration are currently being explored as therapeutic targets.

High-throughput screening of synthetic chemical libraries has identified several novel compounds exhibiting potent activity against intracellular amastigotes with improved selectivity and reduced host toxicity. Drug repurposing has also emerged as an attractive strategy because existing approved drugs possess established pharmacokinetic and safety profiles, substantially reducing development time and cost [14].

Nanotechnology-Based Drug Delivery

Nanotechnology has emerged as one of the most promising innovations in visceral leishmaniasis therapy. Nanocarriers including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, nanoemulsions, and metallic nanoparticles enhance targeted delivery of antileishmanial agents directly to infected macrophages.

These delivery systems improve drug solubility, prolong circulation time, reduce systemic toxicity, increase intracellular drug accumulation, and permit controlled drug release. Liposomal amphotericin B represents the most successful clinical application of nanotechnology in leishmaniasis. Ongoing research is evaluating chitosan nanoparticles, PLGA nanoparticles, gold nanoparticles, silver nanoparticles, and mesoporous silica nanoparticles for improved delivery of amphotericin B, miltefosine, paromomycin, and plant-derived bioactive compounds [7].

Table 2. Emerging Therapeutic Strategies for Visceral Leishmaniasis

Therapeutic Strategy	Target/Principle	Examples	Potential Advantages	Current Research Status
Novel Drug Discovery	Parasite-specific metabolic enzymes and signaling pathways	Trypanothione reductase inhibitors, protein kinase inhibitors, sterol biosynthesis inhibitors	Overcomes resistance, improved selectivity, reduced toxicity	Preclinical and early clinical development
Drug Repurposing	Evaluation of approved drugs for antileishmanial activity	Tamoxifen, Fexinidazole, Azole antifungals, Nitroimidazoles	Lower development cost and shorter approval timeline	Experimental and clinical evaluation
Nanotechnology-Based Drug Delivery	Targeted macrophage drug delivery	Liposomes, PLGA nanoparticles, chitosan nanoparticles, solid lipid nanoparticles, dendrimers	Enhanced bioavailability, reduced toxicity, controlled drug release	Several formulations under preclinical and clinical investigation
Immunotherapy	Enhancement of host cellular immunity	IFN-γ, IL-12, GM-CSF, immune checkpoint inhibitors	Improved parasite clearance and reduced relapse	Experimental and early clinical studies
Host-Directed Therapy	Modulation of immune regulatory pathways	IL-10 inhibitors, PD-1/PD-L1 blockade, TGF-β inhibitors	Restores protective Th1 immune response	Preclinical research
Vaccine Development	Induction of protective long-term immunity	Recombinant protein vaccines, DNA vaccines, viral vector vaccines, live attenuated vaccines	Disease prevention and interruption of transmission	Multiple candidates in Phase I/II clinical trials
Natural Products and Phytochemicals	Plant-derived bioactive compounds	Curcumin, Berberine, Quercetin, Artemisinin derivatives, Ursolic acid	Low toxicity, immunomodulatory effects, novel mechanisms	Extensive preclinical evaluation
Gene Editing and Precision Medicine	Identification of essential parasite genes	CRISPR-Cas9, transcriptomics, proteomics, AI-assisted drug discovery	Identification of novel therapeutic targets and personalized treatment	Emerging research area

Immunotherapy and Host-Directed Therapy

Host-directed therapeutic strategies seek to restore protective immune responses rather than targeting the parasite directly. Cytokine-based therapies utilizing interferon-gamma (IFN-γ), interleukin-12 (IL-12), and granulocyte-macrophage colony-stimulating factor (GM-CSF) have demonstrated enhanced macrophage activation and improved parasite clearance in experimental studies.

Immune checkpoint modulation targeting PD-1/PD-L1, CTLA-4, and regulatory T-cell pathways represents another promising area of investigation. Inhibition of immunosuppressive cytokines such as IL-10 and TGF-β may enhance cell-mediated immunity and improve chemotherapy outcomes.

Combination of immunotherapy with conventional chemotherapy may permit lower drug dosages while reducing relapse rates and treatment failure [42].

Vaccine Development

Despite decades of research, no licensed human vaccine against visceral leishmaniasis is currently available. However, vaccine development remains a global research priority because effective immunization would provide long-term protection and substantially reduce disease transmission.

Current vaccine candidates include killed whole-parasite vaccines, live attenuated vaccines, recombinant protein vaccines, DNA vaccines, viral vector vaccines, and nanoparticle-based vaccine platforms. Prominent antigen candidates include KMP-11, gp63, HASPB, LeIF, A2 proteins, and cysteine proteases.

Several vaccine candidates have demonstrated encouraging immunogenicity in preclinical studies by inducing strong Th1-mediated cellular immune responses characterized by increased IFN-γ production and enhanced macrophage activation. Clinical trials continue to evaluate their safety, immunogenicity, and protective efficacy.

Natural Products and Phytotherapeutics

Natural products remain an important source of novel antileishmanial compounds. Numerous medicinal plants have demonstrated promising activity owing to alkaloids, flavonoids, terpenoids, phenolics, saponins, and essential oils capable of disrupting parasite metabolism or enhancing host immunity.

Bioactive compounds such as curcumin, quercetin, berberine, artemisinin derivatives, betulinic acid, ursolic acid, and various plant-derived essential oils have exhibited significant antileishmanial activity in experimental studies. Although these compounds possess favorable safety profiles, further pharmacokinetic studies, toxicity evaluation, and well-designed clinical trials are required before routine therapeutic use [24].

Gene Editing and Precision Medicine

Recent advances in CRISPR-Cas9 technology have transformed functional genomic studies in Leishmania. Gene-editing approaches enable identification of essential parasite genes responsible for virulence, immune evasion, and drug resistance, facilitating development of highly specific therapeutic targets [18].

Precision medicine approaches integrating parasite genomics, host genetics, transcriptomics, metabolomics, and artificial intelligence are expected to enable individualized treatment strategies based on parasite species, resistance profiles, and host immune characteristics.

Future Perspectives

The future management of visceral leishmaniasis will likely rely on integrated therapeutic strategies combining effective chemotherapy, host-directed immunotherapy, targeted nanomedicine, and prophylactic vaccination. Advances in molecular diagnostics, artificial intelligence-assisted drug discovery, systems biology, and precision medicine are expected to accelerate the development of safer and more effective interventions. Continued international collaboration, sustained investment in translational research, and equitable access to innovative therapies will be essential for achieving the World Health Organization's goal of eliminating visceral leishmaniasis as a public health problem.

Acknowledgement

All the authors would like to express the profound sense of gratitude and cordial thanks to Nibha Institute of Pharmaceutical Sciences for providing the necessary valuable guidance and support throughout the work.

Conflict of Interest

The authors declare no conflict of interest.

Funding

The authors did not receive any fundings from any private or government sources.

Ethical Approvals

This study does not involve experiments on animals or human subjects.

References

1. Guerin PJ, Oliaro P, Sundar S, Boelaert M, Croft SL, Desjeux P, et al. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. Lancet Infect Dis. 2002;2(8):494-501.
2. Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling RW, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? Nat Rev Microbiol. 2007;5(11):873-82.
3. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 2012;7(5):e35671.
4. Sundar S, Chakravarty J. Leishmaniasis: an update of current pharmacotherapy. Expert Opin Pharmacother. 2013;14(1):53-63.
5. Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert Opin Pharmacother. 2015;16(2):237-52.
6. Monge-Maillo B, López-Vélez R. Therapeutic options for visceral leishmaniasis. Drugs. 2013;73(17):1863-88.
7. Alves F, Bilbe G, Blesson S, Goyal V, Monnerat S, Mowbray C, et al. Recent development of visceral leishmaniasis treatments: successes, pitfalls, and perspectives. Clin Microbiol Rev. 2018;31(4):e00048-18.
8. Davidson RN. Visceral leishmaniasis in clinical practice. J Infect. 1999;39(2):112-6.
9. Baily GG, Nandy A. Visceral leishmaniasis: more prevalent and more problematic. J Infect. 1994;29(3):241-7.
10. Boelaert M, Criel B, Leeuwenburg J, Van Damme W, Le Ray D, Van der Stuyft P. Visceral leishmaniasis control: a public health perspective. Trans R Soc Trop Med Hyg. 2000;94(5):465-71.
11. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. Clin Diagn Lab Immunol. 2002;9(5):951-8.
12. Sundar S, Rai M. Advances in the treatment of leishmaniasis. Curr Opin Infect Dis. 2002;15(6):593-8.
13. Singh OP, Sundar S. Developments in diagnosis of visceral leishmaniasis in the elimination era. J Parasitol Res. 2015;2015:239469.
14. de Ruiter CM, van der Veer C, Leeflang MMG, Deborggraeve S, Lucas C, Adams ER. Molecular tools for diagnosis of visceral leishmaniasis: systematic review and meta-analysis. J Clin Microbiol. 2014;52(9):3147-55.
15. Boelaert M, Verdonck K, Menten J, Sunyoto T, van Griensven J, Chappuis F, et al. Rapid tests for diagnosis of visceral leishmaniasis. Cochrane Database Syst Rev. 2014;(6):CD009135.
16. Zijlstra EE, Musa AM, Khalil EA, el-Hassan IM, el-Hassan AM. Post-kala-azar dermal leishmaniasis. Lancet Infect Dis. 2003;3(2):87-98.
17. Kaye P, Scott P. Leishmaniasis: complexity at the host-pathogen interface. Nat Rev Microbiol. 2011;9(8):604-15.
18. Jahangir MA, Taleuzzaman M, Kala C, Gilani SJ. Advancements in polymer and lipid-based nanotherapeutics for cancer drug targeting. Current Pharmaceutical Design. 2020 Nov 1;26(40):5119-27.
19. Sacks D, Noben-Trauth N. The immunology of susceptibility and resistance to Leishmania major. Nat Rev Immunol. 2002;2(11):845-58.
20. Murray HW, Berman JD, Davies CR, Saravia NG. Advances in leishmaniasis. Lancet. 2005;366(9496):1561-77.
21. Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis. 2004;27(5):305-18.
22. Ready PD. Epidemiology of visceral leishmaniasis. Clin Epidemiol. 2014;6:147-54.
23. Burza S, Croft SL, Boelaert M. Leishmaniasis. Lancet. 2018;392(10151):951-70.
24. WHO Expert Committee. Control of the leishmaniases. World Health Organ Tech Rep Ser. 2010;949:1-186.
25. Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med. 2002;347(22):1739-46.
26. Jahangir MA, Jain P, Verma R, Taleuzzaman M, Ahsan MJ, Chettupalli AK, Muheem A, Mirza MA. Transdermal nutraceuticals delivery system for CNS disease. CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders). 2022 Dec 1;21(10):977-93.
27. Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B

for visceral leishmaniasis. N Engl J Med. 2010;362(6):504-12.

28. Croft SL, Sundar S, Fairlamb AH. Drug resistance in leishmaniasis. Clin Microbiol Rev. 2006;19(1):111-26.
29. Croft SL, Olliaro P. Leishmaniasis chemotherapy—challenges and opportunities. Clin Microbiol Infect. 2011;17(10):1478-83.
30. Singh N, Kumar M, Singh RK. Leishmaniasis: current status of available drugs and new potential drug targets. Asian Pac J Trop Med. 2012;5(6):485-97.
31. Kedzierski L. Leishmaniasis vaccine: where are we today? J Glob Infect Dis. 2010;2(2):177-85.
32. Kedzierski L, Evans KJ. Immune responses during visceral leishmaniasis. Parasitology. 2014;141(12):1549-63.
33. Singh OP, Hasker E, Sacks D, Boelaert M, Sundar S. Asymptomatic leishmania infection: a new challenge. Trends Parasitol. 2014;30(7):324-9.
34. Banuls AL, Hide M, Prugnolle F. Leishmania and the leishmaniases: a parasite genetic update. Trends Parasitol. 2007;23(12):600-6.
35. Jahangir MA, Khan S, Kala C. Phytonutrients and technological development in formulations. J Pharm Res Sci Technol 2022; 6 (1): 159. doi: 10.31531/jprst. 2022 Feb 7;1000159:39.
36. Bates PA. Transmission of Leishmania metacyclic promastigotes by phlebotomine sand flies. Int J Parasitol. 2007;37(10):1097-106.
37. Kamhawi S. Phlebotomine sand flies and Leishmania parasites. Cell Microbiol. 2006;8(6):934-44.
38. Akhoundi M, Kuhls K, Cannet A, Votýpka J, Marty P, Delaunay P, et al. A historical overview of the classification, evolution, and dispersion of Leishmania parasites. PLoS Negl Trop Dis. 2016;10(3):e0004349.
39. Srivastava P, Dayama A, Mehrotra S, Sundar S. Diagnosis of visceral leishmaniasis. Trans R Soc Trop Med Hyg. 2011;105(1):1-6.
40. Jahangir MA, Muheem A, Anand C, Imam SS. Traditional and modern applications of honey: An insight. InTherapeutic Applications of Honey and its Phytochemicals: Vol. 1 2020 Dec 22 (pp. 151-169). Singapore: Springer Singapore.
41. Hasker E, Kansal S, Malaviya P, Gidwani K, Picado A, Singh RP, et al. Latent infection with Leishmania donovani. PLoS Negl Trop Dis. 2013;7(4):e2170.
42. Costa CHN. How effective is dog culling in controlling zoonotic visceral leishmaniasis? PLoS Negl Trop Dis. 2011;5(7):e1238.
43. Jahangir MA, Taleuzzaman M, Beg S, Verma S, Gilani SJ, Alam P. A review of eugenol-based nanomedicine: Recent advancements. Current Bioactive Compounds. 2021 Feb 1;17(3):214-9.
44. Bern C, Maguire JH, Alvar J. Complexities of assessing the disease burden attributable to leishmaniasis. PLoS Negl Trop Dis. 2008;2(10):e313.
45. Dantas-Torres F. Canine leishmaniosis in South America. Parasit Vectors. 2009;2(Suppl 1):S1.
46. Sundar S, Singh A. Chemotherapeutics of visceral leishmaniasis: present and future developments. Parasitology. 2018;145(4):481-9.
47. Ponte-Sucre A, Gamarro F, Dujardin JC, Barrett MP, López-Vélez R, García-Hernández R, et al. Drug resistance and treatment failure in leishmaniasis. PLoS Negl Trop Dis. 2017;11(12):e0006052.
48. Jahangir MA, Imam SS, Muheem A, Chettupalli A, Al-Abbasi FA, Nadeem MS, Kazmi I, Afzal M, Alshehri S. Nanocrystals: characterization overview, applications in drug delivery, and their toxicity concerns. Journal of Pharmaceutical Innovation. 2022 Mar;17(1):237-48.
49. WHO. Leishmaniasis fact sheet. Geneva: World Health Organization; 2024.
50. Jahangir MA, Gilani SJ, Muheem A, Jafar M, Aslam M, Ansari MT, Barkat MA. Quantum dots: next generation of smart nano-systems. Pharmaceutical nanotechnology. 2019 Jun 1;7(3):234-45.
51. Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. Trends Parasitol. 2006;22(12):552-7.
52. Kumar R, Engwerda C. Vaccines to prevent leishmaniasis. Clin Transl Immunology. 2014;3(3):e13.
53. Singh N, Mishra J, Singh R, Singh S. Animal models of visceral leishmaniasis. Indian J Med Res. 2016;143(4):394-406.
54. Muheem A, Shakeel F, Jahangir MA, Anwar M, Mallick N, Jain GK, Warsi MH, Ahmad FJ. A review on the strategies for oral delivery of proteins and peptides and their clinical perspectives. Saudi Pharmaceutical Journal. 2016 Jul 1;24(4):413-28.
55. Goto H, Lindoso JAL. Immunity and immunosuppression in experimental visceral leishmaniasis. Braz J Med Biol Res. 2004;37(4):615-23.
56. Jahangir MA, Anand C, Muheem A, Gilani SJ, Taleuzzaman M, Zafar A, Jafar M, Verma S, Barkat MA. Nano phytomedicine based delivery system for CNS disease. Current Drug Metabolism. 2020 Aug 1;21(9):661-73.
57. Murray HW. Clinical and experimental advances in treatment of visceral leishmaniasis. Antimicrob Agents Chemother. 2001;45(8):2185-97.

58. Sundar S, Singh OP. Molecular diagnosis of visceral leishmaniasis. Mol Diagn Ther. 2018;22(4):443-57.
59. Ansari MJ, Aldawsari MF, Zafar A, Soltani A, Yasir M, Jahangir MA, Taleuzzaman M, Erfani-Moghadam V, Daneshmandi L, Mahmoodi NO, Yahyazadeh A. In vitro release and cytotoxicity study of encapsulated sulfasalazine within LTSP micellar/liposomal and TSP micellar/niosomal nano-formulations. Alexandria Engineering Journal. 2022 Dec 1;61(12):9749-56.
60. Burza S, Sinha PK, Mahajan R, Lima MA, Mitra G, Verma N, et al. Five-year field assessment of visceral leishmaniasis elimination in the Indian subcontinent. PLoS Negl Trop Dis. 2014;8(1):e2610.