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Harnessing The Ocean Against Leishmaniasis: Immunobiological Insights, Disease Trends, And Therapeutic Strategies

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Abstract: Leishmaniasis, which manifests as visceral, cutaneous, and mucocutaneous forms with considerable morbidity and death in endemic areas, is still one of the most neglected tropical illnesses (Alvar et al., 2012). Elimination goals are still hampered by chemotherapy limitations, developing drug resistance, toxicity, and the lack of a human vaccine, despite decades of control efforts (Kaye & Scott, 2011). While marine environments have become a viable source of structurally unique bioactive chemicals with antileishmanial potential, recent developments in immunobiology have improved our understanding of host-parasite interactions (Sacks & Noben-Trauth, 2002). This review incorporates recent advancements in marine-derived therapies and vaccine development, as well as important immunological pathways underpinning illness progression and protection. Multidisciplinary approaches combining immunology and marine natural product chemistry, and systems biology to address existing research gaps and enable sustainable control of leishmaniasis.

***Index Terms* -** Leishmaniasis, Kala azar, Phlebotomine sandflies , Visceral leishmaniasis , Cutaneous leishmaniasis , Mucocutaneous leishmaniasis, Marine Bioactives

1.Introduction

The different types of Leishmania protozoan parasites are the causative agents of a group of illnesses called ‘Leshmaniasis’. These parasites are often found in human beings and animals like cats, dogs, rodent and foxes. Disfiguring skin ulcers and fatal illnesses [fever, weight loss and organ enlargement] are the most commonly seen symptoms in Leishmaniasis patients. Poor and inadequate sanitation in the tropical and rural areas is the main cause for spread of this disease.

The parasitic disease Leishmanisis is transmitted by the stinging of female phlebotomine sandflies harbouring protozoa from the genus *Leishmania*. Visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL) are the three main clinical manifestations of the disease; each has a different severity, immunopathology, and prognosis. While CL and MCL result in disfiguring lesions and long- term psychological repercussions, VL, the most severe form, is frequently fatal if left untreated. The diagnosis include traditional methods, serological tests and advanced molecular methods. Despite tremendous advancements in our knowledge of parasite biology and host immunity, current treatments are constrained by toxicity, expense, lengthy treatment schedules, growing resistance and patient’s geographical area of residence. These challenges highlight the need for revised evaluations that incorporate new therapeutic approaches, especially those originating from neglected marine resources, with developing immunobiological insights. The therapies that are based on derivatives derived from marine resources are cost –effective and sustainable, therefore have a promising future for the treatment of this deadly disease.

2.CURRENT EPIDEMIOLOGICAL SITUATION

Leishmaniasis poses a substantial global health burden, with endemicity reported in approximately 88 countries and an estimated 350 million people at risk worldwide. Annually, around 500,000 new cases of visceral leishmaniasis and 1–1.5 million cases of cutaneous leishmaniasis are reported, although the true burden is likely underestimated due to underreporting and limited surveillance in endemic regions (Alvar et al., 2012).

High-burden countries include India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil, where socio-economic factors intersect with ecological conditions favourable for sand-fly vectors. Epidemiological patterns are shifting from zoonotic to anthroponotic transmission in several regions, driven by urbanization, deforestation, climate change, and human migration. Co-infection with HIV significantly increases susceptibility and complicates treatment outcomes, while malnutrition and poor housing conditions further exacerbate disease risk (Kaye & Scott, 2011).

Current control strategies rely on early case detection, chemotherapy, vector control measures such as indoor residual spraying and insecticide-treated bed nets, and reservoir management. However, these measures alone are insufficient, highlighting the urgent need for improved diagnostics, safer drugs, and preventive vaccines.

Table 1: Comparison of Clinical Forms of Leishmaniasis

Form	Affected Organs	Severity	Outcome if Untreated
Visceral (VL)	Liver, spleen, bone marrow	High	Often fatal
Cutaneous (CL)	Skin	Moderate	Scarring
Mucocutaneous (MCL)	Mucosa, skin	High	Severe disfigurement

As shown in Table 1 provides a comparative overview of the three major clinical manifestations of leishmaniasis—visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL)—highlighting differences in target organs, disease severity, and clinical outcomes.

Visceral leishmaniasis is the most severe form of the disease, primarily affecting internal organs such as the liver, spleen, and bone marrow. If left untreated, VL is often fatal due to progressive immunosuppression, severe anemia, and secondary infections. Its high mortality rate underscores the urgent need for early diagnosis and effective treatment strategies.

Cutaneous leishmaniasis predominantly involves the skin and typically presents as localized ulcers at the site of sandfly bites. Although CL is generally not life-threatening, it often leads to permanent scarring and disfigurement, resulting in significant psychological and social consequences for affected individuals.

Mucocutaneous leishmaniasis represents a more aggressive disease form, in which parasites spread from the skin to mucosal tissues of the nose, mouth, and throat. This form is associated with severe tissue destruction and facial deformities, leading to functional impairment and reduced quality of life. The comparison emphasizes that while clinical severity varies, all forms contribute substantially to disease burden and require tailored therapeutic interventions.

3. Marine Bioactives as Anti-Leishmanial Agents

Marine environments harbor immense chemical diversity, offering a rich source of bioactive compounds with unique structural features not commonly found in terrestrial organisms. Several marine-derived compounds, including sulfated polysaccharides, alkaloids, terpenoids, and fucoidans, have demonstrated promising in vitro and in vivo antileishmanial activity. These compounds act through diverse mechanisms, such as disruption of parasite membranes, inhibition of arginase and other metabolic enzymes, induction of oxidative stress, and modulation of host immune responses.

Marine bioactives offer notable advantages, including novel molecular scaffolds that reduce the likelihood of cross-resistance with existing drugs. Additionally, some compounds exhibit immunomodulatory properties that enhance macrophage-mediated parasite killing. Nonetheless, challenges remain, particularly regarding sustainable supply, complex extraction processes, pharmacokinetic limitations, and potential toxicity. Advances in marine biotechnology, synthetic biology, and semi-synthetic modification are increasingly addressing these barriers, strengthening the case for marine compounds as viable antileishmanial leads.

Table 2: Conventional Drugs vs Marine-Derived Compounds

Parameter	Conventional Drugs	Marine Bioactives	Remarks
Source	Synthetic / Semi-synthetic	Marine organisms	Novel scaffolds
Toxicity	High	Low–Moderate	Needs validation
Resistance	Increasing	Low (expected)	Early-stage data
Cost	High	Potentially lower	Scalable biotech needed

As shown in Table 2 compares currently used conventional antileishmanial drugs with emerging marine-derived bioactive compounds across key parameters, including source, toxicity, resistance potential, and cost.

Conventional antileishmanial drugs, such as pentavalent antimonials, amphotericin B, and miltefosine, are largely synthetic or semi-synthetic compounds. While these drugs remain effective in many settings, their clinical use is often limited by high toxicity, lengthy treatment regimens, and increasing reports of drug resistance, particularly in endemic regions.

In contrast, marine-derived bioactive compounds originate from diverse marine organisms and possess novel chemical structures that differ significantly from existing antileishmanial agents. These unique molecular scaffolds are expected to reduce the likelihood of cross-resistance. Preliminary studies suggest that several marine compounds exhibit lower toxicity and additional immunomodulatory effects that enhance host-mediated parasite clearance.

However, the table also highlights that marine bioactives are still largely in the experimental stage. Challenges such as scalable production, comprehensive toxicity evaluation, and clinical validation remain to be addressed. Overall, the comparison illustrates the potential of marine bioactives as promising alternatives or adjuncts to conventional therapies, particularly in the context of sustainable and resistance-aware drug development.

4. Immunobiology and Recent Advances

Protective immunity against *Leishmania* infection is primarily mediated by a Th1-type immune response. Interferon-gamma (IFN-γ) produced by $CD4^+$ T cells, along with interleukin-12 (IL- 12) from dendritic cells, activates macrophages to produce nitric oxide and reactive oxygen species that kill intracellular parasites. In contrast, disease progression is associated with Th2- biased responses and elevated levels of immunosuppressive cytokines such as IL-10.

Leishmania parasites employ sophisticated immune evasion strategies, including the expression of virulence factors such as gp63 and lipophosphoglycan (LPG), which inhibit phagosome maturation, oxidative burst, and antigen presentation. Regulatory T cells and high titers of non-protective anti-*Leishmania* IgG further contribute to an immunosuppressive milieu. Emerging research highlights the role of innate-like T cells, including mucosal- associated invariant T (MAIT) cells, metabolic reprogramming of macrophages, and host microbiome composition in shaping disease susceptibility and outcomes.

5. Vaccine Development Landscape

Despite extensive research, no licensed human vaccine against leishmaniasis is currently available. First-generation vaccines based on killed parasites or recombinant proteins, such as Leish-111f and LACK, demonstrated limited efficacy in clinical trials. Second-generation approaches focus on live-attenuated parasites, viral vectors, and DNA vaccines targeting conserved antigens to elicit durable cellular immunity.

Adjuvant development has emerged as a critical component of vaccine design, with toll-like receptor (TLR) agonists and CpG oligodeoxynucleotides showing promise in skewing immune responses toward protective Th1 profiles. Several vaccine candidates are currently undergoing Phase I and II clinical trials, although challenges remain related to antigenic diversity among *Leishmania* species, long-term protection, and regulatory complexities.

6. Future Directions and Research Gaps

Future leishmaniasis control strategies must integrate omics-driven antigen discovery with marine-derived therapeutic leads to accelerate drug and vaccine development. Systems immunology approaches can elucidate complex host–parasite interactions and identify correlates of protection. Additionally, implementation research that combines vector control with community-based screening and surveillance is essential for translating scientific advances into public health impact.

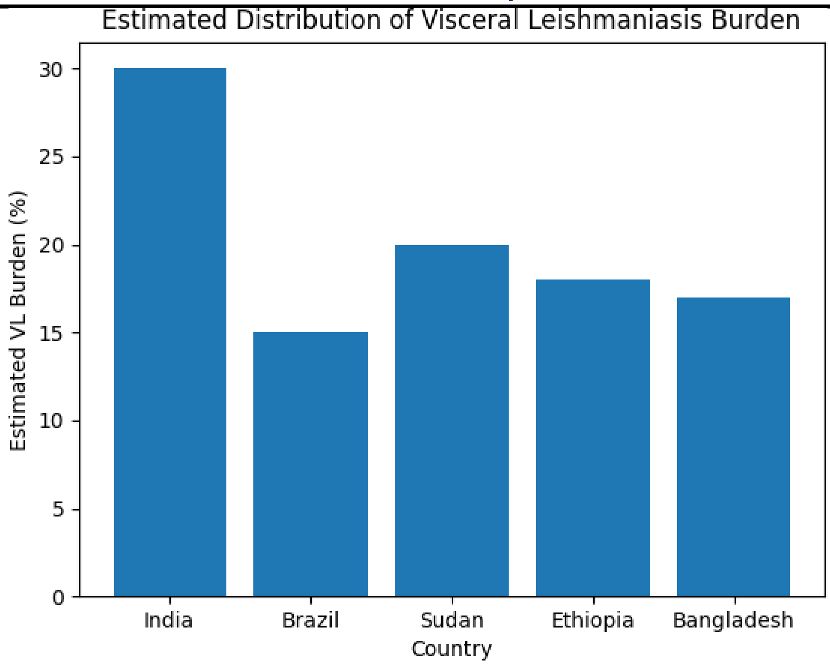
7. Global Distribution of Visceral Leishmaniasis Burden

As Shown in Figure 1 illustrates the estimated distribution of the global visceral leishmaniasis (VL) burden across selected high-endemic countries. The chart highlights the unequal geographical concentration of VL cases, with a substantial proportion of infections occurring in a limited number of regions.

India accounts for the highest estimated share of VL cases, reflecting its long-standing endemicity, dense population, and persistent socio-economic and environmental risk factors that favor sandfly transmission. Countries such as Sudan, Ethiopia, Bangladesh, and Brazil also contribute significantly to the global burden, emphasizing that VL remains a major public health concern across South Asia, East Africa, and parts of South America.

The figure demonstrates that VL distribution is strongly influenced by factors such as poverty, malnutrition, inadequate housing, climate conditions suitable for vector breeding, and limited access to healthcare services. Additionally, regional instability, population migration, and HIV co-infection further intensify disease transmission and complicate control efforts in several of these countries.

Overall, Figure 1 underscores the need for geographically targeted interventions, including strengthened surveillance, improved access to diagnostics and treatment, vector control strategies, and region-specific research priorities. Concentrating resources and public health efforts in high-burden countries is essential for achieving meaningful reductions in visceral leishmaniasis incidence and mortality.



8. CONCLUSIONS

Leishmaniasis continues to pose a major global health challenge, demanding innovative and interdisciplinary solutions. Advances in immunobiology and the discovery of marine bioactive compounds offer renewed hope for effective therapeutics and vaccines. A coordinated effort spanning epidemiology, marine chemistry, immunology, and vaccinology is essential to achieve sustainable control and eventual elimination of leishmaniasis.

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