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Review Article

Comparative Efficacy of Current and Emerging Therapies for Cutaneous and Visceral Leishmaniasis: A Global Perspective

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Abstract: Leishmaniasis treatment has faced challenges with pentavalent antimonials, historically used but now showing resistance and high failure rates. The World Health Organization (WHO) recommended higher doses, but resistance in Nepal and misuse persist. Antimonials are no longer the preferred treatment for visceral leishmaniasis (VL) in the Indian subcontinent but are still used for cutaneous leishmaniasis (CL). Amphotericin B, especially liposomal amphotericin B (L-AmB), has become the preferred treatment for VL in the Indian subcontinent, with high efficacy and shorter treatment courses. Genetic insights into leishmaniasis reveal that parasite species and host immune responses are key factors in disease variation. Genetic analysis of atypical parasite isolates shows that genetic variations can lead to different disease patterns. Whole genome sequencing and proteomic analyses offer fresh insights into how parasite genes and proteins impact drug resistance, post-kala-azar dermal leishmaniasis (PKDL), and unusual disease presentations. Variations in hereditary unit copy numbers and single nucleotide polymorphisms contribute to genetic diversity and distinct tissue distribution, leading to distinct disease patterns. Genomic markers for drug resistance in Leishmania parasites include ATP-binding cassette (ABC) transporters, amino acid permease 3 (AAP3), and proteins like phosphoglycerate kinase (PGK) and mitogen-activated protein kinase (MAPK). These markers are associated with efflux of thiols and metals, antimony resistance, and protection against oxidative stress. Additionally, key proteins and enzymes in antioxidant defense mechanisms, such as iron superoxide dismutase-A (FeSOD-A), folate transporter 1 (FT1), and heat shock protein 83 (HSP83), play roles in drug resistance and parasite survival.

Keywords: Antimonial Resistance, Antioxidant Defense Mechanisms, Drug Resistance Markers, Genetic Insights, Leishmaniasis Treatment, Parasite Genetic Variation.

1. INTRODUCTION

Cutaneous leishmaniasis (CL) has remained prevalent for decades, Millions of cases have been reported globally, particularly in regions that are developing or underdeveloped. The disease exists in two main forms, categorized based on the causative species: New World and Old World CL. Although both forms generally heal on their own, without treatment, they can lead to significant scarring and complications, such as mucosal involvement. The traditional gold conventional therapy for both types typically involves the intralesional or injectable use of antimonial drugs (Azim, Khan, Ullah, Ullah, & Anjum, 2021)**.** The varying responses to current therapies for cutaneous leishmaniasis have emerged as a significant

challenge in disease control. Additionally, the lack of comprehensive analyses on the outcomes of such treatments hampers a deeper understanding of the issue (Madusanka, Silva, Karunaweera, & therapy, 2022)**.** Not all Leishmania species are responsive to the presently available treatment options. Therefore, accurately identifying the specific species is essential for predicting the clinical outcome in patients with cutaneous or mucocutaneous leishmaniasis caused by an unidentified species (Hodiamont, Kager, Bart, de Vries, & van Thiel, 2014).

Despite the availability of various antileishmanial drugs in recent decades, antimonials remain the primary treatment for cutaneous leishmaniasis (CL) in most countries, regardless of the species involved or the clinical presentation of the lesions. The two main antimonial formulations used for CL treatment are sodium stibogluconate (SSG) and meglumine antimoniate (MA). Antimonials work through multiple mechanisms, including a dual action against CL: they activate macrophages to eliminate the parasites, and the prodrug Sb (V) is converted into its active form, Sb (III), which inhibits trypanothione reductase, ultimately causing the parasite's death (Krauth-Siegel & Comini, 2008).

Several genes contribute to the development of drug-resistant forms of the parasite, the most notable include aquaglyceroporin 1 (AQP1), multidrug resistance protein A (MRPA), γ-glutamylcysteine synthetase (γ-GCS), trypanothione reductase (TR), and thiol-dependent reductase 1 (TDR1). (Malvolti, Malhame, Mantel, Le Rutte, & Kaye, 2021).

Thermotherapy is an affordable and straightforward treatment option for cutaneous leishmaniasis, requiring fewer sessions and resulting in minimal side effects and scarring. It is particularly valuable in medically underserved region (Refai *et al*., 2017)**.** Berman *et al*., and Sacks *et al*., have shown that thermotherapy can inhibit the multiplication of Leishmania parasites when temperatures exceed 39 °C(Berman, Neva, & hygiene, 1981; Sacks, Barral, Neva, & hygiene, 1983).

Drug treatment is crucial, but conventional anti-leishmaniasis medications can cause significant adverse effects and toxicity, leading to therapeutic failure or patient discontinuation. Therefore, there is a need to develop new immunomodulatory therapies to effectively treat cutaneous leishmaniasis (Pavanelli, Demarchi, & Microbiology, 2022)**.**Immunotherapy aims to stimulate a robust immune response to quickly control the disease. Recent research suggests that a single dose of an appropriate therapeutic vaccine can lead to rapid and sustained recovery in patients. This approach not only significantly reduces drug toxicity and the development of resistance but also serves as an effective complement to chemotherapy. Compared to monotherapy, it offers a safer and more potent treatment option, potentially leading to both preventive and therapeutic cures for leishmaniasis (Akbari, Oryan, & Hatam, 2021).

Immune system therapy for leishmaniasis is based on the idea that converting an ineffective immune response into a protective one can improve disease control. This can be accomplished using immune-regulating substances or specially designed Leishmania antigens. As a result, immunotherapeutic strategies may include the use of Leishmania antigens, recombinant cytokines and antibodies, or compounds that target crucial immunoregulatory pathways (Ikeogu *et al*., 2020).

Therapies aimed at immunosuppressive agents such as PD-1 have been utilized to treat Leishmania infection in mouse models. In 2019 study with BALB/c mice suffering from chronic L. amazonensis infection, da Fonseca Martins *et al*., demonstrated that treatment with anti-PD-1 and anti-PD-L1 monoclonal antibodies markedly boosted IFN-γ production by CD4+ and CD8+ T cells, resulting in improved contagion control in the mice (da Fonseca-Martins *et al*., 2019).

2.1. Challenges and Shifts in Leishmaniasis Treatment with Pentavalent Antimonials

Historically, pentavalent antimonials, which includes sodium stibogluconate (SSG) and meglumine antimonials (MA), have been used to deal with leishmaniasis. However, a widespread cure failure charge of 30% used to be determined in Bihar, India, prompting a panel of specialists to endorse a revised dosage regimen. This at first accelerated therapy costs however later declined (Berbert *et al*., 2018). Higher doses had been encouraged with the aid of the World Health Organization (WHO), however these have additionally confirmed ineffective, with resistance said in Nepal and misuse contributing to the problem(Pacific, 2023). Antimony resistance is a big problem, with a number mechanisms proposed, along with decreased drug absorption and improved expression of sure proteins(Maharjan, Singh, Chatterjee, Madhubala, & hygiene, 2008). Given these challenges and the hazard of cardiotoxicity, antimonials are no longer the therapy of preference for visceral leishmaniasis (VL) in the Indian landmass. In Africa, they are solely endorsed in aggregate with paramomycin for VL and as monotherapy for post-kala-azar cutaneous leishmaniasis (PKDL)(Kumari, Perveen, Sharma, & Singh, 2021). In the New World, whilst liposomal amphotericin B (L-AmB) is preferred, antimonials are nevertheless used for VL. For CL, antimonials continue to be a main remedy option, given both intralesionally or systemically, on my own or in combination(Shyam Sundar, Chakravarty, & Meena, 2019).

Amphotericin B, a polyene antifungal agent, has been used as first-line remedy in areas with pentavalent antimony (Sbv) resistance. Its deoxycholate shape has amazing remedy charges for visceral leishmaniasis (VL) however has drawbacks such as lengthy length of cure and regular negative reactions(Mishra, Biswas, Jha, & Khan, 1994). Lipid formulations of amphotericin B, especially liposomal amphotericin B (L-AmB), have been developed to limit toxicity and allow shorter remedy courses. L-AmB is the remedy of preference for VL in the Indian subcontinent (ISC), with a single dose of 10 mg/kg reaching an efficacy fee of 95%. In different areas, greater complete doses are recommended(Prakash Singh, Singh, Chakravarty, & Sundar, 2016; S. Sundar & Chakravarty, 2010). L-AmB is additionally advocated for HIV-VL coinfection and has been used efficiently in cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL). Reports of remedy failure with amphotericin B are rare, however resistance mechanisms have been identified, along with loss of ergosterol and mutations in the sterol 14α-demethylase gene (Frézard *et al*., 2022).

Miltefosine (MIL) was the first effective oral antileishmanial drug, registered in India in 2002, with a 94% cure rate for VL. However, concerns about its long half-life and the potential for resistance due to suboptimal compliance have led to indications of MIL resistance in India, Nepal and Bangladesh(Dorlo, Balasegaram, Beijnen, & de Vries, 2012). Mechanisms of resistance include decreased drug uptake and increased efflux, with genetic analyses showing single nucleotide polymorphisms in the MIL transporter gene(Montazami, Aghapour, Farajnia, Baradaran, & biology, 2015). MIL is no longer used alone for visceral leishmaniasis (VL) in ISC but is still advised for treating post-kala-azar cutaneous leishmaniasis (PKDL) and cutaneous leishmaniasis (CL). Paromomycin (PM), an aminoglycoside, has proven effective against leishmaniasis, with a cure rate of 94.6% reported in a phase III trial in India (Younis *et al*., 2023). However, its administration by intramuscular injection for 21 days is challenging in endemic areas. In Africa, paromomycin is used in combination with corticosteroid glycol, and topical formulations are used to treat CL with variable results. Systemic paromomycin has excellent cure rates for crusted leishmaniasis in Brazil but is less effective in treating MCL (Verrest *et al*., 2021). PM resistance is not well documented, but studies suggest that reduced drug absorption and decreased protein synthesis may be associated with resistance (Jhingran *et al*., 2009).

2.2. Enhancing Immune Response: Immunotherapy and Immunomodulators in Leishmaniasis Treatment:

Immunotherapy aims to improve the immune response versus Leishmania parasites, and address the defective immune response observed in some patients. This approach has shown partial success in treating cutaneous leishmaniasis using Leishmania antigens solitary or in blend with other antigens such as BCG. Confit *et al*., and Marinck *et al*., reported cure rates of 76–94% utilizing vaccines derived from whole promastigote formulations for localized cutaneous leishmaniasis (LCL) and mucocutaneous leishmaniasis (ML)(Yadagiri, Singh, Arora, & Mudavath, 2023). Recombinant Leishmania antigens, like Leish111f formulated with MPLA and squalene oil emulsion, have demonstrated promising outcomes in the treatment of treatment-resistant leishmaniasis (Coler, Goto, Bogatzki, Raman, & Reed, 2007). Immunotherapy, with antimonials, may provide an alternative for leishmaniasis, including HIV-Leishmania coinfection, post-kala-azar dermal leishmaniasis (PKDL), and refractory chronic atrophic leishmaniasis. This approach could reduce pharmacotoxicity and the development of resistance when used as an adjunct to long-term immunotherapy(Shah, Shah, Prajapati, & Bilimoria, 2010).

Clinical trials are necessary to confirm the advantages of immunotherapy across various clinical contexts. The immune response mechanisms of New World cutaneous leishmaniasis and cutaneous leishmaniasis indicates that lesion progress is primarily driven by an immune-mediated inflammatory response, with disease progression and severity more closely linked to hypersensitivity than to immunosuppression (Goto & Lindoso, 2010). The finding that early treatment does not significantly shorten recovery time indicates that disease pathogenesis is more closely tied to the inflammatory response rather than the parasite load within the lesion. Inflammatory modulators like TNF-α and IFN-γ are produced at higher levels in cutaneous leishmaniasis compared to other forms of the disease (Clark, Alleva, Mills, & Cowden, 2004; Manamperi *et al*., 2017).

Immunomodulators like pentoxifylline, a tumor necrosis factor alpha inhibitor, have been combined with antimonials in the treatment of mucous and dermal leishmaniasis, demonstrating a decrease in recovery period (de Faria *et al*., 2019). Imiquimod, a Toll-like receptor 7 stimulator and cytokine modulator, has been utilized alongside systemic antimony compounds to administer cutaneous leishmaniasis, resulting in a 90% cure rate in patients who were resistant to pentavalent antimonials (Miranda-Verastegui *et al*., 2009). This conjunction has also shown efficacy in the initial treatment of cutaneous leishmaniasis and was found to be superior to placebo plus pentavalent antimonials in a clinical trial in Peru(Miranda-Verástegui, Llanos-Cuentas, Arevalo, Ward, & Matlashewski, 2005). Combining antimonials with immunomodulators could provide an alternative treatment approach for patients who do not respond to antimonial therapy (Berbert *et al*., 2018). Further evaluation through new research studies is necessary to determine the utilize of these drugs in research practice.

2.3. Genetic Insights into Leishmaniasis: Unraveling the Complexity of Parasite-Host Interactions

Variations in the clinical presentation of leishmaniasis are linked to the specific parasite species and the host's immune response, with the parasite species playing a key role in determining the disease outcome (Elmahallawy, Alkhaldi, Saleh, & Pharmacotherapy, 2021). Research is centered on unraveling the molecular mechanisms that govern tissue homing and exploring how different parasite species or subtypes contribute to visceral, Cutaneous and mucocutaneous types of the disease (G. Volpedo *et al*., 2021) can exhibit uncommon manifestations, and genomic analysis of unusual parasite strains provides valuable insights. For instance, multi-locus sequence typing of Leishmania tropica strains from classical CL cases in Bikaner and unusual VL cases in Bihar has revealed genetic variations that may be associated with these differing disease patterns (Thakur *et al*., 2018). Significant genetic polymorphisms were identified in L. donovani isolates causing visceral leishmaniasis (VL) from Northeast India using multiplex PCR-RFLP and MLMT markers (P. Srivastava, Singh, & Sundar, 2011). Complete genome sequencing of various parasite species, clinical isolates from patients, and laboratory-altered parasite variants has offered new insights into how parasite genes contribute to drug resistance, post-kala-azar dermal leishmaniasis (PKDL) patterns, and atypical disease manifestations (Bharadava *et al*., 2024). Particular parasite genes, gene variants, and variations in gene copy number are linked to distinct disease patterns. A few genes have been identified as differentially expressed in viscerotropic versus skin-tropic species, including some with unknown functions, such as the A2 gene cluster, Ld28.0340, Ld15.0900, and Ld36.2480, which support viscerotropic infection (Depledge *et al*., 2009). Variations in gene copy number and single nucleotide variants play a crucial role in determining genetic variation and tissue orientation, leading to varied disease patterns (Girirajan, Campbell, & Eichler, 2011). Comparisons of whole-genome sequences of VL-leading to strains and unusual cutaneous leishmaniasis (CL)- leading to L. donovani strains from Sri Lanka revealed reduced copy numbers of the A2 virulence gene and mutations in the Rag C GTPase as factors influencing strain vulnerability to CL (W. W. Zhang *et al*., 2014). Proteomic comparisons demonstrated differential expression of proteins involved in translation, biosynthesis, and antioxidant defense, implying that these variations in protein expression may affect pathogenesis (Hoo *et al*., 2019).

Differences in the transcriptome, proteome, and metabolome profiles of parasite isolates with similar genotypes can guide to variations in tissue and virulence distribution. Studies on L. (V.) braziliensis isolates from both mucosal and cutaneous places within the identical patient indicate that the prostaglandin synthesis pathway might contribute to these differences in pathogenesis, as evidenced by the overexpression of heat shock protein 70 (HSP70) and prostaglandin F2 alpha synthase (PGF2s) in cutaneous isolates (Alves-Ferreira, Ferreira, Walrad, Kaye, & Cruz, 2020). Genetic variation and varied gene manifestation are key factors in deciding parasite pathogenicity and medical outcomes (Thakur *et al*., 2021). Clinical isolates of L. donovani responsible for atypical cutaneous leishmaniasis (CL) share identical Hsp70 and 6-PGDH gene sequences with unusual isolates from Sri Lanka, proposing a possible common origin (Thakur *et al*., 2021). Moreover, L. donovani isolates from Himachal Pradesh that cause CL show genetic differences from the MON-2 strain based on GPI and gp63 gene sequences (Lypaczewski *et al*., 2022). Immunocompromised patients often display unusual disease expressions with varying levels of parasite malignancy, emphasizing the importance of host immune status in determining disease outcomes (Grossman, Fox, Kovarik, & Rosenbach, 2012)

2.4. Innovative Approaches in Leishmaniasis Chemotherapy

Peptidases (proteases) are regarded as promising targets for chemotherapy. In Leishmania, the sole aspartic protease is part of the A2 retroviral-like aspartic protease family and is restrained by medications initially created for HIV protease inhibition (Onchieku *et al*., 2018). Leishmania dihydrofolate reductase (DHFR) interacts to form a functional complex with thymidylate synthase (TS), and molecule 571633 has been identified as a potential DHFR-TS inhibitor through in silico virtual screening (Bhattacharya, Leprohon, & Ouellette, 2021). High-throughput screening has also uncovered novel molecular frameworks, with CA272 and CH872 emerging as promising antileishmanial candidates (Siqueira-Neto, Song, Oh, Sohn, & Yang, 2010). Additionally, Prati *et al*., examied the potential of aiming at Leishmania carriers with specially engineered chemical indicators, taking advantage of L. donovani's arginine and lysine auxotrophy. Conjugates with cytotoxic quinone fragments linked to amino acids exhibited toxicity towards the parasites while having minimal effects on mammalian cells (Prati *et al*., 2014).

Recent advancements in the treatment of leishmaniasis and African trypanosomiasis (HAT) underscores the ongoing need for new therapeutic options. Nifurtimox and SCYX-7158 are currently during clinical studies for HAT, with nifurtimox also being evaluated for visceral leishmaniasis (VL) (Nagle *et al*., 2014). Gupta *et al*.. recognized a nitroimidazo-oxazole gied molecule for VL, where DNDI-VL-2098 demonstrated leishmanicidal activity and potential to enhance host-protective immune responses (Gupta *et al*., 2015). Furthermore, new hybrids of heteroretinoid-bisbenzylidine ketones have been developed and tested in vitro against L. donovani, highlighting a previously unrecognized class of antileishmanial agents (Tiwari *et al*., 2015). Additionally, N-substituted β-amino alkanols exhibited leishmanicidal effects by inducing significant mitochondrial swelling and vesiculation in the parasites (Abengózar *et al*., 2015).

An innovative approach using pegylated meglumine antimoniate-loaded liposomes (LMA) in conjunction with non-pegylated LMA has shown increased efficacy against visceral leishmaniasis (VL) in dogs and mice compared to

standard LMA treatments (Reis *et al*., 2017). Additionally, Crovirin, a secretory protein rich in cysteine, is derived from the venom of Crotalus viridis viridis, has exhibited substantial activity against trypanosomes and Leishmania, indicating its potential as a therapeutic agent or drug candidate (Adade *et al*., 2014).

Several natural products have been tested for their leishmanicidal effects. Extracts from plants such as Hyptis pectinata, Aloe vera, Ruta graveolens, Pfaffia glomerata, and Chenopodium ambrosioides have shown direct effectiveness against the extracellular forms of Leishmania (De Queiroz *et al*., 2014). Thymol derivatives have proven more effective than eugenol derivatives in mouse models, with benzoylthymol emerging as the most potent inhibitor with reduced toxicity. Essential oil extracted from the leaves of Artemisia annua. Has also shown leishmanicidal activity against L. donovani both in vitro and in vivo (de Morais *et al*., 2014). Nadhman *et al*., Created silver (Ag)-doped zinc oxide semiconductor nanoparticles that respond to daylight for use in photodynamic therapy (PDT) targeting Leishmania. These nanoparticles enhance cell membrane permeability and induce parasite death upon activation by daylight (Nadhman *et al*., 2014). Daylight-activated photodynamic therapy (DA-PDT) has been effective for treating cutaneous leishmaniasis caused by L. major and L. tropica (Savoia, 2015). Additionally, various macrocycles, including sapphyrin and related heterosapphyrins, are being explored as potential treatments for leishmaniasis (Hooker *et al*., 2012).

2.5. Genomic Markers for Drug Resistance and Treatment Strategies

Recent reports have highlighted the pivotal function of ATP-binding cassette (ABC) transporters in *Leishmania* parasites, which are involved in the efflux of thiols and metals such as antimony (Sb) and arsenic (As), contributing to drug resistance(F. Frézard, R. Monte-Neto, & P. G. Reis, 2014). The transporters LABCI4 and ABCC3 have been reported to be responsible for the efflux of thiol-coupled metals, with LABCI4 being located in both the plasma membrane and mitochondria(Perea *et al*., 2018). The MRPA transporter has also been highlighted for its role in reducing antimony concentration and its presence in resistant *Leishmania* isolates(A. Mukherjee *et al*., 2007). In addition, overexpression of Pgp-like proteins and MRP1 has been shown in antimony-resistant *L. donovani* isolates, leading to decreased intracellular drug concentration and parasite survival(F. Frézard, R. Monte-Neto, & P. G. J. B. r. Reis, 2014). ABCG transporters have also been implicated in drug resistance, with LiABCG6 involved in the efflux of sitamaquine and miltefosine. LABCG4 and LABCG2 transporters are involved in phosphatidylcholine transport and thiolate export with Sb(III), respectively(S. Salari, M. Bamorovat, I. Sharifi, & P. G. N. J. J. o. C. L. A. Almani, 2022). Furthermore, recent research informs us about the role of P4 ATPase and cdc50 in miltefosine efflux. Pentamidine resistance protein 1 (PRP1) and P-glycoproteins (Pgps) have been discussed as additional ABC transporters contributing to drug resistance(Samira Salari *et al*., 2022).

Amino acid permease 3 (AAP3) is highlighted as an arginine transporter that facilitates the uptake of arginine, which is crucial for polyamine biosynthesis and the production of thiols that detoxify antimonial compounds(Muxel *et al*., 2017). The enzyme phosphoglycerate kinase (PGK) is involved in glycolysis and ATP production, and its overexpression in antimony-resistant Leishmania isolates suggests a role in protecting against oxidative stress(Kazemi-Rad *et al*., 2013). Mitogen-activated protein kinase (MAPK) is a key regulator of stress responses and virulence, and its downregulation in antimony-resistant isolates indicates a potential role in cell death pathways(B. Mukherjee *et al*., 2021). Protein tyrosine phosphatase (PTP) is important for cell survival and virulence, and its upregulation in resistant isolates may contribute to apoptosis. Pteridine reductase 1 (PTR1) is essential for the salvage of pteridines, which are critical for parasite growth, and its role in resistance to oxidative stress and antimonial drugs is noted(Faria, 2016). Tryparedoxin peroxidase (TXNPx) is a key enzyme in the defense against oxidative stress, reducing organic hydroperoxides and hydrogen peroxide, and is conserved across *Leishmania* species(Fiorillo, Colotti, Boffi, Baiocco, & Ilari, 2012).

2.6. Key Proteins and Enzymes in *Leishmania* Drug Resistance and Antioxidant Defense Mechanisms:

Iron superoxide dismutase-A (FeSOD-A) is highlighted as a key component of the antioxidant protection system, eliminating superoxide radicals and generating hydrogen peroxide and oxygen(Ana Maria Murta Santi & Murta, 2022). FeSOD-A and FeSOD-B, types of iron-containing superoxide dismutases (FeSOD) found in L. infantum/chagasi, L. donovani, and L. tropica, exhibit high activity, particularly in antimony-resistant strains of L. infantum and L. braziliensis in the lab and in clinical strains of L. donovani (A. M. M. Santi, Silva, Santos, & Murta, 2021). Folate Transporter 1 (FT1), which belongs to the BT1 family, mediates the transport of folate and methotrexate (MTX) in Leishmania. Variations in FT1 manifestation can alter sensitivity to antifolate drugs (S. Salari, M. Bamorovat, I. Sharifi, & P. G. N. Almani, 2022). FT1 is localized in the plasma membrane and has been identified as the primary folate transporter in L. infantum MTX-resistant mutants through gene targeting studies(Richard, Leprohon, Drummelsmith, & Ouellette, 2004). Heat shock protein 83 (HSP83), similar to mammalian HSP90, is involved in regulating the mitochondria-dependent apoptosis pathway and has been shown to be overexpressed in antimony-resistant clinical isolates of *L. donovani*.(Prasanna & Upadhyay, 2021) HSP83 modulates the mitochondrial apoptotic pathway in Leishmania through interactions with other proteins, exhibiting an inverse regulatory effect (Padmanabhan *et al*., 2016). The small kinetoplastid calpain-related protein (SKCRP14.1), a calcium-dependent cysteine protease, was found to be downregulated in L. donovani clinical isolates from India. Overexpression of SKCRP14.1 restored sensitivity to antimonial drugs by inducing programmed cell death (PCD), although it also increased resistance to miltefosine (MIL), highlighting its complex role in drug sensitivity (Vergnes *et al*.,

2007; Saboia-Vahia, de Jesus, Cuervo, & Treatments, 2018). Additionally, LmACR2, a metalloid reductase in L. major, activates antimonial drugs by converting Sb(V) to Sb(III). Transfecting L. infantum with LmACR2 increased susceptibility to Pentostam in intracellular amastigotes (Zhou, Messier, Ouellette, Rosen, & Mukhopadhyay, 2004).

2.7. Vaccination Strategies against Cutaneous Leishmaniasis

Unlike many parasitic infections, individuals who recover from leishmaniasis typically develop protective immunity against reinfection, underscoring the significant role of immunological mechanisms in the disease. This suggests that leishmaniasis, a globally significant disease, could potentially be prevented with vaccines (Malvolti *et al*., 2021). Sand fly vectors, such as Phlebotomus and Lutzomyia species, are of particular concern for their role in inducing immune responses through immunogenic proteins. Notable examples include LJM19 and LJL143 from L. longipalpis and PdSP15 from P. duboscqui (W.-W. Zhang *et al*., 2020).

Currently, there are no licensed vaccines available to prevent human leishmaniasis. The primary methods for managing and preventing the disease are reliant on anticancer agents, which are not only extremely poisonous but also face growing issues with drug resistance. There is an urgent need for the advanement of a safe, efficient, and inexpensive immunization to prevent all forms of this vector-transmitted disease and to interrupt the transfer of the parasite between hosts and vectors (Dinc, 2022). An effective vaccine with 70% efficacy and lasting 10 years could potentially prevent between 41,000 and 141,000 cases of cutaneous leishmaniasis in Latin America, offering a more cost-effective solution compared to the treatment of these cases.

The path to developing an effective vaccine against cutaneous leishmaniasis is challenging because of the intricate relationship between Leishmania parasites and the host immune system (S. Srivastava, Shankar, Mishra, Singh, & vectors, 2016). However, natural recovery from cutaneous leishmaniasis often induces lifelong immunity to the infecting species, suggesting that vaccination is theoretically possible(Khamesipour *et al*., 2005). This supports the historical practice of "leishmania vaccination," in which individuals are immunized with live parasites to safeguard vresus disfiguring lesions caused by natural infection(Okwor, 2014). Although the idea of vaccinating against cutaneous leishmaniasis has largely been abandoned due to safety concerns and challenges with standardization, a live attenuated vaccine that could induce a protective Th1 immune response remains a promising concept (Nagill & Kaur, 2011). Alongside live attenuated vaccines, research has explored various experimental approaches including killed parasites, recombinant proteins, and DNA vaccines, but none have yet led to a licensed vaccine for human use (Jain & Jain, 2015). However, advancements in vaccine technology, particularly those accelerated by the COVID-19 pandemic, may offer new opportunities to address neglected tropical diseases like leishmaniasis.

Different technological platforms have been investigated as potential vaccines for Leishmania, such as live-attenuated or inactivated whole parasites (first generation), recombinant proteins (second generation), and DNA-based vaccines (third generation). Progress in genetic research has greatly supported this development process. In particular, various Leishmania species have been genetically modified to produce live attenuated vaccines, including strains lacking critical virulence or survival genes, such as the Centrin gene-deleted strains of L. braziliensis, L. donovani, L. major, and L. Mexicana (Greta Volpedo *et al*., 2022)

CONCLUSIONS

The management of cutaneous leishmaniasis (CL) presents considerable difficulties, particularly due to varied responses to existing therapies and limited critical analyses of treatment outcomes. This comprehensive research has led to significant findings. Noteworthy drug targets and compounds have been identified, including DHFR-TS-based drugs like molecule 571633 and novel molecular scaffolds such as CA272 and CH872. The potential for targeting Leishmania transporters with specially designed chemical probes has also been explored. Additionally, new compounds, including heteroretinoid-bisbenzylidine ketone hybrids and N-substituted β-amino alkanols, have demonstrated substantial leishmanicidal activity.

Various natural products have been assessed for their leishmanicidal effects, with plant extracts and essential oils showing promising results. Innovative treatment strategies, examples like pegylated meglumine antimoniate-loaded liposomes (LMA) and Crovirin, a cysteine-rich secretory protein (CRISP) derived from snake venom, are gaining attention. As effective alternatives. Furthermore, proteins and enzymes like FeSOD-A, folate transporter 1 (FT1), heat shock protein 83 (HSP83), and small kinetoplastid calpain-related protein (SKCRP14.1) play crucial roles in drug resistance and antioxidant defense mechanisms.

Genetic research has provided valuable insights into parasite-host interactions, disease patterns, and virulence, highlighting the molecular mechanisms behind tissue orientation and the function of particular parasite genes in drug resistance and disease manifestations. In summary, exploring alternative treatments, immunotherapeutic approaches, and

genetic insights into parasite-host interactions offers a promising path to overcoming the challenges of CL treatment and enhancing patient outcomes.

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