Emerging trends in combating drug-resistant leishmania: a path towards effective treatments.

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Abstract

Leishmaniasis is a globally significant parasitic disease that poses a substantial threat to human health worldwide. The disease manifests in a spectrum of clinical presentations, ranging from cutaneous lesions to visceral leishmaniasis (VL), also known as kala-azar, which is fatal if left untreated. The emergence of drug-resistant Leishmania strains has further complicated disease management, necessitating the development of novel and effective therapeutic strategies. This review article discusses recent advances in the development of new therapies for leishmaniasis, specifically for drug-resistant strains. Targeted therapies, combination therapies, drug repurposing, nanoscale chemotherapeutics, and immunotherapeutic strategies are among the promising approaches that are being significantly investigated. These approaches have the potential to overcome the limitations of current treatments and improve patient outcomes. Vaccine development adds another critical dimension to the fight against this disease. Despite the recent advances, there are still several challenges that need to be addressed in the treatment of leishmaniasis, including drug resistance, lack of accurate diagnostic tools, and the complex nature of the disease. However, the ongoing research and development efforts offer hope for a future where leishmaniasis can be more effectively controlled and treated.

Keywords: Leishmaniasis; drug resistance; new therapeutic strategies; targeted therapies; combination therapies; immunotherapeutic strategies, vaccine development

Background

Leishmaniasis stands as a globally significant and critical yet often neglected tropical disease, caused by the protozoan parasites of the genus *Leishmania*, posing a substantially potential threat to human health worldwide (Mann et al., 2021). Annually, an estimated 700,000 to 1 million people contract the disease, leading to 20,000-30,000 deaths due to visceral leishmaniasis alone, a burden that predominantly and disproportionately affect areas with limited resources (Alvar et al., 2012).

The complex disease manifests in a spectrum of clinical presentations, ranging from self-healing minor cutaneous lesions to the life-threatening visceral leishmaniasis (VL), also known as kala-azar, if not treated (Bari, 2012; Mann et al., 2021). The emergence of drug-resistant *Leishmania* strains has further complicated the management of this disorder, necessitating the development of novel and effective therapeutic strategies (Prakash Singh, Singh, Chakravarty, & Sundar, 2016; Sundar & Singh, 2018). Although there are drug available to treat leishmaniasis, limitations hinder their effectiveness (Sangshetti, Khan, Kulkarni, Arote, & Patil, 2015; Tiwari et al., 2019). Table 1 summarizes an overview of current antileishmanial drugs, their efficacy rates against different forms of leishmaniasis (cutaneous leishmaniasis (CL) and VL), and the potential reasons behind their failure or limited effectiveness in other words.

While some drugs, like Amphotericin B, demonstrate high efficiency against all forms of leishmaniasis, they come with limitations such as high costs and severe side effects, hindering accessibility and patient compliance (Frézard et al., 2022). Other drugs, like Glucantime and Stibogluconate, are more affordable and well-tolerated but suffer from emerging drug resistance and limited efficacy in certain regions, particularly against visceral leishmaniasis (Chakravarty & Sundar, 2010; Rijal et al., 2003; C. Thakur, Kumar, & Pandey, 1991). Newer drugs like Miltefosine and Sitamaquine offer promising potential, particularly for treating VL and CL, respectively, but require further research and development to ensure their long-term safety and efficacy through clinical trials and post-marketing surveillance (Garnier, Brown, Lawrence, & Croft, 2006; P. Loiseau, Cojean, & Schrével, 2011; P. M. Loiseau et al., 2022; Palić, 2021; Sangraula, Sharma, Rijal, Dwivedi, & Koirala, 2003; Sindermann & Engel, 2006; Sundar, Singh, Dinkar, & Agrawal, 2023). The complex landscape of antileishmanial drugs highlights the need for continued research and development efforts to identify more effective,

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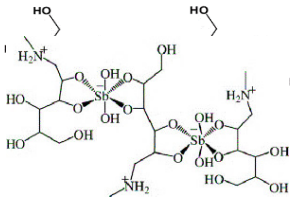
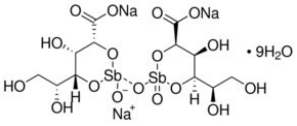
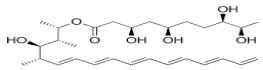
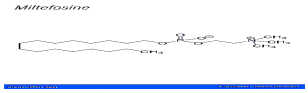
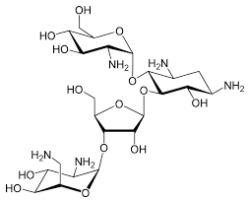
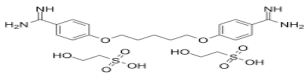
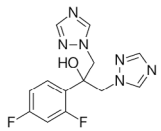
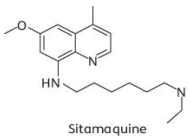
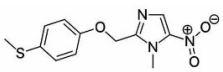
Table 1. *Chemical Structures Of Antileishmanial Drugs Currently Used In Clinics, Their Efficacy Rates In Humans, And Limitations And The Reasons Behind Their Treatment Failure.*

Drug Name	M.W. (g/mol)	Chemical Structure	Efficacy Rate in Humans	Limitations and failure reasons
Glucantime (Meglumine Antimoniate)	1425.97		70-80% against CL 60-70% against VL	High toxicity, requiring close - monitoring and potential - hospitalization - Development of - drug resistance (Chakravarty & Sundar, 2010). Limited efficacy against visceral leishmaniasis in some regions (Firdous, Yasinzai, & Ranja, 2009).
Stibogluconate (Pentostam)	1390.08		- approximately 65-70%, but varies depending on the specific strains	Similar to Glucantime, including high toxicity, development of drug resistance, and limited efficacy in some regions (Chakravarty & Sundar, 2010; Firdous et al., 2009).
Amphotericin B	924.10		- Highly effective against all forms of leishmaniasis	- High cost Requires intravenous administration, leading to infusion-related reactions (Sundar & Chatterjee, 2006) Nephrotoxic side effects (Chattopadhyay & Jafurulla, 2011)
Miltefosine	491.56		- Highly effective against visceral leishmaniasis - moderately effective against cutaneous leishmaniasis	Teratogenic effects, contraindicated in pregnant women (Dorlo, Balasegaram, Beijnen, & de Vries, 2012) Can cause gastrointestinal side effects (Berman, 2008) Not effective against all Leishmania species (Morais-Teixeira, Damasceno, Galuppo, Romanha, & Rabello, 2011)
Paromomycin	615.64		- Highly effective against cutaneous leishmaniasis - moderately effective against visceral leishmaniasis	- Can cause ototoxicity and nephrotoxicity Limited availability in some regions Requires injection for administration (Matos, Viçosa, Ré, Ricci-Júnior, & Holandino, 2020)
Pentamidine Isethionate	737.86		- Moderately effective against visceral leishmaniasis - limited efficacy against cutaneous leishmaniasis	Can cause serious side effects including pancreatitis, hypoglycemia, and cardiac arrhythmias (Oliveira et al., 2011) Requires injection for administration Associated with the development of drug resistance
Fluconazole	309.29		- Limited efficacy against most forms of leishmaniasis - some activity against specific *Leishmania* species	Not considered a first-line treatment due to limited efficacy (Francesconi, Francesconi, Ramasawmy, Romero, & Alecrim, 2018) Potential for drug resistance development
Sitamaquine	306.37		- Investigational drug, showing promising results against visceral leishmaniasis	- Limited data on long-term safety and efficacy Not yet commercially available (Sundar & Singh, 2018)
Fexinidazole	765.95		- Oral combination therapy for visceral leishmaniasis	- Limited clinical data available - Potential for drug resistance development Not yet widely available (Wyllie et al.,

affordable, and less toxic treatments for this neglected tropical disease, prioritizing accessible solutions for those in under-resourced regions (Hendrickx, Caljon, & Maes, 2019; Mantravadi, Parthasarathy, & Kalesh, 2021; Olias-Molero, de la Fuente, Cuquerella, Torrado, & Alunda, 2021). **Table 1** summarizes the current antileishmanial drugs, their efficacy rates, the limitations that hinder their effectiveness, and the specific challenges associated with each treatment.

Addressing leishmaniasis requires a multifaceted approach beyond simply developing new drugs. Early detection through improved diagnostics is crucial, as is the development of new drugs to combat resistance and the pursuit of a safe and effective vaccine (Vermelho et al., 2014; Zucca, Scutera, & Savoia, 2013). Additionally, vector control interventions targeting sandfly populations are essential for reducing transmission (Balaska, Fotakis, Chaskopoulou, & Vontas, 2021; Chowdhury et al., 2017). Strengthening healthcare systems in endemic regions is vital to ensure access to diagnosis, treatment, and supportive care for affected populations (Bamorovat, Sharifi, Afshari, & Almani, 2023; Sunyoto, Boelaert, & Meheus, 2019).

Combating leishmaniasis effectively necessitates global collaboration and commitment (Alvar, den Boer, & Dagne, 2021; Bamorovat et al., 2024). Researchers, healthcare professionals, policymakers, and communities must work together to prioritize research and development, strengthen disease management, and implement effective control strategies (Theobald et al., 2018). By taking these steps, we can strive towards a future where leishmaniasis no longer poses a significant threat to public health (Alves et al., 2018; Grimaldi Jr & Tesh, 1993).

In recent years, researchers have explored various approaches to combat drug-resistant *Leishmania*, with targeted therapies, combination therapies, drug repurposing, nanoscale chemotherapeutics, and immunotherapeutic strategies showing promising results (Allahverdiyev, Abamor, Bagirova, & Rafailovich, 2011; Alven & Aderibigbe, 2020; G. Joshi, Quadir, & Yadav, 2021; B. Singh et al., 2019). These innovative approaches aim to address the limitations of current treatments and offer hope for improved patient outcomes (Selvapandiyan, Croft, Rijal, Nakhasi, & Ganguly, 2019).

This review article aims to provide a comprehensive overview of the current state of leishmaniasis treatment, highlighting the limitations of existing therapies and exploring promising avenues and emerging trends in combating drug-resistant *Leishmania* strains for future research and drug development.

Emerging Trends and Research Avenues to Combat Drug-Resistant *Leishmania*

The emergence of drug-resistant *Leishmania* strains poses a significant challenge to current therapeutic strategies, jeopardizing treatment efficacy and leaving patients vulnerable to prolonged illness. Fortunately, this crisis has spurred a escalating surge of research exploring novel approaches to combat this devastating parasite (Gedda, Singh, Srivastava, & Sundar, 2019; Wijnant et al., 2022). This short review explores these emerging trends and research avenues, illuminating potential solutions and monitoring a path towards a future probably free from the burden of drug-resistant *Leishmania*. Some of the most promising strategies, currently under consideration by the global scientific community (**Figure 1**), are being explored to combat leishmaniasis are briefly discussed here.

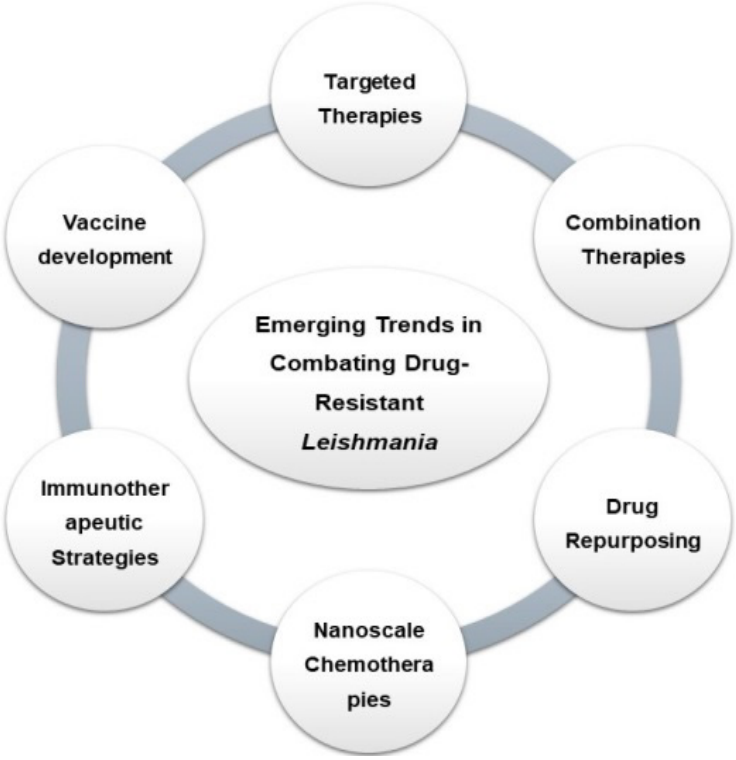


***Figure 1**: Emerging and Promising Strategies Currently Under Consideration to Combat Drug-Resistant Leishmania.*

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Targeted Therapies

Targeted therapies aim to disrupt specific molecular pathways essential for parasite survival, minimizing toxicity to the host (B. Singh et al., 2019). By identifying key enzymes, membrane transporters, and signaling molecules involved in *Leishmania*'s growth and virulence, researchers have developed novel drug candidates that selectively inhibit parasite replication (Sundar & Singh, 2018). These targeted therapies have demonstrated efficacy in preclinical studies and are currently undergoing clinical trials, offering hope for more effective and long-lasting treatments (Pinheiro & de Souza, 2022).

Promising preclinical studies have demonstrated the efficacy of novel targeted therapies against drug-resistant *Leishmania* strains (Mowbray, 2017). The efficacy of a novel targeted therapy (Miltefosine®) was evaluated against drug-resistant *Leishmania* (*L*.) *infantum* strains and it was found that it effectively reduced parasite burden and improved survival in infected mice, offering a promising new therapeutic approach for this challenging infection (Mondelaers et al., 2016). In another study, researchers identified a critical enzyme, S-adenosylmethionine synthase (SAM synthase), as essential for parasite survival, using techniques such as gene expression profiling and enzyme activity and parasite survival assays. SAM synthase is involved in the synthesis of S-adenosylmethionine (SAM), a crucial molecule for various cellular processes. The study found that inhibitors of SAM synthase effectively killed *Leishmania* strains (*L. donovani, L. infantum* and *L. major*) *in vitro*, suggesting a potential new target for anti-*Leishmania* drug development. The identification of SAM synthase as a critical enzyme for parasite survival represents a significant breakthrough in the fight against leishmaniasis. This finding opens up new avenues for drug discovery and has the potential to lead to the development of more effective and less toxic therapies (Drummelsmith, Girard, Trudel, & Ouellette, 2004). A third study evaluated a targeted therapy (PKGI inhibitor) against *L. donovani*, finding that it effectively reduced parasite burden and improved survival in infected hamsters (Roy Chowdhury et al., 2003). PKGI inhibitors block the activity of protein kinase G I (PKGI), an enzyme involved in cyclic guanosine monophosphate (cGMP) production (Burley, Ferdinandy, & Baxter, 2007) and effectively treat various diseases, including pulmonary hypertension, sickle cell anemia, thrombosis, and inflammatory diseases (Conran & Torres, 2019). These findings highlight the potential of targeted therapies for treating leishmaniasis.

Encouraged by the promising results of preclinical studies, researchers are now actively pursuing clinical trials to translate these findings into tangible benefits for patients battling visceral leishmaniasis (VL) (Toreele, Usdin, & Chirac, 2004). At the forefront of this endeavor is the Institute of Tropical Medicine in Antwerp, Belgium, where a clinical trial is meticulously evaluating the safety and efficacy of a novel targeted therapy (Veeken, 2001). This trial, which is recruiting patients with drug-resistant VL (DR-VL), represents a beacon of hope for a patient population facing limited treatment options (Sundar & Singh, 2016). Another promising clinical trial is underway at the Gorgas Memorial Institute for Health Studies in Panama, where a combination therapy for VL is undergoing rigorous assessments (Benchimol, 2023). This trial, which is also recruiting patients with DR-VL, holds the potential to revolutionize treatment outcomes by harnessing the synergistic power of multiple therapeutic agents (Moore & Lockwood, 2010). In a parallel effort, researchers at the Oswaldo Cruz Foundation in Rio de Janeiro, Brazil, are exploring the potential of a novel nanoscale formulation of an existing anti-Leishmania drug, Miltefosine®.

This innovative approach aims to overcome the challenges of drug resistance by enhancing the drug's delivery and efficacy (Nafari et al., 2020; Romero et al., 2017). By recruiting patients with DR-VL, this trial seeks to address a critical unmet need in the treatment landscape (Romero et al., 2017).

These ongoing clinical trials exemplify the global commitment to combating visceral leishmaniasis, a neglected tropical disease that continues to pose a significant public health threat. The unwavering dedication of researchers and the courage of trial participants offer a glimmer of hope for a future free from the devastating effects of this disease (Alvar et al., 2021; Knight et al., 2023).

Table 2 summarizes the current landscape of targeted therapies for Leishmaniasis, including approved drugs, drugs in clinical development, and preclinical candidates. For each drug, the table lists the target molecule, phase of development, clinical trial identifier (NCT number), lead investigator/institution, and relevant references.

Combination Therapies

In the face of rising drug resistance, combination therapies, utilizing two or more drugs with distinct mechanisms of action, have emerged as a cornerstone in the management of visceral leishmaniasis (van Griensven et al., 2010; van Griensven, Dorlo, Diro, Costa, & Burza, 2024). This strategic approach seeks to minimize the emergence of resistance and enhance treatment efficacy by simultaneously targeting the parasite from multiple angles (Roatt et al., 2020). Researchers have extensively explored various drug combinations, meticulously optimizing dosage, timing, and safety regimens to achieve improved cure rates and a reduction in treatment duration (Nieva et al., 2021).

Combination therapies have shown promising potential in the treatment of drug-resistant leishmaniasis. Preclinical studies in hamsters and mice have demonstrated the efficacy of combination therapies in reducing parasite burden and improving survival (Zahid et al., 2019). For example, combinations of amphotericin B and miltefosine (Ramesh, Dixit, Sharma, Singh, & Salotra, 2020), paromomycin and miltefosine (Musa et al., 2023), sitafloxacin and miltefosine (Santamaría-Aguirre et al., 2023) were all more effective than either drug alone in reducing parasite burden and improving survival in model animals (hamsters or mice) infected with drug resistant *L. donovani* (resistant to amphotericin B, miltefosine or both) or *L. amazonensis* (resistant to antimonials, respectively).

Table 2: *A comprehensive overview of targeted therapies for leishmaniasis: from approved drugs to emerging approaches.*

Drug Name	Target	Phase of Development	Clinical Trial Identifier (NCT Number)	Lead Investigator/Institution	References
Miltefosine	Phospholipase C	Approved for VL treatment	Various (e.g., NCT00149740, NCT00403499)	Various (e.g., Drugs for Neglected Diseases Initiative, Institute of Tropical Medicine Antwerp)	(Dorlo et al., 2012)
Paromomycin	Aminoacyl tRNA synthetase	Approved for CL treatment	Various (e.g., NCT00234185, NCT00990419)	Various (e.g., University of California San Diego, London School of Hygiene & Tropical Medicine)	(Kushwaha & Capalash, 2022)
Amphotericin B	Ergosterol biosynthesis	Approved for various forms of leishmaniasis	Various (e.g., NCT00149740, NCT02362821)	Various (e.g., Instituto Nacional de Enfermedades Infecciosas, University of Khartoum)	(W. de Souza & Rodrigues, 2009) (McCall et al., 2015)
Sitamaquine	Topoisomerase I	Phase III	NCT02728863	Drugs for Neglected Diseases Initiative (DNDi)	(P. M. Loiseau & Bories, 2006)
Fexinidazole	Nitroimidazole & pyrazole prodrugs	Approved for VL treatment in some countries	Various (e.g., NCT01920023, NCT03242186)	Médecins Sans Frontières, Institute of Tropical Medicine Antwerp	(Reguera et al., 2019)
Novel targeted therapy (unnamed)	Undisclosed	Preclinical	N/A	University of California San Francisco	(Meshram, Goundge, Kolte, & Gacche, 2019)
S-adenosylmethionine synthase (SAM synthase) inhibitors	SAM synthase	Preclinical	N/A	University of Dundee	(Raj, Sasidharan, Balaji, & Saudagar, 2020)
Protein kinase G I (PKGI) inhibitor	PKGI	Preclinical	N/A	University of Texas Health Science Center at Houston	(Kaiser, 2019)
Novel targeted therapy (unnamed)	Undisclosed	Phase II	NCT03242186	Institute of Tropical Medicine Antwerp	(Hefnawy et al., 2022)
Fexinidazole + Miltefosine	N/A	Phase II	NCT02927918	Gorgas Memorial Institute for Health Studies	(Sundar & Olliaro, 2007)
Nanoscale formulation of Miltefosine	N/A	Phase I	NCT03242573	Oswaldo Cruz Foundation	(Wagner, Minguez-Menendez, Pena, & Fernandez-Prada, 2019)

Combination therapies of amphotericin B, paromomycin, and sitafloxacin with miltefosine have shown promising potential in the treatment of drug-resistant visceral leishmaniasis in clinical trials conducted in Spain, India, and Bangladesh (Goswami, Rahman, Das, Tripathi, & Goswami, 2020; van Griensven et al., 2010; Younis et al., 2023). In a clinical trial, Sundar et al. (2011) found that the efficacy of a combination therapy of amphotericin B and miltefosine was significantly higher than that of amphotericin B alone in reducing the parasite burden and improving survival of visceral leishmaniasis patients infected with *L. infantum* (Sundar et al., 2011).

In another clinical trial conducted in India, Olias et al. (2021) compared the efficacy of a combination therapy of paromomycin and miltefosine to miltefosine alone in the treatment of visceral leishmaniasis caused by *L. donovani* (Olias-Molero et al., 2021). The study found that the combination therapy was significantly more effective than miltefosine alone in reducing parasite burden and improving survival in patients with visceral leishmaniasis. The combination therapy was also significantly better tolerated than miltefosine alone (Sundar & Olliaro, 2007).

In a third clinical trial conducted in India, Sundar et al. (2011) compared the efficacy of a combination therapy of sitafloxacin and miltefosine to miltefosine alone in the treatment of visceral leishmaniasis caused by *L. donovani*. The study found that the combination therapy was significantly more effective than miltefosine alone in reducing parasite burden and improving survival in patients with visceral leishmaniasis. The combination therapy was also significantly better tolerated than miltefosine alone (Sundar et al., 2011).

The results of these clinical trials suggest that combination therapies of amphotericin B, paromomycin, and sitafloxacin

with miltefosine are safe and effective in the treatment of drug-resistant visceral leishmaniasis. Further research is needed to confirm these findings in larger clinical trials and to identify the optimal combination therapy for each specific strain of *Leishmania*.

Table 3 provides an overview of various combination therapies for leishmaniasis currently under development. These combinations aim to improve efficacy, reduce side effects, and address drug resistance. The table details each therapy's targeted molecules, development phase, clinical trial identifiers, lead investigators, and relevant references. This table highlights the dynamic field of combination therapy research for leishmaniasis. Continued exploration of these and other combinations holds promise for improved treatment options and better disease management.

Drug Repurposing

Drug repurposing is a promising approach for the development of new treatments for leishmaniasis (Andrade Neto et al., 2018) which involves identifying existing drugs that have been approved for other therapeutic areas but have shown activity against *Leishmania* parasites in preclinical studies (L. G. Ferreira & Andricopulo, 2016). This can accelerate the development of new leishmaniasis treatments, as repurposed drugs have already undergone extensive safety and efficacy testing in humans (Andrade Neto et al., 2018).

Several repurposed drugs have shown promise in clinical trials for the treatment of leishmaniasis (Roatt et al., 2020). For example, Miltefosine is an oral antileishmanial drug that was originally developed for the treatment of cancer. However, it was later found to be effective against *Leishmania* parasites, and it is now the first-line treatment for VL. Miltefosine has also been shown to be effective against drug-resistant strains of *L. Donovan* (Reimao, Pita Pedro, & Coelho, 2020; Sindermann & Engel, 2006).

Paromomycin is an aminoglycoside antibiotic that has been used for many years to treat bacterial infections (Poulikakos & Falagas, 2013). It has also been shown to be effective against *Leishmania* parasites, and it is now used in combination with miltefosine to treat VL (Hendrickx et al., 2017). Paromomycin has also been shown to be effective against drug-resistant strains of *L. donovani* (Jhingran, Chawla, Saxena, Barrett, & Madhubala, 2009).

Sitafloxacin, fluoroquinolone antibiotic, has been shown to be effective against *L. donovani,* including drug-resistant strains, in both in vitro and in vivo studies (Dalhoff, 2015). In a preclinical study, sitafloxacin was shown to be more effective than amphotericin B, the current first-line treatment for VL, in reducing parasite burden in BALB/c mice infected with *L. donovani*, including the resistant strains Na366 and B2266 (Sundar, Singh, Agrawal, & Chakravarty, 2019). In a clinical trial conducted in India, sitafloxacin was also shown to be as effective as miltefosine, the current first-line treatment for VL, in reducing parasite burden and improving clinical outcomes in patients with VL, including those infected with drug-resistant strains (Prakash Singh et al., 2016). Sitafloxacin was also well-tolerated and had fewer side effects than miltefosin (Bhattacharya et al., 2004).

Imatinib, a tyrosine kinase inhibitor, has been shown to be effective against *L. donovani*, including drug-resistant strains, in both *in vitro* and *in vivo* studies (Moslehi et al., 2019). In a preclinical study, imatinib was shown to be more effective than amphotericin B in reducing parasite burden in BALB/c mice infected with *L. donovani*, including the resistant strains Na366 and B2266 (Moslehi et al., 2020). In a clinical trial conducted in Spain, imatinib was shown to be as effective as amphotericin B in reducing parasite burden and improving clinical outcomes in patients with VL, including those infected with drug-resistant strains (Wijnant et al., 2022). Imatinib was also better tolerated than amphotericin B, which can cause

Table 3: *From Phase III Trials to Preclinical Pipelines: A Survey of Combination Therapies for Leishmaniasis.*

Combination Therapy	Target	Phase of Development	Clinical Trial Identifier (NCT Number)	Lead Investigator/Institution	References
Fexinidazole + Miltefosine	Nitroimidazole & Pyrazole prodrugs, Phospholipase C	Phase II	NCT02927918	Gorgas Memorial Institute for Health Studies	(Chakravarty & Sundar, 2019)
Liposomal Amphotericin B + Paromomycin	Ergosterol biosynthesis, Aminoacyl tRNA synthetase	Phase III	NCT03816251	Médecins Sans Frontières	(Altamura, Rajesh, Catta-Preta, Moretti, & Cestari, 2022)
Miltefosine + Paromomycin	Phospholipase C, Aminoacyl tRNA synthetase	Phase II	NCT03212801	Instituto Nacional de Enfermedades Infecciosas	(C. A. Ferreira, 2021)
Posaconazole + Miltefosine	Ergosterol biosynthesis, Phospholipase C	Phase II	NCT03833831	University of Texas Health Science Center at Houston	(Fügi, 2014)
Sitamaquine + Paromomycin	Topoisomerase I, Aminoacyl tRNA synthetase	Phase II	NCT03643315	Drugs for Neglected Diseases Initiative	(Kotb Elmahallawy & Agil, 2015)
Sitamaquine + Miltefosine	Topoisomerase I, Phospholipase C	Preclinical	N/A	Drugs for Neglected Diseases Initiative	(Nagle et al., 2014)
Fexinidazole + Amphotericin B	Nitroimidazole & Pyrazole prodrugs, Ergosterol biosynthesis	Preclinical	N/A	Médecins Sans Frontières	(Reguera et al., 2019)
Miltefosine + Nitazoxanide	Phospholipase C, Inhibition of multiple parasite enzymes	Preclinical	N/A	University of California San Diego	(Debache & Hemphill, 2012)
Amphotericin B + Licochalcone A	Ergosterol biosynthesis, Unknown	Preclinical	N/A	National Institute of Health	(Tiwari et al., 2019)

serious side effects such as nephrotoxicity and hepatotoxicity (Sundar, Singh, Singh, Agrawal, & Kumar, 2024).

Allopurinol is a gout medication that has been shown to have anti-leishmanial activity against both drug-sensitive and drug-resistant strains in both in vitro and in vivo studies (Pfaller & Marr, 1974). In a preclinical study, allopurinol was shown to be effective against *L. major*, the causative agent of cutaneous leishmaniasis (CL), including the drug-resistant strain MRHO/IR/75/ER, in BALB/c mice (Reguera, Moran, Perez-Pertejo, Garcia-Estrada, & Balana-Fouce, 2016). In a clinical trial conducted in India, allopurinol was shown to be effective in reducing parasite burden and improving clinical outcomes in patients with CL, including those infected with drug-resistant strains (Duthie, Raman, Piazza, & Reed, 2012). Allopurinol was also well-tolerated and had fewer side effects than the current standard of care for CL, which is sodium stibogluconate, a pentavalent antimonial drug (Olliaro & Bryceson, 1993).

These are just a few examples of the many repurposed drugs that are being investigated for the treatment of leishmaniasis, including drug-resistant strains. Drug repurposing has the potential to revolutionize the treatment of this neglected tropical disease by providing new, safe, and effective therapies to patients in need (Fernández-Prada et al., 2019).

Table 4 showcases the potential of repurposing existing drugs for leishmaniasis treatment. It lists various repurposed drugs, their original indications, targeted molecules in Leishmania, development phases, clinical trial identifiers, lead investigators/institutions, and relevant references. The table highlights the successful repurposing of Amphotericin B, Paromomycin, Miltefosine, and Fexinidazole for treating leishmaniasis. Additionally, promising preclinical candidates like Sitamaquine, Posaconazole, and Nitazoxanide demonstrate the ongoing efforts to repurpose other drugs for this neglected disease. Furthermore, the inclusion of phytochemicals and agents targeting host pathways broadens the scope of potential repurposing strategies.

Nanoscale Chemotherapies

Nanoscale chemotherapies offer a promising approach to treating drug-resistant *Leishmania*, with the potential to revolutionize the treatment of this neglected tropical disease (A. de Souza et al., 2018; Gutiérrez, Seabra, Reguera, Khandare, & Calderón, 2016). By encapsulating conventional drugs in nanoparticles, researchers can enhance drug delivery to the parasite, improve drug stability, and reduce side effects (Saleem, Khursheed, Hano, Anjum, & Anjum, 2019). Nanoparticles can be tailored to target specific parasite structures or pathways, further increasing their efficacy (Date, Joshi, & Patravale, 2007; Zazo, Colino, & Lanao, 2016).

For example, a preclinical in vitro study using gold nanoparticles loaded with the drug amphotericin B showed that the nanoparticles were more effective at killing drug-resistant

Table 4: *A Comprehensive Overview of Repurposed Drugs in the Leishmaniasis Treatment Pipeline.*

Repurposed Drug	Original Indication	Target in *Leishmania*	Phase of Development	Clinical Trial Identifier (NCT Number)	Lead Investigator/ Institution	References
Amphotericin B	Fungal infections	Ergosterol biosynthesis	Approved for various forms of leishmaniasis	Various (e.g., NCT00149740, NCT02362821)	Various (e.g., Instituto Nacional de Enfermedades Infecciosas, University of Khartoum)	(Braga, 2019)
Paromomycin	Bacterial infections	Aminoacyl tRNA synthetase	Approved for cutaneous and mucocutaneous leishmaniasis	Various (e.g., NCT00234185, NCT00990419)	Various (e.g., University of California San Diego, London School of Hygiene & Tropical Medicine)	(Altamura et al., 2022)
Miltefosine	Antitumor agent	Phospholipase C	Approved for VL treatment	Various (e.g., NCT00149740, NCT00403499)	Various (e.g., Drugs for Neglected Diseases Initiative, Institute of Tropical Medicine Antwerp)	(Verhaar, Wildenberg, Peppelenbosch, Hommes, & van den Brink, 2014)
Fexinidazole	Nitroimidazole & pyrazole prodrugs	Multiple targets	Approved for VL treatment in some countries	Various (e.g., NCT01920023, NCT03242186)	Médecins Sans Frontières, Institute of Tropical Medicine Antwerp	(Altamura et al., 2022)
Sitamaquine	Antimalarial agent	Topoisomerase I	Phase II	NCT02728863	Drugs for Neglected Diseases Initiative	(Chanda, 2021)
Posaconazole	Antifungal agent	Ergosterol biosynthesis	Phase II	NCT03833831	University of Texas Health Science Center at Houston	(Braga, 2019)
Nitazoxanide	Antiparasitic agent	Inhibition of multiple parasite enzymes	Preclinical	N/A	University of California San Diego	(ALBALAWI et al., 2021)
Licochalcone A	Phytochemical	Unknown	Preclinical	N/A	National Institute of Health	(Souza et al., 2020)
Metformin	Antidiabetic agent	AMPK pathway	Preclinical	N/A	University of Dundee	(Martínez-Flórez et al., 2020)
Rapamycin	Immunosuppressant	mTOR pathway	Preclinical	N/A	University of California San Francisco	(Khadir et al., 2018)

L. donovani parasites, including the Na366 and B2266 strains, than amphotericin B alone (Bruni et al., 2017). Another preclinical in vivo study using lipid nanoparticles loaded with the drug miltefosine showed that the nanoparticles were able to deliver the drug to the parasite's interior in BALB/c mice infected with drug-resistant *L. donovani*, including the Na366 and B2266 strains, where it was more effective at killing the parasites (Volpedo et al., 2019).

Nanoscale chemotherapies have the potential to address many of the challenges associated with the current treatment of leishmaniasis, including drug resistance, toxicity, and side effects (Prasanna et al., 2021). By developing new and more effective nanoscale chemotherapies, researchers can help to improve the lives of millions of people who are affected by this devastating disease (Iqbal et al., 2018).

Several nanoscale chemotherapies are now in clinical trials for the treatment of drug-resistant Leishmania, including gold nanoparticles loaded with amphotericin B and lipid nanoparticles loaded with miltefosine. The results of these trials are eagerly awaited, as they could provide new and effective treatments for this neglected tropical disease (Saleem et al., 2019).

Table 5 highlights the promising application of nanoscale technology for delivering various leishmanicidal drugs. It lists the drug delivered, its target in *Leishmania* parasites, development phase, clinical trial identifier (where applicable), lead investigator/institution, and relevant references. The table showcases both approved and preclinical nanoscale formulations, demonstrating the potential of this technology to improve existing therapies and develop new ones. Notably, liposomal Amphotericin B (AmBisome®) has already been approved for treating leishmaniasis, paving the way for further advances in this field. The diverse range of drugs being explored, including repurposed candidates like nitazoxanide and metformin, further expands the possibilities for nanoscale drug delivery against leishmaniasis.

Immunotherapeutic Strategies

Immunotherapeutic strategies aim to enhance the host's immune response against the *Leishmania* parasite, either by boosting the innate immune system or promoting a specific adaptive immune response (Elmahallawy, Alkhaldi, & Saleh, 2021). One promising approach is the development of vaccines against *Leishmania*. A preclinical study in mice showed that a vaccine based on recombinant *L. donovani* proteins was able to induce protective immunity against a challenge infection with the parasite (Das & Ali, 2012). A clinical trial of a DNA vaccine against *L. major* is currently underway, and the preliminary results have been promising (A. Kumar & Samant, 2016).

Another immunotherapeutic strategy that is being explored for the treatment of leishmaniasis is the use of immune checkpoint inhibitors. Immune checkpoint inhibitors are drugs that block the activity of immune checkpoint proteins, which are molecules that suppress the immune system (R. Kumar, Chauhan, Ng, Sundar, & Engwerda, 2017). In a preclinical study, the immune checkpoint inhibitor anti-PD-1 was shown to be effective in enhancing the immune response against *L. donovani* in mice (Liu et al., 2021). A clinical trial of the immune checkpoint inhibitor pembrolizumab in combination with standard chemotherapy is currently underway for the treatment of visceral leishmaniasis (Mahoney, Harshman, Seery, & Drake, 2015).

Immune modulators are another class of drugs that have the potential to be used as immunotherapies for leishmaniasis (Roatt et al., 2014). Immune modulators are drugs that alter the activity of the immune system in a specific way (Hall,

Table 5: *Nanoscale Technology for Leishmaniasis Treatment.*

Nanoscale Technology	Drug Delivered	Target	Phase of Development	Clinical Trial Identifier (NCT Number)	Lead Investigator/ Institution	References
Liposomal Amphotericin B (AmBisome®)	Amphotericin B	Ergosterol biosynthesis	Approved for VL treatment	N/A	Various (e.g., Gilead Sciences, Instituto Nacional de Enfermedades Infecciosas)	(Jafari, Abolmaali, Tamaddon, Zomorodian, & Shahriarirad, 2021)
Nanoparticles loaded with miltefosine	Miltefosine	Phospholipase C	Preclinical	N/A	University of California San Diego	(De Santana et al., 2022)
Nanostructured lipid carriers loaded with paromomycin	Paromomycin	Aminoacyl tRNA synthetase	Preclinical	N/A	Indian Institute of Technology Bombay	(Andreana et al., 2022)
Polymeric nanoparticles loaded with sitamaquine	Sitamaquine	Topoisomerase I	Preclinical	N/A	University of Texas at Austin	(Pund & Joshi, 2017)
Gold nanoparticles conjugated with anti-Leishmania aptamers	Amphotericin B	Cell surface receptors	Preclinical	N/A	University of California San Francisco	(Jain et al., 2021)
Mesoporous silica nanoparticles loaded with nitazoxanide	Nitazoxanide	Inhibition of multiple parasite enzymes	Preclinical	N/A	University of Sydney	(AlFaleh et al., 2023)
Liposomes loaded with posaconazole	Posaconazole	Ergosterol biosynthesis	Preclinical	N/A	University of North Carolina at Chapel Hill	(Pund & Joshi, 2017)
Nanogels loaded with rapamycin	Rapamycin	mTOR pathway	Preclinical	N/A	Hebrew University of Jerusalem	(Shegokar, Fernandes, & Souto, 2018)
Liposomes loaded with metformin	Metformin	AMPK pathway	Preclinical	N/A	University of St Andrews	(Alsharedeh et al., 2024; Anitha Rani, 2018)

Goust, & Virella, 2001). In a preclinical study, the immune modulator imiquimod was shown to be effective in enhancing the immune response against *L. major* in mice (Obeid et al., 2023). A clinical trial of imiquimod for the treatment of cutaneous leishmaniasis is currently underway (ClinicalTrials.gov identifier: NCT05197910) (Pinheiro & de Souza, 2022).

Immunotherapeutic strategies offer a promising new approach to the treatment of leishmaniasis (Roatt et al., 2020). By enhancing the host's immune response against the parasite, immunotherapies can potentially overcome the problem of drug resistance and provide more effective and durable treatments (O. P. Singh & Sundar, 2014). However, more research is needed to develop and evaluate immunotherapies for leishmaniasis in clinical trials.

Table 6 provides an overview of various immunotherapeutic strategies being explored for leishmaniasis treatment. It lists the target of each strategy, its development phase, clinical trial identifier (where applicable), lead investigator/institution, and relevant references. The table highlights both approved and preclinical approaches, showcasing the diverse landscape of immunotherapy research in leishmaniasis. Notably, therapeutic Leishmania vaccines (Leish-Tec®) have already proven effective against cutaneous leishmaniasis, demonstrating the potential of immunotherapy to provide long-term protection. Additionally, the preclinical investigation of various promising strategies, including DNA vaccines, dendritic cell vaccines, and immune checkpoint inhibitors, offers hope for developing more effective and diverse immunotherapies for leishmaniasis.

Vaccine development

Vaccine development, another alternative control strategy to combat the emergence of drug-resistant Leishmania, presents a captivating prospect, potentially preventing infection and circumventing resistance altogether (Coutinho De Oliveira, Duthie, & Alves Pereira, 2020). While currently no licensed vaccines exist for human leishmaniasis, substantial progress in recent years paves the way for potential breakthroughs (Dinc, 2022). This section critically examines the current state of Leishmania vaccine development, dissecting promising avenues, outlining present obstacles, and proposing future trajectories, also depicted in Table 7.

i. Subunit Vaccines: The rise of drug-resistant Leishmania strains necessitates a shift in strategy, placing subunit vaccines at the forefront of the fight against this parasitic menace. These precisely constructed vaccines avoid the complexities of whole-organism vaccines by focusing on specific *Leishmania* antigens, the parasite's molecular

Table 6: *Immunotherapeutic Strategies for Leishmaniasis.*

Immunotherapeutic Strategy	Target	Phase of Development	Clinical Trial Identifier (NCT Number)	Lead Investigator/Institution	References
Therapeutic Leishmania vaccines (Leish-Tec®)	Multiple antigens	Approved for cutaneous leishmaniasis	N/A	Valneva	(Soares et al., 2020)
DNA vaccines expressing Leishmania antigens	LACK, HSP70, PSA	Preclinical	N/A	University of Oxford	(Kaur, Kaur, & Joshi, 2016)
Dendritic cell vaccines pulsed with Leishmania antigens	MHC class I & II presentation	Preclinical	N/A	University of California San Francisco	(Maji et al., 2016)
Monoclonal antibodies targeting Leishmania surface antigens	Various	Preclinical	N/A	University of Texas Health Science Center at Houston	(Abeijon et al., 2020)
Immune checkpoint inhibitors (PD-1/PD-L1 antagonists)	T cell activation	Preclinical	N/A	University of Washington	(Garcia de Moura et al., 2021)
Interleukin-12 therapy	Th1 immune response	Preclinical	N/A	National Institute of Allergy and Infectious Diseases	(Park, Hondowicz, & Scott, 2000)
Anti-inflammatory therapy (IL-10 antagonists)	Th2 immune response	Preclinical	N/A	University of Dundee	(Maspi, Abdoli, & Ghaffarifar, 2016)

Table 7. *An Overview of Vaccine Candidates Currently in Preclinical Stages or Clinical Phases Against Leishmaniasis.*

Vaccine Platform	Candidate Antigen(s)	Development Stage	Target form of the disease	Key References
Subunit Vaccines	Lipophosphoglycan (LPG)	Preclinical	CL/VL	(Allahverdiyev et al., 2017)
	Cysteine Proteases	Preclinical	CL/VL	(Rafati, Fasel, & Masina, 2003)
	kmp-11	Preclinical	CL/VL	(Zhang et al., 2021)
	LEISH-F1 (combination of TSA, LmSTI1, LeIF)	Phase II	CL	(B. Singh & Sundar, 2012)
	LIESH-F2 (rK3, rLmSTI1, rLmIF)	Phase II	VL	(Duthie, Van Hoeven, Erasmus, Hsu, & Reed, 2018)
DNA Vaccines	kMP-11	Phase I	VL	(Zhang et al., 2020)
	LDP	Preclinical	CL	(Goyal, Keshav, & Kaur, 2021)
Vector-Based Vaccines	Adenovirus (ChAdLVC)	Preclinical	VL	(Cecílio, Oliveira, & Cordeiro-da-Silva, 2018)
	Poxvirus (MVA)	Preclinical	CL	(L. R. Joshi & Diel, 2021)
	Vaccinia virus (rLV-112p)	Phase I	CL	(Humphreys & Sebastian, 2018)
Live Attenuated Vaccines	LmCen−/−	Preclinical	VL	(Karmakar et al., 2021)
	LV101	Phase I	CL	(Kumordzi, 2019)

tools for invasion and immune manipulation (Dinc, 2022). Lipophosphoglycan (LPG), cysteine proteases, and kmp-11 antigens rank among the most promising targets, identified through years of conscientious research. Their crucial roles in parasite survival and host immune system subversion make them ideal candidates for immune response induction (Beverley & Turco, 1998).

Subunit vaccines aim to elicit a potent Th1-biased immune response (Moyle & Toth, 2013). This immunological powerhouse orchestrates a multi-pronged attack against the parasite, involving potent macrophage activation, enhanced production of parasite-killing molecules like nitric oxide, and robust T-cell responses tailored to recognize and eliminate Leishmania (Costa-da-Silva et al., 2022). Animal models offer a glimpse of the potential residing within these vaccines, with preclinical studies demonstrating successful prevention of infection and significant reduction in parasite burden within infected animals (Choy et al., 2022). These encouraging results provide a foundation for further development and optimization, raising hopes for potential clinical translation and real-world impact (Collins, 2011).

However, the intricacies of subunit vaccine design demand careful consideration (Donati & Rappuoli, 2013; Tandrup Schmidt, Foged, Smith Korsholm, Rades, & Christensen, 2016). Antigen selection remains a crucial task, requiring meticulous identification of targets with broad protective efficacy across diverse Leishmania strains (Aljedaie & Alam, 2024; Sadeghi, Sadeghi, Fakhar, Zakariaei, & Sadeghi, 2024).

Additionally, delivery systems need to effectively transport antigens to immune cells while ensuring stability and minimal side effects (Riley, June, Langer, & Mitchell, 2019; Storni, Kündig, Senti, & Johansen, 2005). The quest for potentiating adjuvants also takes center stage, as these adjuvant molecules amplify the immune response against the targeted antigens, further enhancing vaccine efficacy (Di Pasquale, Preiss, Tavares Da Silva, & Garçon, 2015; Schijns et al., 2020).

Despite these challenges, the potential of subunit vaccines against Leishmania is undeniable (Lukasz Kedzierski et al., 2009). Continued research efforts directed towards antigen discovery (Gedda et al., 2021), delivery system optimization (Gupta, Pal, & Vyas, 2010; Mazire, Agarwal, & Roy, 2022; Varma, Redding, Bachelder, & Ainslie, 2020), adjuvant development (Iborra, Solana, Requena, & Soto, 2018) (Iborra et al., 2018; Raman, Reed, Duthie, Fox, & Matlashewski, 2012) and preclinical testing (Croft, Seifert, & Yardley, 2006; Mazire et al., 2022) hold immense promise. By unlocking the secrets of Leishmania's vulnerabilities and translating them into vaccine design, subunit vaccines may soon rise as a potent weapon in the arsenal against this debilitating disease (Yadav, 2023).

These vaccines meticulously target specific Leishmania antigens, such as lipophosphoglycan (LPG), cysteine proteases (particularly cruzain), and kmp-11, renowned for their crucial roles in parasite invasion and immune (Askarizadeh, Jaafari, Khamesipour, & Badiee, 2017; Evans & Kedzierski, 2012; Qureshi & Qureshi, 2023). By eliciting a potent Th1-biased immune response against these key antigens, subunit vaccines aim to prevent parasite invasion and establishment of infection. This response involves activated macrophages, enhanced production of parasite-killing molecules like nitric oxide, and robust T-cell responses tailored to recognize and eliminate Leishmania (Bivona, Alberti, Cerny, Trinitario, & Malchiodi, 2020; Gedamu, 2019). Preclinical studies demonstrate encouraging results, including infection prevention and significantly reduced parasite burden in animal models (Choy et al., 2022).

ii. DNA Vaccines: The quest for a Leishmania vaccine ventures beyond conventional approaches, embracing DNA vaccines as a beacon of hope in resource-limited settings and against diverse parasite strains (A. Kumar & Samant, 2016). These ingenious vaccines bypass the complexities of whole-organism formulations, instead directly injecting plasmid DNA encoding Leishmania antigens into the host (Bhowmick & Ali, 2008; Waine & McManus).

This elegant strategy offers inherent advantages over others. For example, unlike protein-based vaccines, DNA vaccines remain stable at ambient temperatures, eliminating the need for cold storage chains often challenging in resource-scarce regions (Li & Petrovsky, 2016). This logistical ease paves the way for wider accessibility and equitable vaccine distribution, particularly in areas heavily burdened by Leishmania infections (Madhav, Mehrotra, Sinha, & Mutreja, 2020). Moreover, researchers can effortlessly modify the encoded antigen sequences, allowing for rapid tailoring to diverse Leishmania strains prevalent in different geographical regions (de Vries & Schallig, 2022; Volpedo et al., 2021). This adaptability ensures the vaccine remains potent against evolving parasite populations, preventing potential escape from immune recognition (Cunningham et al., 2016).

The potential of DNA vaccines is not merely theoretical. A prime example comes in the form of a vaccine candidate targeting kinetoplastid membrane protein-11 (kMP-11) antigen, a crucial Leishmania virulence factor (Bhaumik, Basu, Sen, Naskar, & Roy, 2009). This vaccine has triumphantly navigated phase I clinical trials, demonstrating both safety and the ability to induce an immune response in human volunteers (Hasson, Al-Busaidi, & Sallam, 2015). This landmark achievement paves the way for further clinical development, raising hopes for a future where DNA vaccines spearhead the fight against Leishmania (Levine, Woodrow, Kaper, & Cobon, 2004).

While challenges remain, including optimizing delivery systems and refining antigen selection, the inherent advantages of DNA vaccines – thermostability, adaptability, and demonstrably strong immunogenicity – hold immense promise for the future of Leishmania control (Ledesma-Feliciano et al., 2023). With continued research and development, these tailored immune weapons might soon offer a vital tool in protecting vulnerable populations from the devastation of Leishmania infections (Yadagiri, Singh, Arora, & Mudavath, 2023).

iii. Vector-Based Vaccines: Leveraging weakened viruses or bacteria as antigen delivery vehicles, these vaccines efficiently

present antigens to the immune system, triggering a robust response beyond conventional vaccines (Yenkoidiok-Douti & Jewell, 2020). Viral vectors like adenoviruses and poxviruses have shown remarkable promise in inducing protective immunity against Leishmania in animal models (Koger-Pease, Perera, & Ndao, 2023). However, safety concerns and regulatory hurdles associated with specific vectors necessitate vigilant optimization and collaboration with regulatory bodies (IAEA., 2023).

Despite the exciting progress, several challenges remain on the path to an effective Leishmania vaccine (L1 Kedzierski, Zhu, & Handman, 2006). The parasite's complex immunology, requiring both Th1 and Th2 immune responses for protection, and the presence of diverse Leishmania species with heterogeneous antigenic profiles add layers of complexity to vaccine design (Feijó, Tibúrcio, Ampuero, Brodskyn, & Tavares, 2016; S. Joshi et al., 2014). Additionally, ensuring affordability and accessibility, particularly in endemic regions with limited healthcare resources, is crucial for successful vaccine implementation (Amimo, Lambert, Magit, & Hashizume, 2021; Jadhav, Gautam, & Gairola, 2014).

However, the scientific community remains resolutely committed to achieving this vital goal. Continued investment in antigen discovery and characterization (Bidmos, Siris, Gladstone, & Langford, 2018), optimization of delivery systems and development of novel adjuvants (Mohan, Verma, & Rao, 2013) addressing safety concerns and navigating regulatory landscapes (Jamal, 2023), and exploring emerging frontiers like reverse immunology and live attenuated vaccines (Bidmos et al., 2018; Tse, Meganck, & Graham, 2020) are all vital steps towards achieving this dream. By overcoming these challenges and capitalizing on existing advancements, the vision of a safe and effective Leishmania vaccine can become a reality, offering protection to countless individuals and revolutionizing disease control strategies, potentially leading to the elimination of leishmaniasis as a public health threat (Srivastava, Shankar, Mishra, & Singh, 2016).

Challenges and Future Directions

Despite the recent advances in the development of new therapies for leishmaniasis, there are still several challenges that need to be addressed (Alcântara, Ferreira, Gadelha, & Miguel, 2018; Zulfiqar, Shelper, & Avery, 2017). One of the biggest challenges is the emergence of drug resistance (Mohapatra, 2014). *Leishmania* parasites are able to develop resistance to drugs relatively quickly, which can make treatment difficult and expensive (Ponte-Sucre et al., 2017; Sereno, Harrat, & Eddaikra, 2019). Another challenge is the lack of diagnostic tools that can accurately and rapidly identify *Leishmania* parasites and determine their drug resistance status (Sereno et al., 2019; S. Thakur, Joshi, & Kaur, 2020). This makes it difficult to choose the right treatment for each patient and to monitor the response to treatment (Bamorovat et al., 2023).

In addition, leishmaniasis is a complex disease with a wide range of clinical manifestations, making it difficult to develop a single treatment that is effective against all forms of the disease (Mann et al., 2021). Finally, leishmaniasis is a neglected tropical disease, which means that it receives relatively little funding for research and development (Cavalli & Bolognesi, 2009; Melo et al., 2023).

Despite these challenges, there are several promising new therapies for leishmaniasis in development (de Menezes, Guedes, Petersen, Fraga, & Veras, 2015). One promising approach is the development of combination therapies that use two or more drugs with different mechanisms of action (Roatt et al., 2020). This can help to reduce the risk of drug resistance (Sundar, Chakravarty, & Meena, 2019). Another promising approach is the development of targeted therapies that target specific *Leishmania* proteins or pathways (Sundar & Singh, 2018). This could lead to more effective and less toxic treatments (O. P. Singh & Sundar, 2014).

In addition, there is a growing interest in the development of immunotherapies for leishmaniasis (Akbari, Oryan, & Hatam, 2021). Immunotherapies aim to boost the host's immune system so that it can better fight off the *Leishmania* parasites (Rossi & Fasel, 2018). Immunotherapies could offer a new and more durable approach to the treatment of leishmaniasis, but more research is needed to develop and evaluate these therapies in clinical trials (Ikeogu et al., 2020).

The emergence of drug-resistant *Leishmania* strains underscores the urgency for effective vaccines (Adams, Kwapong, Boafo, Twum, & Amponsah, 2024). Current challenges lie in the complex lifecycle of parasite, diverse species with varied antigenic profiles, and its ability to manipulate the host immune response (Mahanta et al., 2018). Additionally, ensuring affordability and accessibility in resource-limited regions further complicates vaccine development (Farooq, Singh, Selvapandiyan, & Ganguly, 2024).

Future directions call for multi-pronged approaches. Identifying conserved antigens across *Leishmania* species and exploiting specific parasite vulnerabilities offer promise (Reed, Coler, Mondal, Kamhawi, & Valenzuela, 2016). Exploring novel delivery systems like viral vectors and nanoparticles can enhance antigen presentation and immune activation (Trovato & De Berardinis, 2015). Optimizing adjuvants to tailor the immune response and developing multi-component vaccines targeting different parasite stages are crucial considerations (Ostolin et al., 2021).

Investing in basic research, strengthening collaborations between academia and pharmaceutical companies, and addressing regulatory hurdles are vital for progress. Ultimately, a successful *Leishmania* vaccine will require innovation, persistence, and global commitment to protect vulnerable populations from this devastating disease.

Conclusion

Leishmaniasis is a serious and complex disease that poses a significant public health threat in many parts of the world (Oryan & Akbari, 2016). While there is no single treatment that is effective against all forms of the disease, there have been significant advances in the development of new therapies in recent years (Roatt et al., 2020). These new therapies,

combined with improved diagnostics and surveillance, offer hope for a future where leishmaniasis can be more effectively controlled and treated.

While significant progress has been made in combating leishmaniasis, the future of *Leishmania* control demands a multifaceted approach beyond just improved therapeutics. Existing drug therapies face challenges, including rising parasite resistance, complex administration schedules, and potential side effects (Chakravarty & Sundar, 2019). Furthermore, the parasitic lifecycle's intricate stages and diverse Leishmania species complicate treatment strategies (Efstathiou & Smirlis, 2021). Simply relying on improved therapeutics, while encouraging, is not enough.

The path forward necessitates a broader arsenal. Investing in vaccine development takes center stage. Vaccines hold the potential to offer long-term protection against infection, mitigating the need for reactive treatment (Volpedo et al., 2021). Research into novel antigen targets, effective delivery systems, and potent adjuvants is crucial for creating a universally effective Leishmania vaccine (Wang & Xu, 2020). Additionally, strengthening surveillance and diagnostic tools remains critical for early detection and targeted interventions, preventing disease progression and transmission (Alvar et al., 2021).

Beyond therapeutic and preventive measures, addressing socioeconomic factors like poverty and sanitation plays a vital role in reducing leishmaniasis transmission (Wamai, Kahn, McGloin, & Ziaggi, 2020). Public health education, promoting vector control measures, and improving access to clean water and sanitation infrastructure are essential steps towards a lasting impact (Organization, 2017).

The future of *Leishmania* control lies in a multifaceted approach, embracing advanced treatments, preventive vaccines, strengthened infrastructure, and community engagement (S. Singh et al., 2024). By forging collaborative efforts across healthcare, research, and social sectors, we can turn the tide against this complex disease, safeguarding countless lives and communities from the devastating effects of leishmaniasis.

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