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REVIEW

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Current and emerging therapies for the treatment of leishmaniasis

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ABSTRACT

Introduction: Leishmaniasis, a neglected protozoan illness caused by kinetoplastid pathogens encompasses three major clinical subtypes: visceral, cutaneous and mucocutaneous leishmaniasis. Pentavalent antimonials (Sb^V) have long been the preferred treatment worldwide but increased drug resistance, and significant side effects, including cardiotoxicity have limited their use, particularly in visceral leishmaniasis in India. Similarly, other approved alternatives have concerns such as teratogenicity, high cost, and drug resistance.

Areas covered: This review aims to provide an overview of emerging therapy for leishmaniasis, highlighting the latest advancements in the field and discuss their potential impact on the treatment and prevention of this neglected tropical disease. It also discusses the limitation of current treatments and need for novel approaches to address them effectively.

Expert opinion: For almost eight decades, treatment for all forms of leishmaniasis was solely dependent on Sb^V, despite several drawbacks like long treatment regimens, cardiotoxicity, and drug resistance. In the past 20 years, three drugs with antileishmanial activity were developed for human disease, but their distribution to endemic regions and accessibility for patients remain neglected. We sorely need new antileishmanial drugs, and we present here the emerging targets for developing new antileishmanial compounds that could be brought into the clinics.

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Leishmaniasis treatment; drug resistance; drug discovery; drug targets; metabolic pathways; immunomodulation; nanotechnology; *leishmania* vaccines

1. Introduction

WHO has classified twenty different infectious diseases as neglected tropical diseases (NTDs), common with significant morbidity and mortality, however, these have been neglected in terms of attention, funding, and lack of interest of industry and academia [1]. NTDs affect more than one billion people worldwide [2]. After malaria, *leishmania* is the world's second most parasitic killer. Every year, between 700,000 and 1 million new cases are reported worldwide. Therapy remains challenging, and many still rely on drugs with treatment limitations, such as serious toxicities and drug resistance. More than 20 parasite species cause leishmaniasis in different regions of the world, and response to treatment has to be tailored according to regional variations in therapeutic responses [2].

Leishmania infections cause a variety of disorders depending on the species that causes the infection. Human leishmaniasis has been documented in three main forms: visceral, cutaneous, and mucocutaneous [1]. Visceral leishmaniasis (VL), also known as kala-azar, is the most severe form of the illness. It causes fever, splenomegaly, and other malfunctioning of the reticuloendothelial system. If left untreated, most patients die [2].

Cutaneous leishmaniasis (CL) is characterized by the development of slow-healing skin sores in or near the areas of infected sand fly bite. Initially presenting as small red papules, these lesions progress into painless nodules, eventually rupturing to form distinct ulcers. Clinical manifestations and lesion progression in the host ensue following an asymptomatic incubation period, typically lasting 2–8 weeks, though occasionally extending up to 3 years [3]. Throughout this incubation period, the parasites remain localized at the site of infection, resulting in each lesion corresponding to an individual sandfly bite. Predominantly, these infection sites manifest on exposed regions of the body, such as the arms, legs, and face [4].

Mucocutaneous leishmaniasis (MCL) involvement may occur at the same time as skin involvement or appear after the skin lesions have healed, sometimes even many years later. The infection can spread through the bloodstream or lymphatic system. In regions where the disease is prevalent, up to 20% of patients may develop mucosal symptoms. *L braziliensis* is the most common cause of mucocutaneous leishmaniasis (MCL), although other species such as *L amazonensis*, *L guyanensis*, and *L panamensis* can also be responsible [5]. The nasal and oral mucosa are the areas most frequently affected. Lesions in the oral cavity can spread to the back of the mouth and larynx, potentially impacting cartilage and vocal cords. MCL lesions are open sores and can lead to disfigurement. Timely treatment is essential to manage the infection, as the condition can be life-threatening [6,7].

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Article highlights

- Generic pentavalent antimonials were once the first-line treatment for endemic visceral and other forms of leishmaniasis, but drug resistance in the Indian subcontinent, and serious adverse events like cardiotoxicity led to its decline for the treatment of leishmaniasis.
- Miltefosine, paromomycin, and amphotericin B are also approved alternatives, but each one of them has several disadvantages.
- Drug resistance, low success rates, toxicity, and high prices call for new antileishmanial therapeutic options drugs/modalities must be explored due to drug resistance, low success rates, toxicity, and high prices.
- Developing innovative treatments for vulnerable populations is vital. The current study describes major components of existing antileishmanial treatment and current and upcoming therapeutic developments.

Post-kala-azar dermal leishmaniasis (PKDL) often occurs following apparent recovery from VL. While PKDL is mainly linked to *L. donovani* infection in India and Sudan, instances caused by other *Leishmania* species such as *L. infantum* or *L. tropica* have been documented in Mediterranean countries and Latin America [8,9]. PKDL is distinguished by a skin rash on exposed body parts, such as the face, ears, and hands, and can also spread to other areas of the body as it progresses [10]. In some patients, PKDL develops without any prior episode of VL, and inadequate treatment also raises the risk of PKDL occurrence. Although PKDL has relatively low mortality compared to VL, it has significant socioeconomic implications, and PKDL patients act as a reservoir for parasites, thus contributing to parasite transmission and potential new cases of VL [11,12].

Currently, available antileishmanial medications are few, with several limitations. It is critical to devise novel treatment options for the affected population. The current review discusses critical aspects of existing antileishmanial therapy and targets for future therapeutic developments.

2. Existing antileishmanial therapy

2.1. Visceral leishmaniasis (VL)

As stated above, pentavalent antimonial (Sb^V) has been the drug of choice for several decades. Though these compounds are effective in most regions, the necessity of daily parenteral administration, declining efficacy and low safety profile are the major drawbacks. With prevailing widespread resistance to Sb^V in India, amphotericin B (AmB) deoxycholate was used instead of Sb^V. Its efficacy is ~ 100%, but a high incidence of infusion reactions, and relatively less common nephrotoxicity, hypokalaemia, cardiotoxicity, frequent laboratory monitoring and the necessity of 5–6 weeks of hospitalization are its major limitations [13,14]. As oral miltefosine (MF) became available, the Indian control program switched to it for its ease of use in the field. However, difficult procurement, potential teratogenicity, the need for contraception for nearly six months, and significant noncompliance owing to 28 days long treatment, led the Indian control program to switch to a single dose (10 mg/Kg) liposomal amphotericin B (L-AmB) and this is the current treatment of choice in the Indian Subcontinent (ISC) (Table 1) [15]. Its drawbacks are the necessity of refrigeration for storage, intravenous administration and its prohibitively high cost. The makers of L-AmB (AmBisome; Gilead Sciences, Foster City, U.S.A.) have been donating the drug through WHO since 2012, and extended their previous agreement to 2025 [16].

In East African region [17], in a recent study, 14-day treatment with oral miltefosine along with PM was non-inferior to the Sb^V + PM therapy and has been proposed as an alternate first line therapy [18]. For the Mediterranean Basin, Middle East, Central Asia and South America, L-AmB at a total dose of 18–21 mg/kg is recommended [13].

2.2. Cutaneous leishmaniasis

There are different modalities of treatment of CL depending on the etiological species, severity of the lesions, and propensity to progress to mucosal leishmaniasis.

Cutaneous leishmaniasis in Peru, Brazil and Guatemala caused by *L. (V.) braziliensis* has shown 69.6%, 50.8% and 96.0% cure rates, respectively, when treated with Sb^V at a dose of 20 mg/kg/day for 20 days; indicating differential sensitivity of parasite against Sb^V therapy [19–21]. However, when treated with 20 mg/kg of daily dosage for 10 consecutive days showed an improved cure rate in CL caused by *L. panamensis* and *L. braziliensis*. However, *L. (V.) panamensis* causing CL had a 100% cure rate after receiving 20 mg/kg/day

Table 1. Drugs used for treatment of various forms of leishmaniasis and their duration of treatment.

	Drug combination	Disease	Dosing duration	References
1	Amphotericin B (AmB) deoxycholate	VL	5–6 weeks	[13,14]
2	Oral miltefosine	VL	28 days	[13]
3	liposomal amphotericin B (L-AmB)	VL	Single dose (10 mg/Kg)	[15]
4	**Multidrug Therapies (Phase II trials)**			
	Sb^V (Intravascular or Intramuscular) and Intramuscular paromomycin (PM)	VL	17 days	[17]
5	LAmB (5 mg/ml) +Miltefosine	VL	7 days	[15]
6	LAmB (5 mg/ml) + Miltefosine	VL	10 days	
7	LAmB (5 mg/ml) + Miltefosine	VL	14 days	
8	**(Phase III trials) of Multidrug treatment**			
	LAmB (5 mg/ml) + 50 mg Oral Miltefosine **(Phase III trials)**	VL	7 days	[54]
9	LAmB (5 mg/ml) + 11 mg/kg Intramuscular paromomycin (Phase III trials)	VL	10 days	
10	Oral miltefosine (10 days) + 11 mg/kg Intramuscular paromomycin (Phase III trials)	VL	10 days	
11	Sodium stibogluconate (SSG) 20 mg/kg	CL	20–28 days	[19–21]
12	Miltefosine at 1.5–2.5 mg/kg/day	CL	28 days	[27,28]
13	LAmB at 3 mg/kg	CL	5 days	[29]
14	12-week Miltefosine + 70–80 dose of AmB	PKDL	4 months	[44]
15	SSG at 20 mg/kg/day per day	PKDL	2 months	

for 20 days, compared to a lower cure rate of 64% with a dose of 10 mg/kg/day [22]. The most effective treatment regimen for a wide range of CL cases is a 20-day administration of Sb^V at a daily dosage of 20 mg/kg for 20–28 days [19,23]. The emergence of resistance to antimonials brought miltefosine for the treatment of CL.

Miltefosine is recommended for treating cutaneous leishmaniasis caused by *L. guyanensis* and *L. panamensis*, despite conflicting research outcomes for other CL species [24]. *In vitro* assessments showed high efficacy miltefosine for *L. donovani* caused CL, but was ineffective against *L. major* caused CL. In Iran, a 92.9% cure rate was observed compared to 83% with meglumine antimoniate [25]. Another study reported that a 91% cure rate was achieved against CL caused by *L. panamensis* in Colombia. Miltefosine is an effective and safe drug for treating CL caused by these species. Similarly, two Brazilian trials show excellent therapeutic outcomes for CL caused by *L. braziliensis* or *L. guyanensis* when treated with miltefosine, with a recommended regimen of 1.5–2.5 mg/kg/day for 28 days compared to patients treated intravenously with Sb^V [26–28].

Liposomal formulation of amphotericin B at dose of 3 mg/kg for 5 days with an additional dose on the tenth day successfully demonstrated treatment of CL by *L. major* and *L. tropica* with intravenous or intralesional injections [29]. A similar study reported a better cure rate than Sb^V and is recommended as the first-line drug for CL caused by *L. braziliensis* [30]. However, AmB regimens with lower doses have shown inadequacy against *L. braziliensis*, and evidence suggests treatment failure or poor responsiveness of AmB in patients infected with *L. infantum* [31]. The current recommendation is to administer AmB in doses higher than 1.5 mg/kg/day for more than 5 days to achieve satisfactory results. Likewise, a Weekly dose of 7 mg/kg of pentamidine for treating *L. guyanensis* showed improved effectiveness with an increasing number of treatment sessions, achieving a cure rate of 96% [32]. However, the use of intramuscular pentamidine isethionate was less successful compared to intravenous administration in treating CL caused by *L. guyanensis*. The treatment for CL caused by *L. braziliensis* with pentamidine demonstrated promising recovery rates with a 3-day course of 120 mg/mm^2 of the lesion, providing an alternative to Sb treatment [33,34]. Ketoconazole has shown similar effectiveness to parenteral antimonials and is recommended as an initial treatment for CL. However, its topical application is less successful. Currently, formulations with varying concentrations of ketoconazole have shown limited efficacy in treating CL caused by *L. braziliensis* or *L. (V.) panamensis* [35,36]. Itraconazole also has exhibited promising antileishmanial activity in two studies and was successful *in vivo* when used to treat BALB/c mice that were subcutaneously inoculated with *L. major* [37,38]. Nevertheless, its efficacy in treating CL caused by *L. major* is uncertain due to inconsistent findings. Newer azoles, including voriconazole, 3-imidazolyl flavanones, and luliconazole, have also demonstrated significant inhibition of promastigotes and amastigotes of *L. major* in the treatment of CL [39–41].

Old World CL (OWCL) is caused by *L. major* and *L. tropica*. Most CL lesions heal over time. Local therapy with intralesional Sb^V or topical application of ointment containing PM and methyl benzethonium chloride is applied. Cryo and thermo therapy have also been used as local treatment of CL. Whereas systemic Sb^V is used if there are multiple, large lesions and those over face or overlying/close to a joint [13].

New World CL (NWCL) is caused by *L. mexicana, L. guyanensis, L. panamensis, L. amazonensis, L. peruviana*, and *L. venezuelensis*. Local or systemic therapy is administered as for OWCL. However, systemic treatment is also indicated if the causative species of the parasite (*L. braziliensis*) has the potential for the development of mucocutaneous leishmaniasis (ML). In both Old and New World CL, pentoxifylline, PM, allopurinol, azoles and triazoles have been used either alone or in combination with Sb^V, with a varying degree of success [13]. MF is increasingly being used for the treatment of CL in the both the new and old world. However, its efficacy data needs to be confirmed in well-designed controlled clinical trials [13,42].

2.3. Mucocutaneous leishmaniasis

Several studies have reported that the primary treatment for MCL in Brazil was predominantly pentavalent antimonials. Other approaches, including pentamidine, miltefosine, imidazole, paromomycin sulfate, AmB, and various lipid formulations of amphotericin B (such as liposomal, lipid complex, colloidal dispersion), along with combinations involving pentoxifylline, allopurinol, or sulfa have also been used. It was confirmed that antimony remains the most commonly used treatment for MCL, albeit with only moderate effectiveness, which may be potentially improved when combined with pentoxifylline. There is existing evidence supporting the use of miltefosine for MCL, demonstrating a cure rate comparable to that of antimony [43].

Systemic Sb^V is the most commonly used treatment modality for MCL. However, in cases where Sb^V is not effective or unavailable, other medications such as AmB or its lipid formulations may be used as alternative treatments [42].

2.4. Post kala azar dermal leishmaniasis (PKDL)

In India, the recommended treatment regimens include a 12-week course of miltefosine or 60–80 doses of Amphotericin B deoxycholate over 4 months. In East Africa, post-kala-azar dermal leishmaniasis (PKDL) is generally not treated as the majority of cases (85%) resolve on their own within a year. However, patients with severe or disfiguring disease, lesions persisting for more than 6 months, concomitant anterior uveitis, or young children with oral lesions that interfere with feeding may be treated with either SSG (20 mg/kg/day per day) for up to 2 months or a 20-day course of L-AmB at 2.5 mg/kg/day (Table 1) [44].

Subsequent portion includes a brief overview of recent developments and innovative treatment options for leishmaniasis.

3. Emerging therapies for leishmaniasis

3.1. Emerging therapies for cutaneous and mucocutaneous leishmaniasis

As discussed above, every available antileishmanial drug has significant drawbacks. Thus, there is an urgent need for new

antileishmanial drugs that are oral, safe, and affordable, with shorter duration of treatment [42].

3.2. CO2 laser administration and thermotherapy

In Iran, CL is treated using CO2 laser and thermotherapy, which aim to directly eliminate the *Leishmania* parasites and involve applying external heat to affected tissues, causing targeted damage to the parasites. As stated by Asilian et al. [45], CO_2 laser treatment is cost-effective and can be utilized as the primary therapy for CL. Valencia et al. [46] introduced the Handheld Exothermic Crystallization Thermotherapy for CL (HECT-CL) device, a low-cost heat pack that offers safe, reliable, and renewable conduction of heat. The HECT-CL treatment achieved an overall definitive clinical cure rate of 60%, making it a promising option. The use of direct heat can accelerate the healing of skin lesions [13].

The CO_2 laser treatment was more successful (definitive cure 93.7%) than combined cryotherapy and intralesional Sb^V in treating CL with a faster healing time (6 weeks vs. 12 weeks) after a single treatment session [3]. In specific investigations OWCL, thermotherapy performed better in terms of cure rate than intralesional treatment with Sb^V with comparable or fewer adverse events [13,47].

3.3. Cryotherapy

Cryotherapy was initially tested on 30 patients infected with *L. major* in Saudi Arabia using a CO2 cryo-machine. After 4–5 weeks, there was a 100% cure rate with no visible scarring and no recurrence [48]. Cryotherapy involves the use of liquid nitrogen at a temperature of −195°C. When used once or twice weekly on *leishmania* lesions, cryotherapy demonstrated an efficacy of over 95% [49]. The destruction of parasites occurs through the formation of ice crystals within them resulting in membrane lysis and localized ischemic necrosis. Some of the side effects observed included swelling, redness, as well as hyper or hypopigmentation at the treatment site [50]. Therefore, liquid nitrogen can be considered as one of the treatment options for CL.

3.4. Topical nitric oxide derivates

The ability of nitric oxide (NO), produced by activated murine macrophages, to inhibit the growth and cause cell death of various infections, including *Leishmania major*, has been observed in experimental animals [51]. The use of a S-nitroso-N-acetylpenicillamine (SNAP) cream, which generates NO, resulted in the complete healing of all lesions and the regeneration of new skin in CL patients [52]. Conversely, a clinical trial that involved the application of a topical nanofiber nitric oxide (NO) releasing patch for 12 hours a day over 20 days showed limited effectiveness, with only 37.1% of Colombian patients with CL caused by *Leishmania (V.) panamensis* experienced cure [53]. Despite this, the low occurrence of adverse events and the convenience of topical administration support the need for further research and development of new generations of nitric oxide release systems for the treatment of CL.

3.5. Drug administration

PAHO recommends the use of intralesional antimonial therapy in cases where systemic treatment is not suitable. In Turkey, intralesional antimony therapy (Sb^V) for cutaneous leishmaniasis caused by old-world parasites showed a high efficacy of 97.2% and a low relapse rate of 3.9%, with no major adverse events. A study in Pakistan also reported a high cure rate with intralesional Sb^V, but combining it with itraconazole did not show additional benefits. In Brazil, a single-arm phase II clinical trial treated cutaneous leishmaniasis with weekly meglumine antimoniate (MA) intralesional infiltration, resulting in a definitive cure in 87% of patients at day 180, with mostly minor or moderate adverse events. In Colombia, intralesional MA treatment successfully treated the majority of patients with new-world cutaneous leishmaniasis, with local pain and swelling being the most common side effects. In comparison to systemic antileishmanial therapy, intralesional meglumine antimoniate injection has fewer side effects and is equally effective and safe.

4. Emerging therapies for visceral leishmaniasis

4.1. Emerging multi-drug or combination therapy

Treatment of visceral leishmaniasis (VL) is complex because the most effective medication, dosage, and duration of treatment can vary depending on the location where the disease is endemic. Even after completing the prescribed treatment, some patients experience a recurrence of the disease within 6-12 months. It is anticipated that in the future, multidrug therapy will be utilized more frequently for leishmaniasis. This approach offers potential benefits for VL, including enhanced patient compliance due to shorter treatment duration, reduced costs, decreased need for hospitalization, lower risk of toxicity, and a decreased likelihood of developing resistance to either drug [42]. A study conducted in India found that a single dose of LAmB at 5 mg/kg/day alone or in combination with miltefosine resulted in improved cure rates compared to later treatment (91% vs > 96%). In a larger follow-up study involving 626 patients, three different multidrug regimens were evaluated in a randomized Phase III clinical trial. All three arms, which involved a single dose of LAmB (5 mg/kg) followed by miltefosine for seven days, paromomycin for ten days, or a combination of miltefosine and paromomycin simultaneously for 10 days, resulted in a cure rate of over 97% in all three groups [54]. A study in Sudan observed that a 17-day course of Sb^V combined with PM improved survival and initial cure rates significantly more than a 30-day course of Sb^V monotherapy for VL [55]. Another study from Sudan found that a 14-day regimen of miltefosine combined with PM, which involved one less injection each day, reduced the treatment duration, and eliminated the risk of serious adverse events associated with Sb^V, was as effective as a 17-day regimen of PM combined with Sb^V. In a study of HIV/VL coinfected patients from India, combination therapy with intravenous LAmB and oral miltefosine was found to be well tolerated, safe, and effective, and is now recommended by the WHO as a treatment for these patients [56]. The proposed treatment regimen for Southeast Asia involves combination therapy of intravenous LAmB (up to 30 mg/kg at 5 mg/kg on days

1, 3, 5, 7, 9, and 11) and oral miltefosine (100 mg/day for 14 days) for treating VL in HIV-positive patients. For East Africa, miltefosine is administered for 28 days with LAmB [57].

4.2. Combination approach of immunotherapy with chemotherapy

Immunotherapy could be a possible way to treat leishmaniasis. The ultimate destination of *leishmania* parasites in the mammalian host is macrophages. To thrive within the host, l*eishmania* eludes host immune responses. *Leishmania*'s ability to maintain a chronic infectious condition within its host heavily relies on its immune evasion ability. The immune evasion strategies used by *Leishmania* species includes the following.

(I) Preventing the development of C5-9 membrane attack complexes, which inhibits complement system maturation.
(II) Using Lipophosphoglycan to promote macrophage entrance receptors such as Fc and phosphatidylserine receptors.
(III) Altering the TLR2/TLR4 signaling pathway to turn off the cytokine cascade.
(IV) Preventing phagosome-lysosome fusion within macrophages.
(V) Interrupting the V-ATPase pump to control pH inside the phagosome.
(VI) Using specialized iron transporters to provide iron to the parasite.
(VII) Reducing B7 and CD40 expression as critical aspects for T-cell antiparasitic response.
(VIII) Inhibiting cytokine activation signals in macrophages via the JAK/STAT pathway.
(IX) Changing cytokine and chemokine expression levels.

Since, the parasite manipulates multiple immunological processes [30,31], treating the infection using immunomodulation could be an alternative strategy.

IFN- γ is a well-known cytokine that can activate macrophages to eliminate *Leishmania* parasites. The use of IFN- γ as immunotherapy in patients with VL has been found to lead to quicker control of the parasites [58]. However, a larger study in India involving 156 VL patients treated with Sb^V with or without interferon-γ suggested that the additional benefits of IFN- γ in VL are limited. The long-term response rates for Sb^V alone (36%) and Sb^V plus IFN- γ (49%) were unexpectedly low (Figure 1), and there was no significant difference in responses between the two groups [59].

In Venezuela, approximately 11,532 patients with CL were treated with heat-killed *Leishmania* parasites and Bacille Calmette-Guerin (BCG), resulting in a cure rate of 95.7%. Mild adverse reactions were limited to the BCG vaccine alone (Figure 1). Similarly, in Brazil, 542 CL patients were treated with Sb^V, killed *Leishmania* vaccine plus BCG, BCG alone, or a combination [60]. The cure rates were similar for both the therapeutic vaccine and Sb^V chemotherapy, but with fewer side effects and a shorter recovery time [61]. Another study demonstrated that patients treated with Sb^V and a killed *L. amazonensis* vaccine in NWCL fully recovered, indicating that combination therapy was highly effective [62].

Another study from Venezuela found that combining heat-killed *L. amazonensis* promastigotes with live *Mycobacterium*

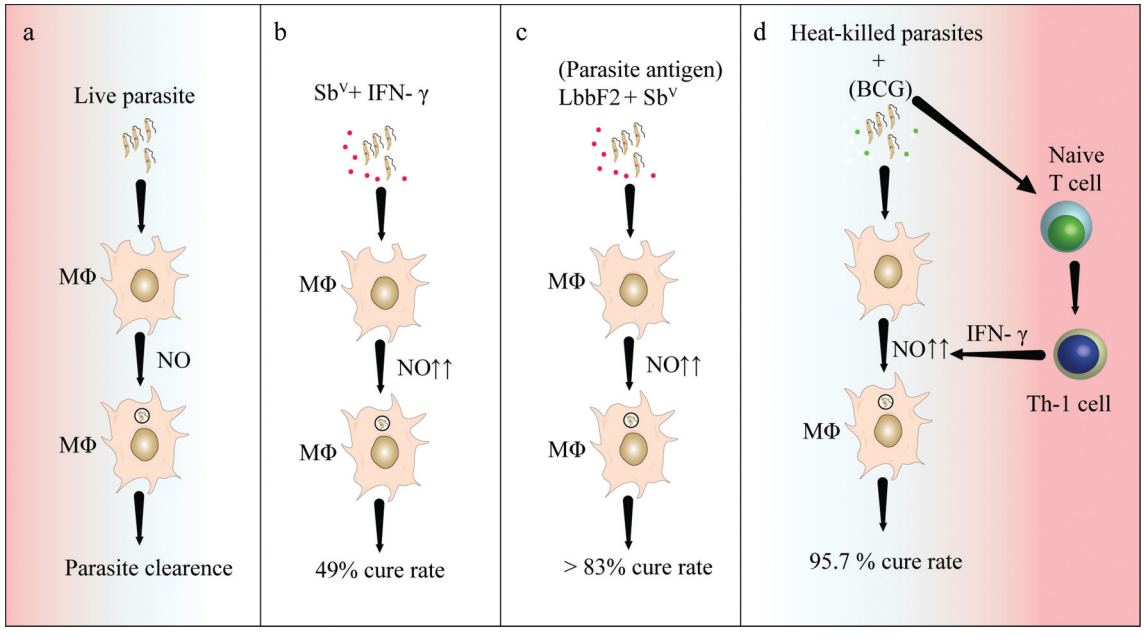

Figure 1. Immunotherapy for the treating *leishmania*sis.

Leishmania, intracellular parasites, are phagocytosed by macrophages. Under the influence of cytokines such as IFN-γ secreted by other immune cells, macrophages activate NOS generation to eliminate the intracellular form of the parasite (a). Treatment of infected macrophages with a cocktail of IFN-γ and pentavalent antimoniate resulted in a 49% cure rate (b). Similarly, treatment with a mixture of parasitic antigens Lbbf2 and Sb^V showed a cure rate of over 83% (c). Additionally, heat-killed *Leishmania*, when administered with BCG, demonstrated a 95.7% cure rate. This outcome is likely attributed to the polarization of naïve T cells into Th-1 cells, which secrete pro-inflammatory molecules like IFN-γ. Subsequently, this activation of macrophages facilitates intracellular parasite clearance (d).

bovis BCG altered the T cell response toward Th1, enhanced IFN- γ production, and the authors concluded that this therapy is safe, cost-effective, and effective for ACL patients [63]. Patients infected with *L. braziliensis* were given a therapeutic vaccine containing parasite-derived antigen Fraction 2 (LbbF2) with Sb^V, and cure rates with immunotherapy and chemotherapy were comparable (>83%) (38). These studies highlight the significance of immunotherapy in improving clinical outcomes.

4.3. Emerging nanotechnology

Recently evolved nanotechnology-based drug delivery systems have been used for leishmaniasis. These efficiently deliver various types of medications to targeted tissues and cells. Because of their unique properties, such as increased bioavailability (Figure 2), targeted drug delivery, reduced toxicity, etc. Various nanotechnology-based techniques and products, such as liposomes, lipid nano-capsules, metal and metallic oxide nanoparticles, polymeric nanoparticles, nanotubes, and nano vaccines, have emerged as potential anti-leishmanial tool [64].

4.3.1. Liposome nanoparticles

Liposome nanoparticles are nano-sized spherical vesicles composed of bilayer phospholipids that provide aqueous support for the adhesion of both hydrophilic and lipophilic medicines [65]. Liposomes can sustain and modulate drug release, and reduce drug dosage and frequency of administration. Liposomes are widely used in the investigation of many predicted therapeutic medications and are an emerging therapeutic technique [66].

LAmB, a formulation of AmB liposome that reduced the adverse effects of amphotericin B, is the best example of a liposome [67]. The effectiveness of liposomal medication when administered to murine model via subcutaneous injection was found to be 90% [68]. Liposomes coupled with mannose and 4-sulfated acetyl galactosamine have been shown to be inhibitors of leishmanial activity [69].

4.3.2. Lipid nano-capsules

Lipid nano-capsules (LNs) are nanocarriers that mimic lipoproteins and range in size from 20 to 100 nm. It is a hybrid structure created by combining liposomes and polymeric nano capsules [70]. LNs are created using a solvent-free process, which gives greater stability and bioavailability. Because of this key advantage of LNs, a significant reduction in doses as well as adverse events were observed [71].

4.3.3. Metallic nanoparticles

There is a diverse variety of metallic nanoparticles employed for antileishmanial activity with low toxicity and high efficacy [72]. AmB was encapsulated in iron oxide (Fe3O4) nanoparticles coated with glycine (peptide) in search of the treatment of VL. A 10–15 nm nanoparticle size was utilized, which allowed for the regulated release of AmB, lowering parasite concentration in treated spleen [73]. Glycine-coated nanoparticles could be used for antileishmanial treatment in the future.

Similarly, zinc oxide nanoparticles (ZnONPs) are widely manufactured and used. ZnONPs were tested *in vitro* against the amastigotes of *L. donovani*, at four different concentrations (0.18, 0.37, 0.75, and 1.5 g/mL). The colorimetric assay

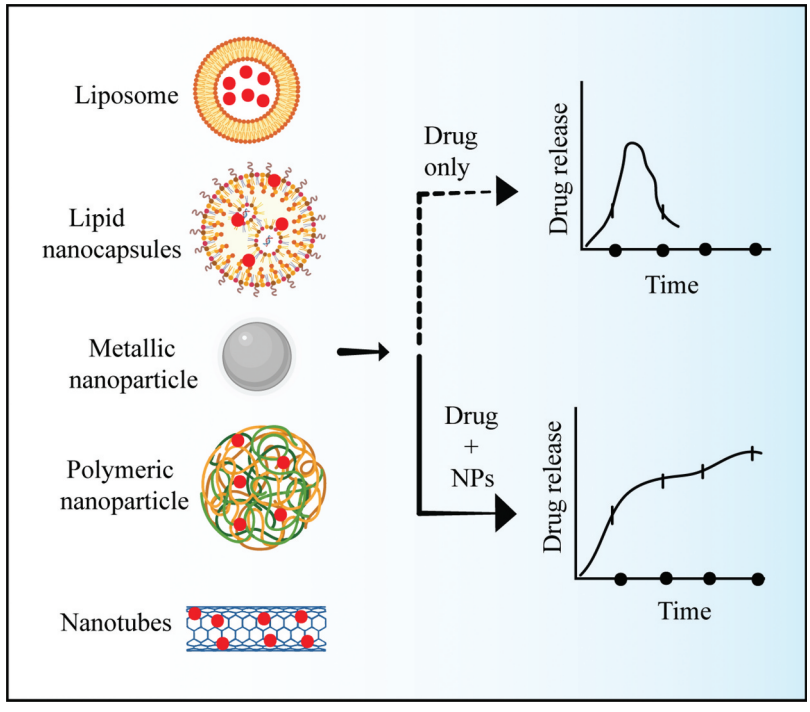

Figure 2. Nanoparticles as a drug delivery system.

Nanoparticles serve a crucial function in extending drug delivery periods by providing controlled release, targeted delivery, protection of drugs from degradation, enhanced solubility, and improved permeability. Their distinctive characteristics enable them to release drugs in a sustained manner, target specific tissues or cells, shield drugs from degradation, enhance solubility, and traverse biological barriers. The illustration demonstrates the controlled release of drugs over time in the absence or presence of nanocarriers.

findings showed that ZnONPs had a cytotoxic effect on the amastigote cells, causing a reduction in their proliferation and inhibiting the parasite's activity. According to the findings, ZnONPs could be a cost-effective approach to developing anti-leishmanial drugs [74]. ZnONPs formulation synthesized using plant leaf extracts of *Verbena officinalis* and *Verbena tenuisecta*, were examined for antileishmanial property. The study found that ZnONPs derived from *Verbena officinalis* exhibited superior antileishmanial activity compared to those from *Verbena tenuisecta*, attributed to their higher phenolic content and smaller particle size [75].

Since ancient times, silver has been widely used in medicine. According to research, silver Nanoparticles (AgNPs) release reactive oxygen species (ROS) that demonstrated a direct toxic effect against promastigotes and amastigotes stage of the parasite [76]. Another study on silver nanoparticles (AgNPs) reported the effectiveness against leishmaniasis by reducing the metabolic activity and proliferation by 1.5 times [71]. Antileishmanial effects of Ag-NPs on *L. tropica* parasites improved the antimicrobial activity of Ag-NPs under UV light [76].

4.3.4. Polymeric nanoparticles (PNP)

These nanoparticles are constructed of biocompatible and biodegradable colloidal particles. Their sizes range between 1 and 1000 nm [77]. PNPs lead to improved bioavailability, enhanced cellular dynamics, biodegradability, and controlled drug delivery [78,79]. PNPs distribute drugs to the target sites via three possible mechanisms. Firstly, through an enzymatic reaction that results in polymer degradation at the targeted location, leading to drug release. Secondly, through swelling of the PNP, followed by hydration and drug release via diffusion. Thirdly, through drug dissociation from the polymer itself [64,80]. Nanoprecipitation was employed to produce Poly DL-lactide-co-glycolide (PLGA) nanospheres, which were subsequently modified on the surface with mannose, mannan, or mannosamine groups using a carbodiimide process. Murine primary macrophages engulf these nanocarriers through clathrin-mediated endocytosis. When macrophages were co-cultured with nanospheres functionalized with carbohydrates, they were stimulated and generated pro-inflammatory cytokines. Mice with VL responded positively to a single dose of amphotericin B carried by nanospheres functionalized with mannan [81].

4.3.5. Nanotubes

Nanotubes are cylindrical hollow molecules made of inorganic and metallic materials. Several studies have been undertaken to demonstrate that nanotubes are good nanocarriers. The antileishmanial activity of AmB in conjunction with carbon nanotubes was investigated. The authors discovered that this formulation outperformed free AmB in terms of targeted killing of *L. donovani* [64,82]. To reduce medication-induced toxicity, in another study combined linked AmB, an antileishmanial agent, with functionalized carbon nanotubes (f-CNTs). This formulation inhibited parasite growth more effectively than AmB, however, significant renal and hepatic toxicity was reported in the kidney and liver of mice [83]. In an *in-vitro* study, the f-Comp-AmB showed significantly enhanced effectiveness against intracellular amastigotes of *L. donovani*, with a 12.2-fold decrease in IC50 values compared to standard AmB. Conversely, f-Grap-AmB and f-CNT-AmB, other modified carbon nanomaterials, exhibited only 7.98- and 6.71-fold improvements, respectively, in their *in vitro* antileishmanial activity compared to conventional AmB [84].

5. Possible drug targets against leishmaniasis

The need to handle diseases quickly encouraged policymakers to establish criteria for evaluating new alternatives. This review section will focus on the studies done to identify novel prospects for use as therapeutic targets.

5.1. Phytoproducts as drug targets

In ancient Mediterranean culture, the usage of plants was correlated with healing. The isolation and extraction of components with a plant origin were made possible by later developments in chemical sciences. The pharmaceuticals made from plant extracts are known as phytomedicines [85].

Alkaloids, flavonoids, phenylpropanoids, steroids, and terpenoids are only a few of the chemicals that have been linked to the biological activity of plant extracts. Different research approaches, including an evaluation of the traditional use, the chemical composition, the toxicity of the plants, or the combination of many factors, may be used to obtain an herbal remedy or an isolated active ingredient [86].

Clearly, plants may provide new antiprotozoal drugs. Nowadays, phytotherapy continues to prosper as a result of the need for inexpensive anti-leishmanial medications with fewer side effects. The chemical variety of plant extracts also makes them pharmacologically appropriate for usage as drugs. Many new studies supporting the use of medicinal herbs for the treatment of leishmaniasis have been published. The most notable studies in this area continue to focus on *Kalanchoe pinnata*, which mostly contains triterpenes, sterols, and flavonoids. Numerous secondary metabolites and compounds with potent antileishmanial activity are described in the literature [87]. In experimental studies, oral administration of the plant derived leishmanicidal substance has been demonstrated to have leishmanicidal activity comparable to that of Sb^V without any adverse side effects. Research findings suggest that *Kalanchoe pinnata* could be a safe and efficient option for orally treating CL. Furthermore, the extract from *aloe vera* leaves have shown potential antileishmanial activity by triggering programmed cell death [85,88]. According to reports, plumbagin, and naphthoquinone inhibits *L. donovani* trypanothione reductase and causes mitochondria-mediated cell death. Naphthoquinone, a secondary metabolite from plants that may have an antileishmanial effect. There are yet more antileishmanial substances to be discovered. Numerous chemical substances produced from plants have demonstrated potential antileishmanial action. However, they are not within the purview of this article [85].

5.2. Antimicrobial peptides as drug targets

The Antimicrobial peptides (AMPs) exhibit various activities, including serving as chemotactic agents for leukocytes and interacting with the microbial membrane to cause autophagy,

necrosis, or apoptosis. These peptides have ability to destabilize the membrane, penetrate intracellular organelles and affect a variety of cellular functions, including bioenergetic function. A number of AMPs, including dermaseptin, phylloseptin, bombinins, temporins, spinigerin, and magainins, have antileishmanial activity [85].

Cathelicidin (Protegrin-1, SMAP-18, −27) and defensin are further classes of AMPs that are expressed in mammals and which affect host inflammatory responses by acting as chemokines or by promoting the production of chemokines by other cells, resulting in the migration of neutrophils, monocytes, and macrophages. Additionally, chemokines are also recognized for their antimicrobial peptide activity against pathogens known as kinocidins [85,89]. Additionally, several AMPs from various species have been reported to affect *Leishmania*. Different mechanisms have been used by these AMPs to cause parasite cell death. According to *in vitro* and *in vivo* research, these AMPs alter ATP concentration, break the membrane potential, and balance the internal and external pH without disturbing the cell membrane [85,90]. Upon caspase-blocking, they trigger the development of vacuoles without altering their activities, demonstrating their capacity to cause autophagy-mediated cell death in parasites. However, other classes of AMPs from the human salivary gland disturbs the potential of the mitochondrial membrane, reduce oxygen consumption, and deplete ATP. It is, therefore, well known that various kinds of AMPs damage parasite membranes, target mitochondria, and delocalize intracellular calcium, which is essential for triggering cell death by altering mitochondrial functions. Parasites' calcium reserves are also affected by intracellular AMPs [85,91]. According to preliminary results from animal studies, these research support further development of AMP-based therapeutic targets against leishmaniasis [92].

5.3. Metabolic pathways as drug targets

Determining the degree of homology between the host and parasite proteins and, consequently, choosing inhibitors that react with parasite proteins without harming the host system remain the main therapeutic goal [93]. Drugs that target energy metabolism were still the preferred option, and several proteins were used as therapeutic targets [94].

Five decades of research on various metabolic pathways in *Leishmania* are summarized as glycolysis, fatty acids and sterol metabolism, polyamine metabolism, folate metabolism, iron metabolism, antioxidant metabolism, and nucleotide metabolism.

The Kreb's cycle, glycolysis, and oxidative phosphorylation occur in the glycosome and mitochondria, respectively. Disruption of any glycolytic process can lead to parasite death by halting glycolysis, as observed in *T. brucei*, which perished instantly when deprived of glucose or exposed to a glucose transporter inhibitor. While fatty acid breakdown in mitochondria is crucial in the *Leishmania* life cycle, glycolysis remains essential. Although the structure of enolase hasn't been fully elucidated, certain unusual residues are identified as potential therapeutic targets. Pyruvate kinase in *L. mexicana* presents a promising drug target with clear selectivity. Glyceraldehyde-3-phosphate dehydrogenase, sharing 30% amino acid sequence with its human counterpart, is a significant candidate for drug designing and discovery. Since most glycolytic enzymes are concentrated inside glycosomes, potential drug targeting could involve inhibiting their transport by interfering with membrane transporters regulating glucose flow through glycosomes [85].

A number of medications target mitochondria, a crucial organ for parasite life. The mitochondrial proteins come from two sources: the nucleus and a little portion of mitochondrial DNA. Experimental data indicate mitochondrial targeting by traditional drugs. Amphotericin B causes membrane permeability and a sharp drop in the potential of the mitochondrial membrane. Pentamidine similarly degrades membrane potential, while cytochrome C oxidase is inhibited by miltefosine [85,95]. However, unlike mammalian cells, *Leishmania's* transmembrane redox system is less responsive to chloroquine and more sensitive to niclosamide, indicating that membrane electron transport and proton pumping may serve as an therapeutic target. Chalcones emerged to be a promising compound that targets the ultrastructure and functions of mitochondria as a consequence of numerous studies on antileishmanial agents [85,96]. Its capacity to inhibit fumarate reductase later made it a viable therapeutic target. Endochin-like quinolones (ELQs), a strong inhibitor of cytochrome bc 1 in *Plasmodium*, have been observed to be toxic to *L. donovani* and *L. mexicana* amastigotes. However, hydroxynaphthoquinone buparvaquone functions as a more powerful inhibitor of electron transport, ATP synthesis, and parasite multiplication, raising beliefs regarding targeting cytochrome bc1 as a possible treatment strategy [85,97]. Other mitochondrial inhibitors included complex II-targeting benzophenone-derived bisphosphonium salt and the antimalarial drug artemisinin, which demonstrated anti-leishmanial efficacy via inducing apoptosis [85]. The major site for fatty acid metabolism is still the mitochondria, where 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase from *L. donovani* has been identified as a possible therapeutic target [98]. Fatty acyl-CoA ligase also controls the cellular homeostasis of lipids and is differentially regulated in antimony resistant *L. donovani*, suggesting it may be an attractive therapeutic target [85].

The synthesis of sterols has been a crucial component of cellular processes and for the maintenance of cell structure. Ergosterol and 24-methyl sterol are the main sterols in trypanosomatids and are crucial for growth and viability. As a result, the metabolic pathway for sterol and fatty acids is a promising area for therapeutic development. Recent studies have proposed combination targeting, in which imipramine and miconazole are used to simultaneously target two processes in sterol biosynthesis [99]. A novel therapeutic target for the treatment of leishmaniasis, edelfosine has recently been shown to disrupt the mitochondrial membrane potential by engaging F0-F1 ATPase in the lipid raft and triggering DNA disruption [99].

Another vital metabolic process required for parasite life is the metabolism of folate. Pteridine reductase, dihydrofolate reductase-thymidylate synthase, folylpolyglutamate synthase,

and serine hydroxymethyl transferase are some of the prospective therapeutic targets from the folate system [85,100].

5.4. Proteasome and cell cycle as drug targets

The proteasome is a multi-subunit protein complex in the cytoplasm and nucleolus that controls cellular protein synthesis and misfolded protein breakdown. The regulatory subunit and the core particle are the two main parts. Proteins that are intended for degradation are coupled with ubiquitin (in eukaryotes) or ubiquitin-like protein (pup) (in prokaryotes) [101]. Numerous studies have been conducted on the protozoan ubiquitin-proteasome system [85]. When proteasome inhibitors were used to affect the parasite's cell proliferation, development, and differentiation in a concentration-dependent way in the 1990s, the proteasome was first studied as a potential therapeutic target [85]. Using 21 M or 51 M MG-132 under *in-vitro* experiments, it was found that the parasites were induced to undergo programmed cell death while the surviving parasites were shorter with rounded apical ends and damaged mitochondria. The viability of the parasite in the macrophages was dramatically reduced after treatment with the traditional proteasome inhibitor lactacystin [85].

Recently, GSK3494245/DDD01305143/compound-8 was developed as a preclinical therapeutic candidate to treat leishmaniasis. The chemical series was optimized to produce a powerful cidal molecule that killed a variety of clinically relevant *L. donovani* and *L. infantum* isolates. Compound 8 has shown a promising pharmacokinetics and *in-vivo* efficacy in mouse models of infection equivalent to miltefosine [102].

Similarly, a molecules known as GNF5343, GNF6702 with good activity for *L. donovani, T. brucei*, and *T. cruzi* cultures were discovered through a high-throughput proteomic analysis at the Genomics Institute of the Novartis Research Foundation (GNF) [103]. GNF6702, a selective kinetoplastid proteasome inhibitor, eradicated parasites in mouse models of leishmaniasis, Chagas disease, and human African trypanosomiasis. Optimization of GNF6702 led to the selection of one (LXE408) compound with remarkable efficacy in murine models of visceral and cutaneous form of leishmaniasis that is currently in Phase 2 human clinical trials. In addition, high-resolution cryo-EM structures of the *L. tarentolae* proteasome in association with L×E408explain the noncompetitive binding of this unique class of kinetoplastid proteasome inhibitors [104]. This drug is in phase II of clinical development.

5.5. Secretory proteins/secretion pathway-based drug targets

The secretory pathway's major organelle, the endoplasmic reticulum (ER), sites where the folding and packaging of proteins for distribution to their intended destinations, is carried out. It also acts as a point of control for proteins that have misfolded, which are then sent to the ubiquitin-proteasome system for destruction. To survive in the hostile macrophage environment, *leishmania* secretes a large variety of proteins into the extracellular milieu [85,105]. These secretory proteins are carried via eukaryotic secretion pathways, where proteins are folded in the endoplasmic reticulum and transported via the Golgi for secretion outside the cell. Therefore, virulence factor processing and secretion remain essential for parasite survival in the host [106]. During host invasion, the parasite produces a substantial number of secretory proteins. Calreticulin, BiP, and protein disulfide isomerase (PDI) are a few proteins that are crucial for protein folding and quality control of ER-mediated chaperoning activity [85]. The ER quality regulation of secretory proteins is greatly aided by calreticulin. However, its overexpression is linked to lower macrophage survival, and changing the activity of the ER chaperone alters protein secretion, making it a prospective drug discovery candidate [107].

5.6. Epigenetic manipulations as drug targets

Given the paucity of information on the impact of epigenetic modifications on host macrophages, most of the evidences, now available, are correlative, and alterations in host epigenetics caused by pathogenic proteins are yet unknown. The potential for directly altering the host's epigenome, stopping pathogen development inside the host, or reducing their virulence with the use of chemical inhibitors, RNAi (RNA interference), gene knockout, etc., could open new avenues for targeting histone-modifying enzymes, DNA methyltransferases, and chromatin, giving science the new concept of 'epigenetic therapy.' However, there is little evidence of the epigenetic impact of *Leishmania* infection on the host cell, but a new study suggests that macrophages may undergo epigenetic remodeling after infection with *L. donovani* [108].

5.7. Iron homeostasis as drug targets

Prokaryotes and eukaryotes both have strictly controlled iron homeostasis. Iron is one of the crucial components of the cell, performing several life-sustaining biological processes. Aconitase, ribonucleotide reductase, cytochromes, and the Fe-S proteins of the electron transport chain are only a few examples of the many proteins that contain active iron [94]. It is additionally utilized as a component of collagen, tyrosine catecholamines, and mammalian immunological responses. Recently, enhanced superoxide dismutase activity and reactive oxygen species have been linked to LIT1 (*Leishmania* iron transporter) up-regulation, which controls parasite differentiation [85,109].

According to RNAi research, iron is also a component of mitochondrial superoxide dismutase, which mediates parasite protection and redox signaling. Further research on genetic deletions confirmed its function in increasing the parasite's vulnerability to ROS-induced stress and differentiation [110]. As a result, the pharmacological target for this molecule should be examined. A fluorescence microscopy and bioinformatics study identified LmABCB3 as a crucial mitochondrial target protein. The synthesis of heme and iron-sulfur clusters, which is dependent on mitochondria, is carried out by an ATP-binding cassette (ABC) half-transporter with a metal binding domain. LmABCB3 transporter is therefore crucial for parasite survival and offers another potential target for leishmaniasis treatment [111].

5.8. Kinome based therapeutics as drug targets

The entire set of the protein kinases encoded by the genome is represented by the kinome. Recent articles have highlighted the importance of protein kinases in the parasite life cycle, including mitogen-activated protein (MAP) kinases, PI3 kinases, and NF-κB signaling [85,112]. Complement receptors, conversely, are crucial in activating protein kinases, which in turn controls host immunological responses.

Among kinases, cyclin-dependent kinases (CDK) are the most extensively researched as a leishmaniasis target. As previously mentioned, CDKs are crucial for controlling the cell cycle; thus, inhibitors aimed at ATP binding to the CDKs' catalytic region [113] may be effective therapeutic targets. Imatinib (an inhibitor of the Abl family of kinases), combined with traditional chemotherapeutic options, may help reduce parasite growth [85]. Casein kinase is one of the other kinases, and it continues to be a key therapeutic target since it is crucial for parasite survival and virulence [85,114].

5.9. Calcium homeostasis as drug targets

All species, from mammals to parasites and non-mammals, depend on calcium as a crucial part of the cellular homeostatic machinery for cell survival. Adenylate cyclase, cAMP phosphodiesterase, protein kinases, and guanylate cyclase are only a few of the enzyme activities that calcium regulates in protozoan parasites, in addition to flagellar, ciliary movements, and exocytosis [85,115–117]. The levels of calcium are controlled by the ER, mitochondria, and acidocalcisome at the cytoplasmic level in trypanosomatids [118]. Calmodulin controls the Ca^{+2}-ATPase membrane channel at the plasma membrane level in trypanosomatids [119], and another transporter promotes calcium-ion buildup in the mitochondrial internal membrane [119,120]. The intracellular calcium homeostasis is maintained by all of these systems of homeostatic machinery in order to act as a signaling messenger. Additionally, calcium has been shown to be essential for parasite differentiation and thermotolerance [121,122].

The greatest calcium storage reservoir, the ER, still has a variety of calcium inflow and efflux mechanisms. In addition to SERCA (Sarcoplasmic reticulum Ca^{+2}-ATPase), which has been shown to have suppressive activities in several trypanosomatids and is a virulence factor in Leishmaniasis [123], calreticulin is a calcium storage protein in the ER and could be a potential therapeutic target.

Targeting calcium transporters may have therapeutic implications due to calcium's important function in controlling the parasite life cycle. Fendiline, mibefradil, lidoflazine, and other calcium channel blockers were discovered to exhibit strong antileishmanial actions in this regard. Bepridil has also demonstrated good effectiveness [124], and verapamil combined with meglumine antimoniate has a synergistic impact on parasite clearance [125].

6. Conclusion

Development of drug design and delivery systems, with reasonable therapeutic effects in many models, has been facilitated by technological advancements in system biology and nanotechnology. There are a number of pathways that can be used as targets for developing therapeutic tools, some of which have been shown to alleviate clinical symptoms and reduce parasite burden. In order to find treatments with fewer side effects, cheaper costs, and greater efficacy against leishmanial infection, efforts must be focused on the appropriate investment in novel drugs and treatment approaches. Strong political has supported VL elimination programs in ISC to ensure that the disease is eliminated from ISC and free treatment is available to the patients of the ISC. Looking at the profiles of the currently available antileishmanial, there is a pressing need to develop alternative therapeutic options that can successfully cure patients with all forms of leishmaniasis.

7. Expert opinion

Leishmaniasis is prevalent in 99 countries of the world. Treatment of various forms of leishmaniasis it still dependent on Sb^V except ISC, it is ironic that Sb^V (urea stibamine), first described in 1920 and used in the treatment of VL in Assam, Bengal, and other states of India, saved the lives of a huge number of VL patients. Despite being associated with severe adverse events like cardiotoxicity and death, it is still being used widely around the world, as there was no option. It is ironic that it took 75–85 years for the LAmB, oral miltefosine, and PM to become available for antileishmanial treatment. We are in dire need of new antileishmanial therapy which is safe, affordable, which can be stored at room temperature, and preferably oral with short regimens. At least in the ISC, LAmB is available at public health facility for free, thanks to the World Health Organization and the donation by the manufacturer for more than 10 years.

Treatment of post kala-azar dermal leishmaniasis (PKDL) and HIV/VL co-infection, human reservoirs for leishmaniasis is very unsatisfactory. For the treatment of PKDL, either 120 days of Sb^V over four months or 60–80 infusions of AmB again for the duration of 4–5 months, was recommended initially. However, these are extremely unsatisfactory and prolonged regimens, with potentially toxic drugs; These modes of PKDL treatment is now abandoned in India. After miltefosine was approved for the treatment of VL in India, based on a small randomized multicentre study using 12 weeks of miltefosine, it was recommended by WHO [126] that oral miltefosine be used for 12 weeks for the treatment of PKDL. However, contraception has to be practiced for six months. But this regimen led to ocular complications in 3.7% of patients with partial visual loss in 1% of patients [127]. Thus, practically, there is no safe regimen for PKDL. PKDL is a human reservoir, and VL outbreaks have been implicated in PKDL patients. We need an urgent treatment regimen for PKDL, which is a safer, shorter, and affordable treatment for these patients; sadly, we have nothing absolutely safe for them. We need to develop either single or multi-drug therapy with newly developed drugs.

For CL, the situation is even worse; we need species-specific therapy against causative organisms. As far as the treatment of cutaneous CL is concerned, the development of

therapy has been sketchy, and there is a lack of well-structured randomized controlled clinical trials for CL. So, with lack of this information, it is difficult to make a recommendation for CL/MCL. The treatment, in use, is based on mostly small and uncontrolled studies. Robust data from well-designed clinical data will be very helpful in deciding the treatment of CL.

As discussed above for the treatment of VL/CL/MCL, we need new antileishmanial compounds and, ways of therapy. There are several new compounds, already in advanced stage of development. But for use in humans, we need data coming out of well-designed clinical trials. Unfortunately, at the moment, there is only one compound in phase 2 clinical trial. Other new molecules with antileishmanial activity need to be found, and then, if their safety and efficacy merit for human consumption, then these could be taken for clinical development. For CL treatment, topical Cryo or Heat therapy and the application of topical PM+ methylbenzethonium chloride ointment looks promising.

The versatility and benefits of colloidal drug carriers such as emulsions, liposomes, and nanoparticles in treating parasite infections are of great interest. Nanoparticles can offer treatment for macrophage-mediated illnesses. Multidrug therapy can prevent drug resistance by reducing duration, doses, and toxicity. Numerous metabolic pathways are being studied as potential targets for drug discovery, targeting structures and ligands to discover new antileishmanial treatments. New targets can boost medication development and disease elimination strategies.

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Declaration of interest

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