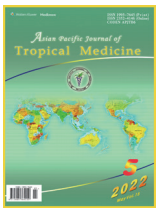

Review Article

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New developments in the treatment of cutaneous leishmaniasis

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ABSTRACT

Leishmaniasis, including the cutaneous form, poses an important public health threat around the world, while no vaccine is currently available against any form of leishmaniasis. The drugs used in the first line treatment of cutaneous leishmaniasis (CL) are commonly pentavalent antimonials despite their toxicities, long-term treatment duration and increasing resistance rates. Other alternatives are amphotericin B, pentamidine, miltefosine and paromomycine. Movement of the population, especially in endemic regions, increases the spread of the parasite and affectes the distribution of causative species, which requires re-evaluation the treatment regimen. Extensive researches are carried out on the treatment of leishmaniasis. The immunotherapeutic and targeted therapeutic approaches, formulations of carrier-loaded active drugs, local thermotherapeutic applications, the combination of antileishmanial drugs/compounds, the use of new synthetic and natural products are promising therapeutic options in the future. Herein, the author reviews the potential treatment modalities of CL with a brief overview of current treatments in the light of ongoing studies around the world.

KEYWORDS: Cutaneous leishmaniasis; Current treatment; Potential treatments; Thermotherapy; Immunotherapy; Natural/synthetic therapy

1. Introduction

Leishmaniasis is a serious, but preventable and treatable parasitic disease caused by *Leishmania* species[1,2]. Depending on host and parasite characteristics, the clinical manifestations of leishmaniasis can be classified as cutaneous, mucocutaneous, and visceral leishmaniasis[3-5]. Leishmaniasis affects about 12 million people all over the world, mostly in developing countries[6]. However, their incidences vary widely amongst their geographical locations. The annual incidence of leishmaniasis is about 2 million cases, 1.5 million cases for cutaneous leishmaniasis (CL) and 500 000 cases for visceral leishmaniasis (VL). The skin lesions in CL tend to heal spontaneously, contrary to VL which can be fatal if not properly treated. CL may result in disfiguring and stigmatizing scars with a considerable impact on quality of life[3,7]. The decision to treat CL, and to initiate a systemic or local treatment, depends on different factors related to the risk-benefit balance[8,9]. The main aim of CL treatment is to decrease the recurrence, to reduce scarring, particularly in cosmetic sites of the body, and to prevent spread of the disease in the community[2]. Diverse *Leishmania* species is known to cause CL, at least five species have been reported on the Eurasian and African continents, and seven species in the Americas. The resolving period and severity of CL depends on the infecting species[10]. The most frequent species causes CL in the western countries are *Leishmania* (*L.*) *mexicana*, *L. amazonensis*, *L. braziliensis*, *L. panamensis*, and *L. guyanensis*, while in the developing countries are *L. tropica*, *L. aethiopica*, and *L. major*[7,11].

No vaccine is currently available against any form of leishmaniasis[12]. In the clinical applications, there are around 25 compounds and formulations showing antileishmanial effects[13]. But, until now, none of the available drugs can be considered ideal due to their high toxicity and the emergence of resistant *Leishmania* associated with the lengthy treatment period[14-16]. The standard treatment recommendation is impossible due to the diversity of *Leishmania* infections worldwide. Optimal treatment regimens are best defined in consideration of demonstrated regional efficacy, available resources, and risk-benefit assessments for major syndrome in each geographic region[9]. Currently, the traditional approach in the treatment of CL is to use pentavalent antimonials;

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Table 1. Current therapy protocol of cutaneous leishmaniasis[7, 9,13].

Treatment	Administration	Regimen
Pentavalent antimony (Sodium stibogluconate or meglumine antimoniate)	IV, IM, and IL	20 mg/kg/day for 20 days
Amphotericin B	IV	1 mg/kg daily or alternately for 15-20 days
Pentamidine	IM	4 mg/kg three times a week for 3-4 weeks
Miltefosine	PO	50 mg single dose for patients weighing less than 25 kg; twice daily for patients more than 25 kg for 28 days
Paromomycin	IM	14 mg/kg daily for 20 days
	Topical cream (15%)	Twice daily application for 10-30 days

IM: intramuscularly; IV: intravenously; IL: intralesionally; PO: orally.

however, several other treatment modalities could be proposed based on epidemiological and geographical features of the regions[3].

Treatment is required if lesions are: multiple, in different locations, and large than 5 cm; complicated, metastatic spread to the lymph nodes; mucosal involvement and exposed skin in location; more invasive (*e.g.*, those failing to respond to topical treatment); and patients are immunocompromised[9].

The population relocation related to several reasons such as wars and socio-economic anxiety, and environmental aspects like climate change result in the exposure of unimmunized individuals to different species of the parasite[17,18]. Even if species-level diagnosis for guiding treatment has limited value by the current treatment methods, this kind of risk factors contribute to an epidemiological diversity and increased frequency of infection which requires to revise the treatment policy[16]. On the other side, rapid advances are made on the treatment of leishmaniasis, some of which represent new avenues for more effective, safer, easier and cheaper applications.

This review focuses on potential treatment modalities of CL with a brief overview of current treatments in the light of ongoing studies around the world.

2. Current treatments for cutaneous leishmaniasis

2.1. Pentavalent antimonials

The drug of choice for all types of the infections caused by *Leishmania* species are pentavalent antimonials (Sb^V)[13], which are found as sodium stibogluconate and methylglucamine antimoniate (MA) formulations. Although the drugs has inhibitory effects on the glycolytic and oxidative pathways of fatty acids in amastigotes, their action mechanism is still not understood completely[19].

The drug is mainly administered intramuscularly (IM), intravenously (IV), or intralesional (IL). Generally, an uncomplicated CL treatment is initiated by local therapy, whereas systemic therapy is warranted for complicated CL[19]. Recommended dose by IM and IV is 15-20 mg Sb^V/kg of body weight daily for 21-28 days (Table 1). It is distributed in high concentration in the plasma, liver and spleen, and 50% of the drug is excreted in 24-76 hours through urine[13,20].

However, painful injection, high toxicity and the emergence of significant resistance due to the long-course treatment of the drug have reduced the use of antimonials[13,14].

The therapeutic response is affected by multiple factors, including the host immune status, and *Leishmania* species. Decreased response to pentavalent antimony has been observed among *Leishmania* species, together with some geographic changeability[19]. Data obtained from various reports using intralesional methylglucamine antimoniate therapy show that the cure rates ranged between 50% and 92%[21–28]; otherwise, intralesional sodium stibogluconate ranged from 58.3% to 94.6%[29–33] in CL patients.

Amphotericin B, pentamidine, miltefosine and paromomycin are the second line drugs for especially pentavalent antimony contraindicated or refractory patients (Table 1)[13]. On the other hand, there are limitations for their use for CL treatment: the therapeutic efficacies of these second line drugs are less than the antimonials[13,14,19]. Besides, they have various toxicities in systemic or local therapy[14,34,35].

2.2. Other drugs clinically used

Over the last 35 years, many compounds have been investigated for their efficacies against leishmaniasis, including rifampicin, tamoxifen, doxycycline, monomycine, trimethoprim, some azole-derivatives, allopurinol (a purine analogue), and sitamaquine (an 8-aminoquinoline analogue). However, safisfying impact has not been observed in the cure results[4,13]. Use of cryotherapy is another treatment choice, but often restricted to diseases caused by *L. tropica* and *L. major et al*. Cryotherapy with liquid nitrogen consists of a freeze, thaw, and freeze cycle, which causes destroy of parasites and other cells[21,36]. Rifampin has been used at higher doses for CL, without reports of increased adverse effects, supporting the idea that the majority of rifampin's adverse effects are idiosyncratic and not dose-related[37].

3. New therapeutic alternatives for CL treatment

Increasing resistance to the current drugs, long-term treatment necessity, and the toxicity problems have resulted in the need to investigate new therapeutic alternatives, such as immunotherapy,

local hyperthermic administrations, antileishmanial synthetic and natural products, and combination therapy[6,9,33,38-42]. Some of these treatments has shown high effectivity, however, there is no standardized protocol.

3.1. Immunomodulatory and targeted therapeutic approaches

Macrophages are very important not only as effectors and antigen-presenting cells, but also as host cells for some microorganisms[12]. By inhibition of phagosome-endosome fusion, the macrophages could serve as hosts for long-term replication, survival and parasite spread (referred as "Trojan horse")[43]. T lymphocytes also play a critical role in shaping the host immune response to direct both protective and non-protective immunity. The disease progression in CL is driven largely by the production of Th2-associated cytokines IL-4, IL-10, IL-13, and TGF-β[44]. In the experimental non-healing and disseminating infection models by *L. major*, a parasite-driven Th2 polarized response was observed[45]. Otherwise, the infection control is mainly mediated by IL-12-driven Th1-type immune response. The production of IFN-γ by $CD4^+$ T cells plays a critical role in the activation of macrophages to kill the parasites by a nitric oxide mediated condition[44]. Despite these basic immunological mechanisms, the regulation of resistance varies widely between species, even within a given species. For example, *L. mexicana* and *L. amazonensis*, unlike *L. major*, have developed mechanisms to survive in conditions of limited Th1 immune responses in the host[46].

3.2. Immunotherapeutic/targeted approaches

The immunotherapy is experiencing a renaissance in various fields[47]. The immunotherapy of leishmaniasis, including CL, is not naive to this renaissance. In this context, the idea of modulation the immune response by the activation of macrophages and the increase of nitric oxide production and other mechanisms to eliminate the parasites has led to new investigations to supply an effective immune response[48,49].

To achieve these goals, one of the approaches in the treatment of leishmaniasis is targeted therapy. Targeted therapies act by blocking basic biochemical or signaling pathways essential for growth and survival of the parasite[6]. In an experimental study, Cummings *et al*. demonstrated that PI3Kγ mediates the entry of *L. mexicana* into phagocytic host cells[50]; whereas in their another study that used the AS-605240, a PI3Kγ inhibitor, for the treatment of experimental *L. mexicana* infection in mice, it was observed significantly lower parasite burdens and lesion sizes than wild type untreated mice. Therefore, PI3Kγ may be a possible drug target for the management of *L. mexicana* and potentially other obligate intracellular pathogens. Further, in reducing parasite burdens, AS-605240 was as effective as sodium stibogluconate. The results of another experimental study by Oghumu *et al*. revealed that transgenic expression of CXCR3 on T cells exacerbates CL caused by *L. major* in BALB/c mice by amplifying Th2 host immune responses, increasing neutrophil and inflammatory monocyte infiltration to infected sites, and inhibiting monocyte maturation[51]. This observation can lead CXCR3 to be considered as a therapeutic target.

Targeting the mechanisms of which are regulated by *Leishmania* to evade or exploit host immune responses is another promising choice for therapeutic intervention[52]. To reverse the immunosuppressed milieu by parasite-driven Th2 cytokine production, it is important to identify the molecules that control Treg cell. Chowdhury *et al*. reported that Ara-LAM, a potent immunomodulatory which induces pro-inflammatory functions in a toll-like receptor 2-dependent manner, causing IFN-γ secreting $CD4^+$ T cells in *Leishmania*-infected BALB/c mice, potentially correlated with impaired Treg cell functions[53]. Some of the other promising immuno-therapeutic strategies could be used as potential targets in future involve receptors expressed on Treg or its corresponding ligands on effectors cells, programed cell death domain-1 or its ligands (PD-L1, and B7-H1), and cytotoxic T lymphocyte antigen-4[6].

Another promising approach for targeted therapeutic treatment of CL is the release of the drug into macrophages cell to kill parasites reside and multiply within host macrophages. In this way, the drug is expected to improve the therapeutic index by increasing efficacy and reducing toxicity[54,55]. In a study to evaluate *in vitro* efficacy of paromomycin sulfate (PM) against *L. major* and *L. tropica*, Kharaji *et al*. observed that solid lipid nanoparticles (SLN) as delivery system can enhance the capability of PM to penetrate into the macrophage. They reported that the efficacy of PM-loaded SLN is significantly more effective than that of PM in inhibiting parasite propagation and SLN is safe without any cytotoxicity[56]. In a visceral leishmaniasis experiment in mice, it was shown that liposomal resiquimod induced IFN-γ and IL-10, and decreased the parasitic load. The decreased parasitic load is potentially due to the large up-regulation of IFN-γ outweighs that of IL-10[57]. Collier *et al*. formulated AR-12, which is a host-mediated therapeutic investigational new drug-approved by the Food and Drug Administration for cancer treatment, into microparticles, a polymer microparticle coated celecoxib derivative kinase inhibitor (AR-12/MPs) using the novel biodegradable polymer acetylated dextran to use VL treatment. Following the treatment with AR-12/MPs, parasitic loads in liver, spleen, and bone marrow were significantly decreased. Moreover, combinatorial therapies with amphotericin B illustrated more significant effects[58].

A variety of nanomaterials (NMs) are used in the drug release approaching. NMs can act as drug carriers or selective agents against the parasite. NMs reduce the toxic effects, and can be used for any combination therapy or as adjuvants to improve immune response in vaccine studies[59].

In a study to evaluate fractional CO_2 laser-assisted topical rifamycin drug delivery, Lodi *et al*. reported that this technique might be safe and effective in treating CL[60].

We consider that the immunotherapeutic choice against leishmaniasis should be targeted at least one of the three main

goals: stimulation of the immune system to enhance leishmaniacidal activity, prevention of the parasite-driven milieu which promotes parasite survival in macrophages, and inhibition of the cells which act as a "Trojan horse" in order to reduce parasitic load.

In the first report about the use of immunomodulators, Badaro *et al*. observed the superiority of human IFN-γ as an adjunct antimony therapy for VL by explaining an enhanced intracellular killing of the parasites[11]. In murine leishmaniasis model, recombinant IFN-γ given alone or along with sodium stibogluconate resolved the infections caused by *L. major* and developed Th1-type responses. However, administration of anti-IL-12 antibodies reversed the therapeutic effects, which suggesting that IFN-γ promotes cure through an IL-12-dependent mechanism[61]. Tucaresol, an orally bioavailable immunopotentiatory drug, acts against infection caused by *L. donovani* by enhancing TH1 response and the production of IL-12 and IFN- γ levels[62].

It would be logical and important to identify an immunomodulatory compound generating an oxidative burst within *Leishmania*-infected neutrophils to effectively eliminate parasites. It has been reported that berberine chloride has a leishmaniacidal activity both directly by inducing an oxidative burst in parasites and indirectly *via* an increase in IL-12[63]. It has obtained successful clinical outcomes *via* imiquimod, an FDA-approved toll-like receptor 7/8 agonist in treatment of CL[64,65]. It may be beneficial in refractory CL in combination with other drugs[64]. Similarly, an imiquimod derivative and FDA-approved molecule resiquimod has also shown promising outcomes in treating CL. Resiquimod decreases the intracellular parasitic load by inducing the production of nitric oxide although it has no direct effect on the parasite[66]. Also, both of the molecules induce interferon-α, interleukin-1β, IL-6 and tumor necrosis factor-α in macrophages and monocytes[67].

The parasitized neutrophils undergo apoptosis and then will be upregulated by macrophages. Therefore, the parasite drives neutrophils as "Trojan horses" to infect macrophages and dendritic cells and initiate CL[53]. In experimental leishmaniasis models to evaluate whether neutrophils have a protective or non-protective role, inhibition of neutrophil recruitment in the infection site resulted in paradoxical impacts, depending on the genetic background of mice used for the experiments. Depletion of the neutrophils results in a reduced parasite load in BALB/c mice, whereas C57BL/6 mice show an exacerbated infection[68]. In an experimental visceral leishmaniasis study used chemokine receptor 2 antagonist RS-504393, we observed decreased numbers of inflammatory monocytes and parasitic loads in spleen and liver. Besides, there was a decreased inflammatory monocyte response correlated with decreased numbers of IFN-γ+IL-10+$CD4^+$ T cells percentage[69].

3.3. Cytokine therapy

Cytokines have a significant role in the shaping of CL by either the development of Th1 or Th2 response[44]. The idea of using immunostimulatory cytokines (*e.g.*, IFN-γ, IL-12, and GM-CSF) or antibodies that target deactivating cytokines as therapy method in leishmaniasis should be considered an important development[49].

The use of anti-IL-10R mAb in chronic cutaneous *L. major* infection results in eliminated persisting parasites. The apparently enhanced antimicrobial action is mainly related to increased expression of activating cytokines such as IL-12, IFN-γ, iNOS induction, macrophage activation and generalized inflammation[70]. Likewise, in normally susceptible BALB/c mice, exogenous treatment with rIL-12 during *L. major* infection leads to resistance of the mice[71]. Neutralizing IL-10 or blocking its receptors in VL models yielded similar results. Suppression of IL-13, IL-4 and TGFβ inhibited parasite replication[72].

3.4. Dendritic cell–based therapy

Dendritic cells (DCs) are the most potent antigen-presenting cells and play a critical role in the activation of T, B and NK cells[73]. In CL, DCs rather than macrophages prime T cell responses against *L. major* and induce protective immunity[74]. DCs play an important role in initial anti-*Leishmania* T cell responses and promoting their differentiation into memory T cell to achieve long-lasting immunity. Thus, DC-based immunotherapy appears as a promising application for the induction of antigen-specific T cell immunity[6]. In murine VL, dendritic cells- and antimony-based combined therapy has been found highly effective[75].

3.5. Thermotherapy applications in CL treatment

Thermotherapy application is a technique used to increase tissue temperature for whole or regional body. Radiofrequency, electromagnetic energy, ultrasonic waves, and other thermal-conduction-based devices could be used for the heating. The heating increases blood flow which facilitates tissue healing. The thermotherapeutical applications can be used in various medical conditions, including skin infectious lesions[76–79].

Hyperthermia alone can damage *Leishmania* parasites, but more importantly, hyperthermia might potentiate the effectiveness of chemotherapeutics when used in combination[76–79].

The ability of dermatotrophic *Leishmania* species to replicate is limited at higher temperatures, and almost completely eliminated over 39 ℃[80]. Subsequently, thermotherapy has been evaluated in a variety of CL species[81]. The ThermoMed device (Thermosurgery Technologies, Inc., Phoenix, AZ), which utilizes radio-frequency technology has received the United States FDA approval for this purpose[82]. WHO recommended this instrument as an alternative therapy for all American CL species[83]. The device is portable, battery-operated, and delivers superficial heat to 50 ℃ *via* a set of prongs placed directly on the lesion. On other side, local anesthesia is required due to pain during the application[76,83].

Another adapted technology of thermotherapy Hand-held

Exothermic Crystallization Thermotherapy for Cutaneous Leishmaniasis (HECT-CL) (Pristech Products, San Antonio, TX) which is a sodium acetate heat pad calibrated to produce (52±2) ℃ for 3 minutes, in one to three fractions (depending on the pain tolerance of the patient)[76]. It costs less than 3 dollars, is simple to use, and is rechargeable by boiling for recurrent reuse[38]. However, thermotherapy should not be used for lesions with potential for lymphocutaneous or mucosal spread[83].

Although different ratios are represented based on heterogeneity among the applications related to personal experience, the definitive clinical cure rate of HECT-CL was generally reported to be 60%-68.4% in the treatment of CL[38]. For radiofrequency thermotherapy, this rate ranges from 38% to 90% with a variety of species[81–87]. In a meta-analysis of controlled clinical trials, the overall efficacy of thermotherapy was 73.2%, whereas the efficacy of systemic treatment was 70.6%. Thermotherapy presents similar efficacy to that of systemic treatment, being safer, requiring a smaller number of treatments and no laboratory monitoring, improving adherence, and having a lower cost *et al*[88].

Photodynamic therapy (PDT) has become a novel important application for some skin infection, including leishmaniasis and it can also be used as combinations of the existing treatments[89,90].

3.6. Combined therapy choice

The combined treatment of CL is one of the most important strategies, which not only increase antileishmanial effect, but also reduce the potential toxic adverse effects, the length of treatment and decrease drug resistance due to their synergistic effects[6,13,91,92]. Several combinations exist for antileishmanial using, such as liposomal amphotericin B plus miltefosine, miltefosine plus paromomycin, miltefosine plus sodium stibogluconate, other new combinations, including the use of immune-chemotherapy[93–96]. Combinations of drugs eliminate the parasites *via* different modes of action. One drug/compound in the combination could modulate the immunity of the host, while the second drug could target the parasite itself[6]. Using recombinant IFN-γ in combination with pentavalent antimonials has been reported as more effective parasitological and clinical in VL treatment, most probably due to the acceleration of parasitologic effect of Sb^V that depend on activated macrophage by IFN-γ[97]. In a study by Almeida *et al*., combined topically applied GM-CSF and antimony was found as effective and well tolerated in the treatment of relapsed CL[98]. In another study, it was indicated that meglumine antimoniate plus pentoxifylline could be more beneficial than meglumine antimoniate alone in the treatment of CL[39]. In comparison to the killing induced by amphotericin B alone, IL-12, anti-IL-10R or agonist anti-CD40 in combination with amphotericin B was more efficient than monotherapy and led to a reduction of the amphotericin dose[99]. In the patients suffering from *L. donovani* infection, combined chemotherapy of sodium stibogluconate and paromomycin[100] and liposomal amphotericin B combined with miltefosine[101–103] was found highly effective. Some candidates of the combination seems to take part in the future options for therapy of leishmaniasis, such as 1) Th1 cytokines like IL-12, IFN-γ and TNF+sodium stibogluconate; 2) granuloma remodeling exogenous cytokines IL-2 or GM-CSF+potent antileishmanial drug like paromomycin; 3) IL-10-receptor blockers+chemotherapy+sodium stibogluconate/paromomycin; and 4) amphotericin B+miltefosine[104].

Nevertheless, taken together, a lot of promising observations are available through immunomodulators and combined therapeutic approaches for the treatment of CL, their prices are exorbitantly high for especially poor population[13].

3.7. The advancement of promising synthetic and natural products

To identify the structural features and action mechanisms of the important drugs gives rise to develop new drugs, like derivatives, which is less toxic and more effective. The significant progress has been made on the advancement of new drugs due to recent technological advances. Similarly, the design and synthesis of specific inhibitors could control the parasites with minimal damage to the host[105–110]. Topoisomerases[111], kinetoplast[112], mitochondria[113], phosphoinositide 3-kinase gamma[50], fatty acid and sterol pathways of the parasite are amongst the promising targets[114] for these specific inhibitors. Besides, plant extracts and plant-derived compounds are extensively preferred for the treatment of infectious diseases, including leishmaniasis, because of their fewer side effects, lower cost, and higher availability[115]. The plant extracts show biological activity through their various chemical groups such as alkaloids, flavonoids, phenylpropanoids, steroids, and terpenoids[116–121]. Edelfosine and ilmofosine, new alkyl-lysophospholipid derivatives, revealed high *in vitro* activity against *L. donovani*[117]. Azasterols, which are synthetic products, have been demonstrated that are active against amastigotes of *L. amazonensis* by the inhibition of the enzyme sterol 24-methyltransferase[118].

Extensive studies have been carrying out on the activity of natural products sourced from marine, microorganism or more commonly plants against *Leishmania* during the last years. A glycoprotein from the sponge *Pachymatisma johnstonii* showed a high anti-leishmanial activity against promastigotes and amastigotes of various species, including a pentavalent antimonial-resistant strain[119]. A fungal metabolite aphidicolin, isolated from *Nigrospora sphaerica*, was found to be active on both promastigotes and amastigotes[120].

There are so many plants extract from different geographical regions representing anti-leishmanial acts. For example, it was shown that phenylpropanoid dimers isolated from the extract of the twigs of *Nectandra leucantha* have anti-leishmanial activity *via* an nitric oxide-independent mechanism[121]. The anti-leishmanial activities of some essential oil have been evaluated in some researches[122–125]. A

linalool-rich essential oil from the leaves of *Croton cajucara*, a plant used in folk Brazilian medicine, has been found that is a strikingly potent leishmanicidal plant extract, which inhibited the growth of *L. amazonensis* promastigotes at very low concentrations and presented no cytotoxic effects against mammalian cells[126]. Ardic N *et al*., in an unpublished study, have recently observed that *Juniper* tar (cade oil), one of the essential oils obtained from the genus *Juniperus*, inhibited the growth of promastigote forms at very low concentrations *in vitro*.

4. Limitations of this review

The review is not a systematic review study and is vulnerable to selection bias. There are many new various studies mentioned in the article, but for which sufficient data could not be obtained in term of the risk-benefit. The other challenges are 1) most of the treatment methods mentioned are not standardized and 2) the effectiveness of alternative treatment strategies has not been adequately compared.

Cutaneous, and the other forms of leishmaniasis, continues to be a public health problem in many countries of the world. The drug for CL treatment is still for chemotherapeutic approaches, such as pentavalent antimonials, amphotericin B, pentamidine, and miltefosine. A method which is more cost-effective, has less toxicity and easy to use, can prevent resistance and shorten the treatment period, will challenge the others. Understanding of crucial pathways for the parasite survival and the host to combat against the parasite is significant in the development of therapeutic vehicles. The formulations of carrier-loaded active drugs, the combination of antileishmanial drugs/compounds, the use of new synthetic and natural products, thermotherapy applications, the immunotherapeutic and targeted therapeutic approaches are promising therapeutic options.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

RD drafted, conceptualized, and finalized the manuscript structure and contents.

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