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Leishmaniasis: An appraisal of current medications and potential natural sources

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Abstract

Leishmaniasis is one of the neglected tropical diseases prevalent in various developing nations.The information available is very limited in a number of countries so the first in-depth exercise is better to estimate the real impact of leishmaniasis and its approaches to cure. Among the various forms of leishmaniasis, the incidence of visceral leishmaniasis and cutaneous leishmaniasis were more prevalent. This review highlights the current status of antileishmanial drugs along with an insight to herbal and marine moieties for which antileishmanial activity has been documented. Since most of the natural products were bio-compatible and safe to use with few impact of side effects, the evaluation of these natural exudates or extracts and their active constituents is a logical way of approaching for new drugs to treat leishmaniasis.

Key words: Visceral leishmaniasis, Sandfly, Antimonials, Natural sources, Vaccine

Introduction

According to World Health Organization (WHO), Leishmaniasis is one of the 17 neglected tropical diseases in the world [1]. Leishmaniasis is a zoonotic infection caused by the parasite belongs to the various species of *Leishmania*, family *Trypanosomatidae* that causes a wide spectrum of clinical manisfestation in humans. Leishmaniasis is transmitted by certain sandfly species namely, *Lutzomyia* in the new world [2] and *Phlebotomus* in the old world [3]. Traditionally, Leishmaniasis has been classified in three different clinical forms, Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (MCL) and Visceral Leishmaniasis (VL). CL, which causes skin sores, is the most common form of leishmaniasis [4]. In case of MCL, parasite spread from the skin and cause sores in the mucous membranes of the nose (most common location), mouth, or throat. VL, also known as kala azar (black fever), in which the skin of patient may become darkened. It is caused by *Leishmania donovani*, where the parasite migrates to the vital organs such as bone marrow, liver and spleen which may leads to death in 20 months if left untreated. As per WHO, an estimated 20,000-40,000 deaths were occurring every year due to leishmaniasis. Currently, it is considered to be endemic in 88 countries, of which 72 are developing nations.

Leishmaniasis is found in every continent except Australia and Antarctica. Among all 90% of VL cases have been found in Bangladesh, Brazil, India, Nepal and Sudan, where as CL was found more common in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, Syria and the least common MCL was found prevalent in Bolivia, Brazil and Peru. Each year, approximately 0.7-1.2 million people suffering from CL and 0.2-0.4 million people suffering from VL. The resistance of leishmania parasites to antimonial drugs, especially pentavalent antimonials is one of the main causes for rapid spread and exponential rise in number of cases which makes the situation more critical. With increasing international travel, leishmaniasis is being imported into those areas where it was not previously seen and opportunistic infections are now being reported (particularly in AIDS patients) [5].

Life cycle of leishmania parasite

Leishmaniasis is transmitted by the bite of an infected female phlebotomine sandfly. Sandflies are primarily infected by animal reservoir hosts, but humans are also a reservoir for some forms. As the parasitized female sandfly takes the blood meal from a human host, metacyclic promastigote forms of the leishmanial parasite enter into human via

proboscis and get ingested by macrophages. Within the host cell, promastigote forms (lose their flagella and) metamorphose into amastigote forms and reproduce by binary fission. They increase in number until the cell eventually bursts, releasing the amastigotes and further infects other phagocytic cells by blood circulation. The schematic representation of leishmania life cycle was shown in Fig 1.

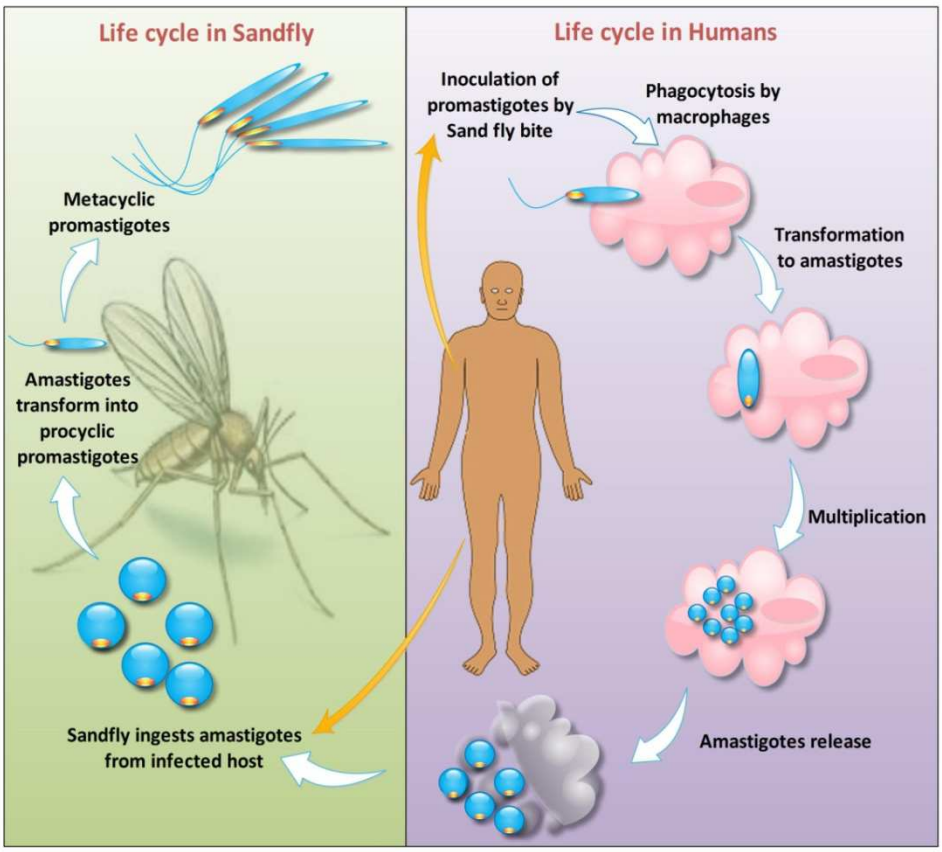


Fig 1: Life cycle of *L. donovani*

Leishmania amastigotes are ingested when another sandfly feeds on an infected host. Within the vector, amastigotes transform into long, flagellated promastigotes. The free living and multiplying promastigotes attach to the gut wall using flagella and develop into mature non-dividing metacyclic promastigotes. The metacyclic promastigotes migrate to the foregut and then to the proboscis. The parasites are transformed to a new host when the sandfly feeds blood meal and thereby the life-cycle continues.

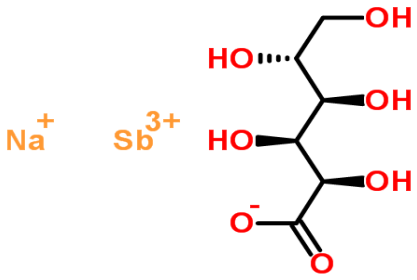
Classical anti-leishmanial therapy

Antimonial compounds

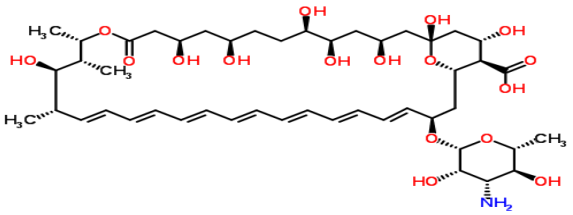
Antimony potassium tartrate (tartar emetic), a trivalent antimonial, was the first drug reported to be effective against CL and VL [6, 7]. Because of the toxicity, difficulty in administration and side effects such as cough, chest pain and depression, tartar emetic was eventually replaced by pentavalent antimonials. Urea stibamine was the oldest pentavalent antimonial compound which had much less toxicity than its trivalent predecessor. It was first described in 1912 and was reported to be effective against *Leishmania donovani* by Brahmchari et al of India in 1922 [8]. Urea stibamine reputed as the first allopathic drug discovered in India. Later on derivatives of phenylstibonic acid sodium salts were prepared which remained the Hobson's choice for all species of leishmania for several decades and saved the millions of lives [9-11]. Compared with trivalent form, pentavalent compounds are less toxic, high doses can be given as they are quickly excreted, and the sodium salt is better tolerated than the potassium one.

The most commonly used organic compounds of antimony (Sb) are antimony sodium gluconate and meglumine antimoniate. Pentavalent antimony compounds are thought to inhibit bioenergetic processes in the pathogen, with catabolism of glucose and inhibition of glycolytic enzymes being the primary sites of action (glucose catabolism is inhibited by 86-94%). This in turn results in inhibition of adenosine triphosphate (ATP)/ guanosine triphosphate (GTP).These compounds continued to be used successfully to treat millions of patients per year throughout the world for more than 50 years. Apart from antimonials, it is obvious that no other heavy metal treatment in any disorder has enjoyed such a reputation and remained unchanged over decades. But the chequered role of antimony in leishmaniasis has reached a climax in 1970's with the emergence of resistance to these drugs. Because of the

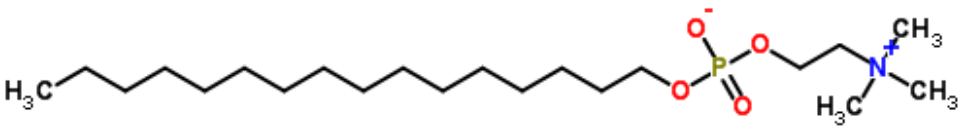
development of more efficacious and newer drugs, antimonial compounds are now used occasionally in treating leishmaniasis.



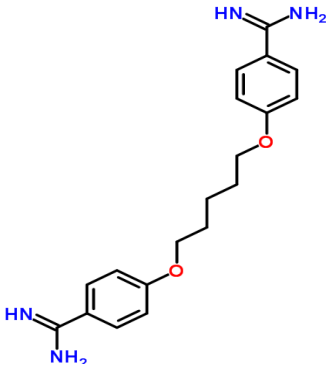
Antimony sodium gluconate



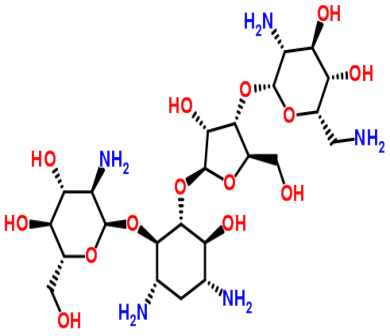
Amphotericin B



Miltefosine



Pentamidine



Paromomycin

Fig 2: Chemical structures of established antileishmanial drugs [12-16]

Amphotericin B and liposomal Amphotericin B

Amphotericin B (AmB), the polyene anti-fungal agent came into universal use as anti-leishmanial agent and became the standard second-line treatment against antimony-resistant VL. AmB appears to interact with ergosterol in the fungal cell membrane. Leishmania resemble fungi in synthesizing 24-substituted sterols such as ergosterol, the major membrane sterol present in the cell membrane and this interaction would predict the efficacy of AmB against Leishmania. It is administered through intravenous (IV) route in the form of desoxycholate. But a special problem associated with AmB is the acute renal toxicity. To reduce toxicity while maintaining therapeutic efficacy, reformulations of AmB were developed with less toxic lipids. Presently three lipid based amphotericin B formulations licensed for clinical use in the treatment of leishmaniasis, liposomal amphotericin B [L-AmB (Ambisome)], amphotericin B colloidal dispersion [ABCD (Amphocil)], and amphotericin B lipid complex [ABLC (Abelcet)]. Low cost of AmB and its greater effectiveness of lipid based formulations made it as a therapeutic alternative against leishmaniasis in the developing nations in which health care resources are limited.

Alkylphosphocholine Analogues

Miltefosine

A major breakthrough in the treatment of leishmaniasis is the development of orally active alkylphosphocholine analogues. Miltefosine is the only oral agent intended for antieishmanial therapy till date. It was initially developed as an anticancer agent and introduced into leishmanial therapy in 1980s. Since 1992, Miltefosine has been recommended by the WHO for the treatment of VL and it was registered in India in March 2002. It is also effective in the treatment of CL and has been registered in Colombia for CL in 2005 [17]. Miltefosine is thought to act by interacting with the protein kinase C enzyme present in the plasma membrane of leishmania parasite by inducing DNA fragmentation and apoptosis in the parasite [18]. An important caveat for patients with miltefosine treatment is the risk of teratogenicity. Although teratogenicity is a concern, considering the limitations with other agents such as parenteral administration and toxicity, miltefosine may become the drug of choice for VL.

Pentamidine

Pentamidine is an aromatic diamidine that was discovered serendipitously as a consequence of the search for hypoglycemic compounds that might compromise parasite energy metabolism. It is formulated as an isethionate salt.

Pentamidine is primarily used to treat *Pneumocystis carinii pneumonia* (PCP). It is used as a second line treatment for the patients resistant to antimonial therapy. Pentamidine interferes with leishmanial DNA synthesis by modifying the morphology of the kinetoplast, and promotes fragmentation of the mitochondrial membrane, killing the parasite [19].Pentamidine is potent and highly toxic compared to antimony. Pancreatic toxicity is the most commonly associated problem with pentamidine therapy. Adverse effects have been reported over 50% of patients, receiving the daily dose of 4 mg/kg which include severe hypotension due to rapid IV administration, dizziness, dyspnea and tachycardia. To avoid sudden drop in blood pressure the administration slowly over a period of 2 hours with recumbent and monitoring of the patient is suggested. Due to high toxicity and recent reports of emergence of drug resistance, other agents are now preferred to pentamidine for the therapeutic intervention of VL.

Paromomycin

Paromomycin, an aminogylcoside aminocyclitol antibiotic in use as an oral agent intended to treat intestinal infections. It is shown to be effective against leishmania parasite, the activity not shared by other aminogycoside antibiotics. The efficacy of paromomycin for CL as a topical treatment was discovered in 1985 and for VL as a parenteral therapy in 1990. Parenteral paromomycin was registered in India in August 2006 for the treatment of VL. The mode of action is related to target the leishmania ribosomes. Recently, it has been observed by Walter Reed Army Institute of Research that the topical formulations containing 15% paromomycin in combination with gentamycin shown better efficacy against CL [20].

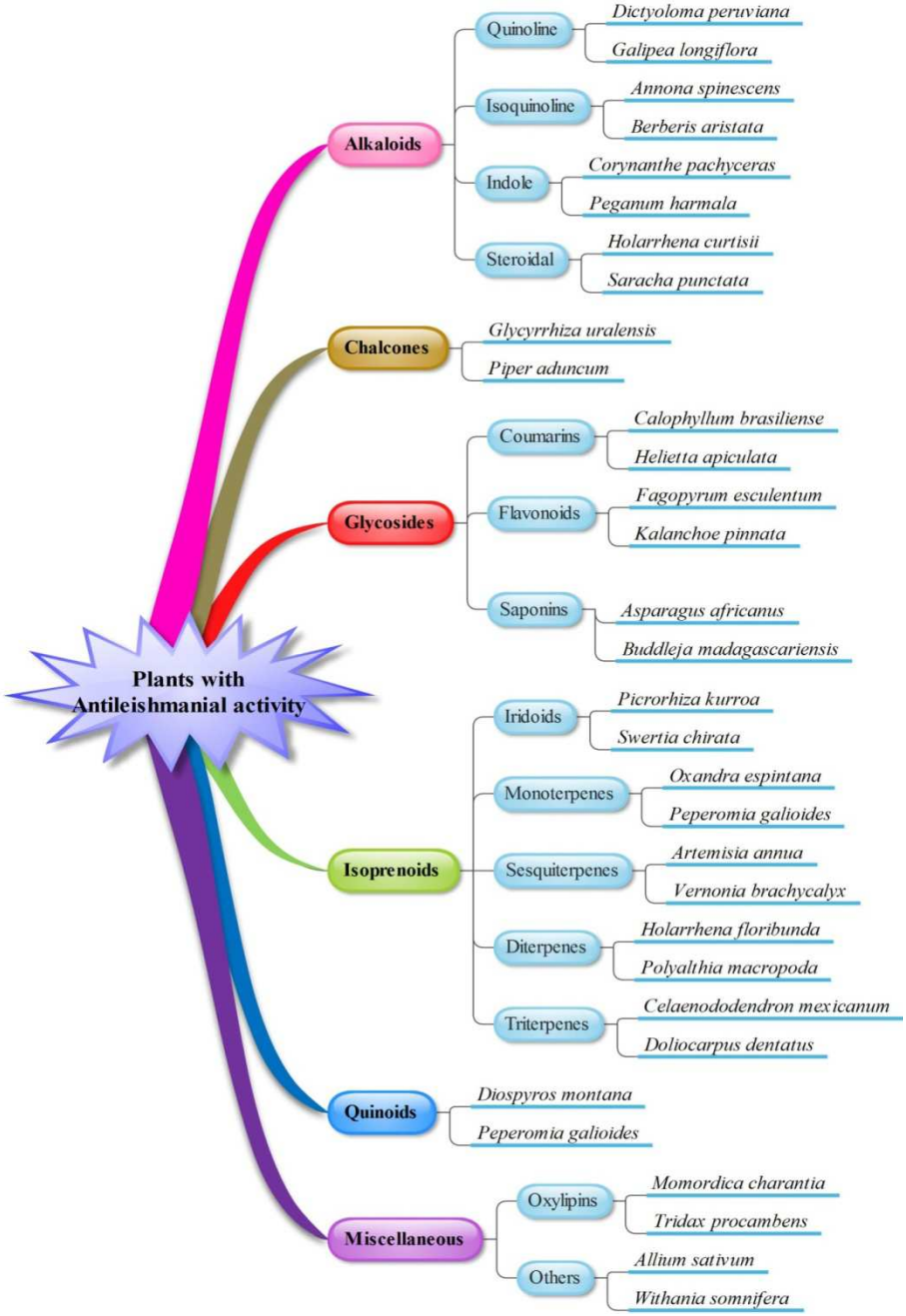


Fig 3: Classification of some medicinal plants with antileishmanial activity

Antileishmanial drugs from natural sources

Herbal sources

Plant products are an abundant source of leads to antileishmanial drugs which can offer potential of therapeutic switching chemotherapy. Epidemiological studies have shown that several plants possess bioactive constituents with leishmanicidal activity. Therefore, elucidation of these phytoconstituents and their medicinal formulas will contribute to a greater extent in the antileishmanial drug development process. Some medicinal plants with antileishmanial activity were listed in Fig 3 and discussed below.

Alkaloids

The most common alkaloids with antileishmanial activity were berberine hydrochloride isolated from the leaves, stem and root bark of *Berberis aristata* [21] ; Dictyolomide A and Dictyolomide B isolated from *Dictyoloma peruviana* [22]; annonine and liriodenine from *Annona spinensis* [23]. Other alkaloids found to be leishmanicidal include 2-phenylquinolines from *Galipea longiflora* [24], indole alkaloids from *Coryanthe pachyceras* [25], *Peganum harmala* [26]; Steroidal alkaloids from *Holarrhena curtisii* [27] and *Saracha punctata* [28].

Chalcones

Licochalcone A isolated from the roots of *Glycyrrhiza uralensis* (Chinese liquorice) [29-32]; 2´, 6´- Dihydroxy-4´-methoxychalcone obtained from *Piper aduncum* found to possess leishmanicidal property [33].

Glycosides

Coumarins may present in the plants in free form and as glycoside form. Coumarin containing plants with antileishmanial activity include *Calophyllum brasiliense* [34] and *Helietta apiculata* [35].Quercetin, a flavonoidal glycoside obtained from *Fagopyrum esculentum* [36] was found to inhibit the growth of *L. donovani* promastigotes, as well as amastigotes in infected macrophages *in-vitro* and induce cell cycle arrest at G1 phase, leading to apoptosis. Leaf aqueous extract of *Kalanchoe pinnata* was found to prevent the growth of lesion after oral dose in BALB/c mice infected with *L. amazonensis* and the effect was long lasting, comparable to the reference drug Glucantime [37].Muzanzagenin, a sapogenin isolated from *Asparagus africanus*, exhibited significant inhibition of the growth of promastigotes of *L.major*. The IC_{50} against leishmania promastigotes was 70 µM [38].

Isoprenoids

Picroliv, a standardized mixture of iridoid glycoside, prepared from the ethanolic extract of the roots and rhizomes of *Picrorhiza kurroa* elicited significant antileishmanial activity [39]. Hydropiperone, a new prenylated dihydroquinone, isolated from *Peperomia galioides* displayed potent antileishmanial activity against promastigote forms of *L. amazonensis*, *L. braziliensis* and *L. donovani* at 25µg/mL with a total lysis of the parasite at 100 µg/mL [40]. Artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* showed antileishmanial activity in *L.major* at the concentration of 30 µM [41]. Its antileishmanial activity is related to the production of free radicals in the parasite due to the presence of an endoperoxide bridge in the structure [42]. 16, 17- dihydroxybrachycalyoxide, a sesquiterpene dilactone isolated from *Vernonia brachycalyx* exhibited antileishmanial activity against the promasitgote of *L.major* (IC_{50} 17µg/mL). But at the same concentration it is found to inhibit the proliferation of human lymphocytes [43]. Epi-oleanolic acid and (24Z)-3-oxotirucalla-7,24-dien-26-oic acid are the triterpenes isolated from the leaves of *Celaenododendron mexicanum* showed antileishmanial activity on promastigotes of *L. donovani* with IC_{50} value of 18.8 µM and 13.7 µM respectively [44]. Betuline aldehyde, a triterpene isolated from the stem of *Doliocarpus dentatus* showed antileishmanial activity against the amastigotes of *L.amazonensis* at the dose of 60µg/mL. But the toxicity of macrophages was observed at this dose [45].

Quinoids

Diospyrin, a bis-naphthoquinone, obtained from the bark of *Diospyros montana* [46] had leishmanicidal activity against the promastigotes of *L.donovani* (minimum inhibitory concentration (MIC) of 1 µg/mL). It mainly acts by binding to the parasites topoisomerase I, thus inhibiting the catalytic activity of the enzyme, or by stabilizing the topoisomerase I-DNA binary complex [47].

Miscellaneous

Momordicartin isolated from *Momordica charantia* exhibited antileishmanial activity against *L.donovani* [48]. (3S)-16, 17-didehydrofalcarinol, an oxylipin, obtained from *Tridax procumbens* displayed marked activity against promastigotes and intracellular amastigotes of *L. mexicana* [49]. Ajoene isolated from *Allium sativum* exhibited activity against *L. mexicana* with IC_{90} value of 50 µM [50]. G3, isolated from the same plant also exhibited anti leishmanial activity with IC_{50} of 18.6 ± 3µg/mL against promastigotes and amastigote forms of *L. donovani* [51]. Withaferine A, a steroidal lactone isolated from *Withania somnifera*, exhibited leishmanicidal activity with IC_{50} of 12.5 ± 4µg/mL against promastigotes and 9.5±3 µg/mL against amastigote forms of *L. donovani*. Its parasiticidal activity is related to the inhibition of protein kinase C (PKC), a central event for the induction of apoptosis following stabilization of the topoisomerase I–DNA complex [51, 52].

Marine sources

4-Acetoxydolastane

(4R, 9S, 14S)-4α-acetoxy-9β,14α- dihydroxydolast-1(15),7-diene is a diterpene isolated from the Brazilian brown alga *Canistrocarpus cervicornis* has exhibited antileishmanial activity with an IC_{50} of 2.0 µg/mL and 4.0 µg/mL for promastigote and intracellular amastigote forms of *L. amazonensis*, respectively. It was also reported that the compound was 93 times less toxic to the macrophage than to the protozoan parasite [53].

Araguspongin C

Araguspongin C, a marine alkaloid obtained from the n-butanol fraction of *Haliclona exigua* inhibited the growth of promastigotes and amastigotes with 35.4 - 61.2% and 21.6 - 48.6% efficacy respectively at a concentrations of 50-100 µg/mL [54].

Coscinamide B

8,9-dihydrocoscinamide B, a marine alkaloid synthesized from a marine sponge, *Coscinoderma sp.,* has shown 99–100% inhibition against promastigotes and 97–98% inhibition against amastigotes forms of *L. donovani* at a concentration of 10 µg/mL [55].

Elatol

Elatol, a sesquiterpene, isolated from Brazilian red seaweed, *Laurencia dendroidea* elicited marked antileishmanial activity against *L. amazonensis* with an IC_{50} value of 4.0 µM and 0.45 µM for promastigotes and intracellular amastigote forms respectively [56].

Holothurin B

Holothurin B, a triterpene glycoside isolated from the coral reef sea cucumber *Actinopyga lecanora* showed marked antileishmanial activity against the *L. donovani.* The glycoside effectively inhibited the growth of promastigotes and amastigotes with 47 - 82 % and 57 - 78 % respectively at a concentration of 50-100 µg/mL [57].

Renieramycin A

Renieramycin A, an active substance of a marine sponge *Neopetrosia sp* also elicited a dose-dependent inhibition against *L. amazonensis* with an IC_{50} value of 0.2µg/mL .

The aqueous, dichloromethane and ethyl acetate extracts of two marine sponges *Ircinia spinosula* and *Sarcotragus sp*., obtained from the Tunisian coastline displayed prominent antileishmanial activity against the promastigotes of *L. major.*

Possible future therapies

Development of vaccine

Vaccination remains the best hope to control all forms of the leishmaniasis. However, there is as yet no effective vaccine for prevention of any form of leishmaniasis. Various subunit recombinant vaccine candidates have been tested and were in preclinical phase which had shown some degree of protection against infection. These vaccines were based on:

- A 46 kD promastigote antigen derived from *L. amazonensis*,
- The Leishmania-activated C kinase (LACK),
- Lipophosphoglycan, a surface glycoconjugate and
- Recombinant surface antigen gp63, a glycoprotein with protease activity.

More recently, Amitabha Mukhopadhyay of the India National Institute of Immunology in New Delhi and his colleagues described a new vaccine that completely blocks the parasite from causing VL in hamsters and mice by targeting a receptor that is common to many forms of the leishmania parasite [58].

Conclusion

As leishmaniasis is a poverty associated disease, efforts should be made to develop drugs that narrow the long dosage regimen and ultimately the cost. The rapid advancement in biology and chemistry has lead to the identification of new targets for antileishmanial therapy. There are more than 100 plants reported to have leishmanicidal activity which are sufficiently high to produce lead molecules. As current therapeutic opportunities were limited to fewer drugs which suffer from resistance, combinatorial advances in biology and chemistry with natural products could provide a better path in finding newer drugs to overcome the resistance. Development of vaccine would be a better feasible alternative for the complete eradication of lesihmaniasis.

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