Exploring the Possible Role of Nature in Curing Leishmaniasis

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Authors’ contributions

This work was carried out in collaboration among all authors. Author RS drafted the protocol. Author VG carried out the literature search. Author VC typed the manuscript and author PC analysed and did corrections in the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Communicable diseases have always been a threat to mankind since times immemorial. Leishmaniasis, an infectious disease caused by protozoan of various species of leishmania, is a major health problem spreading across 98 countries and about 350 million people stand the risk of this infection worldwide. Medical research has struggled a lot to combat this disease.

Objective: Among the various approaches available for treatment of Leishmaniasis, many are costly so there is a need to develop effective but economical and easily available antileishmanial agents.

Methods: Natural products are important source of various new medicaments and their derivatives.
can be used for synthetic modification and bioactivity optimization. Therefore, in order to fulfil the need for novel, economical, more effective and safer chemotherapeutic agents, scientists have explored Mother Nature in detail.

Results: A number of plant species possess inhibitory activity against certain types of parasites such as *Leishmania major*, *Leishmania amazonensis*, *Leishmania aethiopica*, *Leishmania braziliensis*, *Leishmania mexicana*, *Leishmania infantum*, *Leishmania chagasi* and *Leishmania donovani*. Moreover natural products are economical, safer, more effective and without considerable side effects.

Conclusion: The present review highlights the leishmanicidal activity of various natural products with an insight into their possible mechanism.

Keywords: Protozoan; leishmaniasis; chemotherapeutic agents; natural products; infection.

1. INTRODUCTION

Leishmaniasis, an infectious disease, caused by protozoan of various species of *Leishmania* is a neglected tropical parasitic infection placed at ninth position among various diseases worldwide. Its symptoms include skin and mucous membrane lesions to lethal organ infestations [1]. Leishmania is accountable for thousands of death every year and has spread to 98 countries and about 350 million people are prone to this infection [2,3]. Female sandfly which belongs to genus *Phlebotomus* and Trypanosomatidae family transmits the leishmania parasites [4,5]. The parasite has digenetic life cycle (Fig. 1) that alternates between sandfly and mammalian hosts, and has many developmental stages [6]. The disease has been given various different names according to the regions of its prevalence *ulcera de bauru* and *botão de bahia* in Brazil, *ulcera* in Peru, *ulcera de los chicheros* in Mexico and *forest yaws* in the Guyana [7]. The aim of this review is to emphasize that natural products are really effective in curing Leishmaniasis highlighting the in vivo studies and describing their probable mechanism of action.

2. MAIN FORMS OF LEISHMANIASIS

Leishmaniasis manifests mainly in three clinical forms; the one which affects the visceral organs and cause the ocular alterations is called as visceral leishmaniasis (VL) [8,9] and it mainly occur due to different leishmanial species such as *L. donovani*, *L. infantum*, *L. chagasi* and occasionally *L. tropica*. Symptoms include fever, severe weight loss, enlargement of liver and spleen, the other type which affects the skin is called as cutaneous leishmaniasis (CL) [10]. Earlier it was assumed that men are more prone to CL than women. However, modern studies show that except for sylvatic transmission, there exist similar rates of infection in men and women [11]. It is the most common form and is caused by many leishmanial species such as *Leishmania major*, *Leishmania tropica*, and *Leishmania amazonensis* etc. Symptoms are sores and skin ulcers and the third type called as mucocutaneous leishmaniasis (MCL) [12] is caused by *Leishmania infantum*, *Leishmania major*, *Leishmania tropica*, *Leishmania braziliensis* and *Leishmania aethiopica*.

Among the three types of leishmaniasis, visceral leishmaniasis is the most severe type of the disease and may prove fatal if left untreated. On the other hand, CL usually has slighter course and often results into self-healing of ulcers. Few of the visceral cases also develop into a cutaneous form known as post-kala-azar dermal leishmaniasis (PKDL) [13,14].

3. LIFE CYCLE OF LEISHMANIA

The organism responsible for Leishmaniasis mainly occurs in two stages, the motile, flagellated type that proliferates in the gut of the fly is called as promastgote whereas the non-dividing, infective form that resides in the mid-gut and mouthparts of the fly is called as metacyclic and the non-motile form that replicates and lives in a phagolysosomal compartment of mammalian macrophages is called as amastigote. So the life cycle of *Leishmania* takes place in two hosts, the mammalians and sandflies [15,16].

When a sandfly feeds on an infected individual the parasite is consumed with the blood meal and passes directly into the abdominal part of the midgut where the amastigotes are transformed into short oval forms called as procyclics which after 2-3 days post feeding transform into larger slender promastigote form. In the human host, the promastigotes are phagocytized by
Fig. 1. *Leishmania* life cycle [17]

macrophages and get transformed back into the amastigote form [17,18]. The amastigotes then undergo multiplication by binary fission leading to rupturing of macrophage which liberates parasites that mainly affect the reticuloendothelial system including spleen, liver, bone marrow and lymphoid tissues [19,20].

Depending upon the type of leishmania species, the life cycle in the vector varies from 4 to 18 days and is affected by temperature conditions i.e. it gets prolonged at low temperatures or shortened at high temperature [21]. Various other factors such as type of leishmania species, genetic susceptibility of host, hygiene conditions and environment affect the occurrence of disease [22].

After the bite of insects, the components of its saliva determine the local reaction. Shifting of Th1 (T-helper cell) to Th2 causes the adaptive changes in the immune response along with the increased production of interleukin-4, interleukin-6, interleukin-12 and this increased production causes the progression of the disease [23].

4. CONTROL STRATEGIES FOR LEISHMANIASIS

In spite of the high occurrence of the disease, the medicaments to treat leishmaniasis are insufficient and inadequate. Leishmaniasis is considered as neglected disease so like other tritryps diseases pharmaceutical industries have shown minor interest in this area because of lack of substantial profit [24,25]. About 850 new products have been granted licence from 2000 to 2011 but only 4% of these were exclusively targeted for neglected diseases like leishmaniasis. From WHO and NIH databases, it has been found that out of 148445 therapies in development only 1% is for neglected diseases. With the advancement of technology millions of compounds have been tested to identify new leishmanicidal agents, but treatment regimens are still limited due to lack of systematic studies including pharmacokinetics and pharmacodynamics studies moreover no compound is recently developed or registered which shows that there is obvious need for leishmania drug discovery [26,27].
Table 1. Plants acting against promastigote form

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Chemical constituent</th>
<th>Structure</th>
<th>Organism tested</th>
<th>Mechanism of action</th>
<th>Ref. No.</th>
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<tbody>
<tr>
<td><em>Baccharis uncinella</em></td>
<td>Urosolic acid</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Leishmania infantum</em></td>
<td>Urosolic acid: It acts by trigerring immunostimulatory mechanism within the infected cells by NO, the main effector molecule in parasite killing. Though, an aggravated production of these molecules may also lead to tissue damage.</td>
<td>[45-47]</td>
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<td>(Groundsel)</td>
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<tr>
<td><em>Eremurus persicus</em></td>
<td>Aloesaponol III 8-</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Leishmania infantum</em></td>
<td>Aloesponol III 8-methyl ether: It causes alterations in morphological and mitochondrial potential in promastigote form of <em>L. infantum</em> but does not produce significant toxicity in a macrophage cell line.</td>
<td>[48,49]</td>
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<tr>
<td>(Foxtail lilies or</td>
<td>methyl ether</td>
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<td>desert candles)</td>
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<tr>
<td><em>Zingiber zerumbet</em></td>
<td>Zerumbone</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Leishmania infantum</em></td>
<td>Zerumbone: It induces ROS mediated apoptosis in promastigote form of <em>L. donovani</em>, also act on the infected macrophages, and reduce the intracellular amastigotes.</td>
<td>[50,51]</td>
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<tr>
<td>(Awapuhi, bitter</td>
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<td>ginger, shampoo</td>
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<tr>
<td><em>Allium sativum</em></td>
<td>Allicin</td>
<td><img src="image" alt="Structure" /></td>
<td><em>Leishmania donovani,</em></td>
<td>Allicin: Its mechanism of action is due to its rapid reaction with the sulfhydryl groups but the actual intracellular targets</td>
<td>[52,53]</td>
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<tr>
<td>(Garlic)</td>
<td></td>
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<td><em>Leishmania infantum</em></td>
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<td></td>
<td></td>
<td></td>
<td><em>Leishmania major</em></td>
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<td>Plant name</td>
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<td><em>Olea europaea</em> (Wild olive, brown olive, Indian olive)</td>
<td>Oleuropein</td>
<td><img src="image" alt="Oleuropein Structure" /></td>
<td><em>Leishmania donovani</em></td>
<td>Oleuropein: It acts on the <em>in vitro</em> as well as <em>in vivo</em> model of visceral leishmaniasis by inducing reactive oxygen species production. It also elevates the nitric oxide production in <em>ex vivo</em> cultures of spleen as well as liver cells.</td>
<td>[54,55]</td>
</tr>
<tr>
<td><em>Morinda lucida</em> (Brimstone tree)</td>
<td>Molucidin</td>
<td><img src="image" alt="Molucidin Structure" /></td>
<td><em>Leishmania hertigi</em></td>
<td>Molucidin: Normal cells have single set of nucleus and kinetoplast i.e. 1N/1K, but molucidin induce two sets of nucleus and kinetoplast i.e. (2N/2K) in parasitic cells. After division of nuclei and kinetoplast in leishmania parasite, molucidin inhibit cytokinesis process i.e. the cells are not capable to form two distinct daughter cell and this inability of the cell causes the cell cycle arrest and leads to death of parasite.</td>
<td>[56,57]</td>
</tr>
<tr>
<td><em>Euphorbia peplus</em> (Radium Weed)</td>
<td>Simiarenol</td>
<td><img src="image" alt="Simiarenol Structure" /></td>
<td><em>Leishmania donovani</em></td>
<td>Simiarenol: It forms porous channels in the cellular membrane of the parasite that causes leakage of ions</td>
<td>[58,59]</td>
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<td>Plant name</td>
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<tr>
<td><em>Prangos asperula</em></td>
<td>Osthole</td>
<td><img src="image" alt="Structure of Osthole" /></td>
<td><em>Leishmania major</em></td>
<td>Osthole: Results obtained from the <em>in vivo</em> study did not demonstrate recovery of CL lesions in BALB/c mice treated with osthole however, progression of lesions was significantly declined compared to untreated mice.</td>
<td>[60,61]</td>
</tr>
<tr>
<td><em>Banisteriopsis caapi</em> (Ayahuasca, caapi or yagé)</td>
<td>Harmane</td>
<td><img src="image" alt="Structure of Harmane" /></td>
<td><em>Leishmania infantum.</em></td>
<td>Harmane: it acts by inhibiting and blocking kinoplast DNA (kDNA) of the <em>Leishmania infantum.</em></td>
<td>[62,63]</td>
</tr>
<tr>
<td><em>Artemisia annua</em> (Wormwood, sweet annie, sweet sagewort, annual mugwort or annual wormwood)</td>
<td>Artemisinin</td>
<td><img src="image" alt="Structure of Artemisinin" /></td>
<td><em>Leishmania major</em></td>
<td>Artemisinin: Artemisinin is identified as a potent antileishmanial agent against promastigotes and amastigotes. During the leishmaniasis, the cells produce various cytokines like interferon and tumor necrosis factor that facilitate activation of macrophages</td>
<td>[64-66]</td>
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<tr>
<td>Plant name</td>
<td>Chemical constituent</td>
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<tr>
<td><em>Piper regnellii</em></td>
<td>Eupomatenoid 5</td>
<td><img src="image1" alt="Structure" /></td>
<td><em>Leishmania amazonensis</em></td>
<td>Eupomatenoïd 5: It induces cell death in promastigote form by production of reactive oxygen species in addition to hypopolarization of mitochondrial potential.</td>
<td>[67,68]</td>
</tr>
<tr>
<td><em>Plumbago zeylanica</em></td>
<td>2-methyl-5-(3'-methyl-but-2'-enyloxy)-(1,4)naphthoquinone</td>
<td><img src="image2" alt="Structure" /></td>
<td><em>Leishmania donovani</em></td>
<td>2-methyl-5-(3'-methyl-but-2'-enyloxy)-(1,4)naphthoquinone: It acts by disrupting electron-transport chains (ETC) in the mitochondria of the parasite.</td>
<td>[69,70]</td>
</tr>
<tr>
<td><em>Glycyrrhiza glabra</em></td>
<td>18β-glycyrrhetinic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td><em>Leishmania donovani</em></td>
<td>18β-Glycyrrhetinic acid (GRA): It is a natural immunomodulator that mainly acts through nitric oxide (NO) upregulation and mainly affects visceral leishmaniasis.</td>
<td>[71,72]</td>
</tr>
<tr>
<td><em>Tanacetum parthenium</em></td>
<td>Parthenolide</td>
<td><img src="image4" alt="Structure" /></td>
<td><em>Leishmania amazonensis</em></td>
<td>Parthenolide: It increases the cysteine protease activity in promastigote form of</td>
<td>[73-75]</td>
</tr>
<tr>
<td>Plant name</td>
<td>Chemical constituent</td>
<td>Structure</td>
<td>Organism tested</td>
<td>Mechanism of action</td>
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<tr>
<td>(Feverfew or bachelor's buttons)</td>
<td></td>
<td></td>
<td>Leishmania amazonensis</td>
<td>Studies suggest that there is correlation between the megasomes and higher levels of protease activity in <em>leishmania</em>.</td>
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<tr>
<td>Dictyota pfaffii (Dictyota)</td>
<td>Dolabelladienetriol</td>
<td></td>
<td>Leishmania amazonensis</td>
<td>Dolabelladienetriol: NF-κB is a transcription factor that favors the leishmania replication. Dolabelladienetriol reduced the translocation of proteins from the cytoplasm into the nucleus of NF-κB. TGF-β also activate the leishmania replication so dolabelladienetriol diminish these factors and shows leishmanicidal activity.</td>
<td>[76-78]</td>
</tr>
<tr>
<td>Strychnos pseudoquina</td>
<td>Quercetin 3-O-methyl ether, Strychnobiflavone</td>
<td></td>
<td>Leishmania amazonensis</td>
<td>Quercetin 3-O-methyl ether: It act by inhibiting enzyme arginase that plays a central role in biosynthesis of polyamine which is very important and essential for guarding the parasite against oxidative stress and ROS produced via host's defence system.</td>
<td>[79,80]</td>
</tr>
</tbody>
</table>
### Table 2. Plants acting against amastigote form

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Chemical constituent</th>
<th>Structure</th>
<th>Organism tested</th>
<th>Way of use</th>
<th>Mechanism of action</th>
<th>Ref. no.</th>
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</thead>
<tbody>
<tr>
<td>Ferula szowitsiana</td>
<td>7-geranyloxy coumarin</td>
<td><a href="image">Structure</a></td>
<td>Leishmania major</td>
<td></td>
<td>Auraptene or 7-geranyloxy coumarin: It is a coumarin derivative that is believed to act by loss of mitochondrial membrane potential.</td>
<td>[81-83]</td>
</tr>
<tr>
<td>Voacanga africana (Senegal)</td>
<td>Voacamine</td>
<td><a href="image">Structure</a></td>
<td>Leishmania donovani</td>
<td>In vivo</td>
<td>Voacamine: It acts by inhibiting leishmania topoisomerase. The arrangement of DNA is altered by enzyme topoisomerase using three general mechanistic steps. In the first step the DNA binds with the enzyme and in second step one of the strands is cleaved by transesterification and subsequent strand rotation leading to the change in linking number by one or more than one. In the third step, the strand is relegated and enzyme is turned over for the next cycle. voacamine stabilizes the cleavage complex and inhibits the subsequent religation step but has no interaction with the free enzyme.</td>
<td>[84]</td>
</tr>
<tr>
<td>Plant name</td>
<td>Chemical constituent</td>
<td>Structure</td>
<td>Organism tested</td>
<td>Way of use</td>
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<tr>
<td><em>Lindera aggregate</em> (Spice bush)</td>
<td>Boldine</td>
<td><img src="image" alt="Boldine structure" /></td>
<td><em>Leishmania amazonensis</em></td>
<td>In vitro</td>
<td>Boldine: Boldine increases nitric oxide bioavailability in endothelial cells and restores endothelial functions.</td>
<td>[85,86]</td>
</tr>
<tr>
<td><em>Tridex procumbens</em> (Coat Buttons)</td>
<td>16,17-didehydro-falcarinol</td>
<td><img src="image" alt="16,17-didehydro-falcarinol structure" /></td>
<td><em>Leishmania mexicana</em></td>
<td>In vitro</td>
<td>16, 17-didehydro-falcarinol: Its antileishmanial activity is not because of activation mechanisms involving macrophages and NO production; instead it has direct effect on the parasite.</td>
<td>[87]</td>
</tr>
<tr>
<td><em>Picramnia gracilis</em></td>
<td>5,3'-hydroxy-7,4'-dimethoxyflavanone</td>
<td><img src="image" alt="5,3'-hydroxy-7,4'-dimethoxyflavanone structure" /></td>
<td><em>Leishmania braziliensis</em></td>
<td>In vitro/In vivo</td>
<td>5, 3'-hydroxy-7, 4'-dimethoxyflavanone: It is active against the amastigote form of <em>L. panamensis</em>. It acts by causing the chelation of iron thereby depriving the intracellular parasite from essential nutrients.</td>
<td>[88]</td>
</tr>
<tr>
<td><em>Calophyllum rivulare</em> (Santa Maria; mast wood, beauty leaf)</td>
<td>Amentoflavone</td>
<td><img src="image" alt="Amentoflavone structure" /></td>
<td><em>Leishmania amazonensis</em></td>
<td>In vitro</td>
<td>Amentoflavone: It triggers the inhibition of inducible nitric oxide synthase (iNOS) and has a direct cytotoxic action on intracellular form.</td>
<td>[89,90]</td>
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<td>Plant name</td>
<td>Chemical constituent</td>
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<tr>
<td><em>Syzygium aromaticum</em> (Clove)</td>
<td>Eugenol acetate</td>
<td><img src="image" alt="Eugenol Acetate Structure" /></td>
<td><em>Leishmania donovani</em></td>
<td><em>In vitro</em></td>
<td>Eugenol Acetate: Its leishmanicidal effect is found to be mediated by apoptosis, loss of mitochondrial membrane potential as well as reactive oxygen species generation.</td>
<td>[91]</td>
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<tr>
<td><em>Peschiera australis</em></td>
<td>Coronaridine</td>
<td><img src="image" alt="Coronaridine Structure" /></td>
<td><em>Leishmania amazonesis.</em></td>
<td><em>In vitro and In vivo</em></td>
<td>Coronaridine: It mainly affects the intracellular amastigote form of <em>leishmania amazonesis</em> by causing mitochondrial changes. It acts directly or indirectly by common macrophage mitochondrial mechanism like NO production.</td>
<td>[92,93]</td>
</tr>
<tr>
<td><em>Galipea panamensis</em></td>
<td>Phebalosin</td>
<td><img src="image" alt="Phebalosin Structure" /></td>
<td><em>Leishmania panamensis</em></td>
<td><em>In vitro</em></td>
<td>Phebalosin: it is not clear whether the in vitro activity of these metabolites is due to its general cytotoxic activity or if they possess a selective mode of action against L. panamensis.</td>
<td>[94]</td>
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<td>Plant name</td>
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<tr>
<td><em>Baccharis dracunculifolia</em> and <em>Aristolochia pubescens</em> (Birthwort, pipevine)</td>
<td>Neolignan</td>
<td>Neolignan: The neolignan has high <em>in vitro</em> leishmanicidal activity in both promastigote and amastigote forms of <em>L. amazonensis</em>, with minimum cytotoxic effects. It increases the defence potential and volume of endocytic vesicles by activating the lysosomal action in macrophages. Once macrophages reach to the site of infection, they bind to the substrate and start the polymerisation of actin filament and form phagosomes. The phagosomes undergo fusion resulting in the formation of phagolysosome that digest the particles. Neolignin restrain the phagocytic ability and lysosomal volume of macrophages and this contribute to the activity. Production of gaseous, inorganic molecule nitric oxide (NO) in macrophages is another significant mechanism. NO is produced when Stimulation of macrophages by IFN-γ and/or lipopolysaccharide (LPS) produces the NO. Being a free radical NO is exceptionally reactive and causes impairment of proteins and DNA. So according to these parameters the stimulation of</td>
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Ref. No. | [95,96] |
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<th>Plant name</th>
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<tbody>
<tr>
<td><em>Hypericum carinatum</em></td>
<td>Cariphenone A</td>
<td><img src="image1" alt="Structure" /></td>
<td>Leishmania amazonensis</td>
<td>In vitro</td>
<td>The NO release could be involved in anti-leishmanial activity. Cariphenone A and Isouliginosin B: These two compounds act by producing reactive oxygen species along with mitochondrial dysfunction in promastigotes form of <em>L. amazonensis</em>. They also induce low toxicity towards macrophages and red blood human cells, and kill the intracellular amastigote forms by a mechanism independent of nitric oxide.</td>
<td>[97]</td>
</tr>
<tr>
<td><em>Hypericum andinum</em></td>
<td>Isouliginosin B</td>
<td><img src="image2" alt="Structure" /></td>
<td>Leishmania amazonensis</td>
<td>In vitro</td>
<td>The mechanism of action of <em>Hypericum andinum</em> is still under investigation.</td>
<td>[98]</td>
</tr>
<tr>
<td><em>Croton pullei</em></td>
<td>Julio crotine</td>
<td><img src="image3" alt="Structure" /></td>
<td>Leishmania amazonensis</td>
<td>In vitro</td>
<td>Julio crotine: In case of amastigote form it acts on the parasitophorous vacuoles and cause reduction in the number of amastigotes whereas in promastigote form it induces the morphological changes like swelling of the mitochondria.</td>
<td>[99,100]</td>
</tr>
<tr>
<td>Plant name</td>
<td>Chemical constituent</td>
<td>Structure</td>
<td>Organism tested</td>
<td>Way of use</td>
<td>Mechanism of action</td>
<td>Ref. No.</td>
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<tr>
<td><em>Himatanthus sucuuba</em> (Plumeria)</td>
<td>Plumericin</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td><em>Leishmania amazonensis</em></td>
<td>In vitro</td>
<td>Plumericin: It acts by creating pores in the membrane of parasite and this causes the changes in the membrane functions of the cell and ultimately causes lethal effects.</td>
<td>[101, 102]</td>
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<tr>
<td><em>Vitis vinifera</em> (grape vine)</td>
<td>Resveratrol</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td><em>Leishmania amazonensis</em> and <em>Leishmania major</em></td>
<td>In vitro</td>
<td>Resveratrol: It causes alteration in the nucleus-kinetoplast ratio and affects the parasite cell cycle. It also affects the division pattern of the promastigotes.</td>
<td>[103-105]</td>
</tr>
</tbody>
</table>

and membrane structures present near the golgi apparatus.
Pentavalent antimonials represented by sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime) which were the usual treatment for leishmaniasis for several decades, are however being used to a limited extent due to side effects (anorexia, vomiting, dizziness, arthralgia, myalgia, fever) and cost effectiveness [28,29]. Their prospects are further marred by their toxicity profile that prohibits use in the person suffering from cardiac, renal and hepatic diseases and pregnant women [30].

In Europe and developed countries, Liposomal amphotericin B has been used but it is an expensive drug and has serious side effects such as infusion reactions, which include fever, chills, thrombophlebitis and occasionally hypokalemia, nephrotoxicity, myocardi...


23. Chang KP, Reed SG, McGwire BS, Soong L. Leishmania model for microbial virulence: The relevance of parasite


oleuropein is selectively regulated through

E Karampetsou K, Skaltsounis AL, Dotsika

L. infantum

amastigotes of

on promastigotes and intracellular

Domínguez M, Alunda JM

Corral

One. 2016

Zymowme LON4) and BALB/c mice. PloS

using Leishmania major (Sub

vitro

MF, Alkathiri B

Metwally DM, Alk

Infectious Diseases. 2016;20(1):48

oxidative stress. Brazilian Journal o

Zingiber zerumbet

composition and biological activity of the

Cantrell C, Ross SA


Ghaffarifar F, Heydari FE, Dalimi A, Hassan ZM, Delavar M, Mkaeilloo H. Evaluation of apoptotic and antileishmanial activities of Artemisinin on promastigotes and BALB/C mice infected with Leishmania


