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Mini Review

Unravelling Antileishmanial Mechanisms of Phytochemicals: From Mitochondrial Disruption to Immunomodulation

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Abstract

Leishmaniasis is a dangerous yet neglected tropical disease affecting a vast population of the world. Several medicinal plants and their constituents (natural products/phytochemicals) have been considered of prime importance for the management of leishmaniasis over the years. The present review sheds light on the molecular mechanisms of the constituents obtained from medicinal plants that are pre-clinically effective against leishmaniasis. Various mechanisms by which medicinal plant-derived natural products elicit their action against leishmaniasis are illustrated in the literature. The mechanisms identified include: disruption of cytoplasmic and mitochondrial membranes, induction of apoptosis and autophagy, modulation of gene expression and immunological pathways, pro-oxidant effects (disrupting redox balance) with mitochondrial dysfunction, cell cycle arrest, impaired cellular bioenergetics, i.e., adenosine triphosphate production and coagulation of cellular contents within *Leishmania* parasites. Future phytochemical and pharmacological (especially clinical) studies are necessary to further understand the mechanistic details of medicinal plant-derived natural compounds and to develop new phytotherapeutic entities from nature against leishmaniasis.

Introduction

Leishmaniasis is a dangerous disease that is spread by female sandflies of the Phlebotominae subfamily and is caused by protozoa of the genus *Leishmania* in humans. It is considered a neglected tropical disease by the World Health Organization (WHO) and is the second biggest parasitic killer in the world, after malaria. According to WHO estimates, this ailment is present in 88 countries and is responsible for serious health issues, particularly in developing nations, where 350 million people are at risk of contracting the illness and two million new cases are reported annually. The three main disease types are mucocutaneous, cutaneous, and visceral leishmaniasis. Over 90% of new cases of visceral leishmaniasis reported to the WHO in 2020 were found in Bangladesh, Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen. Bolivia, Brazil, Ethiopia, and Peru reported more than 90% of mucocutaneous leishmaniasis cases, and Afghanistan, Algeria, Brazil, Colombia, Iran, Libya, Pakistan, Peru, Syria, and Tunisia documented more than 85% of cutaneous leishmaniasis cases.[1,2]

The *Leishmania* parasite exhibits two morphological forms depending on the stage of its life cycle: amastigotes in the macrophages of the mammalian host and promastigotes in the gut of the sandfly vectors (Fig. 1). *L. donovani* is the cause of visceral leishmaniasis, also generally known as *kala-azar* (black fever). India, Bangladesh, Nepal, Sudan, Brazil, and Ethiopia account for more than 90% of all visceral leishmaniasis cases worldwide. The states of Bihar, Odisha, and Uttar Pradesh have reported the majority of leishmaniasis cases in India. There are more cases of cutaneous and mucocutaneous leishmaniasis in Afghanistan, Saudi Arabia, and some Latin American nations.[2,3]

Pentavalent antimonials (sodium stibogluconate and meglumine antimoniate), amphotericin B, pentamidine, and paromomycin are all effective treatments for human leishmaniasis. The aforementioned synthetic medications have certain drawbacks, such as high costs, the lack of effective oral formulations, or serious side effects that necessitate close patient monitoring. Additionally, it has been noted that the parasites quickly develop resistance, necessitating the development of new treatments to supplement or completely replace those already in use. Treatment has become even more difficult in recent years due to the co-infection of leishmaniasis and the human immunodeficiency virus.[3,4] Hence, identifying effective therapeutic options against leishmaniasis from natural sources appears to be an obvious need.

There are numerous reports on medicinal plants and their constituents (natural products/phytochemicals) effective pre-clinically

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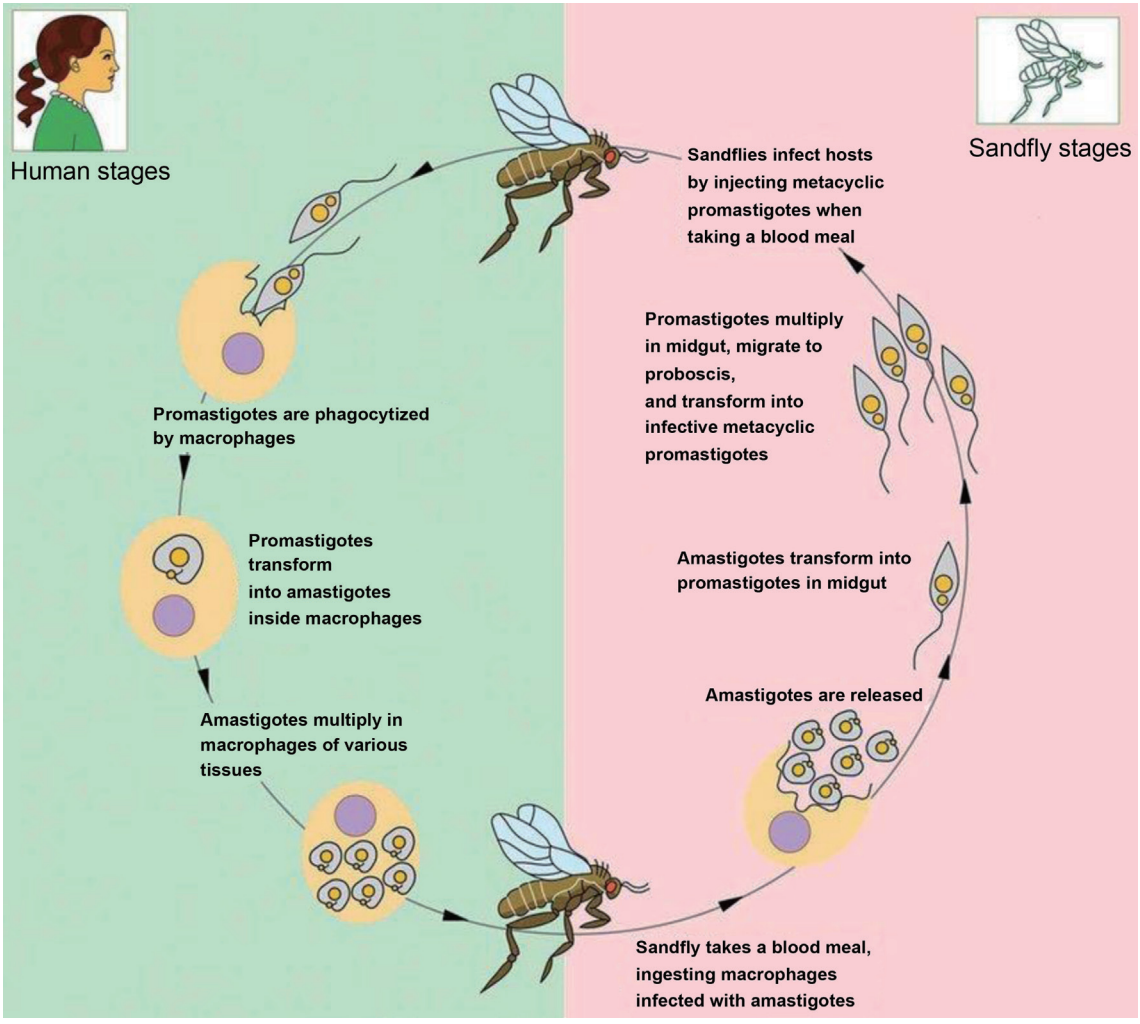

Fig. 1. *Leishmania* life cycle: When sandflies bite a mammalian host, the parasite *Leishmania* is transmitted. The flagellated parasitic form, known as a promastigote, enters the mammalian host. The disease leishmaniasis is caused by the parasites, which, inside the host, develop into immotile, non-flagellated amastigote forms.

against leishmaniasis, but their mechanisms of action were neither deduced nor stated in most cases.[1,3] There are several reviews collecting such pre-clinical studies on medicinal plants and their constituents against leishmaniasis, merely indicating their mechanisms in a succinct or diffuse way,[1,5] but there is no recent compilation dedicatedly deliberating on their mechanistic aspects. The goal of the current article was to carefully extract and illustratively review the mechanisms behind the antileishmanial effects of medicinal plant-derived natural constituents from the relevant literature.

Internet-based scanning of scientific literature was conducted by probing through an array of online bibliographic databases, including Google, Google Scholar, PubMed, Toxnet, Wiley, and Science Direct, using keywords and phrases such as "natural products", "natural constituents", "natural compounds", "phytochemicals" (their generic or chemical names) against "leishmaniasis", "*Leishmania sp*.", "antileishmanial", and "leishmanicidal", in various viable combinations. In the present review, experimental pre-clinical research articles published in English over the past 17 years (2007–2024) explicitly mentioning the observed antileishmanial mechanisms of plant-derived natural products (phytochemicals) that could be traced online were appraised. Representative articles describing key mechanisms were prototypically selected for illustration (Fig. 2). Only articles written exclusively in English were considered. Only pure natural products occurring in higher plants were included; plant extracts/fractions were not considered. Clinical studies were not included. Papers with vague or speculative antileishmanial mechanisms were excluded. Articles that were not peer-reviewed but were hosted on specific web portals as preprints were excluded. Mixtures of phytochemicals/natural products with other substances were also excluded from the current analysis.

Mechanism of action of medicinal plant-derived constituents

Various dietary, medicinal, and aromatic plants and their constituents have been reported to possess significant potential against leishmaniasis at the pre-clinical stage.[1,5] Most studies on medicinal plants do not furnish any mechanistic insights. However, some studies, as selected by the foregoing method, on medicinal plant-derived natural constituents or phytochemicals explicitly indicate their mechanisms of antileishmanial action in several ways (Fig.

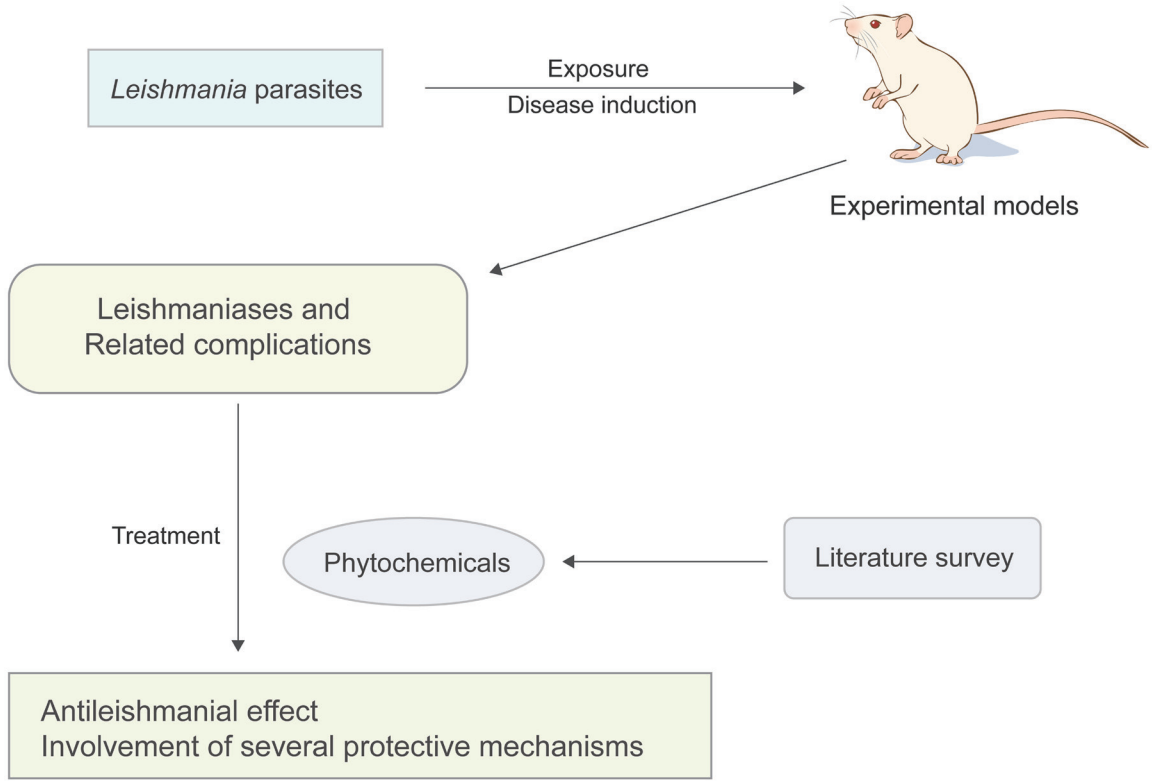

Fig. 2. Literature study on medicinal plant-derived constituents against leishmaniasis.

2). The mechanisms of those natural products are now illustratively discussed below (Fig. 3).

Some medicinal plants contain volatile or essential oils rich in various hydrophobic molecules (terpenes and terpenoids) that can easily diffuse across cytoplasmic membranes and thus reach intracellular targets like membrane-bound organelles. In this way, they can disrupt the integrity of cells and vital cellular structures like the mitochondria of different *Leishmania* parasites. They might

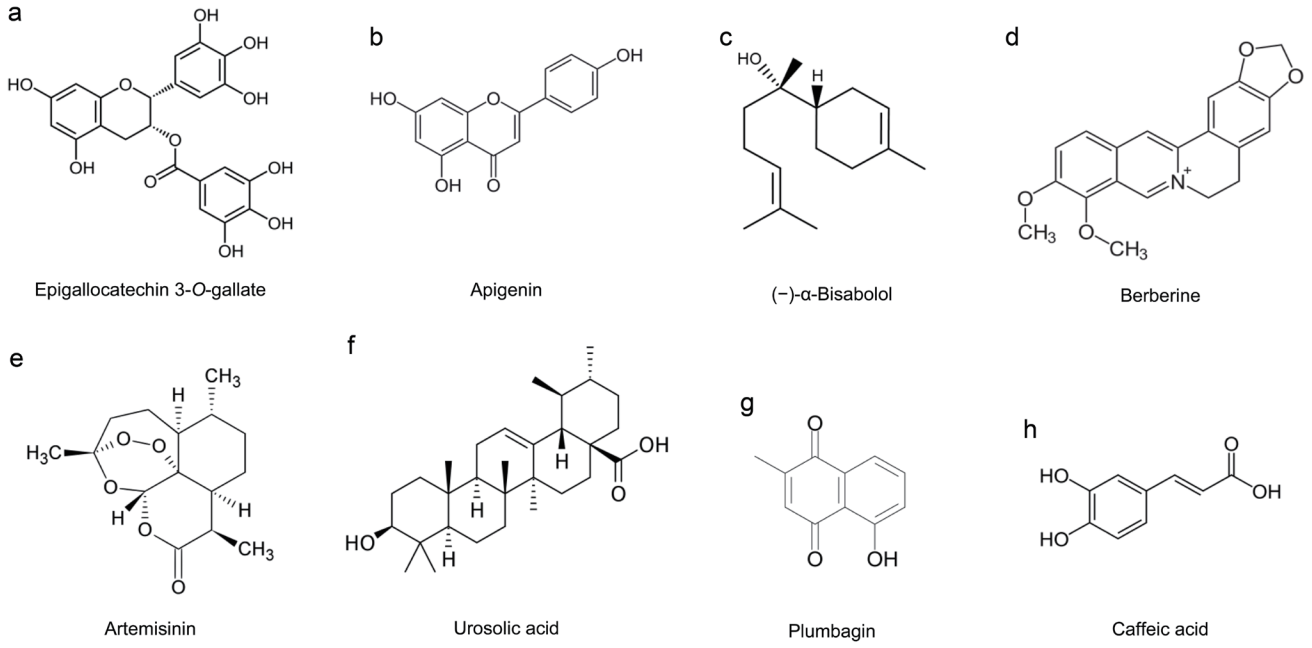

Fig. 3. Some antileishmanial natural constituents obtained from medicinal plants.

also affect ATPases and other key enzymes and proteins that are found in lipid-surrounded cytoplasmic membranes. Additionally, they may interfere with the enzymes needed for the synthesis of cellular structural elements or alter lipid-protein interactions in hydrophobic regions of tissue proteins, leading to cell cycle arrest and parasite death.[6,7]

Induction of apoptosis in *Leishmania* parasites is another notable mechanism of the antileishmanial action of plant-derived natural compounds. Here too, higher terpenoid compounds like sesquiterpenoids and triterpenoids (not constituents of essential oils) play a key role via multiple modes. For instance, the leishmanicidal effect of artemisinin (a sesquiterpene lactone) was deduced to be due to induction of apoptosis, mitochondrial membrane potential disruption (mitochondrial dysfunction), cell cycle arrest, and DNA (deoxyribonucleic acid) fragmentation (i.e., genotoxicity), along with reduced cellular energy, i.e., ATP generation, in *L.donovani* parasites, also causing reduced parasite burden in the spleen of mice.[8–10] Ursolic acid (a pentacyclic triterpenoid) causes mitochondria-dependent, but caspase 3/7-independent, programmed cell death, i.e., apoptosis, in *L. amazonensis* promastigotes. *In vivo*, cutaneous leishmaniasis lesion size and parasite load in affected mice were both decreased by this natural compound.[11] Chromatin condensation, phosphatidylserine externalization, and cytoplasmic membrane damage, all of which are signs of apoptosis, were brought on by (−)-α-bisabolol (a monocyclic sesquiterpenoid) in promastigote forms of two types of *Leishmania* parasites, viz. *L. amazonensis and L. infantum*. Additionally, this natural product precluded both the parasite's cellular bioenergetics, i.e., reduced ATP production, and interfered with the mitochondrial membrane potential, causing mitochondrial disruption.[12,13]

The antioxidant effect of medicinal plants and their constituents is considered responsible for several notable biological benefits.[14,15] Some plant-derived putative antioxidant compounds, on the other hand, are known to exert both antioxidant and pro-oxidant effects by increasing the production of reactive oxygen/nitrogen species (ROS) *in vivo* by hampering endogenous redox homeostasis.[16] Unicellular *Leishmania* parasites are known to possess an inefficient endogenous antioxidative defense system (as they have only one mitochondrion), making them susceptible to oxidative stress-induced deleterious events like mitochondrial dysfunction, DNA damage, apoptosis induction, and cell cycle arrest. Such compounds act by impairing the parasite's mitochondria through the induction of oxidative stress. The well-known antioxidant tea polyphenol epigallocatechin-3-*O*-gallate can raise ROS levels, which lowers the potential of the parasitic mitochondrial membrane and ATP production, causing a decrease in hepatic parasite load in visceral leishmaniasis induced by *L. infantum* in mice.[17] The leishmanicidal effect of apigenin (a flavonoid) in *L. amazonensis* promastigotes is due to increased ROS production, which led to mitochondrial collapse, demonstrated by significant swelling in the parasite mitochondria. This altered the mitochondrial membrane potential, disrupted the trans-Golgi network, and caused vacuolization of the cytoplasm.[18] Apigenin *in vivo* increased intracellular ROS production, which induced the host autophagy pathway via activated macrophages, thereby causing parasite death in *Leishmania*-infected mice.[19] A pro-oxidant effect is also exhibited by another known antioxidant flavonoid compound, namely quercetin, against *L. amazonensis* promastigotes and amastigotes. It induced overproduction of intracellular ROS, leading to parasitic mitochondrial collapse and, eventually, parasite death.[20,21]

Aside from the polyphenolics/flavonoids, other chemical classes of plant-derived natural compounds are also reported to possess pro-oxidant activity in this context.[16] An isoquinoline alkaloid, berberine, has leishmanicidal activity through over-generation of ROS in promastigotes, which increases mitochondrial oxidative stress, induces depolarization of the mitochondrial transmembrane potential, and causes ATP depletion, resulting in mitochondrial dysfunction.[22] Plant-derived quinones and oxylipins also exert their antileishmanial effects owing to their pro-oxidant activity against *Leishmania* parasites. For instance, a pro-oxidant effect via enzyme inhibition is reported to be the mechanism of action of plumbagin (a naphthoquinone) against *L. donovani* promastigotes and amastigotes. It has been demonstrated that trypanothione reductase, a crucial enzyme involved in *Leishmania* redox homeostasis, is inhibited noncompetitively by this compound, increasing ROS, disrupting the redox equilibrium, and inducing oxidative stress in the parasite.[23]

Parasitic mitochondrial damage is also reported to be induced by other plant-derived natural chemicals like seven coumarin derivatives (mammea A/BB (3–6)) isolated from *Calophyllum brasiliense* leaves. These compounds induce mitochondrial damage, as evidenced by mitochondrial swelling, mitochondrial membrane damage leading to depolarization of membrane potential, and aberrant changes in the ultrastructure of *L. amazonensis* promastigotes, resulting in parasite death.[24]

Some phytoconstituents interfere with the biomacromolecules of parasitic cells, leading to inhibition of enzymes, protein synthesis, and cell cycle arrest. For example, diphyllin (a lignan) isolated from *Haplophyllum bucharicum* was reported to exert antileishmanial effects in this manner both *in vitro* and *in vivo*.[25] Higher plant-derived lignans have already been reported to act in this way.[1,5] Two neolignans—threo, threo-manassantin A and threo, erythro-manassantin A—were found to be active against promastigotes and amastigotes of *L. amazonensis* by causing parasite morphological alterations and disrupting plasma membrane and nuclear functions.[26] Niranthin (a lignan) exerted antileishmanial effects in antimony-resistant *L. donovani* promastigotes and amastigotes by DNA topoisomerase I-mediated DNA-protein adduct formation inside the Leishmania cells and induced apoptosis by activation of cellular nucleases, leading to parasite death with minimal toxicity to host (mouse) cells.[27] Macrophage activation with increased phagocytic and lysosomal activity was reported to be the mode of antileishmanial action of 2,3-dihydrobenzofuran (a neolignan) against *L.amazonensis* promastigotes and amastigotes.[28]

Some plant-derived natural compounds are reported to act by multiple mechanisms. For example, caffeic acid (a polyphenol) was able to change the morphology and volume of promastigote cells along with loss of mitochondrial integrity, increased ROS production, exposure of phosphatidylserine, and loss of cytoplasmic membrane integrity, which led to an apoptosis-like process.[29,30] A flavonoid, namely 5,7,3,4-tetrahydroxy-6,8-diprenylisoflavone (CMt), when tested against promastigotes and axenic amastigotes of *L. amazonensis* and *L. infantum*, caused disruption of the parasitic cytoplasmic membrane and its potential, and imposed a pro-oxidant effect through increased ROS production.[31] Modulation of immunochemical pathways and increased expression of relevant transcription factors in macrophages and dendritic cells of mice infected with cutaneous leishmaniasis induced by *Leishmania mexicana* have been reported as the mechanism of antileishmanial action of two steroidal alkaloids, namely solamargine and solasonine, isolated from *Solanum sp*.[32] Immunomodulation was also found to be the antileishmanial mechanism of two diterpenes, namely 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide and 5-epi-icetexone, isolated from *Salvia cuspidata* against *Leish-*

mania amazonensis-infected mice.[33] Thus, different phytochemicals exert a protective role against experimental leishmaniasis in animal systems.

However, all of the foregoing studies and findings are preclinical in nature. The lack of ample relevant clinical studies limits their pharmacokinetic and pharmacodynamic corroboration in humans. The preclinically active natural products should be introduced to the clinical stage, alone or in combination with existing antileishmanial medications, for further compliance.

Future perspective

Isolation and identification of bioactive natural compounds from pertinent higher plants and their clinical evaluation for the treatment of leishmaniasis need to be carried out in future research to further understand the mechanistic details of putative natural products/phytochemicals. This will help develop newer phytotherapeutic entities from nature with minimal or no adverse reactions against leishmaniasis in humans. The growing phytotherapy evidence base offers a promising springboard for future clinical breakthroughs in herbal medicine.

Conclusions

Since the beginning of time, dietary, medicinal, and aromatic plants, as well as their active constituents, have been used to treat a wide range of human ailments worldwide, including leishmaniasis. This practice served as the foundation for modern or contemporary medicine. Several natural compounds obtained from medicinal plants (phytochemicals) have shown strong effects against different *Leishmania* species in preclinical studies under both *in vitro* and *in vivo* conditions. Medicinal plant-derived compounds can effectively manage leishmaniasis by killing the parasite and preventing its growth and transmission to hosts. The mechanisms, as extracted from the scientific literature, include disruption of cytoplasmic and mitochondrial membranes, induction of apoptosis and autophagy, gene expression and immunomodulatory pathways, pro-oxidant effects (disrupting cellular redox equilibrium) with mitochondrial dysfunction, cell cycle arrest, impaired cellular bioenergetics (ATP production), protein/enzyme interaction, and coagulation of cellular contents within the *Leishmania* parasites. The mitochondrion of the parasite (*Leishmania* has only one mitochondrion) is the chief target of most of the active natural products.

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Conflict of interest

Sanjib Bhattacharya is an employee of West Bengal Medical Services Corporation Ltd. The author has no other conflict of interest to note.

Author contributions

SB is the sole author of the manuscript.

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