Chapter 9

Alternative Treatment for Leishmaniasis

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Abstract

Leishmaniasis remains as one of the most important neglected diseases in the world and, after all these years, its treatment is still a problem, mainly because of the side effects caused by the first- and second-line drugs and the indiscriminate treatment, which leads to increasing cases of parasite resistance. The search for alternative therapies for the treatment of leishmaniasis is extremely important. In this context, the use of natural products arises as a promising alternative, combining the empirical knowledge disseminated in the population with researches that aim to scientifically prove the therapeutic effects of plants. Based on this, the use of medicinal plants is considered a desirable and accessible tool in the treatment of these diseases and considered by pharmacognosy as a valuable source for the development of new drugs and as adjuvant for conventional therapies.

Keywords: herbal medicine, *Leishmania* spp., natural products, visceral leishmaniasis, traditional medicine

1. Introduction

Protozoa of the genus *Leishmania* cause a broad spectrum of diseases collectively called Leishmaniasis, which represent a serious public health problem worldwide. Its clinical forms vary from cutaneous leishmaniasis (CL), characterized by tegumentary lesions that can heal and regress spontaneously, to visceral leishmaniasis (VL), more severe and potentially fatal, if not treated [1].

VL is an important zoonosis caused by parasites of the *Leishmania donovani* complex (*L. donovani* in India and Central Africa and *L. infantum* in America, Middle East, Central Asia, China, and the Mediterranean Basin) [2, 3]. It is present in 98 countries but, although widely distributed, more than 90% of cases are restricted to India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil [4, 5]. In the Americas, dogs are considered the main reservoir of the parasites, as well as an important link for the maintenance of the infection in the urban environment [6] (**Figure 1**).

Leishmania species have a complex life cycle, alternating between a permissive insect vector and a susceptible vertebrate host [8]. The transmission of the parasite occurs through the bite of an infected female sandfly, belonging to the genus *Phlebotomus*, in the Old World, or *Lutzomyia*, in the New World [9]. Once inside the vertebrate host, the promastigote forms inoculated by the insect will be phagocytosed by macrophages, transforming into amastigotes. After extensive multiplication, the amastigotes increase in quantity until the cell ruptures, leading to infection of other phagocytic cells, continuing the cycle [10].

Other forms of transmission have already been reported, such as vertical and/or sexual transmission [11], non-vector hematogenous [12, 13], and through other vectors, such as *Rhipicephalus sanguineus* [14], but their role in the maintenance of the disease is not totally clear yet.

In epidemiological terms, the dynamics of disease transmission is very complex and depends on several factors, such as the socioeconomic status of the population (poor living conditions, malnutrition), climate and environmental changes (which leads to sandfly adaptation and spread), host–parasite relationship (immunocompromised individuals, evasion mechanisms employed by the parasite), and population mobility (international travels and/or migration from non-endemic areas to endemic areas), which means that there may be differences in the pattern of disease spread, depending on the place [8, 15–18].

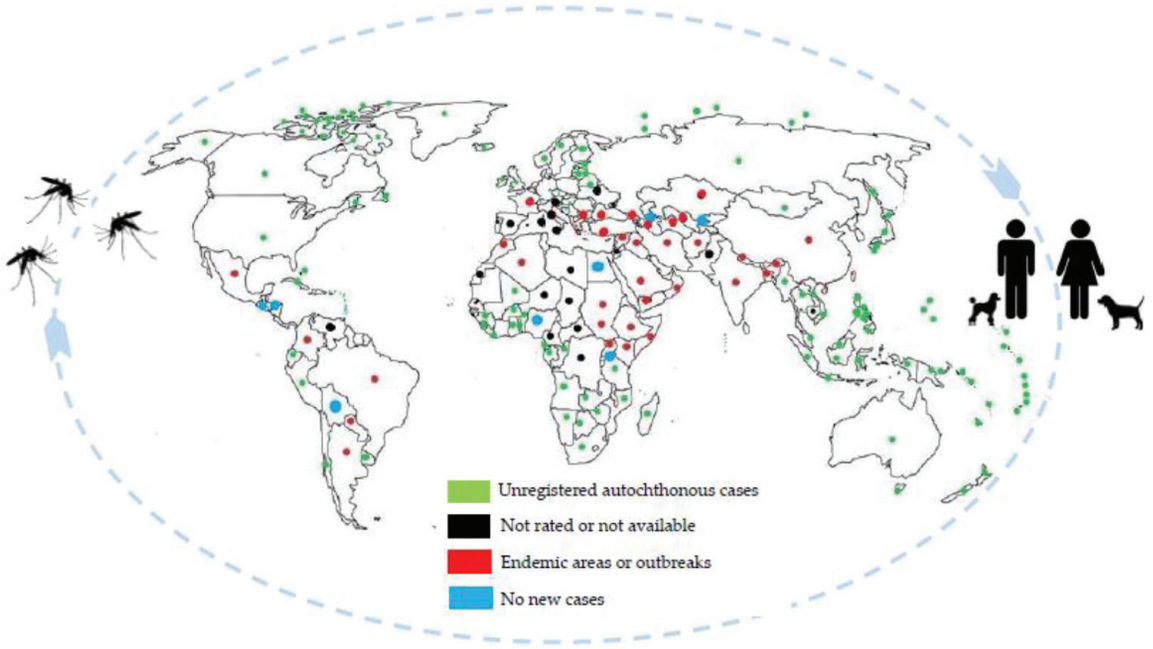

Figure 1. Status of endemicity of visceral leishmaniasis worldwide, 2015. Source: Adapted from WHO (2015) [7].

2. Therapeutic modalities for VL

2.1. Chemotherapy

Despite its importance for both human and animal health, there are few therapeutic options for VL treatment. The bases of therapeutic protocols in humans are the pentavalent antimonials (sodium stibogluconate and meglumine antimoniate), but the need of hospitalization and the severe side effects caused by its administration leads to high dropout rates among the patients, which contributes for parasite resistance in case of disease relapse. Although widely used, the mechanism of action of antimonials is still poorly understood [19, 20].

As a second-line drug, amphotericin B was initially recommended for patients who did not respond to the treatment with pentavalent antimonials. It presents high cure rates, efficacy, and safety, but, once again, needs prolonged hospitalization, for close monitoring of renal functions, and has some adverse effects, such as fever and chills [21, 22].

Miltefosine was the first oral drug used for VL cases, which simplified the treatment in several aspects. It was originally designed for breast cancer and other solid tumors, but the gastrointestinal side effects limited its use [23, 24]. In vitro and in vivo evidences of the antileishmanial activity of miltefosine [25–27] conducted in clinical trials in humans and its release for the treatment of human VL in many countries [28–30]. However, it should not be used in pregnant women due to its teratogenic effect [23]. Besides that, its indiscriminate use, incomplete treatment, and the long half-life of the drug has increased the cases of parasitic resistance, which represents a serious concern [31].

Other drugs are commonly used as therapeutic alternatives for VL, such as paromomycin, pentamidine, and sitamaquine. However, all have variable side effects or cure rates lower than the reference drugs [22, 32–36].

In general, all available drugs have problems related to toxicity and high costs, which hinders the treatment of Leishmaniasis, especially in poor and developing countries, where the great majority of the cases are concentrated [8]. For this reason, it is of great importance the adoption of strategies for the search and development of new candidate drugs. In this context, we emphasize the emergence of phytotherapy as a promising therapeutic alternative, since the use of natural products is widely disseminated in the population [37]. Therefore, it is necessary to combine the empirical knowledge with researches, with the aim to scientifically prove the therapeutic effects of plants—crude extracts, fractions or isolated substances—against *Leishmania* species, especially the causative agents of VL.

2.2. Phytotherapy

Medicinal plants are defined as those administered to man or animals, by any routes, that exert some therapeutical activity [38]. Plants are used as sources of new compounds throughout the history of mankind and, even today, serve as basis of many products used in the medical routine [39].

The use of medicinal plants has become, especially in developing countries, an alternative to traditional health services, both in rural areas, deprived of public health resources, as in

urban areas, as an option or as a complement to allopathic medication [40]. This tradition has been passed on to the populations in every generation, and is configured as a new science, the phytotherapy [41].

In countries with a great diversity of flora, such as Brazil, there is a great potential for the rational exploitation of plant resources and for the diffusion of herbal practices. Such practices are able to generate benefits both in the cultural point of view such as contributions to the scientific validation of the use of plant species [42, 43], since many of these are consumed without their pharmacological properties are, in fact, known [44].

The scientific community reveals a growing interest in this field, recognizing the true health benefit that plants provide [45]. The World Health Organization itself recognizes that the solution to combating numerous diseases, especially the so-called "neglected diseases," lies in the traditional knowledge and in the development of new drugs derived from biodiversity products [46].

Historically, experiments with the use of plants in medicine with therapeutical and healing purposes have been reported, which demonstrates that man began to use plants not only as food but also as a therapeutic resource for many diseases. Currently, many plant drugs are pointed out and described as viable alternatives in the treatment of many diseases [47], progressively abandoning empirical use based on experiments, starting for rational use based on iatrochemistry [48], based on the evident undesirable effects of some synthetic drugs [49].

Tagboto and Townson [50] describe as challenging the path of validation of the use of natural drugs and this includes not only the discovery of new drugs, but also the certification of products already used, culminating in the preservation of biodiversity. These authors report that, due to the widespread use of natural drugs being used, especially in underdeveloped countries, there was a need for certification of these products, and that due to these reasons, in 2000, the World Health Organization created a demand in order to qualify and regulate with scientific bases some medicines whose principles are already known, as well as empirical ones, in order to identify new possibilities within pharmacognosy.

3. Alternate therapies—mechanism of action

3.1. Immunomodulation by antileishmanial plant products

The immunological condition of a patient infected with *Leishmania* represents a determinant point for a favorable treatment. In visceral leishmaniasis, the immune system is markedly shaken by secondary infections and other opportunistic infections associated with the clinical picture of the disease, which emphasizes the need for drugs that not only favor immune recovery but also present a leishmanicidal action [51]. The modern medicine has changed the focus regarding the treatment of several diseases, such as neoplasms and infectious diseases. Traditionally, the drugs were developed to act directly on the microorganisms or neoplastic cells, but now, the main goal is to strengthen the body's defenses. Plants have several secondary metabolites, for example, flavonoids, polysaccharides, lactones, alkaloids, diterpenoids, and glycosides that may activate

the immunological system [52]. Regarding leishmaniosis treatment, Chouhan et al. [53] describe the use of medicinal plants as an alternative for modulating the patient's immune response as an effective device in therapy. A combination of miltefosine and nanoparticles of curcumin displayed lymphocyte proliferation and increased the phagocytic capacity of peritoneal macrophages. This effect was attributed to curcumin [54]. A substance isolated of *Casearia arborea*, tricin, was able to modulate the respiratory burst, which favors the parasite elimination [55].

Awareness of the importance of modulating the immune system has been a crucial point in the prevention and treatment of various diseases, and for this reason, the immunomodulatory properties of plants have been extensively explored so that researchers seek not only to affect the permanence of the pathogen but also have sought to boost both the patient's natural and adaptive defenses [56, 57]. This fact was observed by Almeida-Souza et al. [58], demonstrating a hypothesis that determines compounds obtained by different extraction methods can favor the increase of mediators such as nitric oxide (NO), increasing the functions and abilities of macrophages in the elimination of amastigote forms.

3.2. Reactive oxygen species generation

Against obligate intracellular parasite, macrophages use various mechanisms of action to control infection, as the induction of reactive oxygen and nitrogen species. Hydrogen peroxide is a major source of hydroxyl radicals and other reactive oxygen species, which macrophages produce in greater quantities [59, 60]. Among reactive nitrogen species, nitric oxide (NO) has a potent microbicide effect against intracellular parasites, such as *Leishmania* [61]. NO is a freely diffusible gas produced by the activity of inducible NO synthase (iNOS) enzyme by the conversion of *L*-arginine to *L*-citrulline. iNOS is induced by various pro-inflammatory factors such as cytokines or endotoxins [62]. In its short life, NO acts directly on pathogens by inhibition of proliferation, DNA mutagenesis, disruption of [FeS] clusters, metabolic blockade, and inactivation of virulence factors or molecules associated with infectious pathogens [63]. The functions of NO also include immunostimulatory (pro-inflammatory) effects that together with antimicrobial activity contribute to the killing of intracellular *Leishmania* as previous reported [58].

3.3. Apoptosis-inducing potential

The mechanism of action of leishmanicidal drugs is not well elucidated. It has been reported that both conventional drugs and some plants extracts used in the treatment of visceral leishmaniasis may induce a phenomenon like apoptosis in the parasite. The ethanolic extract of seeds and leaves of *Azadiracta indica* [64] and essentials oils of *Artemisia campestris* and *Artemisia herba-alba* [65] act as an apoptosis inductor in promastigotes of *L. donovani* and *L. infantum,* respectively.

4. Plants with antileishmanial properties

The available drugs against leishmaniasis do not always present a satisfactory result and have been shown as an expressive challenge for current treatment protocols [66]. Many plants that

Plant	Part of plant	Preparation	Species	Reference
Withania somnifera	Leaves; whole plant	Alcoholic fractions F5 and F6; tablets; methanolic extract (fraction A6)	*L. donovani*	Chandrasekaran et al. [68] Kaur et al. [73] Sharma et al. [74]
Inula chritmoides	Not cited	Acetone and dichloromethane extracts	*L. infantum*	Oliveira et al. [75]
Casearia arborea	Leaves	Methanolic extract	*L. infantum*	Santos et al. [55]
Curcuma longa	Rhizome	Oral formulation based on nanoparticles	*L. donovani*	Tiwari et al. [54]
Spergularia rubra	Not cited	Acetone and dichloromethane extracts	*L. infantum*	Oliveira et al. [75]
Ocimum sanctum	Leaves	Ethanolic extract	*L. donovani*	Bhalla et al. [76]; Kaur et al. [73]
Cocos nucifera	Husk fiber	Aqueous extract	*L. donovani*	Bhalla et al. [76]
Sterculia villosa	Bark	Methanolic extract	*L. donovani*	Das et al. [77]
Coccinia grandis	Leaves	Extract	*L. donovai*	Pramanik et al. [78] Das et al. [79]
Morinda citrifolia	Fruits	Aqueous extract Fruit juice	*L. chagasi*	Almeida-Souza et al. [80]
Solanum tuberosum	Tuber	Sodium bisulphite extraction	*L. donovani*	Paik et al. [81] Paik et al. [82]
Moringa oleifera	Flower	Ethyl acetate fraction	*L. donovani*	Singh et al. [83]
Azadirachta indica	Leaves and seeds	Ethanolic fraction and ethyl acetate fraction	*L. donovani*	Chouhan et al. [84]; Dayakar et al. [85]
Croton caudatus	Leaves	Hexanic extract	*L. donovani*	Dey et al. [86]
Artemisia annua	Leaves and seeds	n-hexane fractions	*L. donovani*	Islamuddin et al. [87] Islamuddin et al. [88]
Asparagus racemosus	Whole plant	Tablets	*L. donovani*	Kaur et al. [89] Sachdeva et al. [90]
Syzygium aromaticum	Flower	Essential oil	*L. donovani*	Islamuddin et al. [91]
Croton cajucara	Leaves	Essential oil	*L. chagasi*	Rodrigues et al. [7]
Solanocia mannii	Leaves	Extract	*L. donovani*	Hubert et al. [92]
Solanum torvum	Leaves	Extract	*L. donovani*	Hubert et al. [92]
Coriandrum sativum	Seeds	Oleoresin	*L. chagasi*	Rondon et al. [93]
Lippia sidoides	Not cited	Essential oil	*L. chagasi*	Rondon et al. [93]
Copaifera reticulata	Seeds	Essential oil	*L. chagasi*	Rondon et al. [93]
Spondias mombin	Aerial parts	Ethanolic extract (Sm3 fraction)	*L. chagasi*	Accioly et al. [94]
Annona squamosa	Leaves	Alkaloid and acetogenic extract	*L. chagasi*	Vila-Nova et al. [95]

Plant	Part of plant	Preparation	Species	Reference
Annona muricata	Seeds	Alkaloid and acetogenic extract	*L. chagasi*	Vila-Nova et al. [95]
Aloe vera	Leaves	Extract	*L. infantum*	Rondon et al. [96]
Coriandrum sativum	Seeds	Extract	*L. infantum*	Rondon et al. [96]
Ricinus communis	Leaves	Extract	*L. infantum*	Rondon et al. [96]
Valeriana wallichii	Root	Methanol and chloroform extracts	*L. donovani*	Ghosh et al. [97]
Momordica charantia	Fruit	Crude extract	*L. donovani*	Gupta et al. [98]
Kalanchoe pinnata	Leaves	Aqueous extract	*L. chagasi*	Gomes et al. [99]
Allium sativum	Bulb	Methanolic extract (fraction G3)	*L. donovani*	Sharma et al. [74]
Piper betle	Leaves	Methanolic extract and essential oil	*L. donovani*	Misra et al. [100]
Nyctanthes arbor-tristis	Leaves	Methanolic extract (fraction calceolariosidea)	*L. donovani*	Poddar et al. [101]
Aloe vera	Leaves	Exudate	*L. donovani*	Dutta et al. [102]
Tinospora sinensis	Powdered stem	Ethanolic extract	*L. donovani*	Singh et al. [103]
Chenopodium ambrosioides	Aerial parts	Essential oil	*L. donovani*	Manzote et al. [104]
Annona crassiflora	Stem bark	Exanolic and ethanolic extract	*L. donovani*	Mesquita et al. [105]
Himatanthus obovatus	Root wood	Exanolic and ethanolic extract	*L. donovani*	Mesquita et al. [105]
Guarea kunthiana	Roots	Exanolic and ethanolic extract	*L. donovani*	Mesquita et al. [105]
Cupania vernalis	Leaves	Exanolic and ethanolic extract	*L. donovani*	Mesquita et al. [105]
Serjania lethalis	Root bark	Exanolic and ethanolic extract	*L. donovani*	Mesquita et al. [105]

Table 1. Antileishmanial activity of plants against visceral leishmaniasis.

present anti-infectious characteristics have been studied for the careful detection of new active compounds isolated [67] of antiparasitic action and also as immunomodulators, so that they are shown as a collection of bioactive compounds for the optimization of the treatment of leishmaniasis [68], as well as the presence of active compounds belonging to several chemical groups [69–71], such as flavonoids, isoflavonoids, saponins, alkaloids, sesquiterpenes, polysaccharides, tannins, indoles, and glucans [72].

Much information about plants and formulations employed in popular medicine is contained in the literature, and based on this information, new constituents have been successfully perfected and clinically tested, correlating traditional and modern medicine, combining science and empiricism (**Table 1**). Traditional medicine is based primarily on personal experience, with the use of compounds not yet fully validated, requiring complementary evidence to become safe and effective [106].

5. Conclusion

The drugs available for the treatment of visceral leishmaniasis have adverse effects, a high cost, and, in addition, parasitic resistance is frequent. These facts are a challenge for modern science, which uses traditional medicine as a research source to find a compound that is effective and has minimal side effects. Many studies have been carried out, but the results obtained are not very encouraging. Most of the plants studied did not present leishmanicidal effect but the immunomodulatory effect has often been emphasized. Summarizing, data in the literature show that the substances obtained from the study of plants may be excellent allies in the treatment of leishmaniasis because they have immunomodulatory effects, but none has a direct effect against the parasite.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this chapter.

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