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Native Plants from Argentina Reported as Effective against *Leishmania* spp.

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ABSTRACT

Leishmaniasis represents a spectrum of diseases caused by infection with protozoan pathogens of the genus *Leishmania*. It is a major neglected tropical disease associated with high rates of disability and death, with extended endemic areas in the Americas. Despite current therapeutic approaches, current treatments for leishmaniasis are unsatisfactory due to high associated toxicity, cost, complex administration and the emergence of resistant strains. Because of this, efforts have greatly increased over the last decade to identify novel compounds with anti-leishmanial properties. Thus, one strategy in the search for new compounds is the screening of molecules purified from plant sources. The current work reviewed the available information about the Argentinean natural sources reported as effective against *Leishmania* spp.; including: its relevant chemical compounds, efficiency and applied methodology. Reported studies need to be considered as precursors works to extend the search between the profuse native plants from Argentina.

Keywords: Leishmaniasis, Natural compounds, Argentina, Complementary medicine

INTRODUCTION

Leishmaniasis represents a spectrum of diseases, highly associated to poverty, caused by infection with protozoan pathogens of the genus Leishmania, transmitted to a mammalian host via the bite of an infected female of sand flies [1]. It is a major neglected tropical disease associated with high rates of disability and death with an estimated 2 million new cases annually [2]. Clinically, there are 3 presentations of leishmaniasis: visceral, cutaneous and mucocutaneous. In the Americas, the endemic areas are extended from the South of United States to Argentina. In particular, the disease is endemic in 10 northern provinces of Argentina, and the incidence has been increasing annually since 1980 [3]. Although pentavalent antimonial drugs are the most prescribed treatment, several other interventions have been used with varying success. These include parenteral treatments with drugs such as pentamidine, amphotericin B, aminosidine and pentoxifylline, oral treatments with miltefosine and topical treatments with paromomycin (aminosidine) and aminoglycosides. Other treatments such as immunotherapy and thermotherapy have also been tested [4]. However, current treatments for leishmaniasis are unsatisfactory due to high associated toxicity, cost, complex administration and the emergence of resistant strains. Because of this, efforts have greatly increased over the last decade to identify novel compounds with anti-leishmanial properties [5-8]. Thus, one strategy in the search for new compounds is the screening of molecules purified from plant sources to be used alone or as a complement from the current available treatments.

Recently, Bekhit et al. [9] reviewed many natural derivatives, including: flavonoids, chalcones, naphthoquinones, iridoids, saponins, quinolones, diterpenoids and lignans; with reported *in vivo* and *in vitro* activity; and scarce or null toxicity. No reports about secondary resistance to the mentioned compounds are available. However, as occurs between cancer chemotherapeutics agents, the existence of several acceptable treatment options increases the achievable alternatives in secondary resistant disease cases.

Among the Argentinean natural sources, there are several native plants which evidenced activity against different *Leishmania* species. However, to promote the use of natural

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derivatives, the scientific approaches to determine leishmanicidal properties needs to considerate some particularities.

Plants conditions and origin

In relation to the plant sources, it is known that bioactive compounds are the secondary metabolites defined by the plant physiology status [10]. Then, adaptive features to soils, temperature, light-dark cycles, water salinity and availability are very important determinants of secondary metabolites presence and concentration. For this reason, in the current review, we considered only studies which involved Argentinean native plants grown in the country. In fact, regardless of some properties reported in plants considered as native from Argentina; because they were obtained and harvested in other remote countries, these findings are out of consideration in the present work.

EXPERIMENTAL APPROACHES TO DETERMINE LEISHMANICIDAL ACTIVITY

Other opportune item to consider is related to the experimental methodology used to assign the leishmanicidal activity. *Leishmania* spp. is a digenetic organisms alternating between a flagellated promastigote, in the gut of the sand fly vector; and an intracellular amastigote, in the mammalian host. While, the *in vitro* systems may be potentially used for compounds which have direct lethal action on parasite; other compounds which actions are related to host defense system, cannot be study by this methodology. Therefore, sometimes, *in vitro* assays may not be transferable to *in vivo* situations [11].

In addition, inside of *in vitro* models, it is important to take into account the stages of development of the parasite used experimentally. The promastigotes grown in axenic cultures have been used to screen potential anti-leishmanial agents and the advantages of this system explain its wide popularity. The simplest model to be utilized is the one in which the promastigotes multiply in cell free media [12]. The technique is simple and easily applicable; however, the metabolism and ecology of promastigote differ widely from those of amastigote (target form). In consequence, the screening data obtained from *in vitro* test with promastigote have very little value in animals [13]. Ideally, to be efficient and exhaustive, a drug screening procedure requires conditions that mimic the environment encountered by the target cell. For *Leishmania*, intracellular form of the parasite (amastigotes) might represent the typical conditions. In fact, a direct comparison of the drug susceptibility towards standard anti-leishmanial drugs, between amastigotes and axenic amastigotes, demonstrates a good correlation to many, if not all the drug tested [14].

About the *in vivo* models related to leishmaniasis, when cutaneous forms are studied, the methods to infect animals are intradermal or subcutaneous inoculations [15,16]; while in the visceral forms: intravenous, intraperitoneal and intracardiac inoculations are commonly used [17,18]. The assays outputs can change between lesions measurements, pathological analysis and serological determinations. Usually, blood samples and dissected organs are used to perform DNA, proteins, cytokines or inflammatory cells determinations.

A less common method is the use of bioluminescent parasites to quantify *Leishmania* spp. infection in the ear; which is a more sophisticated and accurate approach compared with the more traditional measurements of lesion diameter, volume, and thickness [19].

Actually, the vast majority of leishmaniasis *in vivo* models use a needle challenge of parasites alone and in large quantities. Moreover, *Leishmania* spp. is transmitted to animals and humans by a sand fly vector. The current use of murine models has been questioned in that it does not represent the clinical disease progression or immune response seen in humans [20].

Argentinean plants effective against *Leishmania* spp.

In **Table 1** are summarized the reported Argentinean plants bioactive against *Leishmania* spp. To be exhaustive, the parasites species and stages, plant sources used and main chemical groups described in the bibliography, are ordered and enumerated.

At least, 8 different species were reported as leishmanicidal agents, included into 5 taxonomic families. All the mentioned plants were reported as used by its ethnopharmacological properties, and none of them were originally related to the leishmaniasis disease.

From a chemical point of view, there are 2 different species without an analytical characterization of metabolites. Both, the methanolic extracts of *Mikania periplocifolia* and *Parietaria debilis* evidenced leishmanicidal activity against *L. mexicana* amastigotes, but not chemical structures were described as related to the induced cytotoxicity. By other side, phenols, and particularly flavonoids, are the most common plant metabolites related to the anti-parasitic activity. The 3-Heptadecyl-5-methoxy-phenol and 1,3-Dimethoxy-5-pentadecyl-benzene derived from *Oxalis erythrorhiza*; 2,8-dihydroxy-7H-furo[2,3-f]chromen-7-one derived from *Tibouchina paratropica*; hispidulin from *Ambrosia tenuifolia*; santin from *Eupatorium buniifolium*; 5-desmethylsinensetin and eupatorin obtained from *Stevia satureiifolia* represent the major group of identified compounds related to the Argentinean anti-leishmanial natural derived compounds. One particular consideration is necessary to embelin, a natural derivative identified from *Oxalis erythrorhiza*. The compound is widely reported as component of herbs used in the traditional medicine of India. Between its described properties, it is relevant to mention the effects on chronic diseases such as tumors, autoimmune inflammatory diseases, parasitic infections, microbial infections, diabetes, obesity and cardio-cerebral vascular

diseases [27]. Finally, lindbergin E, F, G and H isolated from Elaphoglossum lindbergii are the unique acylphloroglucinos which reported cytotoxicity in Leishmania species.

Table 1. Native plants form Argentina reported as effective against *Leishmania* spp.

Plant ID	Plant source	Chemical group	*Leishmania* spp.	Assayed system	References
Oxalis erythrorhiza (Oxalidaceae)	Whole plant	Phenols and Benzoquinones	*L. amazonensis* *L. donovani*	Promastigotes, *in vitro*	[21]
Ambrosia tenuifolia (Asteraceae)	Aerial parts	Flavonoids	*L. mexicana*	Promastigotes, *in vitro*	[22]
Eupatorium buniifolium (Asteraceae)	Aerial parts	Flavonoids	*L. mexicana*	Promastigotes, *in vitro*	[22]
Mikania periplocifolia (Asteraceae)	Aerial parts	None	*L. mexicana*	Amastigotes, *in vitro*	[23]
Parietaria debilis (Urticaceae)	Aerial Parts	None	*L. mexicana*	Amastigotes, *in vitro*	[23]
Tibouchina paratropica (Melastomataceae)	Aerial Parts	Phenols	*L. donovani*	Promastigotes, *in vitro*	[24]
Elaphoglossum lindbergii (Dryopteridaceae)	Rhizomes and roots	Acylphloroglucinols	*L. braziliensis* *L. amazonensis*	Promastigotes, *in vitro*	[25]
Stevia satureiifolia (Asteraceae)	Aerial parts	Flavonoids	*L. braziliensis*	Promastigotes, *in vitro*	[26]

CONCLUSION

The reviewed works provide a several number of promissory compounds; however, to confirm its reported activities, the uses of *in vivo* models result mandatory. Notwithstanding, in most of the cases, the chemical characterization of bioactive molecules could facilitate further researches and promote synthetic molecules production and semi-synthetic modifications destined to enhance the original properties described and its bioavailabitlity. Finally, well conduced researches between Argentinean natural sources are promissory to detect plant derivatives with therapeutic properties against leishmaniasis.

REFERENCES

1. Calderón-Anyosa R, Gálvez-Petzoldt C, García PJ, Carcamo CP (2018) Housing characteristics and leishmaniasis: A systematic review. Am J Trop Med Hyg 99: 1547-1554.
2. WHO (2016) Leishmaniasis. Available from: http://www.who.int/mediacentre/factsheets/fs375/en/
3. Salomon OD, Quintana MG, Mastrangelo AV, Fernandez MS (2012) Leishmaniasis and climate change-case study: Argentina. J Trop Med 2012: 601242.
4. Reveiz L, Maia-Elkhoury ANS, Nicholls RS, Sierra Romero GA, Yadon ZE (2013) Interventions for American cutaneous and mucocutaneous leishmaniasis: A systematic review update. PLoS One 8: e61843.
5. Berbert TRN, de Mello TFP, Wolf Nassif P, Mota CA, Silveira AV, et al. (2018). Pentavalent antimonials combined with other therapeutic alternatives for the treatment of cutaneous and mucocutaneous

leishmaniasis: A systematic review. Dermatol Res Pract 2018: 9014726.

6. Hasnain MG, Nath P, Maruf S, Nabi SG, Hossain AFMA, et al. (2018). Amphotericin B deoxycholate for relapse visceral leishmaniasis in Bangladesh: A cross-sectional study. BMC Res Notes 11: 918.
7. Sunyoto T, Boelaert M, Meheus F (2018). Understanding the economic impact of leishmaniasis on households in endemic countries: A systematic review. Expert Rev Anti Infect Ther.
8. Sereno D, Harrat Z, Eddaikra N (2019). Meta-analysis and discussion on challenges to translate Leishmania drug resistance phenotyping into the clinic. Acta Trop 191: 204-211.
9. Bekhit AA, El-Agroudy E, Helmy A, Ibrahim TM, Shavandi A, et al. (2018) Leishmania treatment and prevention: Natural and synthesized drugs. Eur J Med Chem.
10. Kinghorn AD, Pan L, Fletcher JN, Chai H (2011) The relevance of higher plants in lead compound discovery programs. Nat Prod 74: 1539-1555.
11. Gupta S, Nishi (2011) Visceral leishmaniasis: Experimental models for drug discovery. Indian J Med Res 133: 27-39.
12. Neal RA (1984) *Leishmania major*: Culture media, mouse strains and promastigote virulence and infectivity. Exp Parasitol 57: 269-273.
13. Croft SL, Seifert K, Yardley V (2006) Current scenario of drug development for1eishmaniasis. Indian J Med Res 123: 399-410.
14. Callahan HL, Portal AC, Devereaux R, Grogl M (1997) An axenic amastigote system for drug screening. Antimicrob Agents Chemother 41: 818-822.
15. Vera AM, Casadiego OA, Mantilla JC, Escobar P (2018) Evaluation of ketoconazole formulations for topical use in cutaneous leishmaniasis caused by Leishmania (Viannia). Rev Peru Med Exp Salud Publica 35: 476-482.
16. Koutsoni OS, Karampetsou K, Kyriazis ID, Stathopoulos P, Aligiannis N, et al. (2018) Evaluation of total phenolic fraction derived from extra virgin olive oil for its anti-leishmanial activity. Phytomedicine 47: 143-150.
17. Jawed JJ, Banerjee S, Bandyopadhyay S, Parveen S, Chowdhury BP, et al. (2018) Immunomodulatory effect of Arabinosylated lipoarabinomannan restricts the progression of visceral leishmaniasis through NOD2 inflammatory pathway: Functional regulation of T-cell subsets. Biomed Pharmacother 106: 724-732.
18. Moreira Nd, Vitoriano-Souza J, Roatt BM, Vieira PM, Coura-Vital W, et al. (2016) Clinical, hematological and biochemical alterations in hamster (*Mesocricetus auratus*) experimentally infected with *Leishmania infantum* through different routes of inoculation. Parasit Vectors 9: 181.
19. Schuster S, Hartley MA, Tacchini-Cottier F, Ronet C (2014) A scoring method to standardize lesion monitoring following intra-dermal infection of Leishmania parasites in the murine ear. Front Cell Infect Microbiol 4: 67.
20. Mears ER, Modabber F, Don R, Johnson GE (2015) A review: The current *in vivo* models for the discovery and utility of new anti-leishmanial drugs targeting cutaneous leishmaniasis. PLoS Negl Trop Dis 9: e0003889.
21. Feresin GE, Tapia A, Sortino M, Zacchino S, Rojas de Arias A, et al. (2003) Bioactive alkyl phenols and embelin from Oxalis erythrorhiza. J Ethnopharmacol 88: 241-247.
22. Sülsen VP, Cazorla SI, Frank FM, Redko FC, Anesini CA, et al. (2007) Trypanocidal and leishmanicidal activities of flavonoids from argentine medicinal plants. Am J Trop Med Hyg 77: 654-659.
23. Calderón AI, Romero LI, Ortega-Barría E, Solís PN, Zacchino S, et al. (2010) Screening of Latin American plants for anti-parasitic activities against malaria, Chagas disease and leishmaniasis. Pharm Biol 48: 545-553.
24. Tracanna MI, Fortuna AM, Contreras Cárdenas AV, Marr AK, McMaster WR, et al. (2015) Anti-leishmanial, anti-inflammatory and antimicrobial activities of phenolic derivatives from *Tibouchina paratropica*. Phytother Res 29: 393-397.
25. Socolsky C, Salamanca E, Giménez A, Borkosky SA, Bardón A (2015) Prenylated acylphloroglucinols with leishmanicidal activity from the fern *Elaphoglossum lindbergii*. J Nat Prod.
26. Beer MF, Frank FM, Elso OG, Bivona AE, Cerny N, et al. (2016) Trypanocidal and leishmanicidal activities of flavonoids isolated from *Stevia satureiifolia* var. *satureiifolia*. Pharm Biol.
27. Lu H, Wang J, Wang Y, Qiao L, Zhou Y (2016) Embelin and its role in chronic diseases. Adv Exp Med Biol 928: 397-418.