Plants with anti-*Leishmania* activity: Integrative review from 2000 to 2011

Ana Maria G. Brito, Derivaldo dos Santos, Sheyla A. Rodrigues, Renan G. Brito[1], Lauro Xavier-Filho

Institute of Technology and Research, Department of Biomedicine, Tiradentes University, Aracaju-SE, [1] Department of Physiology, Federal University of Sergipe, São Cristóvão-SE, Brazil

Submitted: 04-10-2012 Revised: 29-12-2012 Published: 01-06-2013

ABSTRACT

The search for more effective new drugs to treat *Leishmaniasis* is undoubtedly relevant. Our objective in this study was to investigate research publications addressing plants with anti-*Leishmaniasis* activity. An integrative review of the literature from 2000 to 2011 was carried out in the databases such as Latin-American and Caribbean Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), and Medical Literature Analysis and Retrieval System Online (MEDLINE). In the initial search, 150 articles were found, with 25 based in LILACS, 68 in SciELO, and 46 in MEDLINE. From these data, after reading the abstracts that were available online, we excluded 12 from LILACS, 39 from SciELO, and 28 from MEDLINE for presenting article duplications. This left 61 articles to be read; however, only 18 of them answered the research questions and determined the final sample of this review. The results showed that research involving the search for new drugs against *Leishmaniasis* should be intensified, especially for the amastigote form, and studies with *in vivo* tests could become a great strategy for successfully finding new treatments for *Leishmaniasis*. It is believed that it is extremely important and urgent to conduct more trials in search of new effective drugs against *Leishmaniasis* that possess minimal adverse effects and that are easily accessible to the public.

Key words: Anti-*Leishmania* activity, natural products, plants, scientific and technical publications

INTRODUCTION

Leishmaniasis caused by protozoan parasites of the genus *Leishmania* is endemic in 88 countries, including Europe and mainly the underdeveloped or developing countries. This potentially fatal tropical disease, whose study is currently being neglected,[1] is considered by the World Health Organization (WHO) as the second most important protozoan in regard to public health.

The main carriers of the parasite referred to above are domestic animals such as dogs, as well as wild animals, with the disease transmitted by the bite of female insects of the genus *Lutzomyia*; during the bite, the parasites are inoculated into the epidermis and dermis of their vertebrate hosts, including humans.[2] In the insect, the parasites are in the infective promastigote form, whereas in their vertebrate hosts, they are found in the amastigote form.[3]

The treatment for *Leishmaniasis* is complicated, since, in humans, the protozoan *Leishmania* is an obligate intracellular parasite of macrophages in the amastigote form.[4]

There is no vaccine available for the disease and the medications of first choice, the pentavalent antimonials, are toxic and administered exclusively by the parenteral route.[4] Moreover, resistance to these medications has been reported, a fact increasing for all forms of *Leishmaniasis* and especially in areas endemic for these threats to human health.[5]

Seifert and Croft,[6] studying the region of Bihar, India, where the prevalence of *Leishmaniasis* is quite pronounced, reported rates over 65% of non-responsiveness to treatment with pentavalent antimonials, which now-a-days are no longer used in these locations.

As second-line treatment in cases of resistance or intolerance to antimonials, amphotericin B is used in the lyophilized

Address for correspondence:
Prof. Ana Maria G. de Brito,
2151. Rua Oceânica. Condomínio Pátio Coroa do Meio,
Bl. Madrid. Apto. 11. Coroa do Meio, Aracaju-SE, CEP:
49.035-000, Brazil. E-mail: profanaguedes@yahoo.com.br

Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/0973-7847.112840

form of sodium deoxycholate – amphotericin B and pentamidine. However, due to the numerous adverse effects frequently developed by amphotericin B in the form of deoxycholate, new formulations have been produced and are currently commercially available. One of these formulations is liposomal amphotericin B. Its high cost, however, does not allow its routine use by health services in developing countries like Brazil.[7]

As for pentamidine, it belongs to the chemical group of diamidines and has been particularly useful in cases that do not respond to antimonials or in cases of individuals suffering from *Leishmaniasis* hypersensitive to antimony; however, its high toxicity becomes a limiting factor, leading to hypoglycemia, hypotension, cardiac abnormalities, nephrotoxicity, and even sudden death, as reported by some users.[8]

Another drug that has proven effective against visceral *Leishmaniasis* is paromomycin, considered an aminoglycoside and administered via parenteral route. It has shown a cure rate of 79% but has not been successful against cutaneous *Leishmaniasis,* besides having high renal toxicity.[9]

In the year 2002, miltefosine, originally developed as an anti-cancer substance, was registered in India to treat visceral *Leishmaniasis,* becoming the first oral treatment and the last leishmanicidal medication placed on the market.[10] In 2007, the medication mentioned above was also registered in Colombia for the treatment of cutaneous *Leishmaniasis*.[11] Since coming into clinical use, no cases of resistance to the treatment of *Leishmaniasis* with miltefosine have been reported. Studies indicate, however, the ease with which this resistance can occur, especially when the medication is used continuously.[12]

Azoles and allopurinol are two of many oral medications that are weakly active against *Leishmania*. These drugs are not useful as a single agent, and there are reports that they can interfere in the efficacy of the treatment of immunocompromised patients when the drugs are used in combination, although clinical trials to test this combination have not yet been performed.[13]

For Oliveira *et al*.,[9] the incidence of millions of new cases of *Leishmaniasis* per year worldwide and deficiencies in current treatment point to an urgent need for new medications to combat the parasitic diseases mentioned above.

According to the WHO, plants are the best and largest source of drugs for humanity, and Brazil has 60.7% of its territory in natural and planted forests, representing the second largest forest area in the world, only behind Russia.[14]

Thus, the purpose of this study was to perform an integrative literature review that consists of one of the research methods used in Evidence-Based Practice in Health and permits the consolidation of findings in care practice. This method can be directed to the definition of concepts, review of theories, or the methodological analysis of studies on a determined subject, helping to improve the knowledge of the research topic.[15]

With this in view, it can be understood that the search for new compounds that offer treatment options for *Leishmaniasis* is imminent. This study, then, asks the following research question: What findings discovered between 2000 and 2011 referred to the use of active ingredients from plants against *Leishmaniasis*?

In this scenario, it is believed that extracts or compounds of plant origin can be incorporated into a valuable starting point for the search of new therapeutic agents, since natural products and their derivatives, according to Basso *et al*.,[16] are the sources of 30% of the global pharmaceutical market. In an attempt to improve that knowledge related to the search for new molecules against *Leishmaniasis,* this study aimed to address research carried out with plants from 2000 to 2011 and published in databases, consolidated in the form of documents or articles that present promising anti-*Leishmania* results.

MATERIALS AND METHODS

In performing this review, we went through the following phases: Identification and selection of the theme of the research question; establishment of criteria for selection of the sampling; definition of information to be extracted from selected studies and ranking of the studies; assessment of the studies included in the integrative review; and finally, explanation of the results and presentation of the review.[17]

The bibliographic research was conducted from January 2012 to April 2012 in the following indexed databases: Scientific Electronic Library Online (SciELO), Latin-American and Caribbean Health Sciences (LILACS), and Medical Literature Analysis and Retrieval System Online (MEDLINE). As for the data search, we used terminologies registered in the descriptive sciences subject headings generated by the Virtual Health Library, standardized from the medical subject headings from the United States-National Library of Medicine, which allows the use of common terminology in English, Portuguese, and Spanish.

The groups of keywords used to search the databases were: *Leishmania*, medicinal plants, and natural products; *Leishmania*, anti-*Leishmaniasis,* and anti-*Leishmania*; leishmanicidal activity; visceral *Leishmania*, plants, and leishmanicidal activity; *Leishmania amazonensis*, anti-*Leishmanial* activity, and medicinal plants.

Table 1: Studies included in the integrative review of trials on plants with anti-*Leishmaniasis* activity. Aracaju, SE, 2012

Code	Article title	Journal/year	Study characteristics
01	Anti-*Leishmanial* activity of a linalool-rich essential oil from *Croton cajucara*	Antimicrobial Agents and Chemotherapy. Year: 2003	Place: Rio de Janeiro/BR Study type: Experimental Tested plants: 01
02	Antiparasitic activities of medicinal plants used in the IC	Journal of Ethnopharmacology. Year: 2004	Place: Zanza/IC Study type: Experimental Tested plants: 17
03	Effects of medicinal plant extracts on growth of *Leishmania (L.) amazonensis* and *Tripanossoma cruzi*	Brazilian Journal of Pharmaceutical Sciences. Year: 2005	Place: Maringá/BR Study type: Experimental Tested plants: 17
04	Anti-*Leishmanial* and trypanocidal activity of Brazilian Cerrado plants	Memórias do Instituto Oswaldo Cruz. Year: 2005	Place: Brasília/BR Study type: Experimental Tested plants: 13
05	Studies on the effectiveness of *Tanacetum parthenium* against *Leishmania Amazonensis*	International Journal on Protistology. Year: 2005	Place: Maringá/BR Study type: Experimental Tested plants: 01
06	Evaluation of the *in vitro* leishmanicidal activity of medicinal plants	Brazilian Journal of Pharmacognosy. Year: 2006	Place: São Luís/BR Study type: Experimental Tested plants: 17
07	*Leishmania* activity of the hydroalcoholic extract and fractions obtained from leaves of Piper *regnellii* (Micah) C. DC. var. *pallescens* (C. DC.) *Yunck*	Brazilian Journal of Pharmacognosy. Year: 2006	Place: Maringá/BR Study type: Experimental Tested plants: 01
08	Anti-*Leishmanial* and antifugal activity of plants used in traditional medicine in Brazil	Journal of Ethnopharmacology. Year: 2007	Place: Juíz de Fora/BR Study type: Experimental Tested plants: 20
09	Antiparasitic activity of some new caledonian medicinal plants	Journal of Ethnopharmacology. Year: 2007	Place: Canala/NC Study type: Experimental Tested plants: 18
10	*In vitro* activity of the alkaloids mixture of *Ervatamia coronaria (Jacq)* Staff. Apocynaceae on *Leishmania braziliensis amastigotes*	Brazilian Journal of Pharmacognosy. Year: 2008	Place: Bogotá/COL Study type: Experimental
11	*In vitro* evaluation of essentials oils activity from Colombians plants on *Leishmania braziliensis*	La Revista Colombiana de Ciencias Químico Farmacéuticas. Year: 2009	Place: Bogotá/COL Study type: Experimental Tested plants: 11
12	Antimicrobial and Anti-*Leishmanial* activity of essential oil from the leaves of *Annona foetida* (ANNONACEAE)	Química Nova. Year: 2009	Place: Manaus/BR Study type: Experimental Tested plants: 01
13	Antimicrobial activity of seeds and leishmanicidal *Pterodon emarginatus* Vogel	Brazilian Journal of Pharmacognosy. Year: 2009	Place: Juíz de Fora/BR Study type: Experimental
14	Evaluation of leishmanicidal action of ethanol extracts of *Crotalaria retusa* L.(Fabaceae)	Brazilian Journal of Pharmacognosy. Year: 2009	Place: Natal/BR Study type: Experimental Tested plants: 01
15	In vitro activity of the essential oil of *Cymbopongon citratus* and its major component (citral) on *Leishmania amazonensis*	Parasitology Research. Year: 2009	Place: Paraná/BR Study type: Experimental
16	Activity of essential oils on the growth of *Leishmania infantum promastigotes*	Flavour and Fragance Journal. Year: 2010	Place: Lisboa/POR Study type: Experimental
17	Chemistry, cytotoxity and anti-*Leishmanial* activity of the essential oil from Piper auritum	Memórias do Instituto Oswaldo Cruz. Year: 2010	Place: Havana/CUB Study type: Experimental Tested plants: 01
18	*In vitro* anti-*Leishmania amazonensis* activity of the polymeric procyanidin-rich aqueous extract from *Syagrus* coronate	Journal of Medicinal Plants Research. Year: 2011	Place: Rio de Janeiro/BR Study type: Experimental Tested plants: 01

BR=Brazil, IC=Ivory Coast, COL=Colombia, CUB=Cuba, NC=New Caledonia

In the initial search, 150 articles were found, with 25 based in LILACS, 68 in SciELO, and 46 in MEDLINE. From these data, after reading the abstracts that were availab le online, we excluded 12 from LILACS, 39 from SciELO, and 28 from MEDLINE for presenting article duplications. This left 61 articles to be read; however, only 18 of them answered the research questions and determined the final sample of this review, as 38 articles studied active ingredients that were not of plant origin.

The selection of the information was based on an instrument that was completed for each article from the final sampling of the review. The tool referred to above presented the following information: Identification of the article and authors, source

Table 2: Some botanical aspects of the plants in the present study

Scientific name	Family	Origin	Plant part used
Adenia lobata	Passifloraceae	Africa	Leaf
Aframomum sceptrum	Zingiberaceae	Africa/Tropical Asian	Leaf
Afrormosia laxiflora	Papilionaceae	Occidental Africa	Leaf/stem
Alchornea cordifolia	Euphorbiaceae	Africa	Leaf
Alstonia boonei	Apocyanaceae	Africa	Leaf/bark
Anacardium occidentale	Anacardiaceae	Brazil	Leaf/bark
Annona crassiflora	Annonaceae	Brazil	Stem/bark
Annona foetida	Annonaceae	Brazil	Leaf
Anogeissus leiocarpus	Combretaceae	Occidental Africa	Leaf/stem/bark
Bridelia ferrugínea	Euphorbiaceae	Africa	Leaf/bark
Cajanus cajan	Fabaceae	Tropical Africa	Leaf/seed
Callitris neocaledonica	Cupressaceae	New Caledonia	Wood
Callitris sulcata	Cupressaceae	New Caledonia	Wood
Carapa procera	Meliaceae	Brazil	Leaf/bark
Casearia sylvestris	Flacourtiaceae	Brazil	Leaf/stem/bark
Chenopodium ambrosioides	Chenopodiaceae	Tropical America	Leaf
Citrus macroptera	Rutaceae	Polynesian Islands	Leaf
Cordia verbenacea	Boraginaceae	Brazil	Leaf
Crotalaria retusa	Fabaceae	India	Leaf
Croton cajucara	Euphorbiaceae	Brazil	Leaf
Cymbopogon citratus	Gramineae	India	Leaf
Curcuma longa	Zingiberaceae	South Africa	Leaf
Dodonea viscosa	Sapindaceae	Brazil/Argentina	Leaf
Ervatamia coronaria	Apocynaceae	India	Leaf/seed
Eugenia uniflora	Myrtaceae	Brazil	Bark
Ficus proxila	Moraceae	Polynesia	Leaf
Hernandia cordigera	Hernadiaceae	France	Bark
Homalinum deplanchei	Flacourtiaceae	France	Bark
Lantana camara	Verbenaceae	Central America	Leaf
Lawsonia inermis	Lythraceae	Africa/India	Leaf
Lippia alba	Verbenaceae	Brazil	Leaf
Lippia multiflora	Verbenaceae	Africa/America	Leaf
Mallotus oppositifolius	Euphorbiaceae	Occidental Africa	Leaf
Manilkara dissecta	Sapotaceae	France	Leaf
Matricaria chamomilla	Asteraceae	Europe	Flower
Mikania glomerata	Asteraceae	Brazil	Leaf
Monodora myristica	Annonaceae	Occidental Africa	Seed
Morinda lucida	Rubiaceae	Nigeria	Leaf/stem
Murraya crenulata	Rutaceae	New Caledonia	Bark
Myoporum crassifolium	Myoporaceae	Australia	Wood
Myoporum tenuifolium	Myoporaceae	Australia	Leaf
Myristica fatua	Myristicaceae	Molucas Islands	Almonds
Ocimum gratissimum	Labiatae	India	Leaf/flower
Opilia celtidifolia	Opiliaceae	Africa	Leaf
Passiflora edulis	Passifloraceae	Tropical America	Leaf
Paullinia pinnata	Sapindaceae	Tropical Africa	Leaf/stem
Piper auritum	Piperaceae	Panama	Aerial part
Piper regnellii	Piperaceae	Panama	Leaf
Premna serratifolia	Laminaceae	France	Bark
Prumnopitys ferruginea	Podocarpaceae	New Caledonia	Leaf
Pterodon emarginatus	Fabaceae	Brazil	Seed
Rosmarinus officinalis	Lamiaceae	Tunisia	Leaf
Scaevala balansae	Goodneniaceae	France	Bark
Schinus terebinthifolius	Leguminosae	Argentina	Leaf
Solanum americanum	Solanaceae	India	Leaf
Syzygium jambolanum	Myrtaceae	India	Leaf
Terminalia glaucescens	Combretaceae	Africa	Leaf/bark
Uvaria afzelii	Annonaceae	Africa	Leaf/stem
Vernonia polyanthes	Fabaceae	Brazil	Leaf
Wollastonia biflora	Asteraceae	France	Leaf

location, purpose, research design, methodology, results, and main conclusions of each study, in accordance with Mendes *et al*.[18]

The articles were numbered according to order of occurrence, and the data were organized according to the concept of information to be drawn from the chosen publications.

Table 3: Plants with anti-*Leishmania* activity

Scientific name	Crude extract/essential oil	CI (50 µg/mL)	Test organism	Author	Year
Adenia lobata	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
		50*			
	Methylene chloride	>100*			
Aframomum sceptrum	Methanolic	50*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	12.5*			
	Alkaloid	>100*			
Afrormosia laxiflora	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
	Alkaloid	>100*			
Alchornea cordifolia	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
	Alkaloid	>100*			
Alstonia boonei	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
	Alkaloid	>100*			
Anacardium occidentale	Hydroalcoholic	5.4*	*L. amazonensis*	Luize *et al*.[20]	2005
		32.3**			
	Methanolic	>250*	*L. amazonensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Annona crassiflora	Crude extract	0.1-4.9*	*L. donovani*	Mesquita *et al*.[22]	2005
Annona foetida	Essential oil	16.2*	*L. amazonensis*	Costa *et al*.[23]	2009
		4.1*	*L. guianensis*		
		27.2*	*L. chagasi*		
		4.1*	*L. brasiliensis*		
Anogeissus leiocarpus	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
		>100*			
Bridelia ferrugínea	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	25*			
Cajanus cajan	Methanolic	62*	*L. amazonensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Callitris neocaledonica	Hydroalcoholic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Callitris sulcata	Hydroalcoholic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Carapa procera	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
Casearia sylvestris	Crude extract	0.1-4.9*	*L. donovani*	Mesquita *et al*.[22]	2005
Chenopodium ambrosioides	Hydroalcoholic	151.9*	*L. amazonensis*	Bezerra *et al*.[25]	2006
Citrus macroptera	Hydroalcoholic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Cordia verbenacea	Methanolic	120*	*L. amazonensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Crotalaria retusa	Crude extract	0.1-4.9*	*L. chagasi*	Rocha *et al*.[26]	2009
Croton cajucara	Essential oil	8.3*	*L. amazonensis*	Rosa *et al*.[27]	2003
		8.7**			
Cymbopogon citratus	Hydroalcoholic	98.0*	*L. amazonensis*	Luize *et al*.[20]	2005
	Hydroalcoholic	95.2*	*L. amazonensis*	Santin *et al*.[28]	2009
Curcuma longa	Hydroalcoholic	26.0*	*L. donovani*	Desrivolt *et al*.[24]	2007
Dodonea viscosa	Methanolic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methylene chloride	>50*			
Ervatamia coronaria	Alkaloid	2.6-12.4**	*L. brasiliensis*	Rodríguez *et al*.[29]	2008
Eugenia uniflora	Methylene chloride	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Ficus proxila	Methanolic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Hernandia cordigera	Methylene chloride	11.5*			
	Methanolic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Homalinum deplanchei	Methylene chloride	11.5*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methanolic	>50*			
Lantana camara	Methanolic	14.5*	*L. brasiliensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Lawsonia inermis	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
Lippia alba	Hydroalcoholic	8.5*	*L. amazonensis*	Luize *et al*.[20]	2005
	Essential oil	57.5**			
Lippia multiflora	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	12.5*			
Mallotus oppositifolius	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			

Contd...

Table 3: Contd...

Scientific name	Crude extract/essential oil	CI (50 µg/mL)	Test organism	Author	Year
Manilkara dissecta	Methanolic	13.4*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methylene chloride	>50*			
Matricaria chamomilla	Hydroalcoholic	98.1*	*L. amazonensis*	Luize *et al*.[20]	2005
		92.7**			
Mikania glomerata	Hydroalcoholic	52.5*	*L. amazonensis*	Luize *et al*.[20]	2005
		97.5**			
Monodora myristica	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
Morinda lucida	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	25*			
		>100**			
Murraya crenulata	Hexane	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Myoporum crassifolium	Methylene chloride	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Myoporum tenuifolium	Methylene chloride	19*	*L. donovani*	Desrivolt *et al*.[24]	2007
Myristica fatua	Methylene chloride	26.5*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methanolic	>50*			
Ocimum gratissimum	Methanolic	>250*	*L. amazonensis*	Braga *et al*.[21]	2006
		71*	*L. chagasi*		
Opilia celtidifolia	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
Passiflora edulis	Hydroalcoholic	150.1*	*L. amazonensis*	Bezerra *et al*.[25]	2006
Paullinia pinnata	Methylene chloride	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Hydroalcoholic	>100*			
	Alkaloid	>100*			
Piper auritum	Essential oil	52.1*	*L. amazonensis*	Monzote *et al*.[30]	2010
		12.8*	*L. donovani*		
		63.3*	*L. mexicana*		
Piper regnellii	Crude extract	167*	*L. amazonensis*	Nakamura *et al*.[31]	2006
	Hydroalcoholic	30*			
Premna serratifolia	Methylene chloride	4.4*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methanolic	>50*			
Prumnopitys ferruginea	Methanolic	>50*	*L. donovani*	Desrivolt *et al*.[24]	2007
Pterodon emarginatus	Essential oil	>100*	*L. amazonensis*	Dutra *et al*.[32]	2009
	Essential oil	>100*	*L. chagasi*		
	Methanolic	>100*	*L. amazonensis*		
Rosmarinus officinalis	Methanolic	44*	*L. amazonensis*	Braga *et al*.[21]	2006
	Methanolic	>250*	*L. chagasi*	Arévalo. *et al*.[33]	2009
Scaevala balansae	Methylene chloride	8.7*	*L. donovani*	Desrivolt *et al*.[24]	2007
	Methanolic	>50*			
Schinus terebinthifolius	Methanolic	55*	*L. amazonensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Solanum americanum	Methanolic	40*	*L. amazonensis*	Braga *et al*.[21]	2006
		>250*	*L. chagasi*		
Syzygium jambolanum	Hydroalcoholic	166.6*	*L. amazonensis*	Bezerra *et al*.[25]	2006
Terminalia glaucescens	Methanolic	>100*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
Uvaria afzelii	Methanolic	12.5*	*L. donovani*	Okpekon *et al*.[19]	2004
	Methylene chloride	>100*			
	Alkaloid	>100*			
Vernonia polyanthes	Methanolic	61*	*L. amazonensis*	Braga *et al*.[21]	2006
Wollastonia biflora	Methanolic	12.6*	*L. donovani*	Desrivolt *et al*.[24]	2007

Forms=(*) Promastigote, (**) Amastigote

Presentation of the results was in the form of a summary chart, two tables, and a descriptive discussion of the information.

RESULTS

Characterization of the studies analyzed

In regard to characterization, the findings from the 18 selected articles were published between 2003 and 2011. All studies had a quantitative approach and experimental character using analytes from plants [Tables 1-3].

We need to understand that studies with the type of approach above are used when seeking answers, such as for new drugs to treat *Leishmaniasis*, because the resistance of these protozoa to the drugs in use has been increasing worldwide,

justifying the relevance of these studies. The data in Table 1 represent the articles selected for this review.

Concerning the articles reviewed, it was noted that most had been published in journals specialized in the area of natural products research.

It was noted that the objectives of the studies were oriented toward testing the active ingredients (crude extract, essential oil, etc.) against the promastigote and amastigote forms of *Leishmaniasis*.

Regarding the origin of the publications, i.e., journal and year of publication, this information is detailed in Table 1. The observation of diverse publications can be justified due to *Leishmaniasis*' presence in 88 countries, with reported cases of drug resistance already existing in all of them.

DISCUSSION

Based on the materials analyzed, we were able to come up with pertinent questions to be answered in relation to research on plants for treatment against *Leishmaniasis*.

In recent years, the reasoning for the search for new anti-*Leishmania* molecules has been developed through basic techniques, such as impeding the growth of promastigotes *in vitro*, according to Liu.[34]

Acestor *et al*.[35] stated that there has been a limited availability of studies on the amastigote form. However, Davis, Murray and Hadman[36] argued that one cannot help noticing that the mechanism of action and interaction of medications in humans are often discovered after their indication and use. These authors also stated that, during the search for new medications, compounds may have been discarded for not demonstrating results *in vitro* or for possibly being pro-drugs.

For Leandro and Campino,[37] the resistance of protozoa such as *Leishmania* to medications used for treatment is increasing in developed countries. These authors believe that, in many cases, resistance is due to the expression of the ABC efflux pump (Adenosine-5-triphosphate (ATP) - binding cassette), since there are several classes of ABC transporters of *Leishmania* spp. protozoa, resulting in different phenotypes in the resistance to medications.

Efforts to investigate new molecules that are effective in treating *Leishmaniasis* include the germicidal potential of compounds derived from plants, as seen by Napolitano *et al*.,[38] who reported that in several regions of the world, many people rely on traditional practices for primary health care, and plants are essential sources of remedies.

For Mendonça-Filho *et al*.[39] and Desjeux,[40] the search for active plant molecules can lead to new strategies for the control of *Leishmaniasis*.

We believe that the scientific community should be more daring and develop innovative, sustainable research projects on the amastigote form *in vivo*, and conduct pre-clinical trials, and not remain content to carry out experiments *in vitro* on the promastigote form.

Through such initiatives, perhaps more robust results can be obtained for the treatment of *Leishmaniasis* that lead to more consolidated expectations that stimulate greater financial investments in research on natural products, not only against *Leishmaniasis* but also to combat other protozoan infectious diseases such as malaria, which is considered the most lethal parasitic disease worldwide.

Final considerations

Through this integrative review, it was possible to note that several researchers are dedicated to the search for new molecules that have efficacy against *Leishmaniasis*; however, it was also evident that, under the conditions of this study, the majority of tests were performed with the promastigote form.

We believe that these studies are undoubtedly important because promastigotes are infective to man and other animals. However, it is urgent that other studies be conducted using more and more compounds derived from plants with the aim of finding anti-amastigote activity, since the morbimortality associated with *Leishmania* is caused by this form.

Although publications have been increasing in recent years with regard to studies on plants that are likely to treat *Leishmaniasis*, it is still necessary that research developers invest more resources in this area, and thus minimize the lack of attention that has been given to these parasitic diseases.

REFERENCES

1. Gil S, Paula JR, Nascimento FR, Bezerra JC. Natural products with leishmanicide potential. J Basic App Pharm Sci 2008;29:223-30.
2. El-Safi S, Kheir MM, Bucheton B, Argiro L, Abel L, Dereure J, *et al*. Genes and environment in susceptibility to visceral *Leishmaniasis*. C R Biol 2006;329:863-70.
3. Marques N, Cabral S, Sá R, Coelho F, Oliveira J, Saraiva da Cunha JG, *et al*. Visceral *Leishmaniasis* and HIV infection in the HAART era. Acta Med Port 2007;20:291-8.
4. Rocha LG, Almeida JR, Macêdo RO, Barbosa-Filho JM. A review of natural products with anti-*Leishmanial* activity. Phytomedicine 2005;12:514-35.
5. Brendle JJ, Outlaw A, Kumar A, Boykin DW, Patrick DA, Tidwell RR, *et al*. Anti-*Leishmanial* activities of several classes of aromatic dications. Antimicrob Agents Chemother 2002;46:797-807.
6. Seifert K, Croft SL. *In vitro* and *in vivo* interactions between miltefosine and other anti-*Leishmanial* drugs. Antimicrob Agents Chemother 2006;50:73-9.

7. BRAZIL. Secretary of the Ministry of health surveillance health department surveillance epidemiology. Manual for the surveillance and control of visceral leishmaniasis/Ministry of health, Department of epidemiological surveillance-Brasilia: Publisher of the Ministry of health, 2006. p. 120.-(Series A. Technical Standards and Manuals).
8. Rath S, Trivelin LA, Imbrunito TR, Tomazela DM, Jesús MN, Marzal PC, *et al*. Antimonials employed in the treatment of leishmaniaisis: The state of the art. Química Nova 2003;26:550-5.
9. Wreje U, Nordgren B, Aberg H. Treatment of pelvic joint dysfunction in primary care: A controlled study. Scand J Prim Health Care 1992;10:310-5.
10. Ahua KM, Ioset JR, Ioset KN, Diallo D, Mauël J, Hostettmann K. Anti-*Leishmanial* activities associated with plants used in the malian traditional medicine. J Ethnopharmacol 2007;110:99-104.
11. Oliveira LF, Schubach AO, Martins MM, Passos SL, Oliveira RV, Marzochi MC, *et al*. Systematic review of the adverse effects of cutaneous *Leishmaniasis* treatment in the new world. Acta Trop 2011;118:87-96.
12. Choudhury K, Zander D, Kube M, Reinhardt R, Clos J. Identification of a *Leishmania* infantum gene mediating resistance to miltefosine and SbIII. Int J Parasitol 2008;38:1411-23.
13. Tempone AG, Martins de Oliveira C, Berlinck RG. Current approaches to discover marine anti-*Leishmanial* natural products. Planta Med 2011;77:572-85.
14. BRASIL. Ministério do Meio ambiente (MMA). Diretoria do programa nacional de conservação da biodiversidade (DCBio). Quarto relatório nacional para a convenção sobre diversidade biológica. Brasilia; 2010. p. 241.
15. Whittemore R, Knafl K. The integrative review: Updated methodology. J Adv Nurs 2005;52:546-53.
16. Basso LA, da Silva LH, Fett-Neto AG, de Azevedo WF Jr, Moreira Ide S, Palma MS, *et al*. The use of biodiversity as source of new chemical entities against defined molecular targets for treatment of malaria, tuberculosis, and T-cell mediated diseases: A review. Mem Inst Oswaldo Cruz. 2005;100:475-506.
17. Souza MT, Silva MD, Carvalho R. Integrative review: What is it? How to do it? Einstein 2012;8:102-6.
18. Mendes KD, Silveira RC, Galvão CM. Integrative literature review: A research method to incorporate evidence in health care and nursing. Texto Contexto – Enferm 2008;17:758-64.
19. Okpekon T, Yolou S, Gleye C, Roblot F, Loiseau P, Bories C, *et al*. Antiparasitic activities of medicinal plants used in Ivory Coast. J Ethnopharmacol 2004;90:91-7.
20. Luize PS, Tiuman TS, Morello LG, Maza PK, Ueda-Nakamura T, Dias Filho BP, *et al*. Effects of medicinal plant extracts on growth of *Leishmania (L.) amazonensis* and *Tripanossoma cruzi*. Braz J Pharm Sci 2005;41:85-94.
21. Braga FG, Bouzada ML, Fabri RL, Matos MO, Moreira FO, Scio E, *et al*. Anti-*Leishmanial* and antifugal activity of plants used in tradicional medicine in Brazil. J Ethnopharmacol 2007;111:396-402.
22. Mesquita ML, Desrivot J, Bories C, Fournet A, Paula JE, Grellier P, *et al*. Anti-*Leishmanial* and trypanocidal activity of Brazilian Cerrado plants. Mem Inst Oswaldo Cruz 2005;100:783-7.
23. Costa EV, Pinheiro ML, Silva JR, Maia BH, Duarte MC, Amaral AC, *et al*. Antimicrobial and Anti-*Leishmanial* activity of essential oil from the leaves of *Annona foetida* (Annonaceae). Química Nova 2009;32:78-81.
24. Desrivot J, Waikedre J, Cabalion P, Herrenknecht C, Bories C, Hocquemiller R, *et al*. Antiparasitic activity of some new caledonian medicinal plants. J Ethnopharmacol 2007;112:7-12.
25. Bezerra JL, Costa GC, Lopes TC, Carvalho IC. Avaliação da atividade leishmanicida *in vitro* de plantas medicinais. Braz J Pharmacogn 2006;16:631-7.
26. Rocha LG, Aragão CF, Loiola MI, Bezerril RA, Paiva NR, Holanda CM, *et al*. Evaluation of leishmanicida action of etanol extracts of *Crotalaria retusa* L.(Fabaceae). Braz J Pharmacogn 2009;19:51-6.
27. do Socorro S Rosa Mdo S, Mendonça-Filho RR, Bizzo HR, de Almeida Rodrigues I, Soares RM, Souto-Padrón T, *et al*. Anti-*Leishmanial* activity of a linalool-rich essential oil from *Croton cajucara*. Antimicrob Agents Chemother 2003;47:1895-901.
28. Santin MR, dos Santos AO, Nakamura CV, Dias Filho BP, Ferreira IC, Ueda-Nakamura T. *In vitro* activity of the essential oil of cymbopogon citratus and its major component (citral) on *Leishmania amazonensis*. Parasitol Res 2009;105:1489-96.
29. Moreno Rodriguez A, Robles Camargo J, Bello Garcia FJ. *In vitro* activity of the alkaloids mixture of ervatamia coronaria (Jacq) staff. Apocynaceae on *Leishmania* braziliensis amastigotes. Braz J Pharmacogn 2008;18:350-5.
30. Monzote L, García M, Montalvo AM, Scull R, Miranda M. Chemistry, cytotoxicity and anti-*Leishmanial* activity of the essential oil from *Piper auritum*. Mem Inst Oswaldo Cruz 2010;105:168-73.
31. Nakamura CV, Santos AO, Vendramett MC, Luize PS, Dias Filho BP, Cortez DA, *et al*. Anti-*Leishmanial* activity of hydroalcoholic extract and fractions obtained from leaves of *Piper regnellii* (Miq.) C. DC. var. *pallescens* (C. DC.). Braz J Pharmacogn 2006;16:61-6.
32. Dutra RC, Braga FG, Coimbra ES, Silva AD, Barbosa NR. Atividades antimicrobiana e leishmanicida das sementes de *Pterodon emarginatus* Vogel. Braz J Pharmacogn 2009;19:429-35.
33. Arévalo Y, Robledo S, Muñoz L, Granados-Falla D, Cuca LE, Delgado G. *In vitro* evaluation of essentials oils activity from Colombians plants on *Leishmania braziliensis*. Rev Colomb Cienc Quím Farm 2009;40:131-41.
34. Liu Y, Wang MW. Botanical drugs: Challenges and opportunities: Contribution to linnaeus memorial symposium. Life Sci 2008;82:445-9.
35. Acestor N, Masina S, Walker J, Saravia NG, Fasel N, Quadroni M. Establishing two-dimensional gels for the analysis of *Leishmania* proteomes. Proteomics 2002;2:877-9.
36. Davis AJ, Murray HW, Handman E. Drugs against *Leishmaniasis*: A synergy of technology and partnerships. Trends Parasitol 2004;20:73-6.
37. Leandro C, Campino L. *Leishmaniasis*: Efflux pumps and chemoresistance. Int J Antimicrob Agents 2003;22:352-7.
38. Napolitano DR, Mineo JR, de Souza MA, de Paula JE, Espindola LS, Espindola FS. Down-modulation of nitric oxide production in murine macrophages treated with crude plant extracts from the Brazilian cerrado. J Ethnopharmacol 2005;99:37-41.
39. Mendonça-Filho RR, Rodrigues IA, Alviano DS, Santos AL, Soares RM, Alviano CS, *et al*. Leishmanicidal activity of polyphenolic-rich extract from husk fiber of cocos nucifera Linn. (Palmae). Res Microbiol 2004;155:136-43.
40. Desjeux P. *Leishmaniasis*: Current situation and new perspectives. Comp Immunol Microbiol Infect Dis 2004;27:305-18.

How to cite this Article: Brito AG, Santos Dd, Rodrigues SA, Brito RG, Xavier-Filho L. Plants with anti-*Leishmania* activity: Integrative review from 2000 to 2011. Phcog Rev 2013;7:34-41.

Source of Support: Nil, **Conflict of Interest:** None declared