

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

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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

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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- <i>Leishmanial</i> activity of a linalool-rich essential oil from <i>Croton cajucara</i>	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 <i>Leishmania (L.) amazonensis</i> and <i>Trypanossoma cruzi</i>	Brazilian Journal of Pharmaceutical Sciences. Year: 2005	Place: Maringá/BR Study type: Experimental Tested plants: 17
04	Anti- <i>Leishmanial</i> 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 <i>Tanacetum parthenium</i> against <i>Leishmania Amazonensis</i>	International Journal on Protistology. Year: 2005	Place: Maringá/BR Study type: Experimental Tested plants: 01
06	Evaluation of the <i>in vitro</i> leishmanicidal activity of medicinal plants	Brazilian Journal of Pharmacognosy. Year: 2006	Place: São Luís/BR Study type: Experimental Tested plants: 17
07	<i>Leishmania</i> activity of the hydroalcoholic extract and fractions obtained from leaves of <i>Piper regnellii</i> (Micah) C. DC. var. <i>pallescens</i> (C. DC.) Yunck	Brazilian Journal of Pharmacognosy. Year: 2006	Place: Maringá/BR Study type: Experimental Tested plants: 01
08	Anti- <i>Leishmanial</i> and antifungal activity of plants used in traditional medicine in Brazil	Journal of Ethnopharmacology. Year: 2007	Place: Juiz 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	<i>In vitro</i> activity of the alkaloids mixture of <i>Ervatamia coronaria</i> (Jacq) Staff. Apocynaceae on <i>Leishmania braziliensis amastigotes</i>	Brazilian Journal of Pharmacognosy. Year: 2008	Place: Bogotá/COL Study type: Experimental
11	<i>In vitro</i> evaluation of essentials oils activity from Colombians plants on <i>Leishmania braziliensis</i>	La Revista Colombiana de Ciencias Químico Farmacéuticas. Year: 2009	Place: Bogotá/COL Study type: Experimental Tested plants: 11
12	Antimicrobial and Anti- <i>Leishmanial</i> activity of essential oil from the leaves of <i>Annona foetida</i> (ANNONACEAE)	Química Nova. Year: 2009	Place: Manaus/BR Study type: Experimental Tested plants: 01
13	Antimicrobial activity of seeds and leishmanicidal <i>Pterodon emarginatus</i> Vogel	Brazilian Journal of Pharmacognosy. Year: 2009	Place: Juiz de Fora/BR Study type: Experimental
14	Evaluation of leishmanicidal action of ethanol extracts of <i>Crotalaria retusa</i> L.(Fabaceae)	Brazilian Journal of Pharmacognosy. Year: 2009	Place: Natal/BR Study type: Experimental Tested plants: 01
15	<i>In vitro</i> activity of the essential oil of <i>Cymbopogon citratus</i> and its major component (citral) on <i>Leishmania amazonensis</i>	Parasitology Research. Year: 2009	Place: Paraná/BR Study type: Experimental
16	Activity of essential oils on the growth of <i>Leishmania infantum promastigotes</i>	Flavour and Fragrance Journal. Year: 2010	Place: Lisboa/POR Study type: Experimental
17	Chemistry, cytotoxicity and anti- <i>Leishmanial</i> activity of the essential oil from <i>Piper auritum</i>	Memórias do Instituto Oswaldo Cruz. Year: 2010	Place: Havana/CUB Study type: Experimental Tested plants: 01
18	<i>In vitro</i> anti- <i>Leishmania amazonensis</i> activity of the polymeric procyanidin-rich aqueous extract from <i>Syagrus coronate</i>	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 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, 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
<i>Adenia lobata</i>	Passifloraceae	Africa	Leaf
<i>Aframomum sceptrum</i>	Zingiberaceae	Africa/Tropical Asian	Leaf
<i>Afrormosia laxiflora</i>	Papilionaceae	Occidental Africa	Leaf/stem
<i>Alchornea cordifolia</i>	Euphorbiaceae	Africa	Leaf
<i>Alstonia boonei</i>	Apocyanaceae	Africa	Leaf/bark
<i>Anacardium occidentale</i>	Anacardiaceae	Brazil	Leaf/bark
<i>Annona crassiflora</i>	Annonaceae	Brazil	Stem/bark
<i>Annona foetida</i>	Annonaceae	Brazil	Leaf
<i>Anogeissus leiocarpus</i>	Combretaceae	Occidental Africa	Leaf/stem/bark
<i>Bridelia ferruginea</i>	Euphorbiaceae	Africa	Leaf/bark
<i>Cajanus cajan</i>	Fabaceae	Tropical Africa	Leaf/seed
<i>Callitris neocaledonica</i>	Cupressaceae	New Caledonia	Wood
<i>Callitris sulcata</i>	Cupressaceae	New Caledonia	Wood
<i>Carapa procera</i>	Meliaceae	Brazil	Leaf/bark
<i>Casearia sylvestris</i>	Flacourtiaceae	Brazil	Leaf/stem/bark
<i>Chenopodium ambrosioides</i>	Chenopodiaceae	Tropical America	Leaf
<i>Citrus macroptera</i>	Rutaceae	Polynesian Islands	Leaf
<i>Cordia verbenacea</i>	Boraginaceae	Brazil	Leaf
<i>Crotalaria retusa</i>	Fabaceae	India	Leaf
<i>Croton cajucara</i>	Euphorbiaceae	Brazil	Leaf
<i>Cymbopogon citratus</i>	Gramineae	India	Leaf
<i>Curcuma longa</i>	Zingiberaceae	South Africa	Leaf
<i>Dodonea viscosa</i>	Sapindaceae	Brazil/Argentina	Leaf
<i>Ervatamia coronaria</i>	Apocynaceae	India	Leaf/seed
<i>Eugenia uniflora</i>	Myrtaceae	Brazil	Bark
<i>Ficus proxila</i>	Moraceae	Polynesia	Leaf
<i>Hernandia cordigera</i>	Hernadiaceae	France	Bark
<i>Homalinum deplanchei</i>	Flacourtiaceae	France	Bark
<i>Lantana camara</i>	Verbenaceae	Central America	Leaf
<i>Lawsonia inermis</i>	Lythraceae	Africa/India	Leaf
<i>Lippia alba</i>	Verbenaceae	Brazil	Leaf
<i>Lippia multiflora</i>	Verbenaceae	Africa/America	Leaf
<i>Mallotus oppositifolius</i>	Euphorbiaceae	Occidental Africa	Leaf
<i>Manilkara dissecta</i>	Sapotaceae	France	Leaf
<i>Matricaria chamomilla</i>	Asteraceae	Europe	Flower
<i>Mikania glomerata</i>	Asteraceae	Brazil	Leaf
<i>Monodora myristica</i>	Annonaceae	Occidental Africa	Seed
<i>Morinda lucida</i>	Rubiaceae	Nigeria	Leaf/stem
<i>Murraya crenulata</i>	Rutaceae	New Caledonia	Bark
<i>Myoporum crassifolium</i>	Myoporaceae	Australia	Wood
<i>Myoporum tenuifolium</i>	Myoporaceae	Australia	Leaf
<i>Myristica fatua</i>	Myristicaceae	Molucas Islands	Almonds
<i>Ocimum gratissimum</i>	Labiatae	India	Leaf/flower
<i>Opilia celtidifolia</i>	Opiliaceae	Africa	Leaf
<i>Passiflora edulis</i>	Passifloraceae	Tropical America	Leaf
<i>Paullinia pinnata</i>	Sapindaceae	Tropical Africa	Leaf/stem
<i>Piper auritum</i>	Piperaceae	Panama	Aerial part
<i>Piper regnellii</i>	Piperaceae	Panama	Leaf
<i>Premna serratifolia</i>	Laminaceae	France	Bark
<i>Prumnopitys ferruginea</i>	Podocarpaceae	New Caledonia	Leaf
<i>Pterodon emarginatus</i>	Fabaceae	Brazil	Seed
<i>Rosmarinus officinalis</i>	Lamiaceae	Tunisia	Leaf
<i>Scaevola balansae</i>	Goodeniaceae	France	Bark
<i>Schinus terebinthifolius</i>	Leguminosae	Argentina	Leaf
<i>Solanum americanum</i>	Solanaceae	India	Leaf
<i>Syzygium jambolanum</i>	Myrtaceae	India	Leaf
<i>Terminalia glaucescens</i>	Combretaceae	Africa	Leaf/bark
<i>Uvaria afzelii</i>	Annonaceae	Africa	Leaf/stem
<i>Vernonia polyanthes</i>	Fabaceae	Brazil	Leaf
<i>Wollastonia biflora</i>	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
<i>Adenia lobata</i>	Methanolic	>100* 50*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
<i>Aframomum sceptrum</i>	Methylene chloride	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methanolic	50*			
<i>Afrormosia laxiflora</i>	Methylene chloride	12.5*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Alkaloid	>100*			
<i>Alchornea cordifolia</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	>100*			
<i>Alstonia boonei</i>	Alkaloid	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methanolic	>100*			
<i>Anacardium occidentale</i>	Methylene chloride	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Alkaloid	>100*			
<i>Annona crassiflora</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	>100*			
<i>Annona foetida</i>	Hydroalcoholic	5.4* 32.3**	<i>L. amazonensis</i>	Luize et al. ^[20]	2005
	Methanolic	>250* >250*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
<i>Annona crassiflora</i>	Crude extract	0.1-4.9*	<i>L. donovani</i>	Mesquita et al. ^[22]	2005
<i>Annona foetida</i>	Essential oil	16.2*	<i>L. amazonensis</i>	Costa et al. ^[23]	2009
		4.1* 27.2* 4.1*	<i>L. guianensis</i> <i>L. chagasi</i> <i>L. brasiliensis</i>		
<i>Anogeissus leiocarpus</i>	Methanolic	>100* >100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
<i>Bridelia ferruginea</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	25*			
<i>Cajanus cajan</i>	Methanolic	62* >250*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
<i>Callitris neocaledonica</i>	Hydroalcoholic	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Callitris sulcata</i>	Hydroalcoholic	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Carapa procera</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	>100*			
<i>Casearia sylvestris</i>	Crude extract	0.1-4.9*	<i>L. donovani</i>	Mesquita et al. ^[22]	2005
<i>Chenopodium ambrosioides</i>	Hydroalcoholic	151.9*	<i>L. amazonensis</i>	Bezerra et al. ^[25]	2006
<i>Citrus macroptera</i>	Hydroalcoholic	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Cordia verbenacea</i>	Methanolic	120* >250*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
<i>Crotalaria retusa</i>	Crude extract	0.1-4.9*	<i>L. chagasi</i>	Rocha et al. ^[26]	2009
<i>Croton cajucara</i>	Essential oil	8.3* 8.7**	<i>L. amazonensis</i>	Rosa et al. ^[27]	2003
<i>Cymbopogon citratus</i>	Hydroalcoholic	98.0*	<i>L. amazonensis</i>	Luize et al. ^[20]	2005
	Hydroalcoholic	95.2*	<i>L. amazonensis</i>	Santin et al. ^[28]	2009
<i>Curcuma longa</i>	Hydroalcoholic	26.0*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Dodonea viscosa</i>	Methanolic	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
	Methylene chloride	>50*			
<i>Ervatamia coronaria</i>	Alkaloid	2.6-12.4**	<i>L. brasiliensis</i>	Rodríguez et al. ^[29]	2008
<i>Eugenia uniflora</i>	Methylene chloride	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Ficus proxila</i>	Methanolic	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Hernandia cordigera</i>	Methylene chloride	11.5*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
	Methanolic	>50*			
<i>Homalinum deplanchei</i>	Methylene chloride	11.5*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
	Methanolic	>50*			
<i>Lantana camara</i>	Methylene chloride	14.5* >250*	<i>L. brasiliensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
	Methanolic	>250*			
<i>Lawsonia inermis</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
<i>Lippia alba</i>	Hydroalcoholic	8.5*	<i>L. amazonensis</i>	Luize et al. ^[20]	2005
	Essential oil	57.5**			
<i>Lippia multiflora</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	12.5*			
<i>Mallotus oppositifolius</i>	Methanolic	>100*	<i>L. donovani</i>	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
<i>Manilkara dissecta</i>	Methanolic	13.4*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
	Methylene chloride	>50*			
<i>Matricaria chamomilla</i>	Hydroalcoholic	98.1*	<i>L. amazonensis</i>	Luize et al. ^[20]	2005
		92.7**			
<i>Mikania glomerata</i>	Hydroalcoholic	52.5*	<i>L. amazonensis</i>	Luize et al. ^[20]	2005
		97.5**			
<i>Monodora myristica</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	>100*			
<i>Morinda lucida</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	25*			
<i>Murraya crenulata</i>	Hexane	>100**	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
		>50*			
<i>Myoporum crassifolium</i>	Methylene chloride	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Myoporum tenuifolium</i>	Methylene chloride	19*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Myristica fatua</i>	Methylene chloride	26.5*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
	Methanolic	>50*			
<i>Ocimum gratissimum</i>	Methanolic	>250*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
		71*			
<i>Opilia celtidifolia</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Methylene chloride	>100*			
<i>Passiflora edulis</i>	Hydroalcoholic	150.1*	<i>L. amazonensis</i>	Bezerra et al. ^[25]	2006
<i>Paullinia pinnata</i>	Methylene chloride	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
	Hydroalcoholic	>100*			
<i>Piper auritum</i>	Essential oil	>100*	<i>L. amazonensis</i> <i>L. donovani</i>	Monzote et al. ^[30]	2010
		52.1*			
<i>Piper regnellii</i>	Crude extract Hydroalcoholic	12.8*	<i>L. amazonensis</i> <i>L. mexicana</i>	Nakamura et al. ^[31]	2006
		63.3*			
<i>Premna serratifolia</i>	Methylene chloride Methanolic	167*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
		30*			
<i>Prumnopitys ferruginea</i>	Methanolic	4.4*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
<i>Pterodon emarginatus</i>	Essential oil	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
		>100*			
<i>Rosmarinus officinalis</i>	Essential oil	>100*	<i>L. amazonensis</i> <i>L. chagasi</i>	Dutra et al. ^[32]	2009
		>100*			
<i>Scaevola balansae</i>	Methanolic	>100*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
		44*			
<i>Schinus terebinthifolius</i>	Methanolic	>250*	<i>L. amazonensis</i> <i>L. chagasi</i>	Arévalo. et al. ^[33]	2009
		8.7*			
<i>Solanum americanum</i>	Methylene chloride	>50*	<i>L. donovani</i>	Desrivolt et al. ^[24]	2007
		>50*			
<i>Syzygium jambolanum</i>	Methanolic	55*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
		>250*			
<i>Terminalia glaucescens</i>	Methanolic	40*	<i>L. amazonensis</i> <i>L. chagasi</i>	Braga et al. ^[21]	2006
		>250*			
<i>Uvaria afzelii</i>	Hydroalcoholic	166.6*	<i>L. amazonensis</i> <i>L. donovani</i>	Bezerra et al. ^[25]	2006
		>100*			
<i>Vernonia polyanthes</i>	Methylene chloride	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
		>100*			
<i>Wollastonia biflora</i>	Methanolic	>100*	<i>L. donovani</i>	Okpekon et al. ^[19]	2004
		12.5*			
<i>Vernonia polyanthes</i>	Methanolic	61*	<i>L. amazonensis</i>	Braga et al. ^[21]	2006
<i>Wollastonia biflora</i>	Methanolic	12.6*	<i>L. donovani</i>	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-Brasília: Publisher of the Ministry of health, 2006. p. 120.-(Series A. Technical Standards and Manuals).
8. Rath S, Trivelin LA, Imbrunite TR, Tomazela DM, Jesús MN, Marzal PC, *et al.* Antimonials employed in the treatment of leishmaniasis: 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. Brasília; 2010. p. 241.
15. Whittemore R, Knafelz 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, Tiunan 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 antifungal activity of plants used in traditional 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 essential oils activity from Colombian 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.

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