Pharmacogn Rev. 2020;14(27):53-61
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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Review Article

Medicinal Plants Containing Coumarin or Essential Oils from the Brazilian Biome May be New Option for Treating Leishmaniasis?

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ABSTRACT

Leishmaniasis is a neglected tropical disease that is among the 13 most common chronic infections in the world. Current chemotherapy for the treatment of leishmaniasis presents several limitations. Medicinal plants containing coumarins or essential oils have been recognized as products with antiprotozoal and anti-inflammatory activities. Our objective was to collect and analyze the data from the literature on the anti-leishmanial effects of Brazilian medicinal plants, focusing on species that contain coumarins and/or essential oils. A systematic review of the literature on the anti-leishmanial activity of the 94 species of plants listed in the National List of Medicinal Plants Relevant to the Brazilian National Health System and/or "Farmácias Vivas" Program was performed. We searched for original results published by international peer-reviewed journals using three databases (PubMed, ScienceDirect and Scielo), theses and books. We identified 23 plant species belonging to 11 botanical families with anti-leishmanial activity. The medicinal plants (essential oil, crude extract and/or purified fractions) higher leishmanicidal effect *in vitro* were *Bidens pilosa, Eugenia uniflora* and *Ageratum conyzoides* ($IC_{50} \leq 3.4$ µg/ml). *Chenopodium ambrosiodes* (essential oil) stands out for its antileishmanial activity *in vitro* and *in vivo*. Few studies evaluate leishmanicidal activity *in vivo* models and chemical characterization of natural products is often not carried out or insufficient. The mechanisms of anti-leishmanial action have been related mainly to immunomodulatory activity. This study points to the urgent need to increase research on species that have shown promising leishmanicidal effect. We intend this review to be useful for future researches aiming to develop a new generation of drugs for the treatment of leishmaniasis with low toxicity.

Key words: Aromatic plants, Coumarin, Leishmaniasis, Phytomedicine, Terpene.

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History

- Submission Date: 27-01-2020;
- Review completed: 25-02-2020;
- Accepted Date: 04-04-2020.

DOI : 10.5530/phrev.2020.14.9

Article Available online
http://www.phcogrev.com/v14/i27

INTRODUCTION

Leishmaniasis is a disease endemic to more than 98 countries, transmitted by vectors and caused by more than 30 species belonging to the genus Leishmania, among which, 15 infect humans in the Americas.[1] Leishmaniasis is a neglected infectious disease since it occurs in low-income countries, especially among the most vulnerable populations that have restricted access to health services. The majority of cases occur in Africa, Asia and the Americas where the high incidence and wide geographic distribution is a challenge to national and regional programs since it requires a great technical, operational and political effort to keep systematic disease surveillance, prevention and control actions.[2] In the Americas, leishmaniasis is present in 18 countries and the most common form is cutaneous leishmaniasis (CL), while the most severe is visceral leishmaniasis (VL), which is fatal in almost all untreated cases. Another frequent form is the mucosal leishmaniasis (ML) that evolves chronically causing serious deformations and sequels, e.g. total and irreversible loss of skin, mucosa and cartilage.[3,4] In Brazil, the incidence of cutaneous/mucosal and visceral leishmaniasis is high (15.8 cases and 5.05 per 100,000 people between the years 2016 and 2018, respectively), with CL concentrated mainly in the northern region and VL in the northeast region (Figure 1).

Although there are no universally applicable therapies for leishmaniasis, a few treatment options are available. The systemic pentavalent antimony (SbV) sodium stibogluconate (Pentostam®) is used in the United States of America and in Europe, while meglumine antimoniate (Glucantime®) is used in Latin America and Africa. These medicines are the first choice drugs for the treatment of all forms of leishmaniasis since the decade of 1940 in many countries.[5,6] However, resistance to the treatment with antimony generated critical health issues in the majority of endemic areas and so novel drugs were adopted.[7] Among them, amphotericin B, miltefosine and paromomycin are used but only as second-line drugs due to excessive adverse effects and toxicity.

This scenario has led to the search for novel alternative therapies. Natural products are a source of a variety of substances with biological activity, thus

Cite this article: Silveira ES, Rodrigues NLDC, Machado NJ, Fonseca FRM, Teixeira MJ, Leal LKAM. Medicinal Plants Containing Coumarin or Essential Oils from the Brazilian Biome May be New Option for Treating Leishmaniasis?. Pharmacog Rev. 2019;14(27):53-61.

the search for active pharmacological compounds from medicinal plants for the treatment of diseases has been prioritized by the World Health Organization (WHO).[8,4] Approximately 40% of all currently available medicines were directly or indirectly developed from natural sources, the majority of which from plants.[9,10]

In Brazil, the Ministry of Health published the National List of Medicinal Plants Relevant to the Brazilian National Health System (RENISUS, in the Portuguese acronym). This list includes medicinal plants with the recognized potential to generate products that can be used by the National Health System. The creation of this list is important for increasing the focus of clinical research on a limited number of species.[11] In parallel, the Federal University of Ceará (UFC), Ceará, Brazil, created the "Farmácias Vivas" project almost three decades ago, listing plants with a therapeutic value from the observation of the use of the local flora by the population of Northeastern Brazil with no access to health services. The project aims at promoting pharmaceutical social assistance to the local communities based on the scientific use of medicinal plants and plant-based medicines following the guidelines of the WHO.[12]

There are several studies in the literature reporting anti-inflammatory, immunomodulatory and antiparasitic activity of coumarin derivates and essential oils.[13-15] Among the species listed on RENISUS and "Farmácias Vivas", the plants containing coumarins and/or essential oils may be interesting for the treatment of leishmaniasis, considering that inflammation and the immune system play a pivotal role in the pathophysiology of the disease.[16,17] Our objective was to collect and critically analyze the data from the literature on the anti-leishmanial effects of medicinal plants of interest for the Brazilian national health system, focusing on species that contain coumarins and/or essential oils in order to guide the prioritization of future research efforts.

MATERIALS AND METHODS

Search strategies

Studies (research articles, books and dissertations) published in English, Portuguese, or Spanish were searched on the databases Pubmed, Science Direct, Scientific Electronic Library Online (SciELO) and CAPES (Brazilian Government's Coordination for the Improvement of Higher Education Personnel) Platform. Studies published between 1995 and 2017 were included and the search was carried out between June and December 2018. The descriptors used for the search were the scientific names of the plants included in the RENISUS and "Farmácias Vivas" lists and the term "leishmania".

The search was carried out in three stages. Firstly, the plants in which the presence of coumarins was reported or classified as aromatic were pre-selected. Secondly, among these plants, the ones in which leishmanicidal activity was reported were selected. Lastly, the studies identified to describe leishmanicidal activity in these plants were double-checked one-by-one by reading the title and abstract and a decision was made to include them or not.

Inclusion and exclusion criteria

The inclusion criteria were pre-established as follows: studies that evaluated the leishmanicidal activity of coumarin or aromatic plants that are listed in RENISUS and "Farmácias Vivas", or their derivates and/or isolated molecules.

The exclusion criteria were pre-established as the following: Revisions, case reports, editorials, studies that do not provide access to the full text and duplicate registries.

RESULTS

The search for data resulted in the inclusion of 56 studies published between 1999 and 2017, of which 49 are research articles and 7 are thesis or dissertations. Five of these studies evaluated 2 plants and one study evaluated 3 plants, while all others evaluated one plant each. Among the species listed in RENISUS and/or "Farmácias Vivas", 23 were identified to possess coumarins and/or essential oil and exert leishmanicidal activity (Table 1).

The family with the highest number of species with reported leishmanicidal activity was Asteraceae (7 species) following by Lamiaceae with 4 species (Table 1). The majority of the studies (59%) were from Brazil and Cuba (21%) (Figure 2).

As described in Table 2, the most studied species of leishmania were *L. amazonensis* and *L. donovani*. Half of the studies used only the promastigote form of the parasite and only eight (approximately 14%) studies evaluated the leishmanicidal activity *in vivo* (*L. amazonensis*, *L. infantum, L. donovani*, *L. braziliensis*). On the effective concentrations to achieve leishmanicidal activity (*in vitro*), we unsurprisingly observed a wide range of concentrations, from 1.5 µg/mL to 250 µg/ml. The medicinal plants that showed the best leishmanicidal activity, based on the IC_{50} values, against the promastigote form were *Bidens pilosa* (organic extract: 1.5 µg/ml) and *Eugenia uniflora* (essential oil: 1.75 µg/ml) and against the amastigote form were *Ageratum conyzoides* (dichloromethane extract: 3.4 µg/ml) and *Eugenia uniflora* (essential oil:

Table 1: Brazilian Medicinal plants containing coumarin or essential oil listed in RENISUS and/or "Farmácias Vivas".

Scientific name	Family	Active principle
Ageratum conyzoides L.	Asteraceae	Coumarin / Essential oil
Amburana cearensis	Fabaceae	Coumarin / Essential oil
Artemisia absinthium	Asteraceae	Essential oil
Bidens pilosa	Asteraceae	Coumarin / Essential oil
Calendula officinalis	Asteraceae	Essential oil
Chamomilla recutita	Asteraceae	Coumarin / Essential oil
Chenopodium ambrosioides	Amaranthaceae	Essential oil
Copaifera spp	Fabaceae	Coumarin
Croton cajucara	Euphorbiaceae	Essential oil
Curcuma longa	Zingiberaceae	Essential oil
Eugenia uniflora	Myrtaceae	Essential oil
Lippia sidoides	Verbenaceae	Essential oil
Mentha piperita	Lamiaceae	Essential oil
Mikania glomerata	Asteraceae	Coumarin
Myracrodruom urundeuva	Anacardiaceae	Essential oil
Ocimum gratissimum	Lamiaceae	Essential oil
Plectranthus amboinicus	Lamiaceae	Coumarin / Essential oil
Plectranthus barbatus	Lamiaceae	Essential oil
Psidium guajava	Myrtaceae	Coumarin
Punica granatum	Punicaceae	Coumarin
Ruta graveolens	Rutáceas	Coumarin / Essential oil
Schinus ter-ebinthifolius	Anacardiaceae	Essential oil
Tagetes minuta	Asteraceae	Essential oil

Table 2: Plants with anti-Leishmania activity.

Plant species	plant part used	Substance, extract or essential oil	concentration/dose	Leishmania species (form tested)	type of study	Reference
Ageratum conyzoides L.	NI	Dichloromethane extract (DE)	IC_{50}: 3.4 µg/ml	*L. donovani* (AA)	*In vitro*	[18]
	Aerial parts	Crude extract	IC_{50}: 107 µg/ml	*L. amazonensis* (P)	*In vitro*	[19]
Amburana cearensis	Stem Bark	Coumarin	50 µg/ml (Effect- LA, LB, LD)	*L. amazonensis*, *L. braziliensis*, *L. donovani* (P)	*In vitro*	[14]
	Seed	Saponin, Coumarin	Saponin (IC_{50}): 5.2% Coumarin (IC_{50}): 6.1 µg/ml	*L. chagasi* (P)	*In vitro*	[20]
Artemisia absinthium	Aerial parts	Ethanol extract	Effect: 101 mg/ml	*L. major* (P)	*In vitro*	[21]
	Aerial parts	Essential oil	400 µg/ml (91% death)	*L. infantum* (P)	*In vitro*	[22]
	Leaf	Essential oil	P (MIC): 0.1565 µg/ml (LD), 0.1565 µg/ml (LAE) AA (IC_{50}): 42.0 µg/ml (LD), 7.94 µg/ml (LAE)	*L. aethiopica, L. donovani* (P, AA)	*In vitro*	[23]
	Aerial parts	Ethanol extract	No effect	*L. infantum* (IA)	*In vitro*	[24]
Bidens pilosa	Leaf, Bark, Root, Flower	Fraction: Ethyl acetate	Root (IC_{50}): 52.3 µg/ml (LC), 102.1 µg/ml (LB), 64.3 µg/ml (LA) Flower (IC_{50}): 41.4 µg/ml (LC), 150.5 µg/ml (LB), 55.3 µg/ml (LA)	*L. chagasi*, *L. braziliensis*, *L. amazonensis* (P)	*In vitro*	[25]
	Leaf	Hydroalcoholic extract	P (IC_{50}): 20.2 µg/ml IA (IC_{50}): 42.6 µg/ml	*L. amazonensis* (P, IA)	*In vitro*	[26]
	Aerial parts, Root	Fraction: N-hexanic (NH); Dichlooromethane (DI), Methanol (ME)	Aerial parts (IC_{50}): 16.1 µg/ml (NH), 18.2 µg/ml (DI), 13.7 µg/ml (ME) Root (IC_{50}): 1.5 µg/ml (NH)	*L. amazonensis* (P)	*In vitro*	[27]
Calendula officinalis	Flower	Methanolic extract	P (IC_{50}): 108.19 µg/ml IA:108 µg/ml (67% death)	*L. major* (P, IA)	*In vitro*	[28]
Chamomilla recutita	NI	Alpha-bisabolol	100 µg/ml (100% de death)	*L. infantum* (P)	*In vitro*	[29]
Chenopodium ambrosioides	Leaf	Ethanol extract	IC_{50}: 151.9 µg/ml	*L. amazonensis* (P)	*In vitro*	[30]
	NI	Aqueous extract	100 µg/ml (82.1 % de death)	*L. amazonensis* (P)	*In vitro*	[31]
	Aerial parts	Essential oil	IC_{50}: 27.8 mg/ml	*L. amazonensis* (P)	*In vitro*	[32]
	Aerial parts	Essential oil	P (IC_{50}): 3.78 µg/ml IA (IC_{50}): 4.68 µg/ml Intraperitonial: 30 mg/kg/day	*L. amazonensis* (P, IA)	*In vitro* / *In vivo*	[33]
	Aerial parts	Essential oil	EO x Amphotericin B (EC_{50}): 0.03 µg/ml EO x Pentamidine (EC_{50}): 0.37 µg/ml	*L. amazonensis* (P)	*In vitro*	[34]
	Aerial parts	Essential oil	P (IC_{50}): 4.45 µg/ml IA (IC_{50}): 5.1 µg/ml	*L. donovani* (P, IA)	*In vitro*	[35]
	Aerial parts	Essential oil	Oral (EC_{50}): 5.55 µg/ml Intraperitonial (EC_{50}): 6.71 µg/ml	*L. amazonensis* (P)	*In vivo*	[36]
	Aerial parts	Essential oil	150 mg/kg/day (100% death)	*L. amazonensis* (P)	*In vivo*	[37]
	Aerial parts	Essential oil	P (IC_{50}): 3.7 µg/ml IA (IC_{50}): 4.6 µg/ml	*L. amazonensis* (P, IA)	*In vitro*	[38]
	Aerial parts	Essential oil, Ascaridole (AS), Carvacrol (CA), Caryophyllene oxide (CO)	EO: effect compared with untreated animals No effect: AS, CA, CO	*L. amazonensis*	*In vivo*	[39]
	Leaf	Hydroalcoholic extract	Topical: reduced the parasite load Orally: no effect	*L. amazonensis*	*In vivo*	[40]
	Leaf	Hydroalcoholic extract ointment	No effect	*L. amazonensis* (P)	*In vivo*	[41]

Copaifera spp	Stalk	Oil nanoemulsions	P (IC_{50}): 0.16 µL/mL (LA, 24H) 0.18 µL (LA,48H), 0.18 µL (LI, 24H) 0,2 µL (LI, 48H). IA: 0.3 µL/mL (LA), 0.18 µL/mL (LI)	*L. amazonensis* / *L. infantum* (P, IA), Mice balb/c	*In vitro* / *In vivo*	[42]
	Leaf	Oil rich in diterpenes (C2, C3), Oil rich in sesquiterpenes (C1, C4), β-caryophyllene (CAR)	P (50 µg/ml): no effect (C1, C4), reducion parasites (C2, C3) IA (IC_{50}): 2.9 µg / ml (C1), 2.3 µg / ml (C4), 1.3 µg / ml (CAR)	*L. amazonensis* (P, IA)	*In vitro*	[43]
	Bark	Essential oil from: *Copaifera reticulata* - Pará (CRP), *C. reticulata* - Acre (CRA), *C. martii* (CM), *C. cearensis* (CC), *C. paupera* (CP), *C. langsdorfii* (CL),*C. officinalis* (CO), *C. multijuga* (CM)	P (IC_{50}): 5.0 g / ml (CRP), 22.0 g / ml (CRA), 14.0 g / ml (CM), 18.0 g / ml (CC), 11.0 g / ml (CP), 20.0 g / ml (CL), 20.0 g / ml (CO), 10.0 g / ml (CM) AA (IC_{50}): 15,0 g / ml (CRP) IA (IC_{50}): 20,0 g / ml (CRP)	*L. amazonensis* (P, AA, IA)	*In vitro*	[44]
	NI	Oil rich in diterpenes (C2, C3), Oil rich in sesquiterpenes (C1, C4), β-caryophyllene (CAR)	P (50 µg / ml): C1 (65 % death), C2 (91.3 % death), C3 (97.5 % death), C4 (56 % death), CAR (68.3 % death) IA (IC_{50}): 2.9 µg / ml (C1), 2.3 µg / ml (C4), 1.3 µg / ml (CAR)	*L. amazonensis* (P, IA)	*In vitro*	[45]
Croton cajucara	Leaf	Essential oil (EO), Linalol (LI)	P (IC_{50}): 8.3 ng / ml (EO), 4.3 ng / ml (LI) IA (IC_{50}): 22.0 ng / ml (EO), 15.5 ng / ml (LI)	*L. amazonensis* (P, IA)	*In vitro*	[46]
	Stem Bark	Trans-dehydrocrotonin (DCTN), trans-crotonin (CTN) and acetyl aleuritolic acid (AAA)	P (IC_{50}): 12.07 µg/mL (DCTN), 41.7 µg/mL (AAA), 48.0 µg/mL (CTN) AA (IC_{50} – 24hr): 19.98 µg/mL (DCTN), 41.44 µg/mL (AAA), 58.25 µg/mL (CTN) IA (DCTN): 0.47 µg/ml (24h), 0.28 µg/ml (48H), 0.16 µg/ml (72H)	*L. amazonensis* (P, AA, IA)	*In vitro*	[47]
	Leaf	Essential oil (EO), 7-hydroxycalamenene purified fraction (7-HPF)	P (IC_{50}): 66.7 µg/mL (EO), 1.37 µg/mL (7-HPF). IA (EO): 250 µg/mL (30 % death)	*L. chagasi* (P, IA)	*In vitro*	[48]
Curcuma longa	Cortex	Turmerone-Rich Hexane Fractions (RHIC, RHIWC), Liposomal formulations (LipoRHIC, LipoRHIWC), ar-turmerone (AT)	CIM: 125 µg / mL (RHIC), 250 µg / mL (RHIWC), 5,5 µg / mL (LipoRHIC), 12,5 µg / mL (LipoRHIWC), 50 µg / mL (AT)	*L. amazonensis* (P)	*In vitro*	[49]
	NI	Curcumin (C), Indiun curcumin (IC), Diacetil curcumin (DC), Galium curcumin (GC)	38 µg/Ml (C), 32 µg/mL (GC), 26 µg/mL (IC), 52 µg/mL (DC)	*L. major* (P)	*In vitro*	[50]
	NI	Curcumin	P (IC_{50} - local strains):): 4.3 µM (LM), 5.9 µM (LT), 5.9 µM (LI) P (IC_{50} - reference strains): 4.5 µM (LM), 5.7 µM (LT), 5.9 µM (LI) AA (IC_{50} - reference strains): 10.0 µM (LM)	*L. major*/ *L. Tropica*/ *L. infantum* - local and reference strains (P, AA)	*In vitro*	[51]
Eugenia uniflowera	Leaf	Methanolic extract	IC_{50} > 250 µg/ml	*L. amazonensis*/ *L. chagasi* (P)	*In vitro*	[52]
	Leaf	Essential oil	LB (IC_{50}): 11.03 µg/ml LA (IC_{50}): 24.39 µg/ml LC (IC_{50}): 40.52 µg/ml	*L. chagasi*, *L. braziliensis*, *L. amazonensis* (P)	*In vitro*	[53]
	Stem Bark	Extract	IC_{50} > 50 µg/ml	*L. donovani* (P)	*In vitro*	[54]
	NI	Hexanic extract	No effect	*L. amazonensis* (P)	*In vitro*	[55]
	Leaf	Essential oil	P (IC_{50}): 6.96 µg/ml (24H), 3.4µg/ml (48H) 1.75µg/ml (72H) IA (IC_{50}): 1.92µg/ml	*L. amazonensis* (P, IA)	*In vitro*	[56]

Lippia sidoides	Leaf	Carvacrol-rich essential oil (CEO), Thymol -rich essential oil (TEO), Carvacrol (C), Thymol (T)	IC_{50} (72H): 54.8 µg/ml (CEO),74.1 µg/ml (TEO), 2.3 µg/ml (C), 9.8 µg/ml (T),	*L. chagasi* (P)	*In vitro*	[57]
	Aerial parts	Essential oil (EO) Thymol (TH)	P (IC_{50}): 44.38 µg/ml (E0), 22.63 µg/ml (TH) IA: 34.4 µg/ml (E0), No effect (TH)	*L. amazonensis* (P, IA)	*In vitro*	[58]
	Leaf	Essential oil	IC_{50}: 89 µg/ml	*L. chagasi* (P)	*In vitro*	[59]
	NI	Essential oil	P (IC_{50}): 19.76 µg/ml IA (IC_{50}): 5.07 µg/ml	*L. chagasi* (P, IA)	*In vitro*	[60]
Mentha piperita	NI	Ether extract, Chloroformic extract, Methanolic extract	IC_{50} > 16 µg/ml (for all extracts)	*L. donovani* (P)	*In vitro*	[61]
	Leaf	Essential oil	IC_{50}: 50 µg/ml	*L. donovani* (P)	*In vitro*	[62]
Mikania glomerata	NI	Hydroalcoolic extract	P: 100 µg/ml (52,5% death) AA: 100 µg/ml (97,5% death)	*L. amazonensis* (P, AA)	*In vitro*	[63]
Myracrodruom urundeuva	Leaf	Essential oil	PRO: 205 µg/ml AA: 104.6 µg/ml IA: 44.5 µg/ml	*L. amazonensis* (P, AA, IA)	*In vitro*	[64]
Ocimum gratissimum	Leaf	Methanolic extract	LA (IC_{50} >): 250 µg/ml LC (IC_{50}): 71 µg/ml	*L. amazonensis* / *L. chagasi* (P)	*In vitro*	[52]
	Leaf	Methanolic extract	No effect	*L. chagasi*, *L. braziliensis*, *L. amazonensis* (P)	*In vitro*	[25]
	NI	Hydroalcoholic extract	P: 100 µg/ml (54.7 % death) AA: 100 µg/ml (91.5 % death)	*L. amazonensis* (P, AA)	*In vitro*	[63]
	Leaf	Essential oil	P (IC_{50}): 100 µg/ml AA (IC_{50}):135 µg/ml IA (IC_{50}): 150 µg/ml	*L. amazonensis* (P, AA, IA)	*In vitro*	[65]
Plectranthus amboinicus	Leaf	Essential oil	LB (IC_{50}): 12.40 µg/ml, LC (IC_{50}): 12.98 µg/ml, LA (IC_{50}): 23.80 µg/ml	*L. chagasi*, *L. braziliensis*, *L. amazonensis* (P)	*In vitro*	[53]
	Leaf	Essential oil	Reduce the viability similar to Amphotericin No effect *in vivo*	*L. braziliensis* (P)	*In vitro* / *In vivo*	[66]
Plectranthus barbatus	Aerial parts	Dehydroabietane (1), 5,6-didehydro-7-hydroxy-taxodone (2), taxodione (3, 20-deoxocarnosol (4), 6α,11,12,-trihydroxy-7β,20-epoxy-8,11,13-abietatriene (5).	1 (IC_{50} >) 237.0 µM, 2 (IC_{50}) 25.7 µM, 3 (IC_{50}) 25.7 µM, 4 (IC_{50}) 25.6 µM, 5 (IC_{50}) 24.4 Mm	*L. infantum* (IA)	*In vitro*	[67]
	Leaf	Crude extract	LC (EC50): 54.46 µg/ml LA (EC50): >500 µg/ml	*L. chagasi, L. amazonensis*	*In vitro*	[68]
Psidium guajava	NI	Hydroalcoolic extract	P: 100 µg/ml (65,4% death) AA: 100 µg/ml (52,0% death)	*L. amazonensis* (P, AA)	*In vitro*	[63]
Punica granatum	NI	Methanolic extract	IC_{50} > 64.0 µg/ml	*L. infantum* (IA)	*In vitro*	[69]
	Leaf	Hydroalcoolic extract	P: 100 µg/ml (74.4 % death) IA: 69.6 µg/ml (IC_{50})	*L. amazonensis* (P, IA)	*In vitro*	[26]
Ruta graveolens	Aerial parts	Aqueous extract	P: 100 µg/ml (74.4 % death) IA: 10 µg/ml (40.3 % death)	*L. amazonensis* (P, IA)	*In vitro*	[31]
Schinus terebinthifolius	Leaf	Triterpenoid: ácido Z-masticadienóico (1), ácido E-masticadienóico (2), Z-schinol (3)	P: No effect IA (IC_{50}): 66.5 g/Ml (1), 64.9 g/mL (2), 28.9 g/mL (3)	*L. infantum* (P, IA)	*In vitro*	[70]
	Stem Bark	Hydroalcoolic extract	IC_{50}: 201 µg/ml	*L. amazonensis* (P)	*In vitro*	[71]
Tagetes minuta	Leaf / Bark	Methanolic extract	IC_{50}: 30.1 µg/ml	*L. infantum* (IA)	*In vitro*	[72]

1.92 µg/ml). The reference drugs used in the nonclinical studies were amphotericin B, glucantime, mitelphosine, or pentamidine, reflecting the current clinical therapies used in the treatment of leishmaniasis. Among the species investigated *Chenopodium ambrosioides* was the most studied through *in vivo* assays (BALB/c mice infected by *L. amazonensis*). The hydroalcoholic extract of *C. ambrosioides* (leaf) ineffective against leishmania, while its essential oil showed leishmanicidal effect in some experimental conditions (Table 2).

Among the extracts or fractions chemically characterized the following molecules were identified as responsible at least in part for leishmanicidal activity: 1,2 Benzopyrone, thymol, β-caryuohyllene, menthol, eucalyptol, (-)-carvone. However, some studies did not characterize their plant extracts.

The data provided insights on common shortcomings of the studies published in this field: approximately 20.3% of the studies did not register or inform the plant species voucher number, 19.6% did not inform which part of the plant was used and 39.3% did not standardize the plant extract or fractions.

DISCUSSION

Among the plant families included in this review, Asteraceae has approximately 2000 species registered in Brazil and is almost always among the 4 families with the largest number of species of useful flora in ethnobotanical studies. Many of the plants of this family are known for their medicinal properties, especially their analgesic, anti-inflammatory and antimicrobial activities.[12,73] The most studied classes of molecules extracted from this family are terpenoids. However, the great diversity of this family, composed of 1535 genus, also generates a variety of secondary metabolites, including coumarin derivates.[74]

The most studied genus of Leishmania - *L. amazonensis* - causes diffuse cutaneous leishmaniasis, but all clinical forms of the disease were included in our search. Tegumentary leishmaniasis is caused mainly by the species *L. peruviana*, *L. guyanensis*, *L. braziliensis* and *L. mexicana* and dissemination in the mucosa occurs mostly by *L. braziliensis*, a species that also causes the cutaneous and mucocutaneous forms of leishmaniasis, thus, it is considered to be the most harmful species.[1] Not all species of Leishmania are found in all endemic areas and their clinical manifestations after infection also vary by region, thus the treatment may need to be adjusted to each local population.[75]

One positive aspect is that the majority of the studies (89.3%) reported the geographic location of where the plant was obtained, the majority originating from Brazil follow by Cuba. This scenario is probably related to the fact that this review's starting point is a set of two lists of plants used by the Brazilian population although many species also occur in other countries. In Brazil, the geographic origin of the plants coincides with the regions most affected by leishmaniasis (North and Northeastern Brazil).

Most studies evaluate leishmanicidal activity through the evaluation of basic outcomes, such as the evaluation of the effect of test drugs (crude extract, essential oil, purified fraction or molecule) on the growth of the parasite. Moreover, almost half of the studies analyze the effects exclusively on the promastigote stage. In the natural cycle in the life of the Leishmania parasite, the promastigotes are present in a vector of the disease – the female sandfly – and mostly not in infected humans. When the parasite is transmitted to humans, it is internalized by macrophages, it evolves from the promastigote form to the amastigote form and starts multiplying by binary fission. Eventually, the parasite lysis the macrophage and starts infecting other nearby macrophages.[76-78] The research carried out on parasitic forms that do not represent the infection of the human host, i.e. promastigotes, is important for the identification of potential novel therapies but is limited in scope and preliminary.[79] Even studies carried out *in vitro* with the amastigote form frequently do not continue to *in vivo* testing.

We also identified other frequent and important shortcomings in the studies we analyzed. One of them is the lack of specimen registration. These are not most of the studies but still represent a significant part, lowering the reliability of the data presented and creating an important barrier to the reproducibility of those studies. Additionally, more than half of the studies do not standardize the plant products. As widely discussed in the literature, plant products possess a variety of compounds, many of those with pharmacological activity, thus the lack of standardization hampers the identification of the compounds, or groups of compounds, that may exert the leishmanicidal activity described. Other important limitations were found in many of the studies, including the absence of detailed chemical characterization, few *in vivo* studies and the lack of any pharmacokinetic study.

Bidens pilosa, *Eugenia uniflora* and *Ageratum conyzoides* showed promising leishmanicidal effects. *Bidens pilosa* (root) showed leishmanicidal effect (*L. amazonensis*, promastigote form) with the lowest IC_{50} value (1.5 µg/ml) when compared to other species (Table 1). Essential oils from *Eugenia uniflora* showed effects against both promastigote and amastigote forms of *L. amazonensis*, while *Ageratum conyzoides* was effective against *L. donovani* (amastigote form). *Chenopodium ambrosiodes* (essential oil) stands out for being the sole plant species with reported leishmanicidal action both *in vitro* and *in vivo*.

In vitro studies also characterized the leishmanicidal action of *B. pilosa* (leaf, flower, stem bark, aerial parts and root) against *L. chagasi*, *L. braziliensis* and *L. amazonensis*. Based on the IC_{50} values, the best results were obtained with the hexanic fraction of *B. pilosa* (root) (*L. amazonensis* - IC_{50}: 1.5 µg/ml) when compared to hydroalcoholic extract and organic fractions.[25-27] The IC_{50} value of artemisinin, used as the reference drug (*L. amazonensis*- IC_{50}: 13.7 µg/ml), was higher than the *B. pilosa* fraction.[27] The petroleum ether extract of *B. pilosa* (leaves) had its main chemical components identified by GC-MS: triterpenes, including 4,22-cholestadien-3-one, stigmasterol and friedelan-3-one.[80] So, it's possible that terpenoids have a key role in the leishmanicidal effect of *B. pilosa*. However, additional studies are necessary to confirm this hypothesis. Additionally, to confirm the leishmanicidal effect of *B. pilosa* it is essential to evaluate the effects on the amastigote form of the parasite and to carry out *in vivo* studies.

The essential oil from *Eugenia uniflora* (EOEU) inhibited both the promastigote and the amastigote forms of *L. amazonensis* with a IC_{50} value close to the *B. pilosa*. The GC-MS analysis of OEEU allowed to identify as main constituents curzerene, γ-elemene and trans-β-elemenone. The leishmanicidal effect of OEUE seems to not be related to nitric oxide production, but with the ability to modulate the macrophage activation, as observed by the increase in both phagocytic capacity and lysosomal activity.[56]

The dichloromethane extract from *Ageratum conyzoides* showed a leishmanicidal effect against *L. donovani* (axemical amastigote form).[81] Its effect seems to occur through the cooperation of many chemical constituents including coumarin derivates, such as encecalol angelate.[18,82] This hypothesis is corroborated by previous studies that reported *A. conyzoides* to be a rich source of secondary metabolites such as simple coumarin, chromenes, coumarins, monoterpenes, pyrrolizidine alkaloids and flavonoids.[83-85] The simple coumarin (1,2-benzopyrone) has determined its leishmanicidal effect and it occurs in other plants listed in the National List of Medicinal Plants Relevant to the Brazilian National Health System and "Farmácias Vivas" including *Amburana cearensis* and *Justicia pectoralis*.[14,86,87]

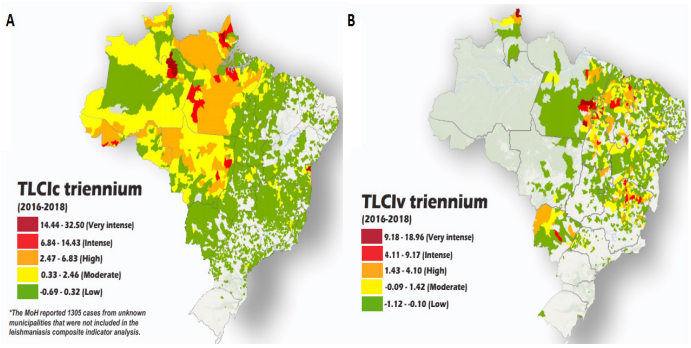

Figure 1: (A) Incidence of Cutaneous and mucosal Leishmaniasis (2016-2018) in Brazil; (B) Incidence of visceral Leishmaniasis (2016-2018) in Brazil. Figure adapted.[4] Source: PAHO/WHO: Data reported by the National Leishmaniasis Programs of the countries.

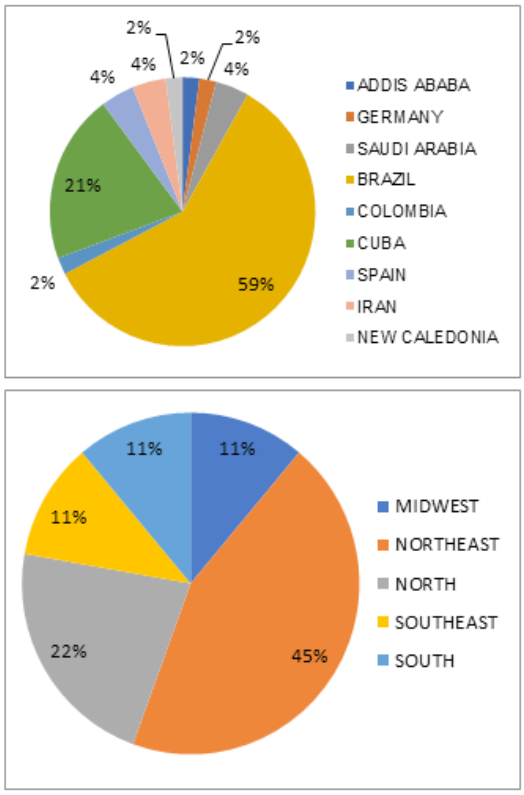

Figure 2: Geographical distribution of the origin of studies in the world (A) and in Brazil (B).

One of the traditional uses of *Chenopodium ambrosioides* is for the treatment of parasites.[88] Its essential oil and major constituents (ascaridole, carvacrol and caryophyllene oxide) exert antileishmanial activity in different *in vitro* and *in vivo* models.[33-39] The essential oil from *C. ambrosiodes* (EOCA) and its major constituents prevented the cutaneous lesion induced by *L. amazonensis* in BALB/c mice. The EOCA showed better antileishmanial activity in comparison with pure terpenoids.[38] Recently, the effect of ascaridole, carvacrol and caryophyllene oxide on mitochondrial functions in Leishmania tarentoloe promastigotes (LtP) was investigated.[89] The EOCA molecules did not show relevant activity on complexes I and II in LtP, whereas complex III was inhibited by caryophyllene oxide in both LtP and submitochondrial particles from bovine heart. Ascaridole and carvacrol did not show a direct immediate effect.

Coumarins and terpenoids have been recognized as anti-leishmanial agents. Simple coumarin and its derivates i.e. 1,2-benzopyrone, auraptene and sesquiterpene coumarins, are active against the genus Leishmania.[14,90,91] and nanoliposomal formulation of coumarins have been developed to improve their pharmacological potential for the treatment of cutaneous.[92]

Several plant-extracted natural products, including crude extracts and isolated molecules (i.e. flavonoids, coumarins and terpenoids) have shown their antileishmanial activity due to a direct action on the parasite and/or on the host immune response.[56,93] Recently, a study reported that the essential oil from *Tetradenia riparia* (EOTR) acts as an immunomodulating drug and presents a leishmanicidal effect.[94] It modulated the production of cytokines, which have a key role in the host's immune response to Leishmania parasite. The EOTR did not interfere in the production of IL-1β, GM-CSF, IL-2, IL-5, IL-10, or TFN-α produced by macrophages infected with *L. amazonensis*, but it induced a significant reduction in the IL-4 levels and an increase in IL-12 levels.

CONCLUSION

The pieces of evidence presented in this review showed that some species have a promising leishmanicidal effect, such us *Bidens pilosa*, *Eugenia uniflora*, *Ageratum conyzoides* and *Chenopodium ambrosioides*. Their effects are related at least in part to the presence of coumarin and/or terpenoids. However, almost all studies halt from investigating leishmanicidal effects further and few research groups explore the *in vivo* effects of crude extracts, purified fractions, or molecules. Consequently, new medicines against leishmaniasis will not be released in the foreseeable future. Among the species identified, *Chenopodium ambrosioides* stands out by its *in vivo* anti-leishmanial activity.

We intend this review to be useful for future researches aiming to develop a new generation of drugs for the treatment of leishmaniasis.

ACKNOWLEDGEMENT

No specific financial support was received for this project

CONFLICT OF INTEREST

The authors declare no conflict of interests

ABBREVIATIONS

AA: Axemical Amastigotes; **EO:** Essential oil; **IA:** Intracellular Amastigotes; **LA:** L. amazonenses; **LAE:** *L. aethiopica*; **LB:** *L. braziliensis*; **LC:** L. chagasi; **LD:** *L. donovani*; **LI:** *L. infantum*; **LM:** L. major; **LT:** L. Tropica; **NI:** Not identified; **P:** Promastigotes.

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Cite this article: Silveira ES, Rodrigues NLDC, Machado NJ, Fonseca FRM, Teixeira MJ, Leal LKAM. Medicinal Plants Containing Coumarin or Essential Oils from the Brazilian Biome May be New Option for Treating Leishmaniasis?. Pharmacog Rev. 2020;14(27):53-61.