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A review of natural products with antileishmanial activity

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Abstract

Infections caused by protozoa of the genus *Leishmania* are a major worldwide health problem, with high endemicity in developing countries. The incidence of the disease has increased since the emergence of AIDS. In the absence of a vaccine, there is an urgent need for effective drugs to replace/supplement those in current use. The plant kingdom is undoubtedly valuable as a source of new medicinal agents. The present work constitutes a review of the literature on plant extracts and chemically defined molecules of natural origin showing antileishmanial activity. The review refers to 101 plants, their families, and geographical distribution, the parts utilized, the type of extract and the organism tested. It also includes 288 compounds isolated from higher plants and microorganisms, classified into appropriate chemical groups. Some aspects of recent antileishmanial-activity-directed research on natural products are discussed.

Keywords: *Leishmania*; Antileishmaniasis; Antileishmanial activity; Leishmanicidal activity; Medicinal plants; Natural products

Introduction

Leishmaniasis is regarded as a major public health problem (WHO, 2002), causing significant morbidity and mortality in Africa, Asia and Latin America. The disease currently threatens about 350 million women, men and children in 88 countries around the world, with about 2 million affected annually. In Brazil, studies report the occurrence of about 20.000 new cases of the illness annually. An increase in the incidence of leishmaniasis can be associated with urban development, forest devastation, environmental changes and migrations of people to areas where the disease is endemic (Carvalho et al., 2000; Patz et al., 2000; Ashford, 2000).

Species of the genus *Leishmania*, a protozoan member of the hemoflagellate group, are the causative agents of human leishmaniasis, which has a reservoir in rodents, dogs, saguins, marsupials and others in the wild animal population, and is transmitted by mosquitoes of the genera *Lutzomia* and *Phlebotomus*. The term leishmaniasis comprises three clearly distinguishable clinical manifestations: generalized visceral infection (visceral leishmaniasis or ''Kala-azar''), cutaneous leishmaniasis (Oriental button), and mucocutaneous leishmaniasis (ulceration of the skin and hyperdevelopment of the mucous membranes) (Garcia-Granados et al., 1997; Ashford, 2000).

Members of the genus *Leishmania* differentiate from proliferative promastigotes in the sandfly vector gut to infective metacyclic promastigotes in the insect foregut. Parasites are inoculated by the vector as the flagellate promastigotes enter the mammalian host, where they infect macrophages, differentiating into nonmotile

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amastigotes and multiplying as such (Araújo et al., 1998; Carvalho et al., 2000). The mechanisms by which visceral and cutaneous manifestations develop have not been fully clarified.

The treatment of leishmaniasis is difficult because of the intramacrophagic location of the infectious form. Victims of this illness present an immune deficiency and are not able to eliminate the parasites through a natural mechanism of defense. Moreover, malnutrition is associated with certain cases of leishmaniasis. Parallel infection with diseases such as malaria and pneumonia increases the fatality of the illness if it is not diagnosed and treated in time. The problem of leishmaniasis has been worsened by the evolution of AIDS due to parallel infections in AIDS patients, as well as by the development of drug-resistance by parasites (Carvalho et al., 2000; Torres-Santos et al., 1999).

In the absence of a vaccine, there is an urgent need for effective drugs to replace/supplement those in current use. The clinically used drugs, many of which are based on pentavalent antimony compounds, were developed before 1959. The toxicity of these agents and the persistence of side-effects even after modification of the dose level and duration of treatment are, however, severe drawbacks. The search for antileishmanial agents has been exhaustive. Alternative drugs, such as amphotericin B and pentamidine, also have unpleasant side-effects (Balana et al., 1998; Carvalho et al., 2000). On the other hand, plant extracts or plant-derived compounds are likely to provide a valuable source of new medicinal agents (Carvalho and Ferreira, 2001; Kayser and Kiderlen, 2001) and the urgent need for alternative treatments has led to a program to screen natural products for potential use in the therapy of leishmaniasis. In fact, the WHO advocated the use of traditional medicine where appropriate health services are inaccessible (Tahir et al., 1998; Weniger et al., 2001; Bhadra, 1993).

Furthermore, the leads obtained from the search for natural products with antileshmanial activity give new impetus for obtaining valuable synthetic compounds (Carvalho et al., 2000).

With the objective of contributing to these studies, a literature search on the use of natural products (crude plant extracts, semi-purified fractions and chemically defined molecules) which have already been evaluated particularly for leishmaniasis, has been carried out.

Materials and methods

The keywords used for the literature search for this review were *Leishmania* × antileishmaniasis × antileishmanial activity × leishmanicidal activity × medicinal plants × natural products. The search was carried out using Biological Abstracts, Chemical Abstracts, and the data bank of the University of Illinois in Chicago NAPRALERT (Acronym for NAtural PRoducts ALERT), updated to December 2001. The references found in the search were then studied in detail.

Results and discussion

Consultation of various literature sources resulted in the elaboration of a list of natural products evaluated for antileishmanial activity (Tables 1 and 2). It should be noted that most of the references cited are not first-hand observations, but compilations copied from other sources. For details on the models or mechanism-based bioassays utilized for selecting crude plant extracts, fractions and pure compounds against the *Leishmania* parasite, the original references should be consulted.

Antileishmanial activity of crude plant extracts and fractions

A plant-screening program for potential leishmanicides was initiated in 1984 in French Guiana, based on the ethnomedical knowledge of the local population. The leishmanicidal activity of several plant extracts was evaluated *in vitro,* by testing on amastigote stages of *Leishmania amazonensis*, and *in vivo* using cutaneous *L. amazonensis* lesions in mice. Among the selected species, *Faramea guianensis* showed activity (Sauvain et al., 1994).

Fourteen plants used topically in folk medicine in Bolivia to treat cutaneous leishmaniasis were collected in the tropical regions of colonization and in the rain forest occupied by Chimane Indians. Two plants employed by those in the colonial region showed an *in vitro* antileishmanial activity: *Bocconia integrifolia* and *B. pearcei.* Three other plants, *Ampelocera edentula*, *Galipea longiflora* and *Pera benensis*, employed by Chimane Indians, were effective in mice infected with *L. amazonensis* (Fournet et al., 1994b).

A preliminary examination of the crude methanol extracts of eight plant species collected from the Sudan revealed that only three plant species had a considerable *in vitro* antileishmanial activity on *L. major* promastigotes at a concentration $<0.5\,\mu g/ml$. The plants *Azadirachta indica*, *Maytenus senegalensis* and *Eucalyptus globulus* showed IC_{50} values of 11.5, 55 and 78 μg/ml, respectively (Tahir et al., 1998).

Singha et al. (1992) evaluated a total of 23 plants from Madras, India, for antileishmanial activity, with *L. donavani* infected hamsters. Extracts derived from five plants (viz., *Alstonia scholaris*, *Swertia chirata*, *Tibouchina semidecandra*, *Tinospora cordifolia* and *Nyctanthes*

Table 1. Plant extracts summary showing antileishmanial activity[a]

Family and botanical name	Origin	Part used	Organism tested	Preparation[b]	Reference
Agavaceae					
Yucca filamentosa L.	Germany	[c]	*L. amazonensis*	Ethanol extract	Plock et al. (2001)
Annonaceae					
Annona glauca Thonn.	Senegal	SD	*L. amazonensis*	Dichloromethane ext	Waechter et al. (1998)
			L. braziliensis	Dichloromethane ext	Waechter et al. (1998)
			L. donovani	Dichloromethane ext	Waechter et al. (1998)
Annona muricata L.	Colombia	PE	*L. braziliensis*	Ethyl acetate extract	Jaramillo et al. (2000)
			L. panamensis	Ethyl acetate extract	Jaramillo et al. (2000)
Annona senegalensis Pers	Senegal	SD	*Leishmania* sp.	Dichloromethane ext	Sahpaz et al. (1996)
Annona aff. spraguei Saff.	Colombia	SD	*L. braziliensis*	Chloroform extract	Saez et al. (1998)
			L. infantum	Chloroform extract	Saez et al. (1998)
			L. panamensis	Chloroform extract	Saez et al. (1998)
Cardiopetalum calophyllum Schldl.	Bolivia	LF + SM	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Duguetia spixiana Mart.	Bolivia	SB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Guatteria foliosa Benth	Bolivia	SB	*L. amazonensis*	Alkaloid fraction	Mahiou et al. (1994)
			L. braziliensis	Alkaloid fraction	Mahiou et al. (1994)
			L. donovani	Alkaloid fraction	Mahiou et al. (1994)
Guatteria schoburgkiana Mart.	Bolivia	RB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Oxandra espintana (Spruce) Baillon	Bolivia	SB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Xylopia aromatica (Lam.) Mart.	Bolivia	LF + SB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Apocynaceae					
Alstonia scholaris R. Br.	India	SM	*L. donovani*	Ethanol extract	Singha et al. (1992)
Holarrhena curtisii King & Gamble	Malaysia	LF	*L. donovani*	Ethanol extract	Kam et al. (1998)
Mandevilla antennacea K. Schum.	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
Peschiera australis Miers.	Brazil	SM	*L. amazonensis*	Chloroform extract	Delorenzi et al. (2001)
Peschiera var. *heurkii* (Muell. Arg.) L. Allorge	Bolivia	LF	*L. amazonensis*	Ethanol extract	Munoz et al. (1994)
			L. braziliensis	Ethanol extract	Munoz et al. (1994)
Picralima nitida Th. & H. Dur.	Nigeria	SD	*L. donovani*	Chloroform extract	Iwu et al. (1992)
Tabernaemontana obliqua (Miers) Leenwenb.	Colombia	LF	*L. amazonensis*	Methanol extract	Weniger et al. (2001)
Araliaceae					
Hedera helix L.	Spain	LF	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)

Oreopanax species	Bolivia	LF	*L. braziliensis*	Ethanol extract	Fournet et al. (1994b)
Asclepiadaceae					
Gongronema latifolia Benth	Nigeria	LF	*L. donovani*	Methanol extract	Iwu et al. (1992)
Periploca graeca L.	Turkey	TG	*L. major*	Methanol extract	Demirci et al. (1998)
Asteraceae					
Acanthospermum hispidum DC.	Bolivia	EP	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
Achyrocline flaccida (Weinm.) DC.	Bolivia	EP	*L. braziliensis*	Ethanol extract	Fournet et al. (1994b)
Ageratina pentlandiana (DC.) K. & R.	Bolivia	LF	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract.	Lockman et al. (1991)
Artemisia herba-alba Asso.	Maroc	[c]	*L. tropica*	Aqueous extract	Hatimi et al. (2001)
Baccharis salicifolia (R. & P.) Pers.	Bolivia	LF	*L. braziliensis*	Ethyl acetate extract	Fournet et al. (1994b)
Chersodoma jodopappa (Sch. Bip.) Cabrera	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Cnicothamnus lorentzii Griseb.	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
Echinacea purpurea Moench	Germany	EP	*Leishmania* sp.	Sap	Parnham (1996)
Inula montana L.	Spain	AP	*L. infantum*	Methanol	Martin et al. (1998)
Jasonia glutinosa DC.	Spain	AP	*L. donovani*	Acetone extract	Villaescusa et al. (1996)
Munnozia fournetii H. Robinson	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Neurolaena lobata R. Br.	Guatemala	LF	*L. mexicana*	Ethanol extract	Berger et al. (2001)
			L. braziliensis	Ethanol extra	Berger et al. (2001)
Ophryosporus piquerioides (DC.) Benth.	Bolivia	EP	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Perezia multiflora Less. (H. & B.) Less.	Bolivia	LF	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Pterocaulon alopecuroideum (Lam.)DC.	Bolivia	EP	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Senecio clivicolus Wedd.	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Stevia yaconensis Hieron.	Bolivia	EP	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
			L.braziliensis	Ethanol extract	Fournet et al. (1994b)
Vernonia squamulosa Hook. & Arn.	Bolivia	SM	*L. braziliensis*	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
			L. amazonensis	Ethanol extract	Fournet et al. (1994b)
Werneria nubigena H.B.K.	Bolivia	LF + SM	*L. braziliensis*	Ethanol extract	Fournet et al. (1994b)

Table 1. (*continued*)

Family and botanical name	Origin	Part used	Organism tested	Preparation[b]	Reference
			L. donovani	Ethanol extract	Fournet et al. (1994b)
			L. amazonensis	Ethanol extract	Fournet et al. (1994b)
Xanthium catharticum L.	Bolivia	RT + SM	*L. braziliensis*	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
			L. amazonensis	Ethanol extract	Fournet et al. (1994b)
Berberidaceae					
Berberis boliviana Lechl.	Bolivia	BK + SM	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Berberis bumeliaefolia Schum	Bolivia	BK	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Berberis cf. laurina Epl.	Bolivia	SM	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Berberis aff. *paucidentata* Rusby	Bolivia	SB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
Bignoniaceae					
Jacaranda copaia D. Don	Fr. Guiana	LF	*L. amazonensis*	Type extract not stated	Sauvain et al. (1993)
Kigelia pinnata DC.	Africa	RB	*L. major*	Type extract not stated	Moideen et al. (1997)
Bombacaceae					
Huberodendron patinoi Cuatrec.	Colombia	BK	*L. panamensis*	Methanol extract	Weniger et al. (2001)
Burseraceae					
Protium amplum Cuatrec.	Colombia	FR	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
			L. infantum	Methylene chloride extract	Weniger et al. (2001)
Caparraceae					
Capparis spinosa L.	Israel	BC	*L. major*	Type extract not stated	Schlein (1994)
Celastraceae					
Maytenus senegalensis (Lam.) Exell	Sudan	SB	*L. major*	Dichloromethane ext	Tahir et al. (1998)
Clusiaceae					
Marila laxiflora Rusby	Colombia	LF	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
Crassulaceae					
Bryophyllum pinnatum Kurz	Brazil	LF	*L. amazonensis*	Aqueous extract	Da Silva et al. (1995)
				Aqueous extract	Rossi et al. (2000)
Dilleniaceae					
Doliocarpus dentatus Kubitzki	Surinam	SM	*L. amazonensis*	Chloroform extract	Sauvain et al. (1996)

Euphorbiaceae					
Pera benensis Rusby	Bolivia	RB + SB	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Ricinus communis V.A. Moshkin	Israel	BC	*L. major*	Type extract not stated	Schlein (1994)
Fabaceae					
Crotalaria barbata R. Grah.	India	EP	*L. donovani*	Ethanol extract	Singha et al. (1992)
Desmodium gangeticum *L.*	Nigeria	LF	*L. donovani*	Methanol extract	Iwu et al. (1992)
Periandra mediterranea Taub.	Brazil	RT	*L. donovani*	Saponin fraction	Santo et al. (1997)
Spartium junceum L.	Israel	BC	*L. major*	Type extract not stated	Schlein (1994)
Gentianaceae					
Swertia chirata Buch. Ham. Ex Wall.	India	EP	*L. donovani*	Ethanol extract	Singha et al. (1992)
Geraniaceae					
Pelargonium sidoides DC.	Germany	[c]	*L. donovani*	Ethanol extract	Kayser et al. (2001a)
Lauraceae					
Aniba canelilla H.B.K.	Bolivia	SM	*L. amazonensis*	Ethyl acetate extract	Fournet et al. (1994b)
			L. braziliensis	Ethyl acetate extract	Fournet et al. (1994b)
Aniba species	Bolivia	SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
Liliaceae					
Allium sativum L.	Iran	BULB	*L. major*	[c]	Ghazanfari et al. (2000)
Malvaceae					
Malva nicaeensis All.	Israel	BC	*L. major*	Type extract not stated	Schlein (1994)
Melastomaceae					
Tibouchina semidecandra Cogn.	India	AP	*L. donovani*	Ethanol extract	Singha et al. (1992)
Meliaceae					
Azadirachta indica A. Juss.	Sudan	SB	*L. major*	Methanol extract	Tahir et al. (1998)
Guarea polymera Little	Colombia	LF	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
Khaya senegalensis A. Juss.	Portugal	[c]	*L. donovani*	[c]	Abreu et al. (1999)
Menispermaceae					
Abuta pahni Mart.	Bolivia	SM	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
Abuta rufescens Aublet	Bolivia	BK	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
Anomospermum bolivianum Kruk. & Mold	Bolivia	BK	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
Tinospora cordifolia (Willd.) Hook.f. & Thoms.	India	SM	*L. donovani*	Ethanol extract	Singha et al. (1992)
Moraceae					
Dorstenia multiradiata Engl.	Nigeria	LF	*L. donovani*	Aqueous extract	Iwu et al. (1992)
Myristicaceae					
Otoba novogranatensis Moldenke	Colombia	LF	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)

Table 1. (*continued*)

Family and botanical name	Origin	Part used	Organism tested	Preparation[b]	Reference
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
			L. infantum	Methylene chloride extract	Weniger et al. (2001)
			L. amazonensis	Methanol extract	Weniger et al. (2001)
			L . braziliensis	Methanol extract	Weniger et al. (2001)
			L. infantum	Methanol extract	Weniger et al. (2001)
Otoba parvifolia (Mgf.) A.H. Gentry	Colombia	BK	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
Myrsinaceae					
Myrsine pellucida Spreng	Bolivia	SB	*L. braziliensis*	Ethanol extract	Lavaud et al. (1994)
Papaveraceae					
Bocconia integrifolia H and B	Bolivia	LF + SB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Bocconia pearcei Hutch.	Bolivia	LF	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
Phytolaccaceae					
Phytolacca dodecandra L'Herit.	Ethiopia	FR	*L. enriettii*	Buthanol extract	Lemma et al. (1972)
Piperaceae					
Peperomia galioides H. B. & K.	Bolivia	EP	*L. amazonensis*	Ethanol extract	
			L. braziliensis	Ethanol extract	Mahiou et al. (1995)
			L. chagasi	Ethanol extract	Mahiou et al. (1995)
			L. donovani	Petroleum ether extract	Mahiou et al. (1995)
Piper aduncum L.	Brazil	IF	*L. amazonensis*	Petroleum ether extract	Torres-Santos et al. (1999)
Piper rusbyi C. DC	Bolivia	EP	*L. amazonensis*	Ethyl acetate extract	Fournet et al. (1994b)
			L. braziliensis	Ethyl acetate extract	Fournet et al. (1994b)
			L. donovani	Ethyl acetate extract	Fournet et al. (1994b)
Rubiaceae					
Faramea guianensis (Aubl.) Bremek	Fr Guiana	LF	*L. amazonensis*	Aqueous extract	Sauvain et al. (1994)
Rutaceae					
Dictyoloma peruvianum Planch.	Bolivia	SB	*L. amazonensis*	Ethyl acetate extract	Lavaud et al. (1995)
			L. braziliensis	Alkaloid fraction	Lavaud et al. (1995)
Galipea longiflora Kr	Bolivia	LF	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994a)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994a)
			L. donovani	Alkaloid fraction	Fournet et al. (1994a)
		LF + RB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994b)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994b)
			L. donovani	Alkaloid fraction	Fournet et al. (1994b)
		RB	*L. amazonensis*	Alkaloid fraction	Fournet et al. (1994a)
			L. braziliensis	Alkaloid fraction	Fournet et al. (1994a)

			L. donovani	Alkaloid fraction	Fournet et al. (1993a)
Swinglea glutinosa Merr.	Colombia	BK	*L amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
			L. infantum	Methylene chloride extract	Weniger et al. (2001)
Sapindaceae					
Serjania tenuifolia Radlk	Bolivia	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
Scrophulariaceae					
Conobea scoparioides (Cham. & Schltdl.) Benth	Colombia	LF	*L. amazonensis*	Methylene chloride extract	Weniger et al. (2001)
			L. braziliensis	Methylene chloride extract	Weniger et al. (2001)
Picrorhiza kurroa Royle, ex Benth	India	RZ + RT	*L. donovani*	Ethanol extract	Mittal et al. (1998)
Scrophularia scorodonia L.	Spain	FL	*L. infantum*	Methanol extract	Martin et al. (1998)
Solanaceae					
Nicotiana glauca Grahm.	Israel	LF + SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Saracha punctata Ruiz & Pav.	Bolivia	LF	*L. amazonensis*	Ethanol extract	Moretii et al. (1998)
			L. braziliensis	Ethanol extract	Moretii et al. (1998)
			L. donovani	Ethanol extract	Moretii et al. (1998)
Solanum actaeabotrys Rusby	Bolivia	LF	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
			L. braziliensis	Ethanol extract	Fournet et al. (1994b)
			L. donovani	Ethanol extract	Fournet et al. (1994b)
Solanum luteum Mill	Israel	BC	*L. major*	Type extract not stated	Schlein (1994)
Sterculiaceae					
Cola attiensis Aubrev. & Pellegr.	Nigeria	SD	*L. donovani*	Chloroform extract	Iwu et al. (1992)
Ulmaceae					
Ampelocera edentula Kulm	Bolivia	SM	*L. amazonensis*	Ethanol extract	Fournet et al. (1994b)
Verbenaceae					
Nyctanthes arbortristis L.	India	AP	*L. donovani*	Ethanol extract	Rathore et al. (1989)
Vitex heterophylla Miq.	India	LF	*L. donovani*	Ethanol extract	Bhakuni et al. (1988)

[a]Only positive plant extract tested for antileishmanial activity were presented in Table 1. Data for negative results is available from the authors on request.
[b]In most cases the reference compound to a positive control were either glucantime or pentamidine.
[c]Date incomplete derived from an abstract; AP, aerial part; BC, branches; BK, bark; EP, entire plant; FL, flowers; FR, fruits; IF, inflorescence; LF, leaves; PE, pericarp; RB, rootbark; RT, roots; RZ, rhizome; SB, stembark; SD, seeds; SM, stem; TG, twig.

Table 2. Chemically defined molecules with antileishmanial activity [a]

Chemical substance[b]	Class	Organism tested	References
Acivicin	Alkaloid	*L. donovani*	Mukherjee et al. (1990)
Agarofuran, beta dihydro: 6-beta-8-beta-diacetoxy-1-alpha-9-alpha-dibenzoyl-oxy-15-(2)-methyl-butyroyl-oxy-2-alpha-hydroxy	Sesquiterpene	*L. tropica*	Perez-Victoria et al. (1999)
Ajmalicine	Alkaloid	*L. major*	Staerk et al. (2000)
Alizarin, 3-methyl	Quinoid	*L. major*	Sittie et al. (1999)
Allopurinol	Alkaloid	*L. donovani*	Werbel and Worth (1980)
Aloe emodin	Quinoid	*L. donovani*	Camacho et al. (2000a)
Amarogentin	Iridoid	*L. donovani*	Medda et al. (1999)
Amentoflavone	Flavonoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Amphotericin B	Miscellaneous lactone	*Leishmania* sp.	Chance (1995)
		L. braziliensis	Chalcat et al. (1965)
		L. braziliensis	Furtado et al. (1960)
		L. donovani	Neal and Croft (1984)
		Leishmania sp.	Lyubimova et al. (1979)
Ancistroealaine A	Alkaloid	*L. donovani*	Bringman et al. (2000)
Ancistroealaine B	Alkaloid	*L. donovani*	Bringman et al. (2000)
Annonacin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
Annonacin A	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
Anonaine, (−)	Alkaloid	*L. amazonensis*	Queiroz et al. (1996)
Anophonin	Lignan	*L. major*	Moideen et al. (1997)
Anthraquinone-2-hydroxymethyl-3-hydroxy	Quinoid	*L. major*	Sittie et al. (1999)
Anthraquinone-2-carbaldehyde	Quinoid	*L. major*	Chan-Bacab and Pena-Rodriguez (2001)
Antioquine	Alkaloid	*L. amazonensis*	Fournet et al. (1993d)
Aphidicolin	Diterpene	*L. donovani*	Kayser et al. (2001b)
Arbortristoside A	Iridoid	*L. donovani*	Tandon et al. (1991)
Arbortristoside B	Iridoid	*L. donovani*	Tandon et al. (1991)
Arbortristoside C	Iridoid	*L. donovani*	Tandon et al. (1991)
Argentilactone	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1997)
Argentinine	Alkaloid	*L. donovani*	Mahiou et al. (1994)
Aristeromycin, (−)	Alkaloid	*L. donovani*	Hiraoka et al. (1986)
Artemether	Sesquiterpene	*L. major*	Yang and Liew (1993)
Artemisinin	Sesquiterpene	*L. major*	Yang and Liew (1993)
Benzofuran, 6-benzoyl-2-(oxomethylphenyl)-3-hydroxy	Oxygen heterocycle	*L. donovani*	Kayser and Kiderlen (1999)
Benzofuranone, 3(2*H*): 4,6-dibenzoyl-2-(phenyl-hydroxy-methyl)	Oxygen heterocycle	*L. donovani*	Kayser and Kiderlen (1999)
Benzofuranone, 3(2*H*): 6-hydroxy-2-(phenyl-methylene)	Oxygen heterocycle	*L. donovani*	Kayser and Kiderlen (1999)
Benzofuranone, 3(2*H*): 6-methoxy-2-(phenyl-hydroxy-methylene)	Oxygen heterocycle	*L. donovani*	Kayser and Kiderlen (1999)
Benzofuranone, 3(2*H*): 6-methoxy-2-(phenyl-methylene)	Oxygen heterocycle	*L. donovani*	Kayser and Kiderlen (1999)
Benzoxazolinone	Alkaloid	*L. donovani*	Carvalho and Ferreira (2001)
Benzoxazol-2(3H)-one	Alkaloid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Berbamine	Alkaloid	*L. amazonensis*	Fournet et al. (1993d)
Berberine	Alkaloid	*L. donovani*	Vennerstrom et al. (1990)

		L. mexicana	Edward et al. (1995)
Berberine, dihydro	Alkaloid	*L. donovani*	Vennerstrom et al. (1990)
Berberine, oxy	Alkaloid	L. donovani	Vennerstrom et al. (1990)
Berberine, tetrahydro	Alkaloid	*L. donovani*	Vennerstrom et al. (1990)
Berberine, tetrahydro: *N*-oxyde	Alkaloid	*L. donovani*	Vennerstrom et al. (1990)
Betuletol	Flavonoid	*Leishmania* sp.	Morales et al. (2000)
Betulin aldehyde	Triterpene	*L. amazonensis*	Sauvain et al. (1996)
Brachycalyxolide, 16,17-dihydro	Sesquiterpene	*L. major*	Oketch-Rabah et al. (1998)
Brachycoumarinone, 2-cyclo epoxide	Coumarin	*L. major*	Oketch-Rabah et al. (1997a)
Brachycoumarinone, 2-epicyclo epoxide	Coumarin	*L. major*	Oketch-Rabah et al. (1997a)
Bractein	Flavonoid	*L. donovani*	Kayser et al. (1999)
		L. donovani	Kayser and Kiderlen (1999)
Bracteoline	Alkaloid	*L. amazonensis*	Queiroz et al. (1996)
Bruceantin	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Brucein A, iso	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Brucein B, iso	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Buchtienine	Alkaloid	*L. donovani*	Kam et al. (1999)
Buddlejasaponin	Triterpene	*L. infantum*	Emam et al. (1995)
Camptothecin	Alkaloid	*L. donovani*	Bodley and Shapiro (1995)
		L. donovani	Bodley et al. (1995)
Chalcone, 2′,6′-dihydroxy-4′-methoxy	Flavonoid	*L. amazonensis*	Torres-Santos et al. (1999)
Chaparrinone	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Chaparrinone, 15-beta-heptyl	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Chimanine A	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
		L. braziliensis	Fournet et al. (1993a)
		L. donovani	Fournet et al. (1994a)
Chimanine B	Alkaloid	*L. amazonensis*	Fournet et al. (1994a)
		L. braziliensis	Fournet et al. (1994a)
		L. donovani	Fournet et al. (1994a)
Chimanine D	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
		L. braziliensis	Fournet et al. (1993a)
		L. donovani	Fournet et al. (1994a)
		Leishmania sp	Munos et al. (1994)
Colchiside 4	Triterpene	*L. infantum*	Mshvildadze et al. (2000)
Colchiside 7	Triterpene	*L. infantum*	Mshvildadze et al. (2000)
Concanavalin B	Proteid	*L. amazonensis*	Barral-Neto et al. (1996)
Conoduramine	Alkaloid	*L. amazonensis*	Munoz et al. (1994)
Conodurine	Alkaloid	*L. amazonensis*	Munoz et al. (1994)
Coreximine, (−)	Alkaloid	*L. amazonensis*	Mahiou et al. (1994)
Coronaridine	Alkaloid	*L. amazonensis*	Delorenzi et al. (2001)
Corydine	Alkaloid	*L. donovani*	Camacho et al. (2000b)
Corynantheidine	Alkaloid	*L. major*	Staerk et al. (2000)
Corynantheidine, dihydro	Alkaloid	*L. major*	Staerk et al. (2000)
Corynanthine	Alkaloid	*L. major*	Staerk et al. (2000)
Coumarin	Coumarin	*L. amazonensis*	Bravo et al. (1999)
Cryptofolione	Miscelaneous lactone	*L. amazonensis*	Schmeda-Hirschmann et al. (2001)
Curcumin	Benzenoid	*L. major*	Rasmussen et al. (2000a)
Curcumin, bisdemethoxy	Benzenoid	*L. major*	Rasmussen et al. (2000a)

Table 2. (*continued*)

Chemical substance[b]	Class	Organism tested	References
Curcumin, demethoxy	Benzenoid	*L. major*	Rasmussen et al. (2000a)
Cusparine	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
Damnacanthal	Quinoid	*L. major*	Sittie et al. (1999)
Damnacanthal, nor	Quinoid	*L. major*	Sittie et al. (1999)
Daphnandrine	Alkaloid	*L. braziliensis*	Chan-Bacab and Pena-Rodriguez (2001)
Decanoic acid	Lipid	*L. donovani*	Cunningham et al. (1972)
Dehydropinifolic acid 15-monomethyl ester	Diterpene	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Diallyl disulfide	Sulfur compound	*Leishmania* sp.	McClure et al. (1996)
Dicentrinone	Alkaloid	*L. donovani*	Camacho et al. (2000b)
Dictyolamide A	Alkaloid	*L. amazonensis*	Lavaud et al. (1995)
Diospyrin	Quinoid	*L. donovani*	Hazra et al. (1995)
Diospyrin, hydroxy	Quinoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Dodeca-4-enoic acid, 4,6-diethyl-3(*S*)-5(*R*)-epidioxy-8-methyl	Lipid	*L. mexicana*	Compagnone et al. (1998)
Dodeca-*cis*-2,4-dienoic acid, 3,6(*R*)-epoxy-4,6-8(*S*)-triethyl: methyl ester	Lipid	*L. mexicana*	Compagnone et al. (1998)
Dodeca-*cis*-2,4-dienoic acid, 4,6-diethyl-3,6(*R*)-epoxy-8(*S*)-methyl: methyl ester	Lipid	*L. mexicana*	Compagnone et al. (1998)
Domesticine, nor:	Alkaloid	*L. amazonensis*	Queiroz et al. (1996)
(*E*)-1-[2,4-Dihydroxy-3-(3-methylbut-2-enyl)-phenyl]-3-[4-hydroxy-3-(3-methyl-but-2-enyl)phenyl]prop-2-en-1-one	Flavonoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Emetine, (−)	Alkaloid	*L. tropica*	Neal (1970)
Emetine, 2,3-dehydro	Alkaloid	*L. tropica*	Neal (1970)
Espintanol	Monoterpene	*L. amazonensis*	Hocquemiller et al. (1991)
Eudesm-4(14)-ene-5-alpha-11(*R*)-12-triol	Sesquiterpene	*L. donovani*	Villaescusa et al. (2000)
Fissinolide	Triterpene	*L. major*	Khalid et al. (1998)
Flavone, iso: 3′,7-dihydroxy-4′-methoxy	Flavonoid	*L. amazonensis*	Araújo et al. (1998)
Formycin B	Alkaloid	*L. donovani*	Neal and Croft (1984)
		L. donovani	Carson and Chang (1981)
		L. major	Neal et al. (1985)
Furan, tetrahydro: 2-(5-(2-hydroxy-undecyl)-2-tetrahydrofuranyl)-5-(14-(5-methyl-2-oxo-2,5-dihydro-3-furanyl)-1,5,12-trihydroxy-tetradecyl)	Oxygen heterocycle	*L. donovani*	Cavé et al. (1990)
Gabunine	Alkaloid	*L. amazonensis*	Munoz et al. (1994)
Germacratien 2,5-epoxy-2beta-hydroxy-8alpha-(2-methylpropenoyloxy)-4(15),10(14),11(13)-12,6alpha-olide	Sesquiterpene	*L. major*	Fuchino et al. (2001)
Glaucafilin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
Glaucanisin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
Glaucaruantine	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Glaucarubin	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Glaucarubinone	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Glauacarubol, 15-beta-glucosyl	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Glucan	Carbohydrate	*L. donovani*	Cook et al. (1980)
Goniothalamicin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
Grifolic acid	Sesquiterpene	*L. amazonensis*	Mahiou et al. (1995)

Grifolin	Sesquiterpene	*L. amazonensis*	Mahiou et al. (1995)
		L. braziliensis	Fournet et al. (1996)
Guattouregidine, iso	Alkaloid	*L. amazonensis*	Mahiou et al. (1994)
Gyrocarpine	Alkaloid	*L. amazonensis*	Fournet et al. (1993d)
Harmaline	Alkaloid	*Leishmania* sp.	Chan-Bacab and Pena-Rodriguez (2001)
Harmine	Alkaloid	*L. donovani*	Kam et al. (1999)
Hederacolchiside A	Triterpene	*L. infantum*	Mshvildadze et al. (2000)
Hederacolchiside A′	Triterpene	*L. infantum*	Mshvildadze et al. (2000)
Hederacolchiside A-1	Triterpene	*L. amazonensis*	Ridoux et al. (2001)
Hederagenin	Triterpene	*L. tropica*	Savornin et al. (1991)
Hederin, alpha	Triterpene	*L. tropica*	Savornin et al. (1991)
Hederin, beta	Triterpene	*L. tropica*	Savornin et al. (1991)
Hederin, delta	Triterpene	*L. tropica*	Savornin et al. (1991)
Heptane, 3-hydroxy-1,7-bis-(4′,4″-dihydro-xyphenyl)	Benzenoid	*L. amazonensis*	Araújo et al. (1998)
Holacurtine	Steroid	*L. donovani*	Kam et al. (1998)
Holacurtine, *N*-demethyl	Steroid	*L. donovani*	Kam et al. (1998)
Holacurtine, 17-epi	Steroid	*L. donovani*	Kam et al. (1998)
Holacurtine, 17-epi-*N*-demethyl	Steroid	*L. donovani*	Kam et al. (1998)
Holacurtinol	Steroid	*L. donovani*	Kam et al. (1998)
Holamine	Steroid	*L. donovani*	Kam et al. (1998)
Holamine, 15-alpha-hydroxy	Steroid	*L. donovani*	Kam et al. (1998)
Hyaluronic acid	Carbohydrate	*L. donovani*	Seneca et al. (1948)
Ibericin	Quinoid	*L. major*	Sittie et al. (1999)
Incomptin B	Sesquiterpene	*L. mexicana*	Guerrero et al. (1995)
Jacaranone	Quinoid	*L. amazonensis*	Sauvain et al. (1993)
Jatrogrossidione	Diterpene	*L. chagasi*	Schmeda-Hirschmann et al. (1996)
Jatrophone	Diterpene	*L. amazonensis*	Schmeda-Hirschmann et al. (1996)
Kutkoside	Iridoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Kudtriol	Sesquiterpene	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Labda-8-*trans*-13-dien-15-oic acid, 18-carboxy: methyl ester (4*S*,9*R*,10*R*)	Diterpene	*L. donovani*	Richomme et al. (1991)
Labda-9-14-diene, 3-beta-acetoxy-8-alpha-13-epoxy-12-oxo	Diterpene	*L. donovani*	Garcia-Granados et al. (1997)
Lapachol	Quinoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Lauric acid	Lipid	*L. donovani*	Cunningham et al. (1972)
Licochalcone A	Flavonoid	*L. donovani*	Chen et al. (1993)
		L. donovani	Chen et al. (1994)
		L. donovani	Chen (1995)
		L. major	Zhai et al. (1995)
Limacine	Alkaloid	*L. braziliensis*	Chan-Bacab and Pena-Rodriguez (2001)
Liriodendronine, *N*-methyl	Alkaloid	*L. donovani*	Camacho et al. (2000b)
Liriodenine	Alkaloid	*L. amazonensis*	Queiroz et al. (1996)
		L. donovani	Waechter et al. (1999)

Table 2. (*continued*)

Chemical substance[b]	Class	Organism tested	References
Lirioresinol B	Lignan	*L. amazonensis*	Fevrier et al. (1999)
Loganin, 6-beta hydroxy	Iridoid	*L. donovani*	Tandon et al. (1991)
Luteolin	Flavonoid	*L. donovani*	Mittra et al. (2000)
Lysicamine	Alkaloid	*L. donovani*	Waechter et al. (1999)
Medioresinol, (+)	Lignan	*L. amazonensis*	Chan-Bacab and Pena-Rodriguez (2001)
Mimengoside A	Triterpene	*L. infantum*	Emam et al. (1996)
Minquartynoic acid	Lipid	*L. major*	Rasmussen et al. (2000b)
Molvizarin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
		L. donovani	Sahpaz et al. (1994)
Monomycin	Carbohydrate	*L. tropica*	Kellina (1964)
		L. tropica	Moskalenko and Pershin (1966)
		L. tropica	Neal (1968)
		L. tropica	Pershin and Moskalenko (1963)
Moschatoline, *O*-methyl	Alkaloid	*L donovani*	Waechter et al. (1999)
Muzanzagenin	Triterpene	*L. major*	Oketch-Rabah et al. (1997b)
Mycobacillin	Proteid	*L. donovani*	Chattopadhyay et al. (1976)
Mycophenolic acid	Miscellaneous lactone	*L. tropica*	Berman and Webster (1982)
Neurolenin B	Sesquiterpene	*L. mexicana*	Berger et al. (2001)
Neurolenin C	Sesquiterpene	*L. mexicana*	Berger et al. (2001)
Nyasol, (+)	Lignan	*L. major*	Oketch-Rabah et al. (1997b)
Nystatin	Miscellaneous lactone	*L. donovani*	Ghosh (1963a)
		L. donovani	Ghosh (1963b)
		L. donovani	Ghosh and Chaterjee (1961)
		L. donovani	Ghosh and Chaterjee (1963)
Obaberine	Alkaloid	*L. braziliensis*	Chan-Bacab and Pena-Rodriguez (2001)
Oleanolic acid, epi	Triterpene	*L. donovani*	Camacho et al. (2000a)
Palmatine	Alkaloid	*L. donovani*	Vennerstrom et al. (1990)
Palmitic acid	Lipid	*L. donovani*	Cunningham et al. (1972)
Pannarine	Depside	*L. amazonensis*	Fournet et al. (1997)
Pannarine, 1′-chloro	Depside	*L. amazonensis*	Fournet et al. (1997)
Paromomycin	Carbohydrate	*L. donovani*	Neal and Croft (1984)
		L. tropica	El-On et al. (1985)
		L. tropica	Moskalenko and Pershin (1966)
		L. tropica	Neal (1968)
Paromomycin I	Carbohydrate	*L. garnhami*	Rezzano de Raffo et al. (1985)
Phaseolinone	Sesquiterpene	*L. donovani*	Roy et al. (1990)
Phenyl-3-(4-hydroxy-3-(3-methyl-2-buthenyl)-phenyl]-prop-*trans*-2-en-1-one,1-[2,4-dihydroxy-3-(3-methyl-2-butenyl)]	Flavonoid	*L. donovani*	Christensen et al. (1994)
Phenylpropane,3,4,5-trimethoxy-8-(3′,5′-dimethoxy-4′-*trans*-propenyl-phenoxy	Phenylpropanoid	*L. donovani*	Barata et al. (2000)
Phorbol-13-acetate,12-*O*-tetradecanol	Diterpene	*L. amazonensis*	Chan-Bacab and Pena-Rodriguez (2001)

Picroliv	Iridoid	*L. donovani*	Mittal et al. (1998)
Picrosid I	Iridoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Pimaricin	Miscellaneous lactone	*L. donovani*	Neal and Croft (1984)
Piperine	Alkaloid	*L. donovani*	Kapil (1993)
Piperogalin	Benzenoid	*L. amazonensis*	Mahiou et al. (1995)
		L. amazonensis	Fournet et al. (1996)
		L. donovani	Kapil (1993))
Piperone, hydro	Quinoid	*L. amazonensis*	Mahiou et al. (1996)
Pleiocarpine	Alkaloid	*L. donovani*	Kam et al. (1999)
Plumbagin	Quinoid	*L. amazonensis*	Fournet et al. (1992a)
		L. braziliensis	Fournet et al. (1992b)
Plumbagin, 3,3′-bi	Quinoid	*L. amazonensis*	Fournet et al. (1992a)
		L. braziliensis	Fournet et al. (1992b)
Plumbagin, 8,8′-bi	Quinoid	*L. amazonensis*	Chan-Bacab and Pena-Rodriguez (2001)
Podocarpusflavone A	Flavonoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Podocarpusflavone B	Flavonoid	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Polymyxin B	Proteid	*L. tropica*	Kellina (1964)
Pregnan-20-one-3-alpha-amino-14-beta-hydroxy	Steroid	*L. donovani*	Kam et al. (1998)
Puertogaline A	Alkaloid	*L. amazonensis*	Mahiou et al. (2000)
Puertogaline B	Alkaloid	*L. amazonensis*	Mahiou et al. (2000)
Pyran, tetrahydro: 2-[beta-para-hydroxy-phenyl)-ethyl]-6-(para-hydroxy-phenyl)	Benzenoid	*L. amazonensis*	Araújo et al. (1998)
Pyrrole-2-carboxaldeide	Alkaloid	*L. mexicana*	Compagnone et al. (1999)
Quercetin	Flavonoid	*L. donovani*	Mittra et al. (2000)
Quinoline, 2-(3,4-dimethoxy-phenyl-ethyl)	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
		L. braziliensis	Fournet et al. (1993a)
Quinoline, 2-(3,4-methylenedioxy-phenyl-ethyl)	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
		L. braziliensis	Fournet et al. (1994a)
Quinoline, 2-*N*-pentyl	Alkaloid	*L. amazonensis*	Fournet et al. (1994a)
		L. braziliensis	Fournet et al. (1993a)
Reserpine	Alkaloid	*L. major*	Staerk et al. (2000)
Ribenol	Diterpene	*L. donovani*	Garcia-Granados et al. (1997)
Rigidusine	Diterpene	*L. donovani*	Morales et al. (2000)
Rollidesin B	Miscellaneous lactone	*L. amazonensis*	Fevrier et al. (1999)
Rolliniastatin 1	Miscellaneous lactone	*L. amazonensis*	Carvalho and Ferreira (2001)
Rolliniostatin 2	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
		L. donovani	Sahpaz et al. (1994)
Rosenolactone, 6-beta-hydroxy	Diterpene	*L. donovani*	Chan-Bacab and Pena-Rodriguez (2001)
Rubiadin-1-methyl ether	Quinoid	*L. major*	Sittie et al. (1999)
Sarachine	Steroid	*L. chagasi*	Moretii et al. (1998)
		L. major	Sahpaz et al. (1994)
Senegalene	Miscellaneous lactone	*L. major*	Chan-Bacab and Pena-Rodriguez (2001)
Sepeerine	Alkaloid	*L. amazonensis*	Mahiou et al. (2000)

Table 2. (*continued*)

Chemical substance[b]	Class	Organism tested	References
Sergeolide	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Sergeolide, 15-acetyl	Triterpene	*L. donovani*	Robert-Gero et al. (1985)
Simalikalactone D	Trterpene	*L. donovani*	Robert-Gero et al. (1985)
Sinefungin	Alkaloid	*L. amazonensis*	Haughan et al. (1993)
		L. braziliensis	Avila et al. (1990)
		L. donovani	Lawrence and Robert-Gero (1993)
		L. donovani	Moulay and Robert-Gero (1995)
		L. donovani	Phelouzat et al. (1995)
		L. donovani	Neal et al. (1989)
		L. mexicana	Haughan et al. (1993)
		L. tropica	Paolantonacci et al. (1987)
Skimmianine	Alkaloid	*L. amazonensis*	Fournet et al. (1993c)
		L. braziliensis	Fournet et al. (1993a)
		L. donovani	Fournet et al. (1994a)
Squamocin	Miscellaneous lactone	*L. amazonensis*	Waechter et al. (1998)
		L. major	Sahpaz et al. (1994)
Striatin A	Diterpene	*L. amazonensis*	Inchausti et al. (1997)
Striatin B	Diterpene	*L. amazonensis*	Inchausti et al. (1997)
Sulfuretin	Flavonoid	*L. donovani*	Kayser et al. (1999)
Surinamensine	Lignan	*L. donovani*	Barata et al. (2000)
Sylvaticin	Miscellaneous lactone	*L. amazonensis*	Fevrier et al. (1999)
Taurin, 8-alpha-hydroxy	Sesquiterpene	*L. donovani*	Cubukcu et al. (1998)
Taxol	Diterpene	*L. major*	Doherty et al. (1998)
Tetradeca-7-11-dienoic acid, 3-6-epidioxy-4,6,8,10-tetraethyl	Lipid	*L. mexicana*	Compagnone et al. (1998)
Tetrandrine, iso	Alkaloid	*L. amazonensis*	Fournet et al. (1993d)
Titucall-3-alpha-hydroxy-7,24-*Z*-dien-26-oic acid	Triterpene	*L. donovani*	Camacho et al. (2000a)
Tyrocidine	Proteid	*L. tropica*	Weinman (1943)
Unonopsine	Alkaloid	*L. donovani*	Waechter et al. (1999)
Ursolic acid	Triterpene	*L. amazonensis*	Sauvain et al. (1993)
Ushinsunine, nor	Alkaloid	*L. amazonensis*	Queiroz et al. (1996)
Usnic acid	Oxygen heterocycle	*L. amazonensis*	Fournet et al. (1997)
Verbascoside	Phenylpropanoid	*L. infantum*	Emam et al. (1995)
Verbascoside, iso	Phenylpropanoid	*L. infantum*	Emam et al. (1995)
Vernodalin	Sesquiterpene	*L. infantum*	Koshimizu et al. (1994)
Vernodalol	Sesquiterpene	*L. infantum*	Koshimizu et al. (1994)
Vernolide	Sesquiterpene	*L. infantum*	Koshimizu et al. (1994)
Vernolide, hydroxy	Sesquiterpene	*L. infantum*	Koshimizu et al. (1994
Voacangine	Alkaloid	*Leishmania* sp.	Bou Habib et al. (1998)
With-5-enolide D, 18-acetoxy-5,6-deoxy	Steroid	*L. brasiliensis*	Bravo et al. (2001)
Yohimbine, alpha	Alkaloid	*L. major*	Staerk et al. (2000)
Zaluzanin C, dehydro	Sesquiterpene	*L. amazonensis*	Fournet et al. (1993b)

[a]Only positive chemical compounds tested for antilesishmanial activity were presented in Table 2. Data for negative results is available from the authors on request.
[b]In most cases the reference compound to a positive control were either glucantime or pentamidine.

arbortristis) showed more than 75% inhibition (at 1 g/kg/day × 5 orally) of multiplication of parasites on day 7 and/or 28 post treatment with an increased survival period (Singha et al., 1992).

Extracts of 11 plants used in Nigerian traditional medicine have been evaluated for possible antileishmanial activity using a radiorespirometric microtest technique based on *in vitro* inhibition of catabolism of $^{14}CO_2$ from a battery of ^{14}C-substrates by promastigotes. Of 13 methanol extracts tested, 5 from *Gongronema latifolia*, *Dorstenia multiradiata*, *Picralima nitida*, *Cola attiensis*, and *Desmodium gangeticum* were active at concentrations of 50 μg/ml or less against a visceral *Leishmania* isolate (Iwu et al., 1992).

Crude extracts collected from different parts of Spain (60 representing 12 species from 7 families) have been screened for antiparasitic activity against *L. infantum*, and 30% of the extracts showed activity. The most promising extracts originate from plants used in traditional medicine, such as *Inula montana*, *Bupleurum rigidum* and *Scrophularia scorodonia* (Martin et al., 1998).

The drugs used currently for treatment of Kala-azar, sodium stibogluconate (SSG) and pentamidine cause severe toxic side-effects and acute immunosuppression in the treated individuals. Picroliv, a standardized mixture of iridoid glycosides, prepared from the alcoholic extract of the root and rhizome of *Picrorhiza kurroa*, has shown strong hepatoprotective activity against several models of hepatotoxicity. Therefore, this study was undertaken to study the effects of picroliv (12.5 mg/kg body wt. × 7 days oral) alone and in combination with SSG on parasitemia, lipid peroxidation and hepatic marker enzymes of golden hamsters during *L. donovani* infection. The results indicated a marked hepatoprotective effect of picroliv in terms of biochemical markers, and a significant antileishmanial activity, implying that it can be utilized as an adjuvant to chemotherapy or in combination therapy of Kala-azar along with SSG, thus enhancing the efficacy of antileishmanials (Mittal et al., 1998).

The ethanolic extract of *Yucca filamentosa*, showed potent activity against *L. amazonensis* at a concentration of 5 μg/ml (Plock et al., 2001). Other plants with marked activity against *L. donovani* were *Khaya senegalensis* and *Anthostema senegalense* with IC_{50} values of 9.8 and 9.1 μg/ml, respectively (Abreu et al., 1999).

Studies carried out in Colombia with *Annona muricata* against *L. braziliensis* and *L. panamenis* showed that its activity was greater than that of meglumine antimoniate (Glucantime®) (Jaramillo et al., 2000). These results show the importance of the investigation of plants with therapeutic potential in the treatment of Leishmaniases.

We found 101 plants described in the literature with antileishmanial activity. The plants are listed in Table 1 in alphabetical order of their family, scientific names, country, plant part used, kind of extract, result and references.

Antileishmanial activity of chemically defined molecules

Four bisbenzyisoquinoline alkaloids, antioquine, berbamine, gyrocarpine and isotetrandrine, were tested in BALB/c mice infected with *L. amazonensis*. The treatments were initiated 1 day after the parasitic infection, with alkaloid at 100 mg/kg body wt./body wt./day for 14 days and the reference compound, Glucantime® at 200 mg/kg body wt./body wt./day. Antioquine, berbamine and gyrocarpine were less potent than Glucantime against *L. amazonensis*. Only isotetrandrine exhibited activity approximately equal to or greater than Glucantime (Fournet et al., 1993d).

A series of aurones with drug-potential for *Leishmania* sp. infections was identified *in vitro* using both a direct cytotoxicity assay against extracellular promastigotes of *L. donovani*, *L. infantum*, *L. enriettii*, and *L. major*, and a test against intracellular amastigote forms of *L. donovani* residing within murine macrophages. The most active aurone, 6-hydroxy-2-[phenylmethylene]-3(2*H*)-benzofuranone had an IC_{50} of 0.45 μg/ml in the extra-, and IC_{50} value of 1.40 μg/ml in the intracellular assay. Other aurones were active between 0.06–12.50 μg/ml and 0.04–7.81 μg/ml, respectively. When tested against murine bone marrow-derived macrophages as a mammalian host cell control, the compounds showed only moderate cytotoxicity (IC_{50} value 2.32 to <25.0 μg/ml) (Kayser and Kiderlen, 1999).

From the hexane extract of roots of *Annona haematantha* an α,β-unsaturated δ-lactone was isolated and identified as argentilactone. This compound exhibited *in vitro* activity against various strains of *Leishmania* sp. at 10 μg/ml. BALB/c mice infected with *L. amazonensis* were treated 4 weeks after infection with argentilactone by oral or subcutaneous routes for 14 days at 25 mg/kg body wt. daily. The reference drug, *N*-methylglucamine antimonate, was administered by subcutaneous injections at 100 mg/kg body wt. for 14 days. Under these conditions, argentilactone showed the same efficacy as the reference drug, reducing by 96% the parasite loads in the lesion and by 50% the parasite burden in the spleen (Waechter et al., 1997).

Compounds isolated from plants with promising activity against the *Leishmania* genera and low toxicity as compared to the pentavalent antimonial drugs include chimanine B; 4-hydroxy-tetralone; 8-8′-biplumbagin; rolliniastatin-1; squamocin; dictyolamide A and B and 2-benzoxazolinone (Carvalho and Ferreira, 2001).

Reviews by Carvalho and Ferreira (2001), Chan-Bacab and Pena-Rodriguez (2001) provide further

information on the antileishmanial activity of chemically defined molecules.

We encountered 239 chemically defined natural molecules reported in the literature, which have been evaluated for antileishmanial activity. The active compounds, which have been isolated and identified, belong to the classes of alkaloids (68), triterpenes (29), sesquiterpenes (19), miscellaneous lactones (18), quinoids (16), flavonoids (13), diterpenes (13), steroids (10), lipids (8), iridoids (8), oxygen heterocycles (7), benzenoids (6), carbohydrates (5), lignans (5), proteids (4), coumarins (3), phenylpropanoids (3), depsides (2), a sulfur compound (1), and a monoterpene (1). The compounds are arranged in Table 2 in alphabetical order. Each entry gives the following information in sequence: chemical name, class, organism tested, and references.

Conclusion

The present study shows a range of plant extracts exhibit interesting antileishmanial properties *in vitro*, seeming to validate their use in folk medicine. The potent leishmanicidal activities of certain chemically defined molecules isolated from natural origins represent an exciting advance in the search for novel antiprotozoal agents at a time when there is an urgent need for new innovative drug leads.

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