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A PERSPECTIVE REVIEW ON THE ALKALOIDS AS POTENTIAL SOURCES FOR DEVELOPMENT OF NEW BIOACTIVE COMPOUNDS AGAINST LEISHMANIA PARASITES. AN UPDATE FOR THE YEARS 1990 TO 2022

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ABSTRACT

Leishmaniasis is one of the most neglected tropical diseases that present areal public health problems worldwide. Chemotherapy has several limitations such as toxic side effects, high costs, frequent relapses, the development of resistance and the requirement for long-term treatment. Effective vaccines or drugs to prevent or cure the disease are not available yet. Therefore, it is important to dissect antileishmanial molecules that present a selective efficacy and tolerable safety. The aim of this review is to update and summarize the investigations that have been undertaken on the antileishmanial activity of alkaloid compounds and their derivatives from January 1990 to September 2022. In this review, 183 alkaloid compounds have been identified with anti-*Leishmania* activities against amastigotes and/or promastigotes of different species. with respect to the test methods, 83.6% of studies were carried in vitro, while 16.4% of them were performed using in vivo assays. For in vitro assay, 153 alkaloid compounds were screened in vitro for anti-leishmanial activities against different Leishmania species (*L. infantum, L. tropica, L. major, L. amazonensis, L. donovani, L. braziliensis, L. panamensis, L. guyanensis, L. chagasi* and *L. mexicana*) and life cycle forms (amastigotes and/or promastigotes). The IC_{50} value for in vitro assay was in a range of 0.13 to 100 µg/ml, among 226 test studied, the highly active was found 62.3% (141), moderately and weak activity represent 31.5% (71) and 6.2 % (14) respectively. For in vivo assay, among 30 alkaloid compounds were studied in vivo against cutaneous and visceral leishmania of different species. The highest activity against cutaneous leishmaniasis was exhibited by Berberine (0.5% cream, twice a day for 35 days, Topically) against *L. major* which produced 99.9% reduction of parasites load in the skin and the highest activity against visceral leishmaniasis was shown by the 2-n-propylquinoline (oral administration at 0.54 mmol/kg for 5 and 10 days) against *L. donvani* which suppresses liver parasites by 87.8 and 99.9%, respectively. In conclusion, numerous alkaloid compounds have demonstrated a diverse range of activities against leishmaniasis with strong activities (IC50 <10 µg/mL). These compounds provide promising potential sources and reasonable starting points for the development of effective and affordable novel drugs.

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INTRODUCTION

Leishmaniasis is considered as one of the most neglected tropical diseases (NTDs) in the world [1], which is second to malaria [2]. it is a group of diseases caused by protozoa parasites from more than 20 Leishmania species. Today, more than 1 billion people live in areas endemic to leishmaniasis and are at risk of infection. An estimated 30000 new cases of visceral leishmania and more than 1 million new cases of cutaneous leishmania occur annually [3]. The parasite is categorized into two main groups: Old World leishmaniasis which is endemic in Africa, Asia, the Mediterranean and the Middle East. *L. tropica, L. major, L. aethiopica* and *L. donovani* are the four common species causing Old World leishmaniasis. New World leishmaniasis is caused by *L. mexicana, L. amazonensis, L. braziliensis, L. panamensis, L. peruviana, L. guyanensis, L. pifanoi, L. venezuelensis, L. shawi* and *L. lainsoni* [4]. There are three clinical forms of leishmaniasis in humans namely cutaneous, mucocutaneous and visceral leishmaniasis. Cutaneous leishmaniasis is a less severe form of the disease which usually manifests in self-healing ulcers. Mucocutaneous leishmaniasis results in disfiguring lesions of mucous membranes in the nose, mouth and throat. Visceral leishmaniasis is the most severe form of the disease which can result in 95% mortality of infected patients if not treated [5]. In 2020, more than 90% of new cases of visceral leishmaniasis reported to WHO occurred in Bangladesh, Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen [3]. Over 90% of mucocutaneous leishmaniasis occurred in Bolivia, Brazil, Ethiopia and Peru, and more than 85% of cutaneous leishmaniasis cases appeared in Afghanistan, Algeria, Brazil, Colombia, Iran, Libya, Pakistan, Peru, Syria and Tunisia [3]. The life cycle of the *Leishmania* parasite starts if a parasitized female sand fly takes a blood meal from a vertebrate host to produce its eggs. As the sand fly feeds, infective promastigotes enter the vertebrate host via the insect proboscis. The promastigotes are then phagocytosed by macrophages which they transform into amastigotes and reproduce by binary fission. They increase in number until the cell eventually bursts and then infects other phagocytic cells to continue the cycle [6]. Over the years, a number of drugs have been employed for the treatment of leishmaniasis. A brief account of the mechanism of action and mode of administration of these drugs has been presented in Table 1 [7].

Table 1: Drugs used for the treatment of leishmaniasis.

Drug	Mode of action	Mode of administration	Adverse effects
Pentavalent antimonials	Inhibition of glycolysis and β oxidation n of fatty acids of parasite	Intralesional for CL, Parenteral	Abdominal pain, erythema, nausea, toxicity (hepatic, pancreas, renal, muscular and skeletal cardiothrombocytopenia or leukopenia)
Amphotericin B	Binding to parasite's membrane sterols and changing its permeability selective to K^+ and Mg^{2+}	Liposomal Formulations, Deoxycholate formulations	Fever, nausea, hypokalemia, anorexia, leukopenia, kidney failure, and heart problems
Pentamidine	Interferes with DNA synthesis and modifies the morphology of kinetoplast	Parenteral, Intramuscular administration	Pain, nausea, vomiting, dizziness, myalgia, hypertension, headache, hypoglycemia and transient hyperglycemia
Miltefosine	Associated with phospholipid biosynthesis and alkyl-lipid metabolism in Leishmania	Oral for VL	Nausea, vomiting, diarrhea and raised creatinine
Paromomycin	Inhibition of protein biosynthesis in sensitive organism	Topical for CL Parenteral for VL	Erythema, pain, edema and ototoxicity (damage to the internal ear)

The current treatment by chemical drugs has several limitations such as toxic side effects, high costs, frequent relapses, the development of resistance and the requirement for long-term treatment [8,9]. Therefore, there is a need for new therapeutic alternatives that are more effective and efficient in terms of parasite elimination and disease resolution and that are safer for patients in terms of better adherence and fewer toxic effects [10,11]. Latest developments in the prevention and treatment permanent solution for leishmaniasis in terms of successful human vaccination is still a major challenge [12]. Historically, natural products have always played a key role in fighting various kinds of diseases [13]. Natural products have been used in the treatment of infectious diseases, especially in developing countries [14], with some displaying anti-leishmanial activities [15]. These activities have been attributed to the terpenes, flavonoids, phenylpropanoids, steroids, quinones, chalcones and a few more, but the most listed in reviews was alkaloids [15].

Therefore, the aim of this review is to update and summarize the investigations that have been undertaken on the antileishmanial activity of alkaloid compounds and their derivatives from January 1990 to September 2022.

Alkaloids are secondary metabolites defined as a nitrogenous organic molecule that has a pharmacological effect on humans and animals. It is one of the largest groups of natural products, represent a highly diverse group of chemical entities. They are divided according to their shapes and origins into three main types of alkaloids: true alkaloids, protoalkaloids and pseudoalkaloids. the structural richness of alkaloids is reflected in their chemical, biological and pharmacological properties [16]. These compounds have important clinical use, such as analgesics, antimalarial, antispasmodics, for pupil dilation, treatment of hypertension, mental disorders and tumors [17]. Also the antiparasitic activity in particular against Leishmania spp have been reported in several studies [15].

METHODS:

The databases used for this article were carried out to select scientific papers available at the PubMed, Google Scholar, Web of Science, Research Gate, SCOPUS, and Scientific Electronic Library Online (SciELO) using the keywords: The keywords used for the literature search for this review were anti-leishmaniasis, anti-leishmanial activity, alkaloids and natural products. We used the search terms separately and in combination with the Boolean operators "OR" or "AND". the year of publication was adjusted for the limit in the year of publication (from 1 January 1990 to 31 May 2022). The search was performed in June 2022 and only articles in English were considered. The data extraction protocol included the scientific and family names, parts of the plant used, name of alkaloids compound, Leishmania species and form, IC50 values, clinical form of leishmaniasis, route, the dose of administration and scheme of treatment, the efficacy of the treatments in the experiment, the authors and year of publication. Exclusion criteria were adopted: the restriction in the year of publication, articles in languages other than English, articles that did not address the proposed theme, that had tested extracts, IC50 >100 µg/mL, which were not available in full and duplicate papers. In the results analysis, highly active alkaloid was considered when the IC50 was less than or equal to 10 µg/mL; moderately active when IC 50 was greater than 10 and less than or equal 50 µg/ml and weakly active when IC50 was greater than 50 µg/ml and less than or equal to 100 µg/mL.

RESULTS AND DISCUSSION:

The alkaloid compounds reported in this review were obtained either from plant, marine or/and synthetic sources. The plant source represents the highest one, as shown in Table 2, 46 plant species distributed in 21 families have been identified with anti-*Leishmania* alkaloid compound(s). The family *Annonaceae* and *Apocynaceae* accounted for the highest percentage (15.2% of each one) followed by *Ancistrocladaceae* (13%) and *Menispermaceae* (8.6%). Table 3 depicts the alkaloid compound(s), that have antileishmanial activity, obtained from marine organisms.

Table 2. Botanical characteristic of the medicinal plants in the present study.

Family name	*Scientific name*	Part used
Acanthaceae	*Acanthus illicifolius*	Leaves
	Ancistrocladus heyneanus	Leaves
	Ancistrocladus benomensis	Leaves
Ancistrocladaceae	*Ancistrocladaceae sp*	Leaves
	Ancistrocladus ealaensis	Leaves
	Ancistrocladus griffithii	Leaves and twigs
	Ancistrocladus likoko	Leaves and roots
	Annona foetida	Bark and root
	Annona spinescens	Bark and root
	Guatteria dumetorum	Leaves
Annonaceae	*Guatteria foliosa*	barks
	Monodora crispata	Leaves
	Monodora brevipes	Leaves
	Unonopsis buchtienii	Stem bark
	Aspidosperma ramiflorum	Stem bark
	Aspidosperna nitidum	Barks
Apocynaceae	*Frompeschiera australis*	Stem
	Geissospermum vellosii	Stem barks
	Kopsia griffithii	Leaves
	Peschirea australis	Stem barks
	Peschiera var heurkii	Stem barks
Aristolochiaceae	*Aristolochia cordigera*	Flower, leaves
Colchicaceae	*Colchicum kurdicum*	Flower
Dioncophyllaceae	*Triphyophyllum peltatum*	Leaves
Euphorbiaceae	*Pera benensis*	Stem bark
Fabaceae	*Prosopis glandulosa*	Leaves
	Senna spectabilis	Flowers
Glusiaceae	*Garcinia lucida*	Stem
Lecythidaceae	*Couroupita guianensis*	Fruits
	Cissampelos sympodialis	Leaves
Menispermaceae	*Limaciopsis loangensis*	Leaves
	Stephania dinklagei	Aerial part

	Triclisia patens	Leaves
Orchidaceae	*Phaius mishmensis*	Whole plant
Oleaceae	*Myctanthes arbortristis*	Seeds
Phyllanthaceae	*Margaritaria nobilis*	Leaves
Piperaceae	*Piper pseudo arboreum*	Leaves
Polygonaceae	*Polygonum tinctorium*	Aerial part
Ranunculaceae	*Thalictrum alpinum*	Whole plant
	Thalictrum flavum L	Roots
Rubiaceae	*Corynanthe pachyceras*	Bark
	Psychotria klugii	Whole plant
	Galipea longiflora	Aerial parts
Rutaceae	*Zanthoxylum chiloperone*	Stem bark
	Zanthoxylum tingoassuiba	Roots
Solanaceae	*Solanum lycocarpum*	Leaves

Table 3. Alkaloid compounds from marine organisms in the present study.

No	*Scientific name*	Alkaloid compound	No	*Scientific name*	Alkaloid compound
1.		Manzamine A			Spongiacidin B
					Dibromopalau'amine
		Manzamine Y			Manzacidin A
		(+)-8-Hydroxymanzamine A	6.	*Cyanobacterium*	Nostocarboline
		Manzamine E	7.	*Haliclona exigua*	Araguspongin C
		Manzamine F	8.	*Ircinia spiculosa*	Tryptophol
	Acanthostrongylophora sp	12,28-oxamanzamine A	9.		Mirabilin B
		12,28-Oxamanzamine E			Norbatzelladine L
		Manzamine A N-oxide		*Monanchora unguifera*	Batzelladine F
		Manzamine J			Batzelladine D
		Neo-kauluamine			Batzelladine L
		Ircinal A	10.	*Neopetrosia sp.*	Renieramycin A
2.	*Agelas mauritiana*	Ageloxime D	11.		Manzamine X
		Ageloxime B		*Petrosiidae sp*	6-Deoxymanzamine X
3.	*Agelas longissima*	Longamide A			
4.	*Aplidium meridianum*	Agelongine	12.	*Streptomyces sp.*	Staurosporine
		Meridianin G			7-Oxostaurosporine
5.	*Axinella verrucosa*	Stevensin	13.	*Ascidian lissoclinum*	Lissoclinotoxin E

With respect to the type of *Leishmania*, 183 alkaloid compounds have been identified with anti-*Leishmania* activities against amastigotes and/or promastigotes of different species. Regarding the test methods, 83.6% of studies were carried in vitro, while 16.4% of them were performed using in vivo assays. Among them, 134 alkaloid compounds were screened in vitro for anti-leishmanial activities against different Leishmania species (*L. infantum, L. tropica, L. major, L. amazonensis, L. donovani, L. braziliensis, L. panamensis, L. guyanensis, L. chagasi* and *L. mexicana*) and life cycle forms (amastigotes and/or promastigotes). The IC_{50} value for in vitro assay was in the range of 0.13 to 100 µg/ml. Among 226 studies, high activity was indicated in 62.3% (141), moderate activity in 31.5% (71) and weak activity in 6.2 % (14) (Tables 3 - 7).

For in vivo assay, 30 alkaloid compounds were evaluated for anti-leishmanial activity against the main clinical forms; cutaneous form of different Leishmania species (*L. venezuelensis, L. major, L. mexicana, L. amazonensis* and *L. braziliensis*) as well as visceral form (*L. donovani* and *L. infantum*). The highest activity against cutaneous leishmaniasis was exhibited by berberine (0.5% cream, twice a day for 35 days, topically applied) against *L. major*. It had a profound effect and resulted in 99.9% reduction of parasites load in the skin. The highest activity against visceral leishmaniasis was caused by 2-n-propylquinoline (oral administration at 0.54 mmole/kg for 5 or 10 days) against *L. donvani*. It suppressed liver parasites by 87.8 and 99.9%, respectively, in 5 and 10 days (Table 8).

Table 4: *In vitro* antileishmanial activity of alkaloids from 1990-1999.

No	Compound name	Organism	Stage	IC50	Data analysis	Reference
1.	Acivicin	*L. donovani*	Amastigotes	8.9 µg/mL	Highly active	[18]
2.	(-) Anonaine	*L. amazonensis*	Promastigotes	6.6 µg/mL	Highly active	[19]
		L. braziliensis	Promastigotes	13.2 µg/mL	Moderately active	
3.	Argentinine	*L. braziliensis*	Promastigotes	<100 µg/mL	Weakley active	[20]
4.	Buchtienine	*L. donovani*	Promastigotes	<1.5µg/mL	Highly active	[21]
5.	Camptothecin	*L. donovani*	Promastigotes	1.1 µg/mL	Highly active	[22]
6.	2-n-propylquinoline	*L. amazonensis*	Promastigotes	27.7 µg/mL	Moderately active	[23]
		L. braziliensis				
		L. donovani				
7.	Chimanine B	*L. Amazonensis*	Promastigotes	13.8 µg/mL	Moderately active	[23]
		L. braziliensis				
		L. donovani				
8.	Chimanine D	*L. amazonensis*	Promastigotes	15.3 µg/mL	Moderately active	[23]
		L. braziliensis				
		L. donovani				
9.	(-) Coreximine	*L. donovani*	Promastigotes	<100 µg/mL	Weakley active	[20]
		L. Braziliensis	Promastigotes	<100 µg/mL	Weakley active	
10.	Conodurine	*L. amazonensis*	Amastigotes	25 µg/mL	Moderately active	[24]
11.	Conoduramine	*L. amazonensis*	Amastigotes	2.5 µg/mL	Highly active	
12.	Gabunine	*L. amazonensis*	Amastigotes	12.5 µg/mL	Moderately active	[24]
13.	Guattouregidine, iso	*L. amazonensis*	Promastigotes	<100 µg/mL	Weakley active	[20]
		L. donovani	Promastigotes	<100 µg/mL	Weakley active	
		L. Braziliensis	Promastigotes	<100 µg/mL	Weakley active	
14.	Harmane	*L. donovani*	Promastigotes	1.1 µg/mL	Highly active	[21]
15.	Liriodenine	*L. amazonensis*	Promastigotes	50 µg/mL	Moderately active	[19]
		L. donovani	Promastigotes	1.5 µg/mL	Highly active	[25]
		L. major	Promastigotes	1.5 µg/mL	Highly active	
16.	Lysicamine	*L. Donovani*	Promastigotes	12.5 µg/mL	Moderately active	[25]
		L. major	Promastigotes	12.5 µg/mL	Moderately active	
17.	Moschatoline,O-methyl	*L. Donovani*	Promastigotes	25 µg/mL	Moderately active	[25]
		L. major	Promastigotes	25 µg/mL	Moderately active	
18.	Piperine	*L. donovani*	Promastigotes	57.1 µg/mL	Weakley active	[26]
19.	Pleiocarpine	*L. donovani*	Promastigotes	25 µg/ml	Moderately active	[21]
20.	Sinefungin	*L. amazonensis*	Promastigotes	6 µg/ml	Highly active	[27]
		L. mexicana	Promastigotes	10 ng/ml	Highly active	
		L. major	Promastigotes	10 ng/ml	Highly active	
		L. Braziliensis	Promastigotes	50 ng/ml	Moderately active	[28]

Table 5: *In vitro* antileishmanial activity of alkaloids from 2000-2009.

No	Compound name	Organism	Stage	IC50	Data analysis	Reference
1.	Ajmalicine	*L. major*	Promastigotes	0.2 µg/mL	Highly active	[29]
2.	Ancistrotanzanine B	*L. donovani*	Amastigotes	1.6 µg/ml	Highly active	[30]
3.	Ancistroealaines A	*L. donovani*	Promastigotes	4.1 µg/ml	Highly active	[31]
4.	Ancistrotanazanine A	*L. donovani*	Amastigotes	1.3 µg/ml	Highly active	[30]
5.	Ancistrocladidine	*L. donovani*	Promastigotes	2.9 µg/ml	Highly active	[32]
6.	Ancistrolikokine D	*L. donovani*	Promastigotes	5.9 µg/ml	Highly active	[30]
7.	Ancistrogriffines A	*L. donovani*	Amastigotes	3.1 µg/ml	Highly active	[33]
8.	Ancistrogriffines C	*L. donovani*	Amastigotes	18 µg/ml	Moderately active	
9.	Ancistroealaine A	*L. major*	Promastigotes	17 µg/mL	Moderately active	[34]
10.	Ancistrocladiniums A	*L. major*	Promastigotes	2.0 µg/mL	Highly active	

11.	Ancistrocladiniums B	*L. major*	Promastigotes	0.5 µg/mL	Highly active	
12.	Anonaine, (-)	*L. donovani*	Promastigotes	10 µg/ml	Highly active	[35]
13.	Araguspongin C	*L. donovani*	Promastigotes	76.1 µg/ml	Weakley active	[36]
14.	Cephaeline	*L. donovani*	Promastigotes	0.3 µg/ml	Highly active	[37]
15.	Coronaridine	*L. amazonensis*	Promastigotes	2.6 µg/ml	Highly active	[38]
		L. amazonensis	Amastigotes	1.2 µg/ml	Highly active	
16.	Corynantheidine	*L. major*	Promastigotes	1.0 µg/mL	Highly active	[29]
17.	Corynanthine	*L. major*	Promastigotes	8.2 µg/mL	Highly active	
18.	Corynantheine	*L. major*	Promastigotes	0.41 µg/mL	Highly active	
			Promastigotes	0.4 µg/mL	Highly active	[39]
19.	Cryptodorine	*L. mexicana*	Promastigotes	0.9 µg/mL	Highly active	[40]
20.	Cocsoline	*L. donovani*	Amastigotes	2.3 µg/mL	Highly active	[41]
21.	Dihydro-Corynantheidine	*L. major*	Promastigotes	0.6 µg/mL	Highly active	[29]
22.	5'-O-demethyl-ent-dioncophylleine A	*L. major*	Promastigotes	11 µg/ml	Moderately active	[34]
23.	Conodurine	*L. amazonensis*	Promastigotes	50 µg/ml	Moderately active	[42]
24.	Ent-Dioncophylleine A	*L. major*	Promastigotes	12 µg/mL	Moderately active	[34]
25.	Dioncophylline C	*L. major*	Promastigotes	13.2 µg/mL	Moderately active	
26.	Emetine	*L. donovani*	Promastigotes	0.42 µg/ml	Highly active	[37]
27.	Chelerythrine, dihydro	*L. donovani*	Promastigotes	0.78 µg/ml	Highly active	[43]
28.	Fangchinoline	*L. donovani*	Promastigotes	0.23 µg/mL	Highly active	[41]
29.	Harmine	*L. donovani*	Promastigotes	25 µg/ml	Moderately active	[44]
30.	Harmaline	*L.infantum*	Amastigotes	0.24 µg/ml	Highly active	[45]
31.	Isocephaeline	*L. donovani*	Promastigotes	0.45 µg/ml	Highly active	[37]
32.	Isodomesticine	*L. mexicana*	Promastigotes	25 µg/ml	Moderately active	[40]
33.	Isoquinolinium	*L. major*	Promastigotes	0.37 µg/ml	Highly active	[34]
34.	Klugine	*L. donovani*	Promastigotes	0.4 µg/ml	Highly active	[37]
35.	Liriodendronine,N-methyl	*L. donovani*	Amastigotes	9.4 µg/ml	Highly active	[46]
36.	Liriodenine	*L. braziliensis*	Promastigotes	16.1 µg/ml	Moderately active	[35]
		L. guyanensis	Promastigotes	5.9 µg/ml	Highly active	
		L. donovani	Amastigotes	7.1 µg/ml	Highly active	[46]
37.	Manzamine A	*L. donovani*	Promastigotes	0.9 µg/ml	Highly active	[47]
38.	(+)-8-Hydroxymanzamine A	*L. donovani*	Promastigotes	6.2 µg/mL	Highly active	[48]
39.	12,28-oxamanzamine A	*L. donovani*	Promastigotes	7.8 µg/mL	Highly active	[48]
40.	Manzamine A N-oxide	*L. donovani*	Promastigotes	1.1 µg/mL	Highly active	[47]
41.	Manzamine F	*L. donovani*	Promastigotes	4.2 µg/mL	Highly active	[48]
42.	Manzamine J	*L. donovani*	Promastigotes	25 µg/mL	Moderately active	[47]
43.	Manzamine E,	*L. donovani*	Promastigotes	3.8 µg/mL	Highly active	[48]
44.	Manzamine E, 6-hydroxy	*L. donovani*	Promastigotes	2.5 µg/mL	Highly active	
45.	12,28-Oxamanzamine E	*L. donovani*	Promastigotes	18 µg/mL	Moderately active	[48]
46.	Manzamine Y	*L. donovani*	Promastigotes	1.6 µg/mL	Highly active	[48]
47.	Manzamine X	*L. donovani*	Promastigotes	5.7 µg/mL	Highly active	[49]
48.	6-Deoxymanzamine X	*L. donovani*	Promastigotes	2.3 µg/mL	Highly active	[49]
49.	Mirabilin B	*L. donovani*	Promastigotes	17.0 µg/mL	Moderately active	[50]
50.	Norisodomesticine	*L. mexicana*	Promastigotes	15 µg/mL	Moderately active	[40]
51.	Nostocarboline	*L. donovani*	Amastigotes	7.47 µg/mL	Highly active	[51]
52.	Reserpine	*L. major*	Promastigotes	9.9 µg/mL	Highly active	[29]
53.	Ramiflorine A	*L. amazonensis*	Promastigotes	1.6 µg/ml	Highly active	[52]
54.	Ramiflorine B	*L. amazonensis*	Promastigotes	4.9 µg/ml	Highly active	
55.	Renieramycin A	*L. amazonensis*	Promastigotes	0.2 µg/mL	Highly active	[53]
56.	Yohimbine, alpha	*L. major*	Promastigotes	8.4 µg/mL	Highly active	[29]

Table 6: *In vitro* antileishmanial activity of alkaloids from 2010-2019.

No	Compound name	Organism	Stage	IC50	Data analysis	Reference
1.	Acridine, 6,9-dichloro-2-methoxy	*L. amazonensis*	Promastigotes	2.6 µg/mL	Highly active	[54]
2.	Ageloxime D	*L. donovani*	Promastigotes	29.2 µg/mL	Moderately active	[55]
3.	Ageloxime B	*L. donovani*	Promastigotes	28.5 µg/mL	Moderately active	
4.	Agelongine	*L. donovani*	Amastigotes	43.2 µg/mL	Moderately active	[56]
5.	(-)-anolobine	*L. donovani*	Promastigotes	5.4 µg/mL	Highly active	[57]
6.	(+)-anolobine	*L. donovani*	Promastigotes	4.0 µg/mL	Highly active	
7.	Armepavine, O-methyl	*L. chagasi*	Promastigotes	23.3 µg/mL	Moderately active	[58]
			Amastigotes	25.4 µg/mL	Moderately active	
8.	Batzelladine L, nor	*L. infantum*	Promastigotes	1.2 µg/mL	Highly active	[59]
9.	Batzelladine F	*L. infantum*	Promastigotes	2.4 µg/mL	Highly active	
10.	Batzelladine D	*L. infantum*	Promastigotes	0.9 µg/mL	Highly active	
11.	Berberine	*L. infantum*	Promastigotes	2.7 µg/mL	Highly active	[60]
			Amastigotes	3.9 µg/mL	Highly active	
		L. tropic	Promastigotes	2.9 µg/mL	Highly active	
			Amastigotes	4.7 µg/mL	Highly active	
		L. tropic	Promastigotes	0.5 µg/mL	Highly active	[61]
12.	Berberine, 8-Trichloromethyldihydro	*L. tropic*	Promastigotes	0.64 µg/mL	Highly active	[61]
13.	Capsaicin	*l. infantum*	Promastigotes	5.01 µg/mL	Highly active	[62]
			Amastigotes	24.2 µg/mL	Moderately active	
14.	Cassine	*L. amazonensis*	Promastigotes	25.2 µg/mL	Moderately active	[58]
15.	Cassine, 3-O-acetyl	*L. amazonensis*	Promastigotes	30.3 µg/mL	Moderately active	
16.	Clioquinol	*L. amazonensis*	Promastigotes	2.55 µg/mL	Highly active	[59]
		L. infantum	Promastigotes	1.44 µg/mL	Highly active	
		L. amazonensis	Amastigotes	1.88 µg/mL	Highly active	
		L. infantum	Amastigotes	0.98 µg/mL	Highly active	
17.	Columbamine	*L. tropic*	Promastigotes	0.86 µg/mL	Highly active	[61]
18.	Cryptolepine	*L. donovani*	Promastigotes	0.37 µg/mL	Highly active	[60]
19.	Cryptolepine, 2,7-dibromo	*L. donovani*	Promastigotes	0.55 µg/mL	Highly active	
20.	Dibromopalauamine	*L. donovani*	Amastigotes	1.09 µg/mL	Highly active	[56]
21.	Flavopereirine	*L. amazonensis*	Promastigotes	0.23 µg/mL	Highly active	[61]
22.	Flindersine, N-methyl-8-methoxy	*L. panamensis*	Promastigotes	14.3 µg/mL	Moderately active	[62]
			Amastigotes	>30 µg/mL	Moderately active	
23.	y-Fagarine	*L. amazonensis*	Promastigotes	7.17 µg/mL	Highly active	[68]
24.	Hyrtiosulawesine	*L. amazonensis*	Promastigotes	14.81 µg/mL	Moderately active	[69]
25.	Hyrtiosulawesine, 3,4-dihydro-	*L. amazonensis*	Promastigotes	17.29 µg/mL	Moderately active	
26.	Ircinal A	*L. donovani*	Promastigotes	4.6 µg/mL	Highly active	[47]
27.	Jatrorrhizine	*L. tropic*	Promastigotes	0.82µg/mL	Highly active	[61]
28.	1,6-Juliprosopine	*L. donovani*	Promastigotes	0.8 µg/mL	Highly active	[70]
			Amastigotes	1.8 µg/mL	Highly active	
29.	Julocrotine	*L. amazonensis*	Promastigotes	21.1 µg/mL	Moderately active	[71]
			Amastigotes	6.2 µg/mL	Highly active	
30.	Neo-kauluamine	*L. donovani*	Promastigotes	4.2 µg/mL	Highly active	[47]
31.	Listeferine	*L. donovani*	Promastigotes	16.6 µg/mL	Moderately active	[62]
32.	Laurotetanine	*L. donovani*	Promastigotes	7.6 µg/mL	Highly active	
33.	Lissoclinotoxin E	*L. donovani*	Promastigotes	0.4 µg/mL	Highly active	[72]
			Amastigotes	2.5 µg/mL	Highly active	
34.	Longamide A	*L. donovani*	Amastigotes	3.85 µg/ mL	Highly active	[56]
35.	Tryptophol	*L. donovani*	Amastigotes	9.6 µg/ mL	Highly active	[73]
36.	Manzacidin A	*L. donovani*	Amastigotes	75.83 µg/mL	Weakley active	[56]
37.	Meridianin G	*L. donovani*	Promastigotes	64.8 µg/mL	Weakley active	[74]

38.	Northalidasine	*L. major*	Promastigotes	27 µg/mL	Moderately active	[75]
39.	Northalrugosidine	*L. major*	Promastigotes	30 µg/mL	Moderately active	[75]
		L. donovani	Promastigotes	0.17 µg/mL	Highly active	[76]
40.	Northalfoetidine	*L. major*	Promastigotes	39 µg/mL	Moderately active	[75]
41.	2,3-dihydro-7H-dibenzo	*L. amazonensis*	Amastigotes	20.6 µg/mL	Moderately active	[77]
	[*de,h*]quinolin-7-one	*L. infantum*	Amastigotes	56.4 µg/mL	Weakley active	
		L. amazonensis	Promastigotes	31.8 µg/mL	Moderately active	
		L. infantum	Promastigotes	42.1 µg/mL	Moderately active	
		L. braziliensis	Promastigotes	48.3 µg/mL	Moderately active	
		L. guyanensis	Promastigotes	16.3 µg/mL	Moderately active	
42.	2,3,8,9,10,11-hexahydro-7H-	*L. amazonensis*	Amastigotes	4.5 µg/mL	Highly active	[77]
	dibenzo[de,h]quinolin-7-one	*L. infantum*	Amastigotes	4.8 µg/mL	Highly active	
		L. amazonensis	Promastigotes	3.6 µg/mL	Highly active	
		L. infantum	Promastigotes	4.4 µg/mL	Highly active	
		L. braziliensis	Promastigotes	4.4 µg/mL	Highly active	
		L. guyanensis	Promastigotes	1.8 µg/mL	Highly active	
43.	Palmatine	*L. tropic*	Promastigotes	0.59 µg/mL	Highly active	[61]
44.	Paenidigyamycin A	*L. major*	Promastigotes	0.4 µg/mL	Highly active	[78]
		L. donovani	Promastigotes	3.7 µg/mL	Highly active	
45.	Piperine	*l. infantum*	Promastigotes	3.03 µg/mL	Highly active	[62]
46.	Phyllanthidine	*L. amazonensis*	Amastigotes	49.11 µg/mL	Moderately active	[79]
			Promastigotes	82.37 µg/mL	Weakley active	
47.	Spectaline	*L. major*	Promastigotes	0.2µg/mL	Highly active	[80]
		L. amazonensis	Promastigotes	15.8 µg/mL	Moderately active	[63]
48.	Spectaline, 3-O-acetyl	*L. amazonensis*	Promastigotes	25.9 µg/mL	Moderately active	[63]
49.	Spongiacidin B	*L. donovani*	Amastigotes	41.5 µg/mL	Moderately active	[56]
50.	Stevensin	*L. donovani*	Amastigotes	75.8 µg/mL	Weakley active	[56]
51.	Thalfoetidine	*L. major*	Promastigotes	17 µg/mL	Moderately active	[75]
52.	Thalrugosidine	*L. donovani*	Promastigotes	0.63 µg/mL	Highly active	[76]
53.	Thaligosidine	*L. major*	Promastigotes	38 µg/mL	Moderately active	[75]
54.	Thalidasine	*L. donovani*	Promastigotes	6.59 µg/mL	Highly active	[76]
55.	Warifteine	*L. chagasi*	Promastigotes	80 µg/mL	Weakley active	[81]

Table 7: *In vitro* antileishmanial activity of alkaloids from 2020-2022.

No	Compound name	Organism	Stage	IC50	Data analysis	Reference
1.	α -Lapachones	*L. infantum*	Promastigotes	0.13 µg/mL	Highly active	[82]
		L. major	Promastigotes	0.32 µg/mL	Highly active	
2.	β-Lapachones	*L. amazonensis*	Promastigotes	0.09 µg/mL	Highly active	[82]
		L. infantum	Promastigotes	0.75 µg/mL	Highly active	
		L. major	Promastigotes	0.09 µg/mL	Highly active	
3.	α - Phthalazinylhydrazone	*L. amazonensis*	Promastigotes	0.2 µg/mL	Highly active	[82]
		L. infantum	Promastigotes	0.49 µg/mL	Highly active	
		L. major	Promastigotes	0.83 µg/mL	Highly active	
4.	β-Phthalazinylhydrazone	*L. amazonensis*	Promastigotes	0.02 µg/mL	Highly active	[82]
		L. infantum	Promastigotes	0.45 µg/mL	Highly active	
5.	Cornigerine	*L. major*	Promastigotes	0.8 µg/mL	Highly active	[83]
			Amastigotes	11.9 µg/mL	Moderately active	
6.	Colchicine	*L. major*	Promastigotes	0.2 µg/mL	Highly active	[83]
			Amastigotes	4.0 µg/mL	Highly active	

7.	Colchicine, 2-Demethyl	*L. major*	Promastigotes Amastigotes	0.4 µg/mL 8.7 µg/mL	Highly active Highly active	[83]
8.	Colchicine, 3-Demethyl	*L. major*	Promastigotes Amastigotes	0.5 µg/mL 10.2 µg/mL	Highly active Moderately active	[83]
9.	Colchicine, N-deacetyl-N-formyl	*L. major*	Promastigotes Amastigotes	0.4 µg/mL 11.1 µg/mL	Highly active Moderately active	[83]
10.	Colchicoside	*L. major*	Promastigotes Amastigotes	5.01 µg/mL 24.2 µg/mL	Highly active Moderately active	[83]
11.	Colchifoline	*L. major*	Promastigotes Amastigotes	0.5 µg/mL 10.2 µg/mL	Highly active Moderately active	[83]
12.	Corynantheol, dihydro	*L. amazonensis*	Promastigotes	38.4 µg/mL	Moderately active	[84]
13.	Demecolcine	*L. major*	Promastigotes Amastigotes	0.7 µg/mL 14.0 µg/mL	Highly active Moderately active	[83]
14.	Flindersin, N-methyl-8-methoxy	*L. panamensis*	Promastigotes Amastigotes	2.8 µg/mL 2.4 µg/mL	Highly active Highly active	[85]
15.	7-Oxostaurosporine	*L. amazonensis* *L. donovani*	Promastigotes Amastigotes Promastigotes	1.7 µg/mL 0.43 µg/mL 0.28 µg/mL	Highly active Highly active Highly active	[86]
16.	(E)- Piplartine, demethoxy	*L. amazonensis*	Amastigotes	2.6 µg/mL	Highly active	[87]
17.	(E)- Piplartine	*L. amazonensis*	Amastigotes	2.6 µg/mL	Highly active	
18.	3-quinolin-ol, 1,2,3,4-tetrahydro-Benzo	*L. panamensis*	Promastigotes Amastigotes	0.67 µg/mL 1.03 µg/mL	Highly active Highly active	[85]
19.	Quinolone, 2-amino-8-hydroxy	*L. panamensis*	Promastigotes Amastigotes	0.25 µg/mL 0.16 µg/mL	Highly active Highly active	[85]
20.	Quinoline, 3,4-dimethyl-3H-imidazol [4.5f]-2-amine	*L. panamensis*	Promastigotes	5.2 µg/mL	Highly active	[85]
21.	Staurosporine	*L. amazonensis* *L. donovani*	Promastigotes Amastigotes Promastigotes	0.37 µg/mL 4.6 µg/mL 0.97 µg/mL	Highly active Highly active Highly active	[86]
22.	Tryptanthrin	*L. amazonensis* *L. infantum* *L. amazonensis* *L. infantum*	Promastigotes Promastigotes Amastigotes Amastigotes	2.7 µg/mL 1.9 µg/mL 18.6 µg/mL 28.5 µg/mL	Highly active Highly active Moderately active Moderately active	[88]

Table 8: *In vivo* anti-leishmanial activity of alkaloids from 1990-2022.

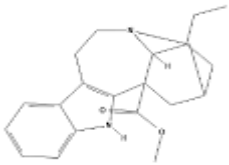
No	Compound name	Organism	Clinical form	Dose, duration and rout of administration	Efficacy	Reference
1.	Isotetrandrine	*L. amazonensis* *L. venezuelensis*	Cutaneous leishmania	100 mg/kg/d for 14 days. (IV)	Effective as pentavalent antimonials at 56mg/Sb/kg against *L. amazonensis* and slightly less active against *L.venezuelensis.*	[89]

2.	Berberine	*L. braziliensis*	Cutaneous leishmania	208 mg/kg/twice a day. (IM)	Produced 56% suppression of lesion area	[90]
		L. major	Cutaneous leishmania	0.5% cream, twice a day for 35 days. (Topically).	Produced 99.9%reduction of parasites load in the skin	[91]
3.	Berberine, 8-cyano dihydro	*L. Donovani*	Visceral leishmania	208 mg/kg/twice a day, for 6 days. (IM)	Produced 54% suppression of hepatic parasite.	[90]
		L. braziliensis	Cutaneous leishmania		Produced 46% suppression of lesion area.	
4.	Berberine, tetrahydro	*L. Donovani*	Visceral leishmania	416 mg/kg/twice a day, for 6 days. (IM)	Produced 50% suppression of hepatic parasite.	[90]
5.	Berberinium iodide, N-methyl tetrahydro	*L. Donovani*	Visceral leishmania	416 mg/kg/twice a day, for 6 days. (IM)	Produced 50% suppression of hepatic parasite.	[90]
6.	Plumbagin, 8,8bi	*L. amazonensis*	Cutaneous leishmania	50 mg/kg/d, once daily for 14 days. Topically.	Produced significant suppression of lesion area (potent as glucantime 400 mg/kg/d).	[92]
7.	2-n-propylquinoline	*L. donvani*	Visceral leishmania	Oral administration at 0.54 mmol/kg for 5 or 10 days.	Suppresses 87.8 and 99.9% of liver parasites, respectively.	[92]
		L. amazonensis	Cutaneous leishmania	100 mg/kg/d, once daily for 14 days. Topically.	More potent than N-methyl glucanmine antimonite.	[93]
		L.donovani	Visceral leishmania	oral treatment of mice at 12.5 mg/kg daily for 10 days	Reduce 66% parasite burdens in liver	[94]
8.	Chimanine D	*L. donvani*	Visceral leishmania	10 days at 0.54 mmol/kg by the (SC) Oral administration at 0.54 mmol/kg for 5 and 10 days.	Produced 86.6% suppression of hepatic parasite lower parasite suppression (72.9%).	[92]
		L. amazonensis	Cutaneous leishmania	100 mg/kg/d, once daily for 14 days. Topically.	More potent than N-methyl glucanmine antimonite.	[93]
9.	2-Styrylquinoline	*L. donvani*	Visceral leishmania	Oral administration at 0.54 mmol/kg for 5 days.	Suppresses 79.6% parasites in the liver	[92]
10.	2-(3,4-methylenedioxy phenylethyl) quinolone	*L. amazonensis*	Cutaneous leishmania	100 mg/kg/d, once daily for 14 days. Topically.	Effective as reference drug	[93]
11.	Cusparine					
12.	2-(3,4-dimethoxy phenylethyl) quinolone					

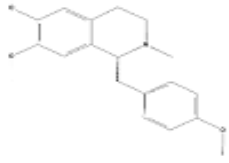
13.	Chimanine B					
14.	Skimmianine					
15.	Sinefungin	*L. braziliensis*	Cutaneous leishmania	4mg/kg/d, once daily for 10 consecutive days. (IP).	Optimal dose found 50-fold lower than LD50	[28]
16.	Harmine	*L. donovani*	Visceral leishmania	1.5, 2.5, 5.0 and 11.8 mg/kg, at interval of 3days. (SC)	The therapeutic dose judged from the reduction in parasite burden of spleen was 1.5mg/kg.	[44]
17.	Araguspongin C	*L. donovani*	Visceral leishmania	100 mg/kg, for5 days. (Orally)	Produced 38.7% suppression of hepatic parasite.	[36]
18.	Canthin-6-one	*L. amazonensis*	Cutaneous leishmania	(I.P)	Decrease of lesion weight by 15.0% and the parasite load by 77.6% in compared with the group of untreated mice.	[95]
19.	Cpd 19	*L. amazonensis*	Cutaneous leishmania	Oral administration at 25 mg/kg twice daily for 15 days	Reduce 89 % parasite burdens in the lesion	[94]
		L. infantum	Visceral leishmania	Oral treatment of mice at 25 mg/kg daily for 10 days	Reduce 49% parasite burdens in spleen	
20.	Cpd 20	*L. amazonensis*	Cutaneous leishmania	Oral administration at 25 mg/kg twice daily for 15 days	Reduce 81 % parasite burdens in the lesion	[94]
21.	Cpd 21	*L. amazonensis*	Cutaneous leishmania	Oral administration at 25 mg/kg twice daily for 15 days	Reduce 90% parasite burdens in the lesion	[94]
22.	Cpd 22	*L. infantum*	Visceral leishmania	Oral treatment of mice at 25 mg/kg daily for 10 days	Reduce 48% parasite burdens in spleen	[94]
23.	Cpd 23	*L. infantum*	Visceral leishmania	Oral treatment of mice at 25 mg/kg daily for 10 days	Reduce 51% parasite burdens in spleen	[94]
		L.donovani	Visceral leishmania	Oral treatment of mice at 12.5 mg/kg daily for 10 days	Reduce 61% parasite burdens in liver	
24.	Cpd 24	*L. infantum*	Visceral leishmania	Oral treatment of mice at 25 mg/kg daily for 10 days	Reduce 57% parasite burdens in spleen	[94]
25.	Cpd 25	*L. amazonensis*	Cutaneous leishmania	Oral administration at 25 mg/kg twice daily for 15 days	Reduce 89 % parasite burdens in the lesion	[94]
26.	(E)-Piplartine	*L. amazonensis*	Cutaneous leishmania	25 mg/kg/day for 4 days, (intra-lesion).	More than 40% reduction in the lesion size and 55% in spleen parasite burden compared to untreated mice group.	[87]

27.	Northalrugosidine	*Visceral leishmania*	Visceral leishmania	2.8, 5.6 and 11.1 mg/Kg. IV	Dose dependent reduction of the parasitic burden in the liver and spleen without over toxicity effect at the doses used.	[76]
28.	2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one	*L. infantum.*	Visceral leishmania	10 mg/kg. IV	Reductions (p ,0.05) in parasite burden in liver and spleen 99% and 78%, respectively	[77]
29.	Solamargine	*L. Mexicana*	Cutaneous leishmania	Topical, 10 µg /d for 6 weeks	71.4% reduction of parasite number	[96]
30.	Solasonine					

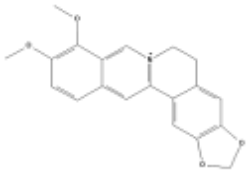
Among 183 alkaloid compounds, 24 compounds seem to be the most promising as they were active against both promastigotes and amastigotes forms (Coronaridine [38], Armepavine, O-methyl [58], Berberine [60], Capsaicin [62], Clioquinol [59], Flindersine, N-methyl-8-methoxy [62, 80],1,6-Juliprosopine [70], Julocrotine [71], lissoclinotoxin E [72], 2,3-dihydro-7H-dibenzo [de,h]quinolin-7-one [77], 2,3,8,9,10,11-hexahydro-7H-dibenzo [de,h]quinolin-7-one [77], Cornigerine[83], Colchicine[83], 2-Demethyl Colchicine[83] , 3-Demethyl Colchicine[83], N-deacetyl-N-formyl Colchicine[83], Colchicoside[83], Colchifoline[83], Demecolcine[83], 7-Oxostaurosporine [86], 1,2,3,4-tetrahydro-Benzo3-quinolin-ol [85], 2-amino-8-hydroxy quinolone [85], Staurosporine [86] and Tryptanthrin [88]). Figure 1. shows the chemical structure of the most promising alkaloid compounds. Furthermore, there are only seven compounds (2-n-Propylquinoline, Chimanine D & B, Berberine, Sinefungin, 2,3-dihydro-7H-dibenzo[de,h] quinolin-7-one and Harmine) that have been investigated both in vitro and in vivo (Figure 2).



Coronaridine



Armepavine, O-methyl



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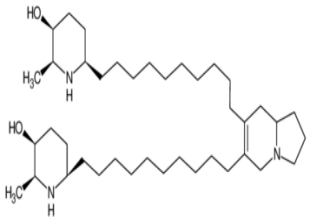
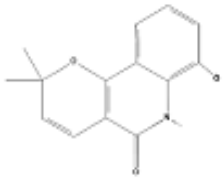


1,6-Juliprosopine



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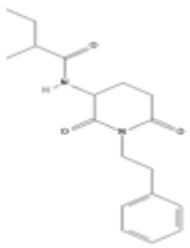
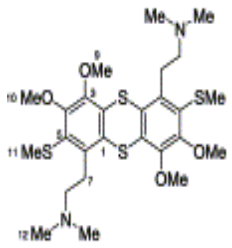


Julocrotine



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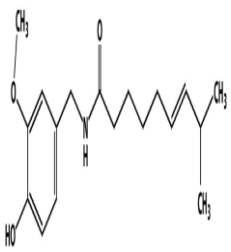

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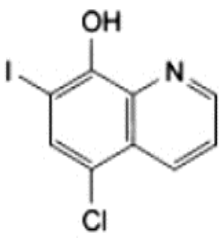

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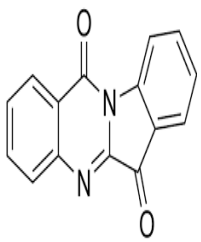

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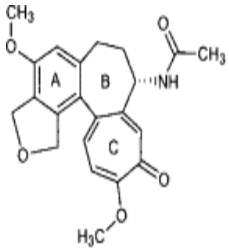
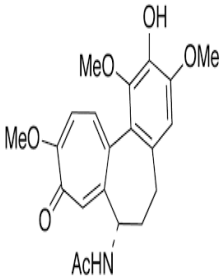
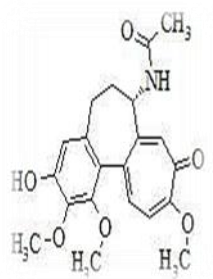


Cornigerine



2-Demethyl Colchicine



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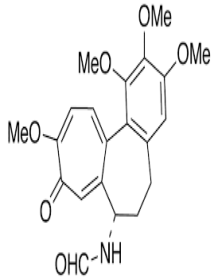
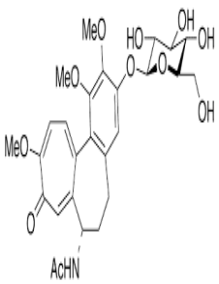
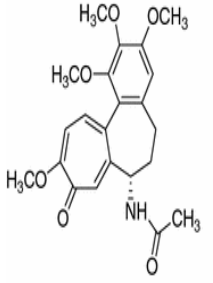


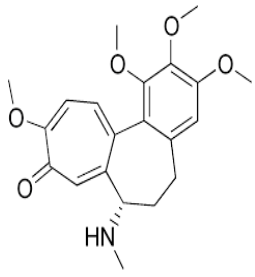
N-deacetyl-N-formyl Colchicine



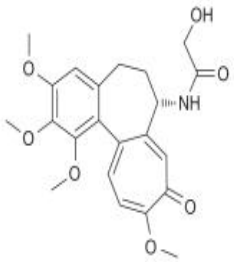
Colchicoside



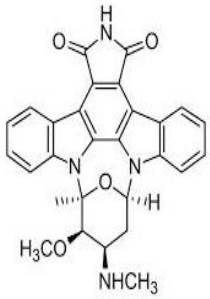
Colchicine



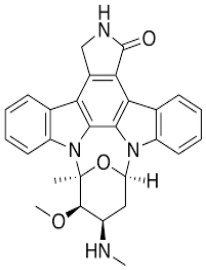
Demecolcine



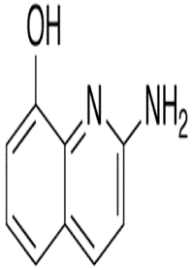
Colchifoline



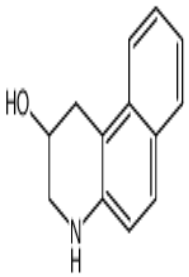
7-Oxostaurosporine



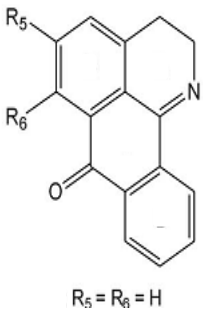
Staurosporine



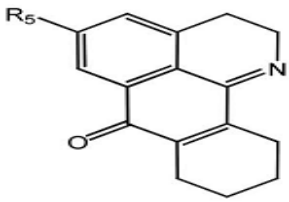
2-amino-8-hydroxy quinolone



1,2,3,4-tetrahydro-Benzo3-quinolin-ol



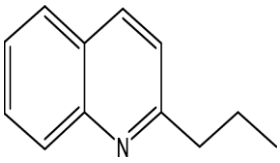
2,3-dihydro-7H-dibenzo [de,h]quinolin-7-one



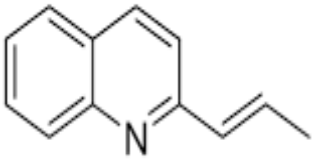
R_5 =H

2,3,8,9,10,11-hexahydro-7H-dibenzo[de,h]quinolin-7-one

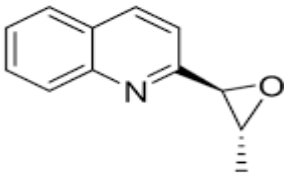
Figure 1: The chemical structure of the alkaloid compounds that are active against both promastigotes and amastigotes forms [38,58, 59, 60, 62, 70, 71, 72, 77, 80, 83,85, 86,88].



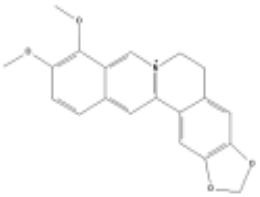
2-n-Propylquinoline



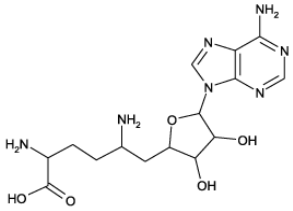
Chimanine B



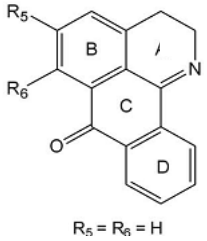
Chimanine D



Berberine

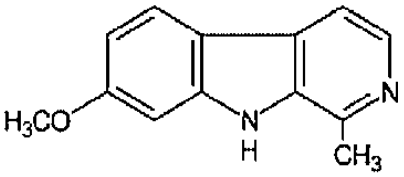


Sinefungin



$R_5 = R_6 = H$

2,3-dihydro-7H-dibenzo [de,h]quinolin-7-one



Harmine

Figure 2: The chemical structure of alkaloids compounds that have been investigated both in vitro and in vivo [28, 44, 60, 77, 93].

Mechanism of anti-Leishmanial actions:

Many types of alkaloids have been described as having biological activities against trypanosomatids, such as Leishmania spp. These compounds act against *Leishmania* via various mechanisms. for example;

- Quinolone alkaloids (Camptothecin), exhibit antileishmanial activity against promastigotes form of *L. donovani*. The mechanism of action of these metabolites is based on the inhibition of the DNA topoisomerase I and also inhibition the incorporation of (3H) thymidine in these parasites [22]. Also Clioquinols, a group of quinolone alkaloids, show activity against amastigotes and promastigotes forms of *L. amazonensis* and *L. infantum*. The mechanism of action of these metabolites is that it induces a discontinuity of the parasite membrane, possibly related to characteristic event of cell death caused by necrosis [64].
- Isoquinoline alkaloid (Berberine) has leishmanicidal activity through a reduction in the viability of promastigotes and stimulated the generation of ROS in these cells. It was also able to increase the levels of mitochondrial superoxide and induce depolarization of mitochondrial transmembrane potential [97].

- Heterocyclic steroids (solamargine and solasonine) induced different immunochemical pathways in macrophages and dendritic cells. Additionally, they were capable of enhancing the expression levels of transcription factors, such as NFκB/AP-1 [96].
- Isoxazol alkaloid (Acivicin), showed antileishmanial activity against amastigotes form of *L. donovani*. the drug irreversibly inactivates carbamyl phosphate synthetase II, the first enzyme of the pyrimidine biosynthetic pathway [18].
- Indole alkaloid (Dihydrocorynantheol) has activity against promastigotes form of *L. amazonensis*. The SEM analysis revealed cell rounding and changes in the flagellum of the parasites. In the TEM analysis, the treated promastigotes showed changes in flagellar pocket and kinetoplast and presence of lipid inclusions [84]. Harmaline, is reported to possess significant antileishmanial activity against amastigotes form of *L. infantum* [45]. The mechanism of action is based on its ability to intercalate DNA or interfer with the metabolism of amino acids in the parasite [20]. The mechanism of action of Corynanthine, a-yohimbine and Reserpine is based on the inhibition of the respiratory chain of the parasite [29].
- Indoloquinazoline alkaloid (Tryptanthrin), induced mitochondrial membrane depolarization observed in Tryptanthrin-treated promastigotes [88]. In terms of mechanism of action, Batzelladine L and Norbatzelladine L caused an increase in the permeability of the Leishmania plasma membrane and depolarization of the mitochondrial membrane. Also Norbatzelladine L, induced a significant increase in the production of reactive oxygen species (ROS), a potential pathway to cell death [59].

Generally, alkaloids compounds may work either alone or in combination with each other against various Leishmania species via various mechanisms. Figure 3 shows some targets for antileishmanial actions of alkaloid compounds.

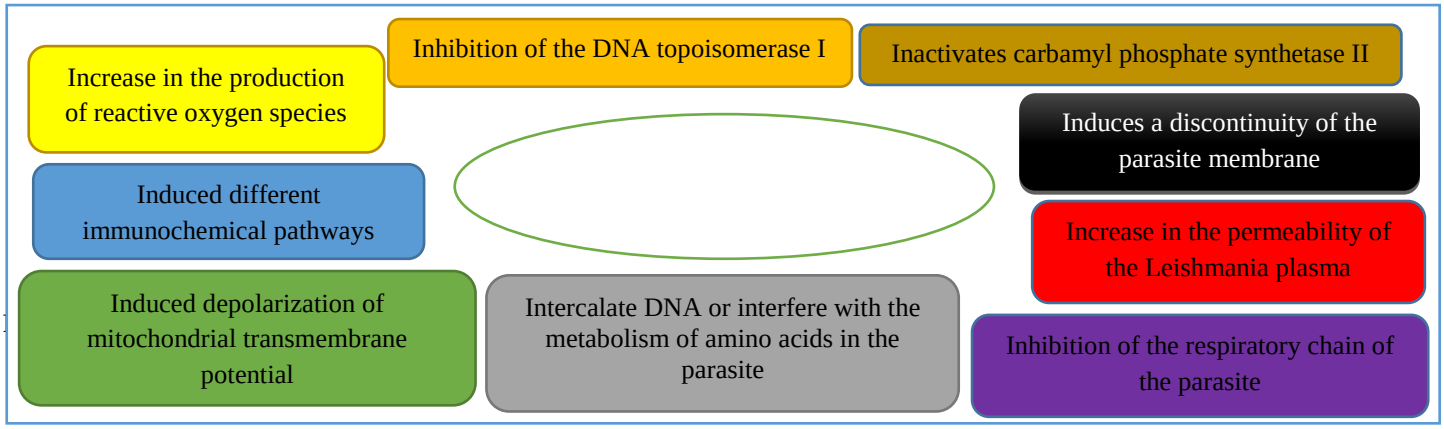


Figure 3: Possible targets of alkaloid compounds for anti-Leishmania actions.

CONCLUSION

As a means to facilitate the accessibility of information, this review updates and summarizes results on alkaloid compounds against different Leishmania species. The alkaloid compounds presented here have demonstrated a diverse range of activities against leishmaniasis with some showing high activity. There are 24 compounds that are most promising alkaloids which are active against both promastigotes and amastigotes forms and seven alkaloid compounds have been investigated both in vitro and in vivo. These compounds could be reasonable starting points and promising sources for further development of effective and affordable drugs against leishmaniasis.

Recommend Future Research:

In vitro studies are valuable for the screening of isolated compounds as well as for investigations of the cellular and molecular modes of action. Since many natural compounds are rapidly metabolized in the human body by liver enzymes and gastrointestinal microflora, animal experiments are indispensable to identify candidates with sufficient half-life times in vivo and anti-leishmanial activities in concentration ranges that are reachable in the human blood. More investigations are required to allow a direct comparison of in vitro and in vivo data. It is pleasing that more and more investigations report on the activity in vivo and more studies are needed in this respect increasing the number of potential candidate compounds for further drug development. Convincing randomized, double-blind placebo-controlled clinical trials in human patients are missing to clarify the therapeutic efficacy and safety (side effects) to reach considerable recognition in the medical world.

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AAH: wrote manuscript draft;
HEK: manuscript editing, supervision of AAH;
AHA, MMM, WGO, AHA: literature collection, manuscript editing;
TE: supervised whole project and wrote, edited and corrected the manuscript.

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The authors declare that there is no conflict of interest.

ABBREVIATION

C.L : Cutaneous Leishmania,
V.L : Visceral Leishmania,
M.C. L : Mucocutaneous Leishmania,
I.M : Intramuscular,
I.V : Intravenous,
S.C : Subcutaneous,
I.P : Intraperitoneal,
I.L : Intralesional,
ROS : Reactive Oxygen Species,
IC_{50} : Half Maximal Inhibitory Concentration,
NTDs : Neglected Tropical Diseases.

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