Asian Pacific Journal of Tropical Disease

journal homepage: http://www.apjtcm.com

Review article https://doi.org/10.12980/apjtd.7.2017D7-215

Antileishmanial activity of medicinal plants from Africa: A review

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ARTICLE INFO

Article history:
Received 19 Sep 2017
Received in revised form 23 Oct, 2nd revised form 31 Oct 2017
Accepted 15 Nov 2017
Available online 29 Nov 2017

Keywords:
Leishmaniasis
Medicinal plants
Antileishmanial activity

ABSTRACT

Leishmaniasis is a serious disease that presents a real public health problem worldwide. Today, antileishmanial therapy remains expensive and has intolerable side effects; therefore, it is important to dissect antileishmanial molecules that present a selective efficacy and tolerable safety. Several studies revealed the accumulative antileishmanial activity of natural substances isolated from medicinal plants. Several organic extracts-essential oils and their constituents have been tested in some African countries for their antileishmanial activities. The aim of this review is to summarize the investigations that have been undertaken on the antileishmanial activities of medicinal plants from Africa. The ethnobotanical surveys revealed the use of several species for leishmaniasis treatment. Furthermore, *in vitro* and *in vivo* experiences have been conducted on medicinal plants and showed cytotoxicity against a variety of *Leishmania* species such as *Leishmania major* (cutaneous leishmaniasis) and *Leishmania infantum* (visceral leishmaniasis).There has been little analysis of the mechanisms of action of natural molecules from medicinal plants against *Leishmania* species, but some studies revealed that these molecules could affect different targeting pathways including apoptosis.

1. Introduction

Leishmaniasis is regarded as a major public health problem, causing significant morbidity and mortality rates 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 millions being affected annually[1]. In recent years, the research on molecules that could be useful for leishmaniasis treatment has been increased. In African countries, as many of the world century, the therapeutic of this disease became dominated since the beginning by antimony derivatives which remain toxic and expensive (pentavalent antimony, amphotericin B)[2]. Indeed, some forms of leishmaniasis (visceral and cutaneous) exhibit, in addition, some degree of resistance against conventional drugs, and sometimes even exhibit total resistance to any treatment[3].

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Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

Hence, it is essential to seek new alternative antileishmanial molecules that would be effective and would present low toxicity. The nature is a veritable candidate that can offer a variety of molecules that possess diverse chemical structures. It has been considered since always as the main source of medicines against diseases. Medicinal plants, due to their ability to synthesize a variety of molecules that have several pharmacological interests, are considered as the major target for screening bioactive molecules in different therapeutic systems including antibacterial[4-8], antiviral[9-11], antitumor[8,12-16], antioxidant[17,18], antifungal[19], anti-inflammatory[20,21], anti-pyretic and antileishmanial activities[22-24]. These natural products extracted from medicinal plants are very diverse as they present several functional structures such as phenols, alcohols and acids[25-27].

Experimental approaches are needed for the evaluation of antileishmanial activity of natural substances from medicinal plants; the viability assay presents a veritable test that is used for the screening of cytotoxicity of organic extracts, essential oils and their derivatives[28,29]. The isolation of molecules that possess an antileishmanial effect can offer some therapeutic applications for leishmaniasis treatment.

In this context, we are interested in identifying and cataloging

African medicinal plants that are used against leishmaniasis. The review is based on the results of the analysis of ethnobotanical (empirical) and pharmacological studies carried out in Africa (experimental *in vitro* and *in vivo* studies).

2. Overview of leishmaniasis

Leishmaniasis is caused by a protozoan parasite, *Leishmania*, which is transmitted by the bite of a small vector Diptera: phlebotomine mosquito belonging to the genus of *Lutzomyia* (New World) and *Phlebotomus* (Old World) and affecting many species of domestic and wild mammals. Various forms of clinical manifestations of human leishmaniasis have been described in the literature[30]. They are due to twenty species of the genus *Leishmania* following biochemical characterization of the strains by enzyme electrophoresis, based on its modern taxonomy[31] which can be grouped into three entities: visceral leishmaniasis (VL, kala azar), cutaneous leishmaniasis (CL, sore oriental, uta, yaws, chiclero's ulcer) and mucocutaneous leishmaniasis (MCL, espundia)[32]. In the New World, leishmaniasis is caused by *Leishmania braziliensis* complex (MCL and CL), the *Leishmania mexicana* complex (CL), *Leishmania peruviana* (CL) and *Leishmania infantum* (*L. infantum*) (VL and CL); while in the Old World, leishmaniasis is caused by *Leishmania donovani* (*L. donovani*) (VL), *L. infantum* (VL and CL), *Leishmania tropica* (*L. tropica*) (CL), *Leishmania major* (*L. major*) (CL) and *Leishmania aethiopica* (CL). *L. infantum* and *L. chagasi* were found to have an identical biochemical genotype and are considered as synonyms[33]. The diseases are mainly zoonoses with two exceptions: the CL due to *L. tropica* in urbanized areas of the Near- and Middle-East and the VL due to *L. donovani* in the Indian subcontinent (North India, Nepal and Bangladesh). Canine leishmaniasis (CanL) is a chronic viscero-cutaneous disease caused by *L. infantum*; *Leishmania chagasi*), for which the dog acts as a reservoir. In some cases, parasites belonging to *Leishmania braziliensis* complex, *L. major* and *L. tropica* have been isolated from the host[34,34].

3. Epidemiology and development cycle of leishmaniasis

Leishmaniasis is caused by parasites of *Leishmania* genus, kinetoplastid protozoa belonging to the family Trypanosomatidae and transmitted by bite of an infected female sandfly[35]. In Africa, these little hairy flies belong to the genera *Phlebotomus* (Table 1), and bite at night, preferably at dusk. Parasites of the *Leishmania* genus exist in two forms. The flagellate form, or promastigote, is found in the digestive tract of the female sandfly, where it multiplies before being transmitted during a blood meal. Under promastigote forms, the parasite is 3 × 15-20 microns. Once humans or other host receptive mammals are bitten, promastigotes are phagocytosed by macrophages, where they proliferate in a vacuole parasitophorous as not strict intracellular flagellate, or amastigote form (3 × 3-4 microns). Twenty *Leishmania* species are divided into two kinds: *Leishmania* and *Viannia*[31](Table 1). Depending on the region and species, the parasite reservoir is either an animal or a human. Humans and canines are the main visceral leishmaniasis reservoirs. Cutaneous leishmaniasis reservoirs, in Africa, are the felines, rodents and Cercopithecidae[36](Table 1). Typically, in humans there is a link between the clinical presentation and the species responsible[37]. In fact, host parasite interaction, including the immune status of the host, appears to play a key role in the evolution of the disease.

4. Clinical forms of the disease in humans

In humans, the immune response plays an important role in

Table 1
The reservoirs and vectors of some *Leishmania* species in the Africa.

Leishmania species	Infection	Reservoirs	Vectors
		Ordre/Family/(Species)	Genus/Subgenus/(Species)
L. major	Cutaneous;Mucosal leishmaniasis	Primates/Cercopithecidae/ (*Cercopithecus aethiops*) / Hominidae/ (*Homo sapiens*) / Canidae/ (*Canis familiaris*) Rodentia/Sciuridae/(*Xerus rutilus*) /Muridae/ (*Tatera gambiana*; *T. robusta*; *T. ngricauda*; *T. indica*; *Taterillus emini*; *Psammomys obesus*; *Rhombomys opimus*; *Meriones shawi*; *M. lybicus*; *M. crassus*; *M. hurricanae*; *M. meridianus*; *M. erythrouros*; *M. persicus*; *Gerbillus pyramidum*; *Arvicanthis niloticus*; *Mastomys erythroleucus*; *M. natalensis*; *Nezokia indica*; *Aethomys kaiseri*	*Phlebotomus*/Phlebotomus/ (*Phlebotomus papatasi*; *P. duboscqi*)
L.donovani	Visceral; Post-kala azar dermal leishmaniasis	Primates/Hominidae/(*Homo sapiens*) /Canidae/(Canis familiaris) /Felidae/(*Felis serval*) /Viveridae/(*Genetta genetta*) Rodentia/Muridae/ (*Acomys albigena*; *Arvicanthis niloticus*; *Rattus rattus*)	*Phlebotomus*/*Paraphlebotomus*/ (*Phlebotomus alexandri*) / *Euphlebotomus*/ (*Phlebotomus argentipes*)
L. tropica	Cutaneous leishmaniasis Mucosal leishmaniasis Visceral leishmaniasis	Primates/Hominidae/(*Homo sapiens*) /Canidae/(*Canis familiaris*) Rodentia/Muridae/(*Rattus rattus*)	*Phlebotomus*/*Paraphlebotomus*/ *Phlebotomus sergenti*) /Larroussius/ (*Phlebotomusperniciosus*; *Phlebotomus ariasi*)
L. infantum	Visceral leishmaniasis Cutaneous leishmaniasis Mucosal leishmaniasis	Primates/Hominidae/(*Homo sapiens*) /Canidae/(*Canis familiaris*; *Canis aureus*; *Canis lupus*; *Vulpes vulpes*) / Felidae/(*Fennecus zerda*; *Felis felis*)	*Lutzomyia*/*Lutzomyia*/(*Lutzomyia longipalpis*) *Phlebotomus*/ Larroussius/(*Phlebotomus perfiliewi*; *P. neglectus*; *P. langeroni*; *P. longipes*; P. *pedifer*) /*Adlerius*/*Phlebotomus chinensis*
Leishmania aethiopica	Cutaneous; Diffuse cutaneous; Mucocutaneous leishmaniasis	Primates/Hominidae/ (*Homo sapiens*) Hyracoidea/ Procaviidae/(*Procavia johnstoni*; *Procavia habessinica*; *Heterohyrax brucei*; *Dendrohyrax arboreous*) Rodentia/Muridae /(*Cricetomys gambianus*)	

the development of the disease. Differences of clinical cases are associated with several species of *Leishmania* and the patient's immunological status[38]. In Africa, symptomatic manifestations of two groups can be described, one having the VL and the other featuring the tegumentary forms in which the parasite remains localized in the skin and mucous membranes; thereof includes those forms of cutaneous leishmaniasis, diffuse cutaneous and mucocutaneous.

4.1. Visceral leishmaniasis (VL)

It is called kala azar or "black fever" and presents the most severe form of the disease. In untreated case, VL is mortal. During the bite of the sandfly, the parasites migrate through the bloodstream and lymphatic system to lymphoid organs (spleen and bone marrow) and liver. Its clinic case is generally characterized by an inflammation of the liver and spleen, causing hepatosplenomegaly, severe abdominal distension, severe weight loss and anemia. Death usually occurs after 6 months to a few years following the progression of the infection[39].

4.2. Cutaneous leishmaniasis (CL)

Formerly known as the "Oriental button", the CL can cause skin lesions on the bite place, pruritic papule. This is followed by an inflammatory reaction with epithelial hyperplasia and necrosis of the dermis leading to ulceration. These ulcers are usually circular with well-defined edges that have a purplish color. They are covered with a thin crust and moving towards a form called "wet" (like "Uta") or "dry". These lesions are usually painless but leave after healing deep non-pigmented scars[39-42].

5. Necessity of screening antileishmanial natural agents

Several chemical agents have been described for the treatment of leishmaniasis. Amongst them, the compounds of antimony, antileishmanial drugs like chloroquine, quinacrine, emetine, metronidazole and minomycline antibiotics, tetracycline and rifampin are used (Table 2)[43-45]. The efficacy of these treatments depends on the parasite strain and determination of specification is important in order to plan control and prevention. However, the use of these chemical agents is almost always limited by side effects, including increased liver enzymes.

5.1. Current treatments and their side effects

In Table 2 we summarize different treatments used in leishmaniasis therapy. Trivalent antimony was the first molecule used against leishmaniasis but was quickly abandoned because of its toxicity. Since 1940, the most commonly used first-line drugs are pentavalent antimony, N-methyl glucamine and sodium stibogluconate. These drugs have many side effects of early anaphylactic treatment as muscle pain, rash, vomiting, hyperthermia, tachycardia and bleeding. The other side effects occur at the end of treatment and result in general signs, cardiac, hepatic, pancreatic, renal and hematological disorders[41,46,64,65]. The duration of treatment ranged from 20 to 28 days by intravenous or intramuscular administration[51]. The problem arises when some leishmanial strains have developed resistance against this drug[66-68]. The emergence of parasites resistance is mainly due to numerous factors such as the immune system status of patients, pharmacokinetic drug elimination, differences in biochemical and structural levels of each species of *Leishmania* that are responsible for selective responses to drugs[55]. Finally, access to treatment is difficult because of the poverty that affects the peoples of underdeveloped countries. This situation facilitates significantly the progression of the disease.

The amphotericin B and pentamidine come as the second-line of treatments. The amphotericin B is a polyene antibiotic which inhibits powerful demethylation of lanosterol. The action of amphotericin is due to the disruption of membrane permeability of *Leishmania*. It is used almost against visceral leishmaniasis, effective with high cure rates administered by intravenous infusion, has significant renal and hematological liposomes toxicity (AmBisome) "lipid formulations of amphotericin B" are less toxic and more effective in patients with visceral leishmaniasis, but the cost is always higher[41,51,69,70].

Pentamidine is a synthesized aromatic diamine which inhibits the synthesis of parasite DNA by blocking the thymidine synthetase and by binding to tRNA. The administration is by slow infusion, and inherent toxic effects of the dose reaching the kidney, pancreas or blood lineages[41].

The Miltefosine is an alkylphospholipid that affects cells signaling pathways and membrane synthesis; it was originally developed as an oral antineoplastic agent aim is licensed for use in visceral leishmaniasis in India[71,70]. Gastrointestinal adverse effects[58], vomiting and diarrhea were more common with miltefosine[59]. Fatal acute pancreatitis has been attributed to miltefosine in a 41-year-old man with visceral leishmaniasis[60].

The Paromomycin is an aminoglycoside that is active against many Gram-negative and Gram-positive strains as well as against some protozoa and tapeworms. It is out of use as an antibiotic, well tolerated and affordable treatment for visceral leishmaniasis (VL) at a dose of 11 mg/kg (base) for 21 days, no nephrotoxicity has been reported with the dose/duration used for VL. The toxicity is infrequently encountered (< 1%), goal audiometric function was not tested in MOST studies and hepatotoxicity is rare (< 1%). Paromomycin has been extensively used as an antibiotic and no serious adverse effects have been encountered. The results of phase IV studies in India showed that the side effects seen after the treatment of *Leishmania* by paromomycin are uncommon and include itching, erythema, edema and tenderness. Because reports of efficacy are confounded by natural healing of CL, the results are mixed; at best, active drug shows a modest benefit over placebo purpose, and it is usually less effective than pentavalent antimonials[54].

Imiquimod, an imidazoquinoline that induces the production of nitric oxide is used in the formulations of creams for genital warts, actinic keratosis and basal cell carcinomas with very high response rates[72-74]. A high concentration of NO is toxic to parasites. Studies of oral administration of this drug have shown cure rates of 60% at a dose of 5 mg/kg in mice infested with *L. donovani*[75]. This medicine was tested topically in combination with antimony showing a decrease healing time for patients with cutaneous leishmaniasis[55,76].

Table 2
Antileishmanial drugs, their side effects and their action sites.

Generic name of drug (chemical type)	Mechanism of action	Side effects	References
Trivalent antimony Pentavalent antimonials: Meglumine antimoniate (Glucantime) Sodium stibogluconate (Pentostame	Active against amastigote but not against promastigotes. Mechanism is not exactly known but suggestions showed that antileishmanial effect might be due to action on host macrophage cell by inhibition of macromolecular biosynthesis in amastigotes, possibly via perturbation of energy metabolism due to inhibition of glycolysis and fatty acid β-oxidation.	Toxicity, muscle pain, rash, vomiting, hyperthermia, tachycardia and bleeding Other side effects in general signs, cardiac disorders, hepatic, pancreatic, renal and hematological	[46] [47] [48] [41] [49] [3]
Amphotericin B (polyene antibiotic)	Complexes with 24-substituted sterols, such as ergosterol in cell membrane, thus causing pores which alter ion balance and result in cell death.	Administration by intravenous infusion and has significant renal and hematological toxicity	[50] [51]
Pentamidine (diamidine)	Accumulated by the parasite; effects include binding to kinetoplast DNA. Inhibits the synthesis of parasite DNA by blocking the thymidine synthetase and by binding to tRNA.	The administration is by slow infusion, and dependent toxic effects of the dose reaching the kidney, pancreas or blood lineages.	[52] [41]
Paromomycin (aminoglycoside antibiotic) (also known as aminosidine or monomycin)	In *Leishmania*, paromomycin also affects mitochondrion.	Itching, erythema, edema and tenderness.	[53] [54]
Miltefosine (hexadecylphosphocholine)	Primary effect uncertain, possible inhibition of ether remodelling, phosphatidylcholine biosynthesis, signal transduction and calcium homeostasis. The intracellular accumulation of the drug appears to be the critical step for its action. It has been found that miltefosine induces an apoptosis-like cell death in *L. donovani* by producing numerous defects.	3% of patients developed adverse effects, mainly gastrointestinal toxicity, and elevated hepatic transaminases and creatinine, gastrointestinal adverse effects vomiting and diarrhea, fatal acute pancreatitis.	[55] [56] [57] [58] [59] [60]
Imiquimod (imidazoquinoline)	Stimulates nitric oxide production from macrophages.	It is applied once a day 5 times a week for at least 6 weeks. Local reactions occur most frequently and include itching, burning, bleeding, vesicles, erosions, ulcerations, excoriations, crusting, induration, edema, and pain. Other side effects include upper respiratory tract infection, flu-like symptoms.	[61] [62]
Paromomycin (aminosidine) is an aminoglycoside with antileishmanial activity	Inhibits protein synthesis and modifies membrane fluidity and permeability. An *in vitro* study showed that following a 72-h exposure of *L. donovani* promastigotes and amastigotes to paromomycin, the mitochondrial potential was decreased, which indicates that mitochondria are the targets of the drug.	Adverse effects were more frequent in the paromomycin-treated group compared with the amphotericin B-treated group (6% *vs*. 2%, resp.); included increased hepatic transaminases, ototoxicity, and pain at injection-site.	[63]

5.2. Natural substances and fight against leishmaniasis

For the reasons of high toxicity of synthetic molecules, the search of other alternative compounds that are free of these problems and disadvantages is necessary. Furthermore, medicinal plant products play a veritable role as source of diverse functional molecules. Indeed, these plants are used since always to fight against leishmaniasis and showed important results[77-83]. In recent years, the screening of antileishmanial compounds from medicinal plants has been studied[23,24,84-88]. The poverty imposes to the underdeveloped countries such as African countries to use medicinal plants to treat diseases as leishmaniasis. Here we report many scientific evidences for the traditional use of plants for leishmaniasis treatment.

5.3. Antileishmanial activity of medicinal plants from Africa

The African countries remain a source of excellence of medicinal plants given the modesty of their economies and in particular the poverty of their populations who do not have the means to purchase the drugs that are still very expensive for a large segment of the African population. In addition, bacterial, viral, fungal and parasitic diseases such as leishmaniasis anthropozoonotic, hydatid disease, brucellose, *etc*. are spreading in all parts of this continent[4,8,23,24]. The scientific research that was conducted by African researchers on medicinal plants used against leishmaniasis *in situ*, *in vitro* or *in vivo* in Africa, led to valuable results and contributed to the discovery of alternative molecules that could be used in the future. The

antileishmanial activity of natural products of medicinal plants has been extensively tested in different African areas[89-96]. This activity depends on the plant used, the type of extract, the part studied and harvest area (Table 3).

Based on Figure 1, the African family plants which has the best antileishmanial effect is the Annonaceae family. Plants belonging to this family seem to have some medicinal properties and contain chemical compounds that have leishmanicidal effects. Plants of this family include *Pistacia atlantica*, *Anonidium mannii*, *Enantia chlorantha*, *Isolona hexaloba*, *Annona glauca*, *Annona senegalensis* and *Annickia kummeriae*.

The bioactive compounds of *Pistacia atlantica* including α-Pinene + α- and Terpinen-4,ol are effective against leishmania because it includes most plants of this family, we tried to introduce the different species of the genus that grow in Africa. There are several species of the genus *Pistacia*, which include *Pistacia lentiscus*.

In addition to the antileishmanial activity of Pistacia, frequency of biological activities such as germicidal, antifungal, viral wiring, antiparasitic and analgesic properties and antioxidant properties of the antibody and the dilation of blood vessels have been demonstrated[107]. Analysis showed that the herb mountain *Pistacia* contains various compounds such as α-pinene + α-thujene, camphene, β-pinene, *p*-cymene, terpinen-4,ol and other compounds[107]. *Pistacia atlantica* has bioactive compounds such as flavonoids[108], fatty acids and triglycerides[109-113], oleoresins[114,115], essential oils[116,117]. Recently, a new hispolone compound has been isolated from the methanolic extract[118].

Another example of a medicinal plants traditionally used in Morocco to fight against leishmaniasis is *Salvia officinalis*[24], its major components are: 1,8-cineole, camphor, borneol, bornyl acetate, camphene, α- and β-thujone, linalool, α- and β-caryophyllene, α-humulene, α- and β-pinene, viridiflorol, pimaradiene, salvianolic acid, rosmarinic acid, carnosolic acid, ursolic acid, *etc*.[119,120]. Several studies showed that some biological properties of the essential oil of *Salvia* depend on camphor, 1,8-cineole, α-thujone, and β-thujone[121]. The essential oil of sage contains about 20% camphor, and as the leaves expand, the camphor content also increases[122]. In another study, the most powerful scavenging compounds were reported to be α-thujone and β-thujone, bornyl acetate, camphor, menthone, and 1,8-cineol in the essential oil. Sage is also a natural source of flavonoids and polyphenolic compounds[23].

In Morocco, antileishmanial activity of medicinal plants has been reported in situ by El Rhaffari *et al.*[77] in the Meknes-Tafilalt Area (Southeastern Morocco), on the use of medicinal plants to fight against leishmaniasis. This study revealed numerous plant species belonging to different botanical families, which are frequently used by the population of this area. Amongst the most cited plants are: *Pistacia atlantica*, *Apium graveolens*, *Nerium oleande*, *Calotropis procera*, *Artemisia herba-alba* Asso, *Launea arborescens*, *Anthemis stiparum*, *Inula viscosa*, *Lactuca virosa*, *Lipidium sativum*. On the other hand, several studies have been conducted by several authors in different countries of Africa based only on ethnobotanical surveys namely Iwu *et al*.[100] in Nigeria *etc*.

The *in vitro* antileishmanial studies were evaluated by different authors. Malebo *et al*.[93] showed an effect of dichloromethane extract from the bark root of the *Annickia kummeriae* (Tanzania) against *L. donovani*. This activity could be due to the presence of phenolic compounds in this plant extract. In fact, phenolic compounds are highly recognized by their antileishmanial activities.

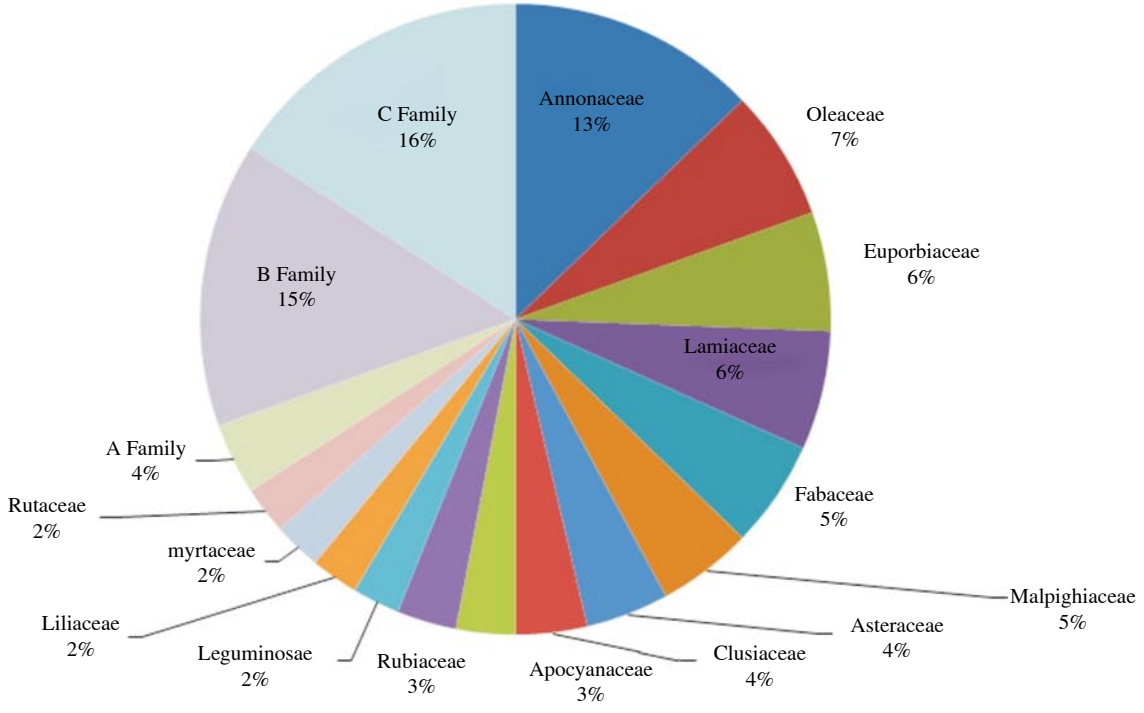


Figure 1. Distribution of medicinal plants species according to their families.
Family A : Anacardiaceae, Menispermaceae; Family B: Aloeaceae, Asclepiadaceae, Brassicaceae, Celastraceae, Chenopodiaceae, Combretaceae, Cupressaceae, Meliaceae, Papillionaceae, Rosaceae, Solanaceae, Verbenaceae; Family C: Acanthaceae, Apiaceae, Cacinaceae, Cactaceae, Caryophyllaceae, Cecropiaceae, Convolvulaceae, Cucurbitaceae, Ebenaceae, Huaceae, Lauraceae, Lecythidaceae, Lithraceae, Moraceae, Myristicaceae, Phytolaccaceae, Piperaceae, Plantaginaceae, Rannunculaceae, Sapindaceae, Sapotaceae, Simaroubaceae, Vitaceae, Zingiberaceae, Zygophyllaceae.

Table 3

Ethnomedicinal and pharmacological properties of African medicinal plants against *Leishmania* species.

Plant family	Plant species	Country	Used part	Type of extraction	*Leishmania* species used	Compounds	Results of biological activity (IC_{50} ± SD)	References
Acanthaceae	*Thomandersia hensii*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	> 64 μg/mL	[95]
Aloeaceae	*Aloe nyeriensis*	Kenya	Leaves	Mehanol extract	*Leishmania major*	n.d	n.d	[94]
				Aqueous extract	*Leishmania major*	n.d	n.d	[94]
Anacardiaceae	*Pseudospondias microcarpa*	Tanzania	Stem bark	Ethanol extract	*Leishmania donovani*	n.d	29.9 ± 4.19 μg/mL	[93]
			Root bark	Ethanol extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
	Pistacia atlantica	Morocco	Gum/Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
	Anonidium mannii	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	> 64 μg/mL	[95]
	Enantia chlorantha		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	10.08 μg/mL	[95]
	Isolona hexaloba		Root bark	Aqueous decoction	*Leishmania infantum*	n.d	32.46 μg/mL	[95]
	Polyalthia suaveolens		Root bark	Aqueous decoction	*Leishmania infantum*	n.d	8.00 μg/mL	[95]
	Annona glauca Thonn.	Senegal	Seeds	Dichloro methane extract	*Leishmania amazonensis* *Leishmania braziliensis*	Annonacin A and Goniothalamicin	n.d	[97]
	Annona senegalensis Pers		Seeds	Dichloro methane extract	*Leishmania* sp.	mono-tetrahydrofuran acetongenins, annosenegalin and annogalene	n.d	[98]
	Annickia kummeriae	Tanzania	Leaves	Petroleum ether extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
			Leaves	Dichloro methane extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
			Leaves	Methanol extract	*Leishmania donovani*	n.d	9.25 ± 0.54 μg/mL	[93]
			Stem bark	Petroleum ether extract	*Leishmania donovani*	n.d	9.74 ± 1.82 μg/mL	[93]
			Stem bark	Dichloro methane extract	*Leishmania donovani*	n.d	18.00 ± 0.42 μg/mL	[93]
			Stem bark	Methanol extract	*Leishmania donovani*	n.d	19.41 ± 1.66 μg/mL	[93]
			Root bark	Petroleum ether extract	*Leishmania donovani*	n.d	14.55+1.1 μg/mL	[93]
			Root bark	Dichloro methane extract	*Leishmania donovani*	n.d	9.79 ± 2.5 μg/mL	[93]
			Root bark	Methanol extract	*Leishmania donovani*	n.d	12.38 ± 1.12 μg/mL	[93]
Annonaceae	*Uvaria afzelii* Sc. Elliot	Ivory Coast	Leaves	Methanol extract	*Leishmania donnovani*	n.d	12.5 μg/mL	[90]
			Roots	Dichloro methane extract	*Leishmania donnovani*	n.d	12.5 μg/mL	[90]
	Polyalthia suaveolens	Gabon	Stem barks	Methanol extract	*Leishmania infantum*	n.d	1.8 μg/mL	[99]
	Monodora myristica	Ivory Coast	Seeds	Methanol extract	*Leishmania donovani*	n.d	>100 μg/mL	[90]
				Dichloro methane extract	*Leishmania donovani*	n.d	>100 μg/mL	[90]
	Uvaria afzelii		Leaves	Methanol extract	*Leishmania donovani*	n.d	12.5 μg/mL	[90]
Apiaceae	*Apium graveolens*	Morocco	Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
	Alstonia boonei	Ivory Coast	Leaves	MeOH	*Leishmania donovani*	n.d	>100 μg/mL	[90]
	Alstonia boonei	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	>64 μg/mL	[95]
	Picralima nitida		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	>64 μg/mL	[95]
	Picralima nitida Th.	Negeria	Seeds	Chloroform extract	*Leishmania donovani*	n.d	n.d	[100]

(*continued on next page*)

Table 3 (*continued*)

Plant family	Plant species	Country	Used part	Type of extraction	*Leishmania* species used	Compounds	Results of biological activity (IC_{50} ± SD)	References
Apocynaceae	*Nerium oleander*	Maroc	Stem/Leaves/ Root	n.d	*Leishmania major*	n.d	n.d	[89]
Asclepiadaceae	*Gongronema latifolia* Benth	Negeria	Leaves	Methanol extract	*Leishmania donovani*	n.d	n.d	[100]
	Calotropis procera	Morocco	Leaves / Stem	n.d	*Leishmania major*	n.d	n.d	[89]
Asteraceae	*Artemisia herba-alba* Asso.		n.d	Aqueous extract	*Leishmania tropica*	n.d	n.d	[101]
	Artemisia annua	Tanzania	Leaves	*n*-Hexane extract	*Leishmania donovani*	n.d	6.4 ± 0.6 μg/mL	[93]
				Ethanol extract	*Leishmania donovani*	n.d	>30.00 μg/mL	[93]
	Launea arborescens	Morocco	Stem	n.d	*Leishmania major*	n.d	n.d	[89]
	Anthemis stiparum		Capitulates	n.d	*Leishmania major*		n.d	
	Inula viscosa		Aerialpart	n.d	*Leishmania major*	n.d	n.d	
	Lactuca virosa		Aerialpart	n.d	*Leishmania major*	n.d	n.d	
Brassicaceae	*Lipidium sativum*	Morocco	Seed	n.d	*Leishmania major*	n.d	n.d	
	Brassica oleraceae		Leaves	n.d	*Leishmania major*	n.d	n.d	
Cacinaceae	*Pyrenacantha klaineana*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	> 64 μg/mL	[95]
Cactaceae	*Opuntia ficus-indica*	Morocco	Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
Caryophyllaceae	*Saponnaria vaccaria*	Morocco	Root / Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
Cecropiaceae	*Musanga cecropioides*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	6.35 μg/mL	[95]
Celastraceae	*Maytenus senegalensis*	Sudan	Stem bark	Dichloro methane extract	*Leishmania major*	n.d	n.d	[80]
	Maytenus senegalensis	Tanzania	Root bark	Ethanol extract	*Leishmania donovani*	n.d	16.5 ± 2.32 μg/mL	[93]
Chenopodiaceae	*Haloxylon scoparium*	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Hammada scoparia		Aerial part	n.d	*Leishmania major*	n.d	n.d	
Clusiaceae	*Garcina punctata*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	32.00 μg/mL	[95]
	Harugana madagascariensis		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	20.32 μg/mL	[95]
	Mammea africana		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	27.27 μg/mL	[95]
	Psorospermum guineense	Mali	Root bark	Dichloro methane extract	*Leishmania major*	n.d	n.d	[91]
	Harungana madagascariensis	Cameroun	Seeds	Methanol extract	*Leishmania donnovani*	n.d	1.60.6 μg/mL	[92]
Combretaceae	*Anogeissus leiocarpus*	Ivory Cost	Leaves	Methanol extract	*Leishmania donovani*	n.d	>100 μg/mL	[90]
	Terminalia glaucescens		Leaves	Methanol extract	*Leishmania donovani*	n.d	>100 μg/mL	[90]
	Combretum comosum	Gabon	Leaves	Methanol extract	*Leishmania infantum*	n.d	>100 μg/mL	[99]
	Combretum cuspidatum		Stem barks	Dichloro methane extract	*Leishmania infantum*	n.d	28.6 μg/mL	[99]
Convolvulaceae	*Calycobolus* sp.	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	32.00 μg/mL	[95]
Cucurbitaceae	*Citrullus oolocynthis*	Morocco	Fruit/Fresh fruit	n.d	*Leishmania major*	n.d	n.d	[89]
Cupressaceae	*Juniperus oxycedrus*	Morocco	Wood	n.d	*Leishmania major*	n.d	n.d	[89]
	Juniperus thurifera	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
Dioscoraceae	*Dioscorea preussii*	Gabon	Leaves	Mehanol extract	*Leishmania infantum*	n.d	68.6 μg/mL	[99]
Ebenaceae	*Diospyros canaliculata*	Cameroun	Stem bark	dichloromethane-methanol (1:1)	*L. donovani*	Betulin, plumbagin, ismailin, gerberinol, and betulinic acid	2.99 μg/mL	[92]

Table 3 (*continued*)

Plant family	Plant species	Country	Used part	Type of extraction	Leishmania species used	Compounds	Results of biological activity (IC_{50} ± SD)	References
Euphorbiaceae	*Alchornea cordifolia*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	32.46 µg/mL	[95]
	Alchornea floribunda		Leaves/Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	>64 µg/mL	[95]
	Drypetes gossweileri		Stem bark	Aqueous decoction	*Leishmania infantum*		>64 µg/mL	[95]
	Jatropha curcas		Root bark	Aqueous decoction	*Leishmania infantum*	n.d	>64 µg/mL	[95]
	Manniophyton fulvum	Congo	Leaves	Aqueous Decoction	*Leishmania infantum*	n.d	50.80 µg/mL	[95]
			Root bark				>64 µg/mL	
			Stem bark				>64 µg/mL	
	Drypetes natalensis	Tanzania	Stem bark	Ethanol extract	*Leishmania donovani*	n.d	19.00 ± 3.27 µg/mL	[93]
			Root bark				29.7 ± 3.52 µg/mL	
	Andrachne telephiooîdes	Morocco	Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
	Euphorbia calyptrata		Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
	Battandiera amaena (Batt) Maire		Bulb	n.d	*Leishmania major*	n.d	n.d	[89]
Fabaceae	*Desmodium gangeticum*	Nigeria	Leaves	Methanol extract	*Leishmania donovani*	n.d	n.d	[100]
	Bobgunnia madagascarensis	Mali	Root bark	Dichloro methane extract	*Leishmania major*	n.d	n.d	[91]
	Entada africana Gill. and Perr.		Roots	Aqueous extract	*Leishmania major*	n.d	n.d	[91]
	Albizia coriara	Kenya	Stem bark	Aqueous extract	*Leishmania major*	n.d	n.d	[94]
	Acacia tortilis		Stem bark	Aqueous extract	*Leishmania major*	n.d	n.d	[94]
	Tephrosia fulvinervis	Cameroun	n.d	n.d	n.d	isoflavonoid (5), 2'-methoxy-4',5'-methylenedioxy-7,8-[2-(1-methylethenyl) furo]isoflavone	n.d	[102]
	Augouardia letestui	Gabon	Stem barks	Methanol extract	*Leishmania infantum*	n.d	>100 µg/mL	[99]
	Dialium lopense	Gabon	Stem barks	Methanol extract	*Leishmania infantum*	n.d	>100 µg/mL	[99]
Fagaceae	*Quercus rotundifolia* Lamk	Morocco	Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
Geraniaceae	*Pelargonium odoratissimum*		Aerialpart	n.d	*Leishmania major*	n.d	n.d	[89]
Huaceae	*Afrostyrax lepidohyllus*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	32.46 µg/mL	[95]
Lamiaceae	*Ocimum gratissimum*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	20.32 µg/mL	[95]
	Ajugea iva	Morocco	n.d	n.d	*Leishmania major*	n.d	n.d	[89]
	Lanvandula multifida		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Marrubium vulgare		Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
	Mentha pilegium		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Ocimum basilicum		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Origanum compactum		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Rosmarinus officinalis		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
			Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
	Salvia clandestina (Batt)		Aerial part	*n*-Hexane extract	*Leishmania major*	n.d	155.43 µg/mL	[23]
					Leishmania tropica	n.d	148.23 µg/mL	
					Leishmania infantum	n.d	14.11 µg/mL	
			Aerial part	Dichloro methane extract	*Leishmania major*	n.d	24.56 µg/mL	[23]
					Leishmania tropica	n.d	33.77 µg/mL	
					Leishmania infantum	n.d	31.57 µg/mL	
			Aerial part	Methanol extract	*Leishmania major*	n.d	>1000 µg/mL	[23]
					Leishmania tropica	n.d	850.76 µg/mL	
					Leishmania infantum	n.d	>1000 µg/mL	

Table 3 (*continued*)

Plant family	Plant species	Country	Used part	Type of extraction	*Leishmania* species used	Compounds	Results of biological activity (IC_{50} ± SD)	References
Lamiaceae	*Salvia officinalis* L.	Morocco	Leaves	*n*-Hexane extract	*Leishmania major*	n.d	>1000 μg/mL	[24]
				Ethanol extract	*Leishmania major*	n.d	>1000 μg/mL	
				Methanol extract	*Leishmania major*	n.d	>1000 μg/mL	
	Thymus satureioides		Aerial part	n.d	*Leishmania major*	n.d	n.d	[89]
Lauraceae	*Cinnamum zeylanicum*	Morocco	Bark	n.d	*Leishmania major*	n.d	n.d	[89]
Lecythidaceae	*Napoleona vogelii*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	5.66 μg/mL	[95]
Leguminosae	*Dalhousiea africana*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	>64 μg/mL	[95]
	Piptadeniastrum africanum		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	6.01 μg/mL	[95]
	Scorodophloeus zenkeri		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	9.51 μg/mL	[95]
	Tetrapleura tetraptera		Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	12.70 μg/mL	[95]
			Fruits	Aqueous decoction	*Leishmania infantum*	n.d	27.70 μg/mL	
Liliaceae	*Allium sativum*	Morocco	Stem/Bulb	n.d	*Leishmania major*	n.d	n.d	[89]
	Allium cepa		Stem	n.d	*Leishmania major*	n.d	n.d	[89]
	Asparagus racemosus	Kenya	Roots	Methanol extract	*Leishmania major*	n.d	n.d	[94]
				Aqueous	*Leishmania major*	n.d	n.d	[94]
Lithraceae	*Lawsonia inermis*	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
Malpighiaceae	*Acridocarpus chloropterus*	Tanzania	Leaves	Petroleum ether extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
				Dichloro methane extract	*Leishmania donovani*	n.d	11.66 ± 1.51 μg/mL	[93]
				Methanol extract	*Leishmania donovani*	n.d	28.80 ± 1.21 μg/mL	[93]
			Stem bark	Petroleum ether extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
				Dichloro methane extract	*Leishmania donovani*	n.d	14.57 ± 1.36 μg/mL	[93]
			Root bark	Petroleum ether extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
				Dichloro methane extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
				Methanol extract	*Leishmania donovani*	n.d	>30 μg/mL	[93]
Meliaceae	*Azadirachta indica* A.	Sudan	Stem bark	Methanol extract	*Leishmania major*	n.d	n.d	[80]
	Pseudocedrela kotschyi	Mali	Roots	Dichloro methane extract	*Leishmania major*	n.d	n.d	[91]
Menispermaceae	*Penianthus longifolius*	Congo	Root bark	Aqueous decoction	*Leishmania infantum*	n.d	32.00 μg/mL	[95]
	Triclisia dictyophylla		Leaves	Aqueous decoction	*Leishmania infantum*	n.d	32.00 μg/mL	[95]
	Triclisia patens Oliv	Ghana	Aerial parts	Methanol extract	*Leishmania donovani*	n.d	1.50 ± 0.16 μg/mL	[103]
Moraceae	*Dortenia multiradiata*	Nigeria	Leaves	Aqueous extract	*Leishmania donovani*	n.d	n.d	[100]
Myristicaceae	*Staudtia kamerunensis*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	> 64 μg/mL	[95]
Myrtaceae	*Psidium guajava*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	32.46 μg/mL	[95]
	Eucalyptus sp.	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Myrtus communis		Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Eugenia caryophyllata		Floral button	n.d	*Leishmania major*	n.d	n.d	[89]
Oleaceae	*Olea europeaea* (Limouni)	Tunisia	Leaves	Methanol extract	*Leishmania amazonensis*	n.d	6.970 ± 0.316 μg/mL	[104]
					Leishmania donovani	n.d	2.130 ± 0.023 μg/mL	
					Leishmania tropica	n.d	17.622 ± 0.651 μg/mL	
					Leishmania major	n.d	14.661 ± 0.380 μg/mL	
	Olea europeaea (Zarrazi)		Leaves	Ethanol extract	*Leishmania amazonensi*	n.d	14.379 ± 1.400 μg/mL	[104]
				Ethanol extract	*Leishmania donovani*	n.d	17.737 ± 1.430 μg/mL	
				Methanol extract	*Leishmania tropica*	n.d	27.707 ± 2.852 μg/mL	
				Methanol extract	*Leishmania major*	n.d	23.889 ± 1.651 μg/mL	
	Olea europeaea (Dhokkar)		Leaves	Mixture (ethanol and methanol) extract	*Leishmania amazonensi*	n.d	2.936 ± 0.021 μg/mL	[104]
				Ethanol extract	*Leishmania donovani*	n.d	16.296 ± 0.63 μg/mL	
				Methanol extract	*Leishmania tropica*	n.d	19.494 ± 0.785 μg/mL	
				Methanol extract	*Leishmania major*	n.d	23.120 ± 1.581 μg/mL	
	Olea europeaea (Toffehi)		Leaves	Ethanol extract	*Leishmania amazonensi*		4.017 ± 1.345 μg/mL	[104]
				Ethanol extract	*Leishmania donovani*	n.d	13.785 ± 0.976 μg/mL	
				Methanol extract	*Leishmania tropica*	n.d	17.761 ± 0.860 μg/mL	
				Methanol extract	*Leishmania major*	n.d	17.681 ± 1.383 μg/mL	
	Olea europeaea (Chemlali Tataouine)		Leaves	Mixture (ethanol and methanol) extract	*Leishmania amazonensi*	n.d	3.894 ± 0.599 μg/ml	[104]
				Methanol extract	*Leishmania donovani*	n.d	6.201 ± 0.939 μg/mL	
				Methanol extract	*Leishmania tropica*	n.d	18.875 ± 1.253 μg/mL	
				Methanol extract	*Leishmania major*	n.d	17.323 ± 1.066 μg/mL	

Table 3 (*continued*)

Plant family	Plant species	Country	Used part	Type of extraction	*Leishmania* species used	Compounds	Results of biological activity (IC_{50} ± SD)	References
	Olea europea	Morocco	Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
Papillionaceae	*Abrus precatorius*	Nigeria	Leaves	*n*-Hexane extract	*Leishmania donovoni*	n.d	15.7 μg/mL	[105]
Papilonaceae	*Neurautanenia mitis*	Tanzania	Tuber	Ethanol extract	*Leishmania donovani*	n.d	8.8 ± 1.06 μg/mL	[93]
Piperaceae	*Piper guineense*	Congo	Leaves	Aqueous decoction	*Leishmania infantum*	n.d	> 64 μg/mL	[95]
Plantaginaceae	*Plantago amplexicaulis* (Cav)	Morocco	Aerialpart	n.d	*Leishmania major*	n.d	n.d	[89]
Polypodiaceae	*Polypodium polycarpon*	Gabon	Leaves	Dichloro methane extract	*Leishmania infantum*	n.d	52.4μg/mL	[99]
Rannunculaceae	*Nigella sativa*	Morocco	Seed	n.d	*Leishmania major*	n.d	n.d	[89]
Rosaceae	*Malus communis*	Morocco	Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
	Rosa sp.		Flower	n.d	*Leishmania major*	n.d	n.d	[89]
Rubiaceae	*Massularia acuminata*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	6.96 μg/mL	[95]
	Sarcocephalus latifolius (Smith) Bruce	Mali	Stem bark	Dichloro methane extract	*Leishmania major*	n.d	n.d	[91]
			Stem bark	Dichloro mehane extract	*Leishmania major*	n.d	n.d	[91]
			Stem bark	Methanol extract	*Leishmania major*		n.d	[91]
	Pavetta crassipes K. Schum	Guinea	Leaves	Alcaloid extract	*Leishmania infantum*	n.d	10.77 μg/mL	[106]
	Corynanthe mayumbensis	Gabon	Stem bark	Dicholoro methane extract	*Leishmania infantum*	n.d	63.2 μg/mL	[99]
	Morelia senegalensis	Gabon	Stem bark	Dicholoro methane extract	*Leishmania infantum*	n.d	34.2 μg/mL	[99]
	Uncaria africana	Gabon	Stem bark	Methanol extract	*Leishmania infantum*	n.d	>100 μg/mL	[99]
Rutaceae	*Citrus aurantium*	Morocco	Fruit	n.d	*Leishmania major*		n.d	[89]
	Citrus limon	Morocco	Leaves Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
	Zanthoxylum zanthoxyloides (Lam.) Zepernick and Timler	Mali	Root bark	Dichloro methane extract	*Leishmania major*	n.d	n.d	[91]
			Root bark	Aqueous extract	*Leishmania major*	n.d	n.d	
Sapindaceae	*Paullinia pinnata*	Ivory Cost	Leaves	Methanol extract	*Leishmania donovani*	n.d	>100 μg/mL	[90]
	Ganophyllum giganteum	Gabon	Stem bark	Dichloro methane extract	*Leishmania infantum*	n.d	15.6 μg/mL	[99]
Sapotaceae	*Autranella congolensis*	Congo	Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	20.32 μg/mL	[95]
Simaroubaceae	*Quassia africana*	Congo	Root bark	Aqueous decoction	*Leishmania infantum*	n.d	5.04 μg/mL	[95]
			Stem bark	Aqueous decoction	*Leishmania infantum*	n.d	>64 μg/mL	
	Irvingia grandifolia	Gabon	Stem bark	Methanol extract	*Leishmania infantum*	n.d	>100 μg/mL	[99]
Solanaceae	*Capsicum annuum*	Morocco	Fruit	n.d	*Leishmania major*		n.d	[89]
	Capsicum frutescens		Fruit	n.d	*Leishmania major*	n.d	n.d	[89]
Sterculiaceae	*Cola attiensis* Aubrev.	Nigeria	Seeds	Chloroform extract	*Leishmania donovani*	n.d	n.d	[100]
	Cola lizae	Gabon	Stem bark	Methanol extract	*Leishmania infantum*	n.d	35.4 μg/mL	[99]
Verbenaceae	*Lippia citriodora*	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]
	Lippia multiflora Moldenke	Ivory Coast	Leaves	Dichloromethane extract	*Leishmania donnovani*	n.d	12.5 μg/mL	[90]
				Ethanol extract			0.108 mg/mL	
Zingiberaceae	*Aframomum sceptrum*	Ivory Coast	Leaves	Dichloro methane extract	*Leishmania donnovani*	n.d	12.5 μg/mL	[90]
Zygophyllaceae	*Zygophyllum gaetullum*	Morocco	Leaves	n.d	*Leishmania major*	n.d	n.d	[89]

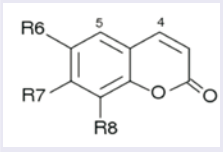
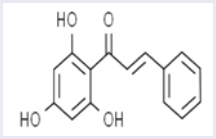
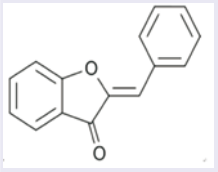
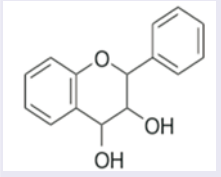
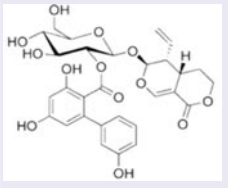
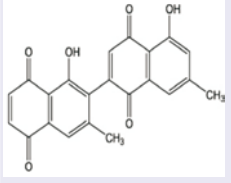
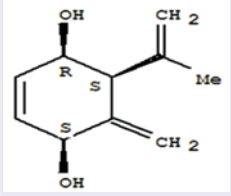
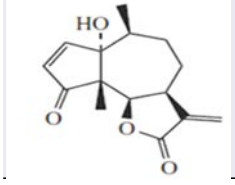
In Congo, a study was conducted by Musuyu Muganza *et al*.[95] on the aqueous extract of the stem bark of *Enantia chlorantha* against *L. infantum*. The study has revealed that the extract give a powerful effect with an IC_{50} = 10.08 μg/mL. Kigondi *et al*.[94] studied the antileishmanial activity of aqueous and methanol extracts of leaves from *Aloe nyeriensis* (Kenya) against *L. major*, and showed low activity with percent mortality at 1 mg/mL of extract are 53.30 ± 5.10 and 68.40 ± 6.30 respectively.

On the other hand, in Côte d'Ivoire, the antileishmanial screening revealed three species, *Lippia multiflora*, *Aframomum sceptrum* and *Uvaria afzelii* with an IC_{50} extract below 25 μg/mL[90]. This difference in results of the antileishmanial activity could be attributed to the chemical composition of plants by active molecules such as phenols, flavonoids, terpenes, *etc*... and which can be influenced and determined by the edaphic factors. Furthemore, the antileishmanial effect can be also affected by *Leishmania* strains used, the methods of extraction and the pharmacological tests.

In Morocco, the study of antileishmanial research has been recently started by Et-Touys *et al*.[23]. *Salvia verbenaca* has been used, which is a medicinal plant from Morocco that has been traditionally used to treat leishmaniasis[89]. In this study, leishmanial cytotoxicity of *n*-hexane, dichloromethane and methanol extracts from *Salvia verbenaca* against *L. major*, *L. tropica* and *L. infantum* promastigotes form using viability assay have been tested[23]. *N*-hexane and dichloromethane extracts showed a highest antileishmanial activity than methanolic extract. Indeed, *n*-hexane showed a half-maximal

Table 4

Mechanisms of action of natural molecules against *Leishmania*.

Molecules	Mechanisms of action	References
Coumarins 	Coumarins (gallic acid) induce apoptotic cell death.	[123]
Chalcones 	Licochalcone A activity is well documented *in vitro* and *in vivo* against *Leishmania donovani* and *L. major* strains. The mechanism of action is related to the inhibition of mitochondrial electron transport. These main targets are the enzymes of the respiratory chain dehydrogenase such as fumarate, succinate dehydrogenase and malate dehydrogenase.	[124]
Aurones 	The aurones share similar anti parasitic activities. Chalcones inhibit the same target sites as chalcone. A planar structure is typical for all aurones and this conformation exhibits strong similarity with compounds that Li *et al*. proposed as a lead structure which is optimal chalcones as protease inhibitors.	[125, 126]
Flavonïds : Flavone, flavanone, isoflavone, glucorhamnosyl-flavone Exemple: 	Specific flavonoids affect the transport mechanisms in *Leishmania*.	[57]
Iridoïds: 	This compound has a leishmanicidal activity by inhibition the activity of DNA-topoisomerase I in *Leishmania donovani*.	[127]
Naphtoquinon: diospyrin 	Naphtoquinone dimer diospyrin extract from *Diospyros montana* (Ebenaceae) was found to be active against *Leishmania donovani*. The inhibition of topoisomerase type for this parasite has been suggested as a mechanism of action.	[128]
Monoterpens : Piquerol A 	The interaction of Piquerol A with the enzymatic system of redox of parasite induce to enzymes inhibition and death of parasite.	[129]
Lactons sesquiterpenics : parthenin 	The parthenin is able to bloc specific targets of parasite responsible for glutathinonylspermidin, trypanothion of cystein and glutathion precursors synthesis in *Leishmania* species.	[130]

inhibitory concentration at IC_{50} = 155.43 μg/mL, IC_{50} = 148.23 μg/mL and IC_{50} = 14.11 μg/mL respectively against *L. major*, *L. tropica* and *L. infantum*. While, dichloromethane has an IC_{50} value at IC_{50} = 24.56 μg/mL against *L. major*, IC_{50} = 33.77 μg/mL against *L. tropica* and IC_{50} = 31.57 μg/mL against *L. infantum*. In another study also conducted by Et-touys *et al*.[23], methanol, *n*-hexane and ethanol extracts from *Salvia officinalis* (medicinal plant largely used in Morocco pharmacopeia) have been tested against *L. major* using MTT assay. *Leishmania* tests showed a similar sensitivity when tested at or above concentrations 1 000 μg/mL.

5.4. Antileishmanial mechanisms of action of molecules from plants

The antileishmanial activity of natural extracts is certainly attributed to the presence of bioactive molecules that can inhibit the growth of these parasites by numerous mechanisms of action. The mechanisms of action depend on the chemical composition, the leishmanial strains tested and the used methods. The spectrum of action of these molecules against leishmanial strains is very variable and comes from the morphological destruction to the regulation levels.

Table 4 summarizes the various antileishmanial modes of action of natural molecules. Phenolic substances such as coumarins have demonstrated their ability to inhibit parasites via induction of apoptosis of a readable manner dose-dependent[123]. While some flavonoids such as flavones, flavonone, isoflavone and glucorhamnosyl-flavone were able to stop the growth of *Leishmania* by affecting the transport mechanisms of this strain, antileishmanial cytotoxicity mechanisms may also affect the energy level of the strains tested by disrupting the electrons chain transport[123]. Indeed, a study carried out by Ray *et al*.[127] showed a cytotoxic activity of iridoids against *L. donovani*. In another work, Zhai *et al*.[124] showed such mechanism by studying the activity licochalcone A (molecules that belong to chalcones) against *L. donovani* and *L. major*. The main targets are the enzymes of the electrons respiratory chain such as fumarate dehydrogenase, succinate dehydrogenase and malate dehydrogenase.

Leishmanicidal mechanisms have been linked to the ability of these compounds to inhibit DNA topoisomerase; the key enzyme in the DNA compaction. Another example of a compound that has been suggested as a topoisomerase inhibitor is that of naphthoquinone (dimer diospyrin). This compound is isolated from the extracts of *Diospyros montana* (Ebenaceae) and shows a strong antileishmanial activity against *L. donovani*[128]. The leishmanicidal activity can also be linked to the disruption of energy levels in the mitochondrial. Indeed, some monoterpenes such as Piquerol A proved to be capable of interacting with the enzymatic system of electrons chain transport of the parasites leading to their inhibitions and falling energetic potential (ATP). This situation induces apoptosis of parasite via mitochondrial signals[129].

6. Conclusion

Medicinal plants are used for the treatment of several illnesses including infectious diseases. *In vitro* and *in vivo* works showed the biological properties of molecules isolated from these plants and some of them are now used as medicaments. The African continent is rich in medicinal plants with very powerful pharmacological properties such as antioxidant, antifungal, anti-inflammatory, antibacterial, antiviral, antitumor and antileishmanial. Several studies were conducted in African countries to reveal antileishmanial activity of secondary metabolites from these plants and the results suggested potential therapeutic applications. Different species are used traditionally to treat leishmaniasis. The *in vitro* assay of extracts from these species was also carried out in some countries and showed promising results. However, the screening and purification or hemisynthesis of bioactive compounds from the extracts with several molecules require much time, strong capital and high curiosity. Future research must be addressed to draw from African medicinal plants pure molecules with specificity against the leishmanial strains to fight against leishmaniasis.

Conflict of interest statement

We declare that we have no conflict of interest.

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