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 cytoxicity 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].

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...
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 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, chilcero’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 viscerocutaneous 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[34,35].

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...
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, diffus 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 at 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 minomycin 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 B 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 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].
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 anthropozoontic, 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*, *Annonidium mannii*, *Enantia chlorantha*, *Isolona hexaloba*, *Annona glauca*, *Annona senegalensis* and *Annickia kummeriae*.

The bioactive compounds of *Pistacia atlantica* including 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-Tafillalt 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 oleander*, *Calotropis procera*, *Artemista herba-alba Asso*, *Launaea arborescens*, *Anthemis stiperum*, *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](https://example.com/fig1.png)

**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, Papilionaceae, Rosaceae, Solanaceae, Verbenaceae; Family C: Acanthaceae, Apiceae, Cacinceae, Cactaceae, Caryophyllaceae, Cercopitateae, Convulaceae, 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 (IC50 ± SD) | References |
|--------------|---------------|---------|-----------|--------------------|-------------------------|-----------|------------------------------------------|------------|
| Acanthaceae  | *Thomandersia hensii* | Congo   | Leaves    | Aqueous decoction  | *Leishmania infantum*   | n.d       | > 64 µg/mL                               | [95]       |
|   | *Aloe nyeriensis* | Kenya   | Leaves    | Methanol extract  | *Leishmania major*       | n.d       | n.d                                      | [94]       |
|   |                     |         | Aqueous extract | *Leishmania major* | n.d                     | n.d       |                                          |            |
| Anacardiaceae | *Pseudoponias microcarpa* | Tanzania | Stem bark | Ethanol extract | *Leishmania donovani*   | n.d       | 29.9 ± 4.19 µg/mL                        | [93]       |
|   |                     | Morocco | Stem bark | Aqueous decoction | *Leishmania donovani*   | n.d       | > 30 µg/mL                               | [89]       |
|   | *Anitia chlorantha* | Congo   | Stem bark | Aqueous decoction | *Leishmania infantum*   | n.d       | > 64 µg/mL                               | [95]       |
|   | *Isolona hexaloba* | Morocco | Stem bark | Aqueous decoction | *Leishmania donovani*   | n.d       | 10.08 µg/mL                              | [95]       |
|   | *Polyalthia microcarpa* | Morocco | Stem bark | Aqueous decoction | *Leishmania donovani*   | n.d       | 32.46 µg/mL                              | [97]       |
|   | *Anonidium mannii* | Congo   | Stem bark | Aqueous decoction | *Leishmania infantum*   | n.d       |                                          |            |
|   | *Enantia chlorantha* | Tanzania | Leaves | Petroleum ether extract | *Leishmania donovani*   | n.d       | > 30 µg/mL                               | [93]       |
|   |                      |         | Leaves | Dichloro methane extract | *Leishmania donovani*   | n.d       |                                          |            |
|   |                      |         | Roots | Dichloro methane extract | *Leishmania donovani*   | n.d       |                                          |            |
|   |                      |         | Stem bark | Petroleum ether extract | *Leishmania donovani*   | n.d       |                                          |            |
|   |                      |         | Stem bark | Dichloro methane extract | *Leishmania donovani*   | n.d       |                                          |            |
|   |                      |         | Stem bark | Methanol 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]       |
|   |                      |         | Root bark | Petroleum ether extract | *Leishmania donovani*   | n.d       | 19.41 ± 1.66 µg/mL                       | [93]       |
|   |                      |         | Root bark | Methanol extract | *Leishmania donovani*   | n.d       | 9.79 ± 2.5 µg/mL                         | [93]       |
|   |                      |         | Root bark | Dichloro methane extract | *Leishmania donovani*   | n.d       | 12.38 ± 1.12 µg/mL                       | [93]       |
| Annonaceae  | *Uvaria afzelii* Sc. Elliot | Ivory Coast | Leaves | Methanol extract | *Leishmania donovani*   | 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]       |
|   | *Uvaria afzelii* | Nigeria | Leaves | Methanol extract | *Leishmania donovani*   | n.d       | 12.5 µg/mL                               | [90]       |
| Apiaceae    | *Aptium 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] |
|   | *Picralima nitida* | Congo   | Stem bark | Aqueous decoction | *Leishmania infantum*   | n.d | >64 µg/mL | [95] |
|   | *Picralima nitida* Th. | Nigeria | Seeds | Chloroform extract | *Leishmania donovani* | n.d | n.d | [100] |

(continued on next page)
| Plant family | Plant species | Country | Used part | Type of extraction | Leishmania species used | Compounds | Results of biological activity (IC50 ± SD) | References |
|-------------|---------------|---------|-----------|-------------------|------------------------|-----------|----------------------------------------|-------------|
| Apocynaceae | Nerium oleander | Morocco | Stem/Leaves/ Root | n.d | Leishmania major | n.d | n.d | [89] |
| Asclepiadaceae | Gomortega latifolia Benth | Nigeria | Leaves | Methanol extract | Leishmania donovani | n.d | n.d | [100] |
| Asteraceae | Calotropis procera | Morocco | Leaves / Stem n.d | Aqueous extract | Leishmania major | n.d | n.d | [89] |
| Artemisia herba-alba Asox | | | | | 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] |
| | Stem | Morocco | n.d | Ethanol extract | Leishmania donovani | n.d | >30.00 µg/mL | [93] |
| Launaea arborescens | | | | | Leishmania major | n.d | n.d | [89] |
| Antheros stipanum | | | | | Leishmania major | n.d | | |
| Inula viscosa | | | Aerialpart | n.d | Leishmania major | n.d | | |
| Lactuca virosa | | | Aerialpart | n.d | Leishmania major | n.d | | |
| Brassicaceae | Lipidium sativum | Morocco | Seed | n.d | Leishmania major | n.d | | |
| Baccharis oleracea | | | Leaves | n.d | Leishmania major | n.d | | |
| Cacinaceae | Pyrenacantha kleiniana | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | > 64 µg/mL | [95] |
| Cactaceae | Opatia ficus-indica | Morocco | Fruit | n.d | Leishmania major | n.d | n.d | [89] |
| Caryophyllaceae | Saponaria vaccaria | Morocco | Root / Leaves n.d | Leishmania major | n.d | n.d | [89] |
| Cereopsisae | Musanga cecropioidees | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | 6.35 µg/mL | [95] |
| Cellaraceae | 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] |
| Clusiaceae | Garcinia punctata | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | 32.00 µg/mL | [95] |
| | Harungana madagascariensis | | | | Leishmania infantum | n.d | 20.32 µg/mL | [95] |
| | Mammea africana | | | | 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 donovani | 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 glanecenec | | | | Leishmania donovani | n.d | >100 µg/mL | [90] |
| | Combretum comosum | Gabon | Leaves | Methanol extract | Leishmania infantum | n.d | >100 µg/mL | [99] |
| | Combretum castipadum | | | | 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 ooloycynthia | 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 preussi | Gabon | Leaves | Methanol extract dichloromethane-methanol (1:1) | Leishmania infantum | n.d | 68.6 µg/mL | [99] |
| | Diospyros canaliculata | Cameroon | Stem bark | Ethanol extract | Leishmania donovani | n.d | 2.99 µg/mL | [92] |
| Plant family | Plant species | Country | Used part | Type of extraction | Leishmania species used | Compounds | Results of biological activity (IC50 ± SD) | References |
|--------------|---------------|---------|-----------|--------------------|------------------------|-----------|------------------------------------------|------------|
| Euphorbiaceae | Alchornea cordifolia | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | 32.46 µg/mL | [95] |
|              | Alchornea floribunda | Congo | Leaves/Stem bark | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|              | Drypetes gosweilleri | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|              | Jatropha curcas | Congo | 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] |
|              | Drypetes natalensis | Tanzania | Stem bark | Ethanol extract | Leishmania donovani | n.d | 19.00 ± 3.27 µg/mL | [93] |
|              | Andrachne telephioïdes | Morocco | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Euphorbia calyptrata | (Batt) Maire | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | 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. | Nigeria | Roots | Aqueous extract | Leishmania major | n.d | n.d | [91] |
|              | Albizia coriaria | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Acacia tortilis | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Tephrosia fulvinervis | Cameroun | n.d | Aqueous decoction | Leishmania infantum | n.d | 20.32 µg/mL | [95] |
|              | 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] |
|              | Quercus rotundifolia | Morocco | Fruit | n.d | Leishmania major | n.d | n.d | [89] |
|              | Pelargonium odoratissimum | Gabon | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Entada africana Gill. and Perr. | Gabon | Roots | Aqueous extract | Leishmania major | n.d | n.d | [91] |
|              | Albizia coriaria | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Acacia tortilis | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Tephrosia fulvinervis | Cameroun | n.d | Aqueous decoction | Leishmania infantum | n.d | 20.32 µg/mL | [95] |
|              | 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] |
|              | Quercus rotundifolia | Morocco | Fruit | n.d | Leishmania major | n.d | n.d | [89] |
|              | Pelargonium odoratissimum | Gabon | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Alchornea floribunda | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | 32.46 µg/mL | [95] |
|              | Drypetes gosweilleri | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|              | Jatropha curcas | Congo | 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] |
|              | Drypetes natalensis | Tanzania | Stem bark | Ethanol extract | Leishmania donovani | n.d | 19.00 ± 3.27 µg/mL | [93] |
|              | Andrachne telephioïdes | Morocco | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Euphorbia calyptrata | (Batt) Maire | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | 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. | Gabon | Roots | Aqueous extract | Leishmania major | n.d | n.d | [91] |
|              | Albizia coriaria | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Acacia tortilis | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Tephrosia fulvinervis | Cameroun | n.d | Aqueous decoction | Leishmania infantum | n.d | 20.32 µg/mL | [95] |
|              | 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] |
|              | Quercus rotundifolia | Morocco | Fruit | n.d | Leishmania major | n.d | n.d | [89] |
|              | Pelargonium odoratissimum | Gabon | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Alchornea floribunda | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | 32.46 µg/mL | [95] |
|              | Drypetes gosweilleri | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|              | Jatropha curcas | Congo | 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] |
|              | Drypetes natalensis | Tanzania | Stem bark | Ethanol extract | Leishmania donovani | n.d | 19.00 ± 3.27 µg/mL | [93] |
|              | Andrachne telephioïdes | Morocco | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Euphorbia calyptrata | (Batt) Maire | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | 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. | Gabon | Roots | Aqueous extract | Leishmania major | n.d | n.d | [91] |
|              | Albizia coriaria | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Acacia tortilis | Kenya | Stem bark | Aqueous extract | Leishmania major | n.d | n.d | [94] |
|              | Tephrosia fulvinervis | Cameroun | n.d | Aqueous decoction | Leishmania infantum | n.d | 20.32 µg/mL | [95] |
|              | 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] |
|              | Quercus rotundifolia | Morocco | Fruit | n.d | Leishmania major | n.d | n.d | [89] |
|              | Pelargonium odoratissimum | Gabon | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Alchornea floribunda | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | 32.46 µg/mL | [95] |
|              | Drypetes gosweilleri | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|              | Jatropha curcas | Congo | 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] |
|              | Drypetes natalensis | Tanzania | Stem bark | Ethanol extract | Leishmania donovani | n.d | 19.00 ± 3.27 µg/mL | [93] |
|              | Andrachne telephioïdes | Morocco | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
|              | Euphorbia calyptrata | (Batt) Maire | Aerial part | n.d | Leishmania major | n.d | n.d | [89] |
| Plant family | Plant species | Country | Used part | Type of extraction | Leishmania species used | Compounds | Results of biological activity (IC₅₀ ± SD) | References |
|-------------|--------------|---------|-----------|-------------------|------------------------|-----------|------------------------------------------|------------|
| Lamiaceae   | Salvia officinalis L. | Morocco | Leaves | n-Hexane extract | Leishmania major | n.d | >0000 µg/mL | [104] |
|             | Thymus satvureoides | Aerial part | n.d | Methanol extract | Leishmania major | n.d | >0000 µg/mL | [89] |
| Laraceae    | Cinamomum zeylanicum | Morocco | Bark | n.d | Leishmania major | n.d | n.d | [89] |
| Lecithinaceae | Napoleon vogelii | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | 5.66 µg/mL | [95] |
| Leguminosae | Dalhousia africana | Congo | Leaves | Aqueous decoction | Leishmania infantum | n.d | >64 µg/mL | [95] |
|             | Piptadeniastrum africanum | Congo | Stem bark | Aqueous decoction | Leishmania infantum | n.d | 6.01 µg/mL | [95] |
|             | Scordophloeus zenkeri | Stem bark | Aqueous decoction | Leishmania infantum | n.d | 9.51 µg/mL | [95] |
| Liliaceae   | Allium sativum | Morocco | Stem/Bulb | n.d | Leishmania major | n.d | n.d | [89] |
|             | Allium cepa | Stem | n.d | Methanol extract | Leishmania major | n.d | n.d | [94] |
|             | Arparagus racemosus | Kenya | Roots | Methanol extract | Leishmania major | n.d | n.d | [94] |
| Liliaceae   | Lawsonia inermis | Morocco | Leaves | n.d | Leishmania major | n.d | n.d | [89] |
| Malpighiaceae | A. indica A. sudanica | Sudan | Stem bark | Methanol extract | Leishmania donovani | n.d | >30 µg/mL | [93] |
| Meliaceae   | A. indica A. sudanica | Sudan | Stem bark | Methanol extract | Leishmania donovani | n.d | >30 µg/mL | [93] |
| Menispermaeae | Pentanthes longifolius | Congo | Root bark | Aqueous decoction | Leishmania infantum | n.d | 32.00 µg/mL | [95] |
|             | Tricalisia dictyophilla | Leaves | Aqueous decoction | Leishmania infantum | n.d | 32.00 µg/mL | [95] |
| Moraceae    | D. multiradiata | Nigeria | Leaves | Aqueous decoction | Leishmania infantum | n.d | 1.50 ± 0.16 µg/mL | [103] |
| Myrtaceae   | Staudia 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] |
| Oleaceae    | Eugenia carophyllata | Leaves | n.d | Methanol extract | Leishmania major | n.d | n.d | [89] |
| Oleaceae    | Olea europea (Lelimouni) | Tunisia | Floral button | n.d | Leishmania amasonensis | n.d | 6.970 ± 0.316 µg/mL | [104] |
| Oleaceae    | Olea europea (Zarrazzi) | Leaves | Ethanol extract | Leishmania amasonensis | n.d | 14.379 ± 1.400 µg/mL | [104] |
| Oleaceae    | Olea europea (Dhokkar) | Leaves | Ethanol extract | Leishmania amasonensis | n.d | 17.373 ± 1.430 µg/mL | [104] |
| Oleaceae    | Olea europea (Toffelli) | Leaves | Ethanol extract | Leishmania amasonensis | n.d | 23.707 ± 2.852 µg/mL | [104] |
| Oleaceae    | Olea europea (Chemlali Tataouine) | Leaves | Ethanol extract | Leishmania amasonensis | n.d | 23.808 ± 1.651 µg/mL | [104] |
Table 3 (continued)

| Plant family | Plant species | Country | Used part | Type of extraction | Leishmania species used | Compounds | Results of biological activity (IC50 ± SD) | References |
|--------------|---------------|---------|-----------|--------------------|------------------------|-----------|------------------------------------------|------------|
| Papilionaceae | *Abies alba* | Morocco | Fruit | n.d | *Leishmania donovani* | n.d | 15.7 µg/mL | [93] |
| | *Uvaria aethiopica* | Morocco | Leaves | n.d | *Leishmania donovani* | n.d | >64 µg/mL | [95] |
| Polysiaaceae | *Polysiphonia stricta* | Morocco | Aerial part | n.d | *Leishmania infantum* | n.d | 8.8 ± 1.06 µg/mL | [93] |
| | *Polysiphonia stricta* | Morocco | Aerial part | n.d | *Leishmania major* | n.d | 8.8 ± 1.06 µg/mL | [93] |
| | *Polysiphonia stricta* | Morocco | Aerial part | n.d | *Leishmania major* | n.d | 8.8 ± 1.06 µg/mL | [93] |
| | *Polysiphonia stricta* | Morocco | Aerial part | n.d | *Leishmania major* | n.d | 8.8 ± 1.06 µg/mL | [93] |

In Congo, a study was conducted by Musuyu Munganza 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 IC50 = 10.08 µg/mL. Kigondi et al.,[94] studied the antileishmanial activity of aqueous and methanol extracts of leaves from *Aloe nieriensis* (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 sceptra* and *Uvaria afzelii* with an IC50 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. Furthermore, the antileishmanial effect can also be 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-Toys 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

| 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 ant 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] |
| Flavonoids: Flavone, flavanone, iso flavone, glucorhamnosyl-flavone Exemple: | Specific flavonoids affect the transport mechanisms in *Leishmania*. | [57]       |
| Iridoids:          | 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]      |
| Monoterpenes: 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 glutathionylspermidin, trypanothion of cystein and glutathon 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 1000 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 mitochondrion. Indeed, some monoterpene 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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