



NATURAL PRODUCTS IN ANTILEISHMANIAL DRUG DISCOVERY: A REVIEW

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ABSTRACT

*Leishmaniasis is a disease caused by the protozoan parasites, which belong to the genus Leishmania. Some known species of Leishmania include L. tropica, L. donovani, L. mexicana, L. aethiopica, L. Infantum, L. donovani, L. mexicana, L. braziliensis, L. chagasi and L. amazonensis. Leishmaniasis is transmitted through the bite of phlebotomine sandflies. The existence of Leishmaniasis has been recorded in several countries in the Mediterranean, Central and South America, Asia, Africa, the Middle East, China, India and the Caribbean. Chemotherapy and vector control are the known available means of combating the Leishmaniasis as the development of effective vaccines are still under way. Crude solvent extracts and isolated compounds from certain plants have however, shown significant activity against leishmanial parasite. Some of the plants reported to have antileishmanial activity include *Tridax procumbens*, *Urechites andrieuxii* Muell.-Arg. (Apocynaceae), *Desmodium gangeticum*, *Pseudelephantopus spicatus*, *Himantanthus cucuuba*, among others. Of the antileishmanial plants, the greatest number belonged to the Apocynaceae. Methanol extracts of the plants were mostly found to possess antileishmanial activity. The level of activity exhibited by the crude solvent extracts or the isolated constituent(s) depended largely on the type of solvent used for the extraction and also on the plant part used. The array of plants that have demonstrated antileishmanial activity suggests that the hope to discover novel antileishmanial drugs is high.*

Keywords: Antileishmanial activity; leishmaniasis; natural products; Leishmania species, cutaneous leishmaniasis; visceral leishmaniasis.

INTRODUCTION

The Disease

Leishmaniasis is vector-borne disease caused by a protozoan endo-parasite species belonging to the genus *Leishmania* that live in the blood and tissues of the host. The disease basically affects animals but finds its way into the human population when man, flies and the animal reservoirs coexist in the same environment. A broad range of clinical manifestations involving the skin, mucous membranes and visceral organs with devastating consequences have been diagnosed among infected humans. Cutaneous leishmaniasis and visceral leishmaniasis have been reported to be the two major forms of leishmaniasis in humans. The latter happens to be the dreaded or severe form of the disease that in certain cases can record 100% mortality of infected persons when not treated. Cutaneous leishmaniasis unlike visceral leishmaniasis has been found to be less severe. The less severity of cutaneous leishmaniasis has been attributed to self-healing ulcers (Bryceson, 1996). In other texts, another form of leishmaniasis called Muco-cutaneous leishmaniasis, which causes an extensive disfiguring lesion of the nose, mouth and throat mucous membranes have also been reported (Boakye *et al.*, 2005). Other authors however, argue that muco-cutaneous leishmaniasis is a subset of cutaneous leishmaniasis (The Center for Food Security & Public Health., 2009).

Leishmaniasis has been reported to be one of the world's most neglected diseases with about twelve (12) million reported cases with an estimated infection rate of two (2) million new cases yearly (about 75% cases of cutaneous leishmaniasis and 25% cases of visceral leishmaniasis) (Luciana *et al.*, 2012). The World Health Organization (WHO) also reports that, about 350 million people are considered to be at risk of contracting leishmaniasis especially among people living in the developing countries (World Health Organisation, 2010).

Causes of Leishmaniasis

Leishmaniasis is a disease caused by the protozoan called *Leishmania species*. *Leishmania species* are obligate unicellular parasites that exist in two distinct forms. They exist as non-flagellar amastigote in humans and other hosts while in culture and gut of sandflies (vector) the flagellar or the promastigote form is visible (Chang *et al.*, 1985). Some known species of *Leishmania* include *L. tropica*, *L. donovani*, *L. mexicana*, *L. braziliensis*, *L. aethiopica*, *L. Infantum*, *L. donovani*, *L. mexicana*, *L. braziliensis*, *L. chagasi* (Arfan and Simeen, 2008). The *Leishmania* parasites are said to be motile and slender reaching about 10 to 15 μm in length with a single anterior flagellum. The electron microscopic studies of the *Leishmania* parasites reveal that the amastigotes have a double membrane supported by a layer of sub-pellicular fibrils of which one of the membranes is lost when the transformation of the amastigotes takes place. The fibrils are however retained and a short flagellum may be seen arising from the kinetosome. These parasites run a spiral course from the region of the flagellar base towards the posterior apical end (Arfan and Simeen, 2008).



Symptoms of Leishmaniasis

Clinical studies conducted on leishmaniasis have revealed diverse clinical manifestations of the disease. The diverse clinical manifestations of the disease have been attributed to the reaction between the virulence of the parasite species and the host's immune response (Boakye *et al.*, 2005). Leishmaniasis is characterized by a wide range of clinical manifestations that include ulcerative skin lesions developing at the site of the sand fly bite (localized cutaneous leishmaniasis), multiple non-ulcerative nodules (diffuse cutaneous leishmaniasis), destructive mucosal inflammation (mucosal leishmaniasis), and disseminated visceral infection (visceral leishmaniasis) (Richard *et al.*, 2007).

Existing Means of Control/Treatment

Before the introduction of oral and topical treatment alternatives for cutaneous leishmaniasis, the pentavalent antimonials have been the recommended drugs used for the treatment of both cutaneous leishmaniasis and visceral leishmaniasis (Richard *et al.*, 2007). The pentavalent antimonials were discovered over 60 years ago (Simon and Vanessa, 2006). Three new drug formulations, liposomal amphotericin B (AmBisome), miltefosine and paromomycin for the treatment of visceral leishmaniasis, have all been reported to suffer from limitations of cost, specific toxicities or parenteral administration (Simon and Vanessa, 2006). Although, new oral and topical treatment alternatives for the treatment of cutaneous leishmaniasis have been introduced within the past few years, a vaccine is yet to be developed (Richard *et al.*, 2007). The idea to develop a single drug formulation effective for the treatment of all forms of leishmaniasis have been said to be unlikely to be achieved mainly due to the intrinsic variation in drug sensitivity of the 17 *Leishmania* species known to infect humans and the different pharmacokinetic requirements imposed on the drugs to be used by the visceral and the cutaneous sites of infection (Simon and Vanessa, 2006). However, further reports have shown that the advances made so far have been significant as the concept of choice for treatment is now real (Simon and Vanessa, 2006). It has also been reported in other tests that, chemotherapy and vector control are the available means of combating leishmaniasis as the development of effective vaccines are still under way Chawla and Madhubala (2010). Some authors believe that the prevention and control of cutaneous leishmaniasis have proven to be difficult because of the complexity of cutaneous leishmaniasis epizootology and the few options available for effective vector control (Richard *et al.*, 2007). According to a recent report The Center for Food Security & Public Health. (2009) has it that, the parasites *Leishmania species* do not remain viable outside a host or *in vitro* culture but can however, be inactivated by 1% sodium hypochlorite, 2% glutaraldehyde, or formaldehyde and they are also susceptible to heat at a temperature of about 50–60°C (The Center for Food Security & Public Health., 2009).

Mode of Transmission

The transmission of *Leishmania* parasites is largely influenced by characteristics of the vector involved in the transmission. These characteristics include the tendency of the vector to take blood



from humans and/or animals as well as the capability of the ingested parasites to develop to the infective stages within the specific vector (Bryceson, 1996). Leishmaniasis is a vector-transmitted disease. The mode of transmission of *Leishmania* parasites is through the bite of *Phlebotomine* sandflies. These sand flies (vector) have been reported to be widely distributed in the tropics and other warm mainland areas and extend northwards to latitudes in the region of 50° N (Sewice, 1980). The vector (sand fly) belongs to the subfamily of *Phlebotominae* with about 600 species distributed in five genera of which species in three genera (*Phlebotomus*, *Lutzomyia* and *Sergentomyia*) are responsible for the transmission of the *Leishmania* parasites in vertebrates. However, only *Phlebotomus* and *Lutzomyia* genera transmit disease to man (Morsy, 1996).

Adult *Phlebotomine* sandflies are readily identified by their minute size (2-5 mm in length), their hairy appearance, relatively large eyes and their relatively long and stilt like legs. Sandflies have been reported to live in rodent burrows, crevices, holes in river banks, trees and houses in the Old World whereas in the New World, sandflies dwell in the tree canopies and forest litter (Kendrick, 1986). Sewice (1980) also described sandflies as small brownish hairy flies that are identified by the presence of erect narrow wings covered with hair (Sewice, 1980). Sandflies have a characteristic hopping type of flights and are said to exhibit nocturnal activity (Arfan and Simeen, 2008).

Geographical Distribution

The distribution of leishmaniasis is highly dependent on the distribution of appropriate vector species (Boakye *et al.*, 2005). With the exception of the Antarctica, *Leishmania species* (which cause leishmaniasis) have been reported on almost every continent with their presence being primarily endemic in tropical and sub-tropical regions (The Center for Food Security & Public Health., 2009). The Centre for Food Security & Public Health. (2006), reported cases of the occurrence of leishmaniasis in many countries in the Mediterranean, Central and South America, Asia, Africa, the Middle East, China, India and the Caribbean. The report went further to say that cases in the United States are rare and typically occurred in individuals returning from countries that have the disease and/or the vector (sand flies) (The Centre for Food Security & Public Health., 2006). However, sand flies capable of spreading the disease have been reported to be found in Southern Texas and leishmaniasis has been reported in 21 states and Canada foci (The Centre for Food Security & Public Health., 2006). An updated report in 2009 provided that, reported cases of leishmaniasis in Europe appear to be spreading northward from its traditional foci (The Center for Food Security & Public Health., 2009).

In Africa, leishmaniasis is endemic to countries mostly found in the North Africa, Central Africa, East Africa, and West Africa as well as countries found in the Horn of Africa (Sheik-Mohamed and Velega, 1999). Leishmaniasis has been reported in countries like Niger (Desjeux *et al.*, 1981), Mali (Lefrou, 1948), Nigeria (Dyce, 1924), Senegal (Riou and Advier, 1993), and Cameroon (Rageu, 1951). Other countries that also have reported cases include Burkina Faso, Mauritania,



Gambia and Guinea. Based on available information, cutaneous leishmaniasis is proposed to be endemic in a belt running from Mauritania, Gambia and Senegal in the west to Nigeria and Cameroon in the east. Though the cutaneous leishmaniasis belt mentioned cuts across the northern part of Ghana no report of the disease was heard in Ghana until in 1999 when some chronic ulcers were diagnosed as cutaneous leishmaniasis in the Volta Region (Boakye *et al.*, 2005). Unfortunately, in spite of the long history of the disease in West Africa, it happens to be one of the less recognized or over-looked parasitic infections in this region (Desjeux *et al.*, 1981). Richard *et al.* (2007) also suggested that, cutaneous leishmaniasis has become one of the so-called neglected diseases, with little interest by financial donors, public-health authorities, and professionals to implement activities to research, prevent, or control the disease perhaps due to the fact that it is rarely fatal (Richard *et al.*, 2007). The most devastating form of cutaneous leishmaniasis (muco-cutaneous leishmaniasis) that involves the mucous membranes of the nose, mouth and throat as well as the deadly visceral form are reported to be rare in West Africa. However, there have been two reported cases of muco-cutaneous leishmaniasis in Senegal (Strobel *et al.*, 1978) and some reported cases of the deadly visceral leishmaniasis have been recorded in Togo (de Campos *et al.*, 1979), Burkina Faso (Andre *et al.*, 1978), and the Gambia (Conteh and Desjeux, 1983; Greenwood *et al.*, 1984).

Conteh and Desjeux (1983) suggested that fevers and splenomegaly in countries neighboring the Gambia could be due to visceral leishmaniasis (Conteh and Desjeux, 1983). Sirol *et al.* (1972) are of the opinion that visceral leishmaniasis could be common in West Africa (Sirol *et al.*, 1972). Some cases of visceral leishmaniasis have been reported in South Asia, the Mediterranean, the Middle East, Latin America and parts of Asia (The Center for Food Security & Public Health., 2009).

Plants with Antileishmanial Activity

Methanol extract of *Tridax procumbens* L. (the whole plant) have been reported to exhibit significant leishmanicidal activity (Peraza-Sanchez *et al.*, 2007). *In vitro* studies on activity of *Tridax procumbens* extracts against promastigotes of *Leishmania mexicana* revealed significant activity (Zhelmy *et al.*, 2009). The methanol extract of *Tridax procumbens* showed inhibition of promastigotes growth of *Leishmania mexicana* with a 50% inhibitory concentration (IC₅₀) of 3 µg/ml while oxylipin (3*S*)-16,17-didehydrofalcarninol, an isolated compound from *Tridax procumbens* exhibited the highest inhibition at IC₅₀ of 0.478 µg/ml. Toxicity test conducted on the extract and oxylipin (3*S*)-16,17-didehydrofalcarninol however, revealed insignificant or no effect on mammalian cells. Using the standard drugs amphotericin B and pentamidine as references, pentamidine and oxylipin (3*S*)-16, 17-didehydrofalcarninol exhibited similar antileishmanial activity (Zhelmy *et al.*, 2009). The use of *Urechites andrieuxii* Muell.-Arg. (Apocynaceae) in traditional medicine for the treatment of cutaneous leishmaniasis in the Yucatan Peninsula has been reported (Pulido and Serralta, 1993; Argueta, 1994). It has been said that while Mayan traditional healers recommend washing the lesion with a root infusion of *Urechites andrieuxii*, and then applying the



powdered dry root over the area, other traditional doctors recommend the direct application on the lesion with dried, ground leaves of *Urechites andrieuxii* (Jiu, 1966). Crude methanol extracts of from the leaves and roots of *Urechites andrieuxii* Muell.-Arg. growing in four different natural populations have also been reported to exhibit antileishmanial activity on three species of *Leishmanial* parasites namely, *L. braziliensis*, *L. amazonensis* and *L. donovani* with extracts from the roots showing strongest activity (Manuel *et al.*, 2003). The first population was collected from an area characterized by high humidity and flooded soils, second and third populations from an area with warm humid climate and sporadically soils respectively while the fourth population was obtained from an area characterized by a dry climate with well drained soils and low humidity. In this study, crude methanol extracts from the roots of *Urechites andrieuxii* Muell.-Arg. obtained from the four different natural populations in the Yucatan Peninsula all showed antileishmanial activity against the named *Leishmanial species* but at different levels at a concentration of 200 µg/mL with *Urechites andrieuxii* Muell.-Arg collected from the first population showing a strongest antileishmanial activity against the three *Leishmania species*. *Urechites andrieuxii* Muell.-Arg collected from the second showed a weak antileishmanial activity while those (*Urechites andrieuxii* Muell.-Arg) obtained from the third and fourth populations exhibited weakest antileishmanial activity. This was revealed in an *in vitro* activity of methanol extracts of the four populations of *Urechites andrieuxii* against strains of promastigotes forms of *L. braziliensis*, *L. amazonensis* and *L. Donovani* (Manuel *et al.*, 2003). The difference in the activity among the different populations suggests that biological activities of plants are influenced by environmental factors to some extent. This falls in line with earlier report that, the production of plant bioactive secondary metabolites is influenced by environmental, ontogenetic and genetic factors (Vanhalen *et al.*, 1991). The most active methanol extract of the roots (from the first population) has been reported to be cytotoxic to ovary carcinoma cells, human epidermoid carcinoma cells, cervix carcinoma cell and colon carcinoma cells while methanolic extracts from the leaves exhibited cytotoxicity in cervix carcinoma cells only (Manuel *et al.*, 2003).

Manuel *et al.* (2003) however suggested that, toxic activity observed for the most active extract against *Leishmania* promastigotes, might in fact be due to the presence of metabolites with cytotoxic, but not necessarily antileishmanial activity (Manuel *et al.*, 2003). Manuel *et al.* (2003) further suggested the presence of biologically active natural products with selective toxic activity against *Leishmania* parasites in the methanol extract of the leaves *Urechites andrieuxii* (Manuel *et al.*, 2003). The root extract of *Urechites andrieuxii* has been reported in other literature to have depressant, antiatherogenic and anti-inflammatory activities (Jiu, 1966). Extracts from the plant *Urechites andrieuxii* has further been reported in other texts to have toxic activity against *Leishmania mexicana* (Viscencio *et al.*, 1995). Another plant that has been reported to have antileishmanial activity is *Desmodium gangeticum* (Iwu *et al.*, 1992). It has been reported in the work carried out by Nasib *et al.* (2005) to determine the efficacy of *Desmodium gangeticum* extract and its fractions (hexane, *n*-butanol and aqueous) against experimental visceral leishmaniasis, showed that the *n*-butanol fraction had moderate antileishmanial activity when tested against



established infection of *Leishmania donovani* in hamsters whiles the crude ethanolic extract as well as hexane and aqueous fractions of the same plant showed insignificant inhibition of parasite multiplication. Also, the *n*-butanol fraction of *Desmodium gangeticum* has been reported to have the highest efficacy of *Leishmania donovani* challenge followed by the crude methanolic extract in a chemoprophylactic efficacy study when administered at a dosage of 250 mg/kg to hamsters 7 days prior to the *Leishmania donovani* infection and also on the 7th day after infection as booster dose. The *n*-butanol fraction have further been reported to show significant ($P < 0.001$) non-specific resistance to peritoneal macrophages against *Leishmania* infection (promastigote form) whiles the methanol extract, hexane and aqueous fractions showed no activity. Other results have also revealed the *n*-butanol fraction of *Desmodium gangeticum* to be the most efficient over the other fractions against established infection of *Leishmania donovani* in a chemotherapeutic efficacy study when administered orally with five doses of 100 mg/kg (Nasib *et al.*, 2005).

Pseudelephantopus spicatus is another plant that has been reported to possess antileishmanial activity (Odonne *et al.*, 2011). Isolated compounds 8,13-diacetyl-piptocarphol, 8-acetyl-13-*O*-ethylpiptocarphol and ursolicobatained from *Pseudelephantopus spicatus* in an *in vitro* study exhibited activity against *Leishmania amazonensis* axenic amastigotes with the compounds 8,13-diacetyl-piptocarphol, and 8-acetyl-13-*O*-ethylpiptocarphol exhibiting significant activity than Amphotericin B which was used as the positive control (Odonne *et al.*, 2011). Cytotoxicity studies conducted on the most active compounds, 8,13-diacetyl-piptocarphol and 8-acetyl-13-*O*-ethylpiptocarphol showed that these compounds are not cytotoxic when tested on HeLa, L929 and B16F10 cell lines at a concentration of 50 μ M (Buskuhl *et al.*, 2010).

The bark of *Himatanthus succuba* has been reported to show significant direct activity against the intracellular form of *Leishmania amazonensis* axenic amastigotes (Villegas *et al.*, 1997). Two known spiro-lactone iridoids; plumericin and its isomer isoplumericin obtained from bio-guided isolation of the stem bark's ethanol extract of *Himatanthus succuba* have been reported to show strong activity against *Leishmania amazonensis* axenic amastigotes at IC₅₀ of 5 μ g/ml in amastigotes. These two compounds have further been reported to exhibit less toxicity on mice peritoneal macrophages and on tumoral cells than in their activity on *Leishmania* amastigotes in cytotoxicity evaluation. However, in the case of the tumoral assays isoplumericin is more toxic than plumericin. *In vitro* study of plumericin and its isomer isoplumericin on infected macrophages, isoplumericin exhibited toxicity against infected macrophages which did not allow an evaluation of its activity against intracellular amastigotes whiles plumericin caused a reduction of the macrophage infection similar to Amphotericin B, at IC₅₀ of 0.9 μ M for plumericin and 1 μ M for Amphotericin B (Castillo *et al.*, 2007). Crude methanol extract of the plants *Azadirachta indica*, *Maytenus senegalensis*, *Eucalyptus globulus*, *Pseudocedrelakotschy* and *Balanites aegyptiaca* have also been reported to possess antileishmanial activity against *Leishmania major* promastigotes (Ahmed *et al.*, 1998). *Azadirachta indica*, *Maytenus senegalensis* and *Eucalyptus globulus* among the plants showed the highest antileishmanial activity against *Leishmania major* promastigotes at a



concentration <0.5 mg/mL while *Pseudocedrelakotschy* and *Balanitesaegyptiaca* exhibited moderate activity (Ahmed *et al.*, 1998). Report further has it that, liquid–liquid partitioning of the methanol extracts showed that fractions of *M. senegalensis* in dichloromethane and ethyl acetate had the highest antileishmanial activity at 5 mg/mL. Study conducted on the effect of crude extracts on the proliferation of lymphocytes with the addition of phytohaemagglutinin stimulator showed inhibition of lymphocyte proliferation by *A. indica* and *P. kotschy* extracts at high concentrations (<50 mg/mL). *M. senegalensis* on the other hand, showed no significant toxic effect. Preliminary phytochemical evaluation of the dichloromethane fraction of *M. senegalensis* revealed the presence of terpenoids and traces of phenolic principles but no alkaloid, tannins or flavonoids (Ahmed *et al.*, 1998). Perhaps the antileishmanial activity of this could be as a result of the presence of these phytochemicals (Ahmed *et al.*, 1998).

Peschiera australis (Muñ. Arg.) Miers, is another known plant species with antileishmanial activity (Delorenzi *et al.*, 2001). The chloroform fraction and an isolated indole alkaloid identified as Coronaridine obtained from crude ethanolic stem extract of *Peschiera australis* have been reported to show significant activity against both the promastigote and amastigote forms *Leishmania amazonensis*. Hexane and aqueous fractions however, showed insignificant activity towards both forms of the parasite. Transmission electron microscopic assessment of promastigotes and amastigotes treated with chloroform fraction or coronaridine revealed marked alterations in their mitochondria (Delorenzi *et al.*, 2001). *In vitro* study on the antitrypanosomal and antileishmanial activity of plants used in Benin in traditional medicine and bio-guided fractionation of the most active extract revealed that the dichloromethane extracts of aerial parts of *Acanthospermum hispidum*, DC. (Asteraceae) has preferable antileishmanial activity against *Leishmania mexicana* to the methanolic and aqueous extracts. Further results have also shown that, the dichloromethane extracts of the leaves and twigs of *Keetialeucantha* (K. Krause) Bridson (syn. *Plectronialeucantha* Krause) have also exhibited antileishmanial activity (Joanne *et al.*, 2011). Methanolic extract from *Lantana ukambensis* has also showed significant activity against promastigotes form of *Leishmania donovani* with an inhibitory concentration (IC₅₀) of 6.9 µg/mL in an *in vitro* antileishmanial evaluation (Sawadogo *et al.*, 2012). Other study has showed that *Lantana ukambensis* contained a high concentration of polyphenols, triterpenes, and saponins (Sawadogo *et al.*, 2011). Perhaps the antileishmanial effect of this plant could be attributed to one of these groups of compounds (Sawadogo *et al.*, 2012). The methanol and chloroform extracts from roots of ‘Indian Valerian’ *Valeriana wallichii* have shown activity against *Leishmania donovani* promastigotes and both promastigotes and amastigotes of *Leishmania major* (Ghosh *et al.*, 2011).

Isolated Compounds from Plants with Antileishmanial Activity

Oxylipin (3*S*)-16, 17-didehydrofalcarinol isolated from *Tridax procumbens* has been reported by Zhelmy *et al.* (2009) to have significant activity against *Leishmania Mexicana*. The structure of Oxylipin (3*S*)-16, 17-didehydrofalcarinol was identified by infrared spectroscopy (Nicolet, Protegé



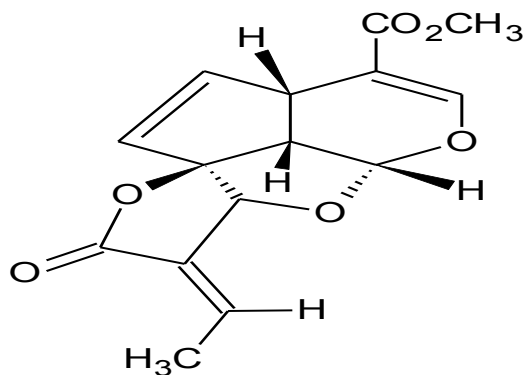
460), nuclear magnetic resonance experiments [^1H and ^{13}C NMR, BrukerAvance 400 (400 and 100MHz, respectively)], and mass spectrometry (Agilent Technologies gas chromatographer 6890N coupled to a mass detector 5975B) (Zhelmy *et al.*, 2009).

X-ray crystallography has also confirmed the presence of plumericin and isoplumericin from bio-guided fractionation of the stem bark of *Himatanthussucuuba*. Both compounds in *in vitro* showed marked activity against *Leishmania amazonensis* axenic amastigotes (Castillo *et al.*, 2007). In other works, the antileishmanial activity exhibited by *Pseudelephantopuspicatus* has been attributed to the presence of 8,13-diacetyl-piptocarphol and the 8-acetyl-13-O-ethyl-piptocarphol and ursolic acid (Odonne *et al.*, 2011). Two isolated compounds identified as oleanolic acid and ursolic acid obtained from bio-guided fractionation of the twigs extract of *Keetialeucantha* (K. Krause) Bridson (syn. *Electronialeucantha* Krause) have been reported to have antileishmanial activity (Joanne *et al.*, 2011). According to other results, evaluation of the antileishmanial activity of ursolic acid showed activity against promastigotes of *Leishmania amazonensis* at IC_{50} of 43.8 $\mu\text{g}/\text{mL}$ and 5 $\mu\text{g}/\text{mL}$, depending on the test (Torres-Santos *et al.*, 2004; Gnoatto *et al.*, 2008) and also against promastigotes of *Leishmania donovani* at IC_{50} of 3.5 $\mu\text{g}/\text{mL}$ (Moulisha *et al.*, 2010). Oleanolic acid has also exhibited antileishmanial activity against promastigotes of *Leishmania amazonensis* at $\text{IC}_{50} = 10 \mu\text{g}/\text{mL}$ (Torres-Santos *et al.*, 2004).

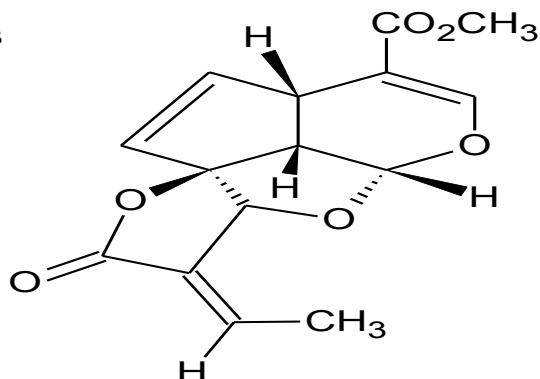
Naphthoquinones and naphthofuranes have been identified as responsible for the antileishmanial activities from *Chondodendrontomentosum* bark and *Cedrelaodorata* (González *et al.*, 2011). Citral has been reported to be the main active component responsible for the antileishmanial activity of the essential oil of *Cymbopogon citratus* on *Leishmania amazonensis* (Santin *et al.*, 2009). Again 16 α -Hydroxycyclohexa-3,13 (14)*Z*-dien-15,16-olide an isolated compound from *Polyalthialongifolia* has been found to be orally active against *leishmaniadovani* parasites and non-cytotoxic (Pragya *et al.*, 2010). Another bioactive compound obtained through the chromatographic fractionation of the CH_2Cl_2 phase from methanol extract from the leaves of *Pentacaliadesiderabilis* (Vell.) Cuatrec. (Asteraceae) and identified as jacaranone [methyl (1-hydroxy-4-oxo-2,5cyclohexandienyl) acetate] have also showed significant activity against promastigotes of *Leishmania (L.) chagasi*, *Leishmania (V.) braziliensis*, and *Leishmania amazonensis* (Thiago *et al.*, 2012). Also, polygodial (a derivative of a sesquiterpene) isolated from stem barks of *Drimys brasiliensis* Miers (Winteraceae) has been reported to show leishmanicidal effect against the promastigotes of *Leishmania braziliensis*, *Leishmania amazonensis*, and *Leishmania chagasi* (Daniela *et al.*, 2011). Other results have shown that isolated constituents from *Tridax precumbens* L (an antileishmanial plant) are saturated and unsaturated fatty acids (Gadre and Gabhe, 1988), flavonoids (Yadava and Saurabh, 1998; Ali *et al.*, 2001; Akbar *et al.*, 2002), lipids (Verma and Gupta, 1988), and polysaccharides (Raju and Davidson, 1994). Perhaps the antileishmanial activity exhibited by this plant is as a result of the presence of some and/or combination of these compounds.



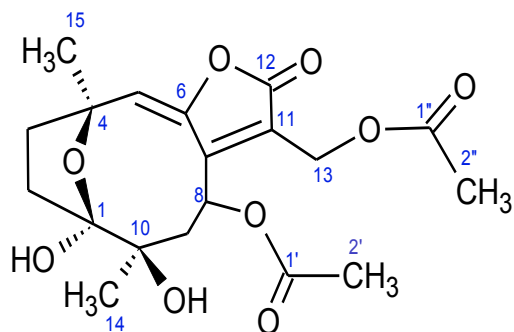
Structures of Some Isolated Compounds with Antileishmanial Property



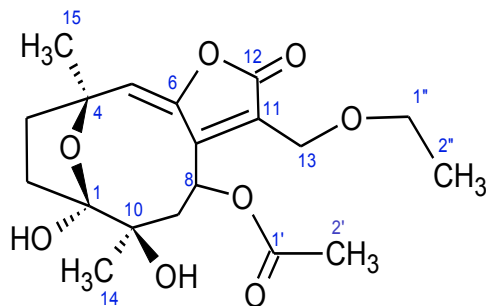
isoplumericin



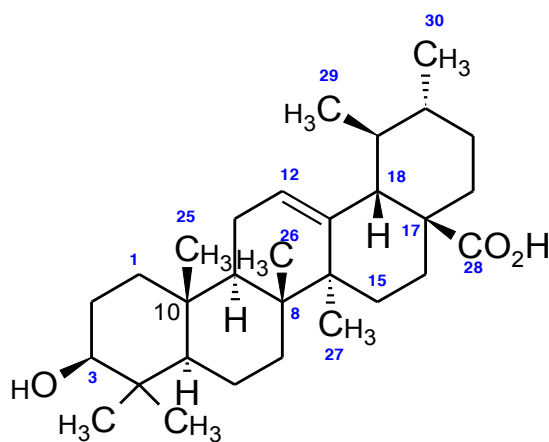
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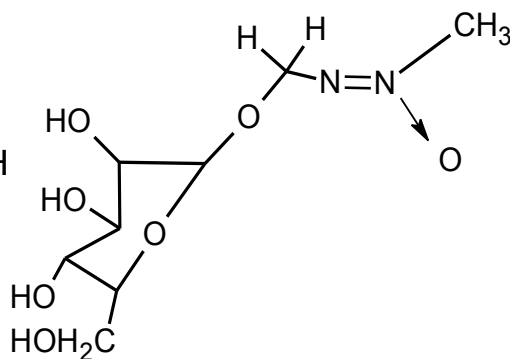
(+)-8,13-Diacetyl-piptocarhol



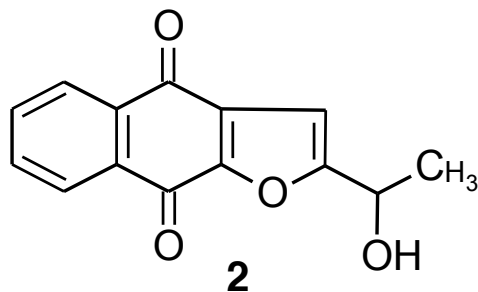
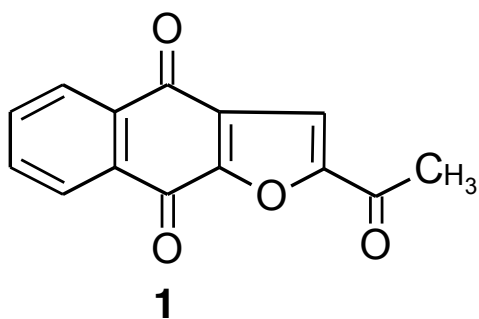
(+)-8-Acetyl-13-O-ethyl-piptocarphol



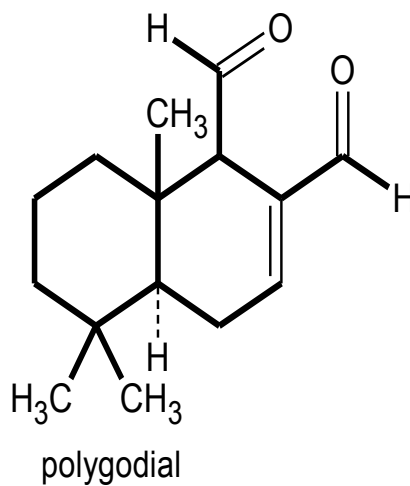
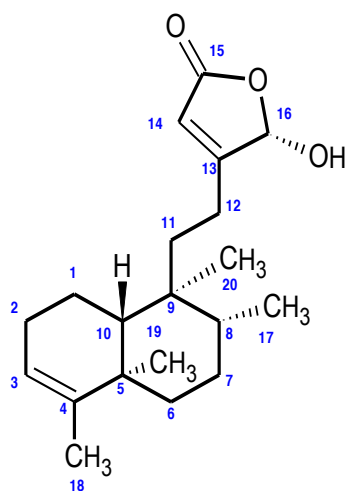
Ursolic acid



Cycasin

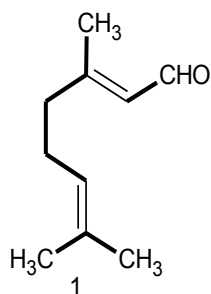


Napthoquinones (1 and 2)

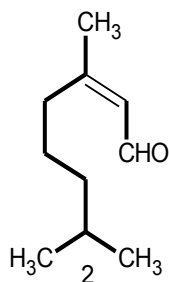


16a-hydroxycycleroda-3,13 (14)Z-dien-15,16-olide

polygodial

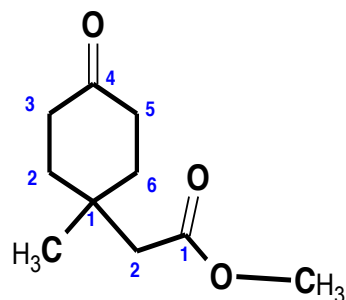


Geranial (citral a)



Neral (citral b)

stereoisomers of citral (1 and 2)



methyl (1-methyl-4-oxocyclohexyl)acetate

(jaracanone)

Table-1. List of plants with antileishmanial property.

Plants with antileishmanial activity.	Plant Family	Part(s) used	Solvent used	References
<i>Tridax procumbens</i>	Asteraceae	Whole plant	Methanol	Sánchez <i>et al.</i> , 2007; Zelmyet <i>et al.</i> , 2009).
<i>Urechites andrieuxii</i>	Apocynaceae	Leaves and roots	Methanol	Pulido and Serralta, 1993; Argüeta <i>et al.</i> , 1994; Manuel <i>et al.</i> , 2003
<i>Desmodium gangeticum</i>	Fabaceae	Whole plant	<i>n</i> -butanol	Iwuet <i>et al.</i> , 1992; Nasibet <i>et al.</i> , 2005
<i>Pseudelephantopus spicatus</i>	Asteraceae	Leaves, aerial parts	Ethanol	Odonneet <i>et al.</i> , 2011;
<i>Himatanthus succubus</i>	Apocynaceae	Stem bark,	Ethanol	Villegas <i>et al.</i> , 1997; Castillo <i>et al.</i> , 2007
<i>Azadirchta indica</i>	Meliaceae	Stem bark	Methanol	Ahmed <i>et al.</i> , 1998;
<i>Maytenus senegalensis</i>	Celasteraceae	Stem bark	Methanol	Ahmed <i>et al.</i> , 1998;
<i>Pseudocedrela kotschyana</i>	Meliaceae	Stem bark	Methanol	Ahmed <i>et al.</i> , 1998;
<i>Balanites aegyptiaca</i>	Balanitaceae	Seeds, stem bark	Methanol	Ahmed <i>et al.</i> , 1998;
<i>Eucalyptus globulus</i>	Myrtaceae	Seeds	Methanol	Ahmed <i>et al.</i> , 1998;
<i>Acanthospermum hispidum</i>	Asteraceae	Aerial parts	Dichloromethane	Joanne <i>et al.</i> , 2011
<i>Cymbopogon citratus</i>	Poaceae	Leaves	Fresh leaves were steam distilled using Clevenger's apparatus	Santinet <i>et al.</i> , 2001
<i>Peschiera australis</i>	Apocynaceae	Stem	Ethanol	Delorenziet <i>et al.</i> , 2000
<i>Lantana camara</i>	Verbenaceae	Stem, leaves	Methanol	Sawadogo <i>et al.</i> , 2012
<i>Chondodendron tomentosum</i>	Menispermaceae	Bark and leaves	Ethanol	González-Coloma <i>et al.</i> , 2011
<i>Cedrela odorata</i> L.	Meliaceae	Bark	Chloroform, hexane	González-Coloma <i>et al.</i> , 2011
<i>Pentacaliadesiderabilis</i>	Asteraceae	Leaves	Methanol	Thiago <i>et al.</i> , 2012
<i>Drimys brasiliensis</i> Miers	Winteraceae	Stem barks	Hexane	Daniela <i>et al.</i> , 2011).
<i>Polyalthia longifolia</i>	Annonaceae,	Leaves	Ethanol	Pragya <i>et al.</i> , 2010
<i>Valeriana wallichii</i>	Valerianaceae	Roots	Chloroform, methanol	Ghosh <i>et al.</i> , 2011

CONCLUSION

The antileishmanial activity of the plants reported in this piece of work suggests that these plants can be used to treat leishmaniasis. It should however be emphasized that, reported results in this work have shown that, the level of activity of a particular plant depends largely on the solvent used for extraction and to some extent the part of the plant used. Isolation and characterization of extracts from some plants reported in this work to have antileishmanial activity have also shown the presence of one or more natural product(s). Perhaps the antileishmanial activity of these plants could be due presence of the natural product(s).

Isolated compounds from *Pseudelephantopuspicatus* (Odone *et al.*, 2011) and *Keetialeucantha* (K. Krause) Bridson (syn. *Electronialeucantha* Krause) (Joanne *et al.*, 2011) have both shown the presence of ursolic acid. Perhaps, that is the reason why both exhibit antileishmanial activity. Furthermore, the report that the antileishmanial activity of *Lantana ukambensis* could be due to the presence of polyphenols, triterpenes, and saponins (Sawadogo *et al.*, 2012), is in line with other results that diterpenoids and triterpenoids (Tan *et al.*, 2002), saponins (Ridoux *et al.*, 2001), and polyphenols (Kolodziej, 2001) are phytochemical compounds with antileishmanial effect.

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