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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), Desmodiumgangeticum, Pseudelephantopusspicatus, Himatanthussucuuba,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 spices, 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 Organistion, 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 cutaneousleishmaniasis and visceral leishmaniasis (Richard *et al.*, 2007).Thepentavalent antimonials werediscovered 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 reportedto 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 epizoology 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 influence 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^{o} 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, sandfliesdwell 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 Velema, 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 the 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 casesof 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 onactivity of *Tridax procumbens* extracts against promastigotes of *Leishmaniamexicana* 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 (IC_{50}) of 3µg/ml whiles oxylipin (3*S*)-16,17-didehydrofalcarinol, an isolated compound from *Tridax procumbens* exhibited the highest inhibition at IC_{50} of 0.478 µg/ml. Toxicity test conducted on the extract and oxylipin(3*S*)-16,17-didehydrofalcarinol 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-didehydrofalcarinol 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 thelesion 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 humidityand flooded soils, second and third populations from an area with warm humid climate and sporadically soils respectively whiles 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 whiles those (*Urechites andrieuxii* Muell.-Arg) obtained from the third and fourth populations exhibited weakest antileishmanial activity. This was revealed in an *in vitro* activityof methanol extracts of the four populations of *Urechitesandrieuxii* 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, theproduction of plant bioactive secondarymetabolites 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 andcolon carcinoma cells whiles 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 *Urechitesandrieuxii* (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 *Desmodiumgangeticum* (Iwu et al., 1992). It has been reported in the work carried out by Nasib *et al*. (2005) to determine theefficacy of *Desmodiumgangeticum*extract and its fractions (hexane, *n*-butanol and aqueous) againstexperimental visceral leishmaniasis, showed that then-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 *Desmodiumgangeticum* has been reported to have the highest efficacy of *Leishmaniadonovani* 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 *Desmodiumgangeticum*to be the most efficient over the other fractionsagainst established infection of *Leishmania donovani* in a chemotherapeutic efficacy study when administered orally with five doses of 100 mg/kg (Nasib *et al.*, 2005).

Pseudelephantopusspicatus is another plant thathas been reported to possess antileishmanial activity (Odonne *et al.*, 2011). Isolated compounds 8,13-diacetyl-piptocarphol, 8-acetyl-13-*O*-ethylpiptocarpholand ursolicobatained from *Pseudelephantopusspicatus*in an *in vitro* study exhibited activity against *Leishmaniaamazonensis*axenic amastigotes with the compounds8,13-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 50µM (Buskuhl *et al.*, 2010).

The bark of *Himatanthussucuuba* has been reported toshow significant direct activity against the intracellular form of *Leishmania amazonensis* axenic amastigotes (Villegas *et al.*, 1997). Two known spirolactoneiridoids; plumericin and its isomer isoplumericin obtained from bio-guided isolation of the stem bark's ethanol extract of *Himatanthussucuuba* have been reported to show strong activity against *Leishmania amazonensis* axenic amastigotes at $IC_{50}$of 5µg/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 assaysisoplumericin 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 IC_{50} of 0.9µM for plumericin and 1 µM for Amphotericin B (Castillo *et al.*, 2007). Crude methanol extract of the plants *Azadirachtaindica, Maytenussenegalensis,Eucalyptus globulus, Pseudocedrelakotscifye*and *Balanitesaegyptiaca*have also been reported to possess antileishmanial activity against *Leishmania major* promastigotes (Ahmed *et al.*, 1998).*Azadirchtaindica, Maytenussenegalensis*and *Eucalyptus globulus* among the plants showed the highest antileishmanial activity against *Leishmania major* promastigotesat a concentration <0.5 mg/mL while*Pseudocedrelakotscifye*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 phytohaemagglutininstimulator showed

inhibition of lymphocyte proliferation by*A. indica* and *P. kotscifye* 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).

Peschieraaustralis(Mu¨ll. 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 *Peschieraaustralis* have been reported to show significant activityagainst both thepromastigote 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 *Acanthospermumhispidum*, DC. (Asteraceae) has preferable antileishmanial activity against *Leishmanial 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 promastigotesformof *Leishmania donovani* with an inhibitory concentration (IC_{50}) 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 methanoland chloroform extracts fromroots of 'Indian Valerian' *Valerianawallichii*have shown activity against *Leishmaniadonovanipromastigotes* and both *promastigotes and amastigotes of Leishmaniamajor* (Ghosh et al., 2011).

Isolated Compounds from Plants with Antileishmanial Activity

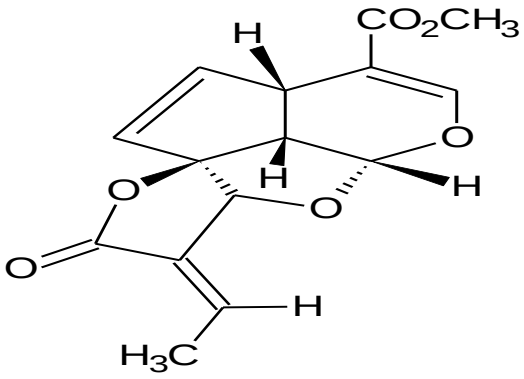
Oxylipin (3*S*)-16, 17-didehydrofalcarinol isolated from *Tridax procumbens* has been reported by Zhelmy *et al.* (2009) to have significant activity against *Leishmanial Mexicana*. The structure of Oxylipin (3*S*)-16, 17-didehydrofalcarinol was identified by infrared spectroscopy (Nicolet,Protegé 460), nuclear magnetic resonance experiments [1H and 13C 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

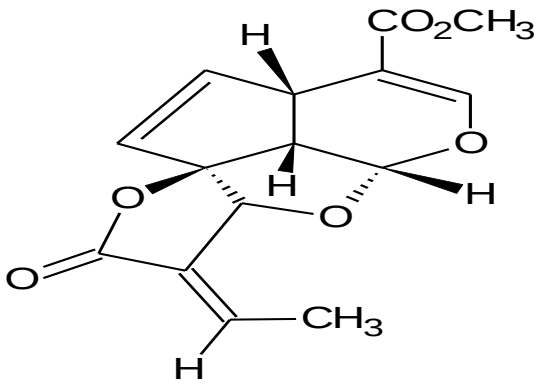
marked activity against *Leishmania amazonensis* axenic amastigotes (Castillo *et al.*, 2007).In other works, the antileishmanial activity exhibited by *Pseudelephantopusspicatus* has been attributed to the presence of 8,13-diacetyl-piptocarphol and the 8-acetyl-13-O-ethyl-piptocarphol and ursolic acid (Odonne *et al.*, 2011).Two isolated compoundsidentified as oleanolic acid and ursolic acid obtained from bio-guided fractionation of the twigs extract of *Keetialeucantha* (K. Krause) Bridson (syn. Plectronialeucantha 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 43.8µg/mL and 5 µg/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 µg/mL (Moulisha *et al.*, 2010). Oleanolic acid has also exhibited antileishmanial activity against promastigotes of *Leishmania amazonensis*at IC_{50} = 10 µg/mL (Torres-Santos *et al.*, 2004).

Naphtoquinones and naphtofuranes have been identified as responsible for the antileishmanial activities from *Chondodendrontomentosum*bark and *Cedrelaodorata* (González *et al.*, 2011). Citral has been reported to the he main active component responsible for the antileishmanial activity of the essential oil of *Cymbopogoncitratus* on Leishmania amazonensis (Santin *et al.*, 2009). Again 16a-Hydroxycleroda-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 *Drimysbrasiliensis*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.

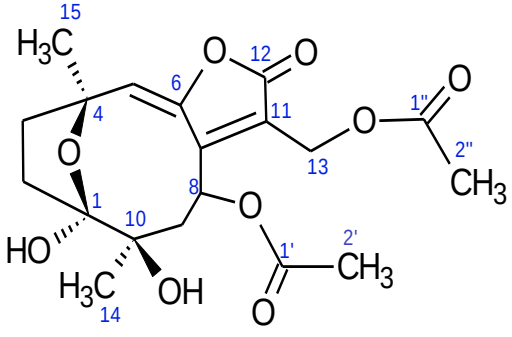
Structures of Some Isolated Compounds with Antileishmanial Property



isoplumericin



plumericin



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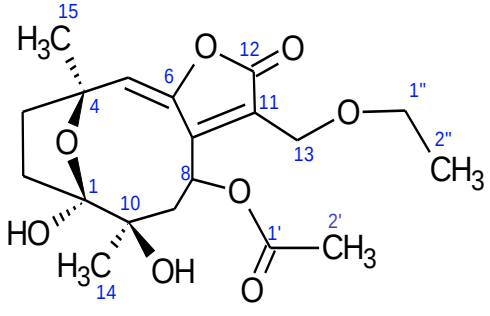

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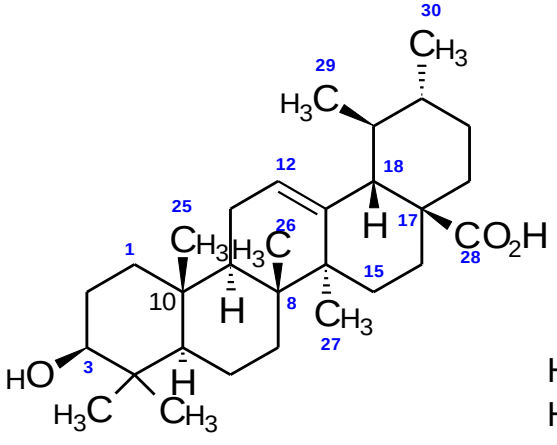
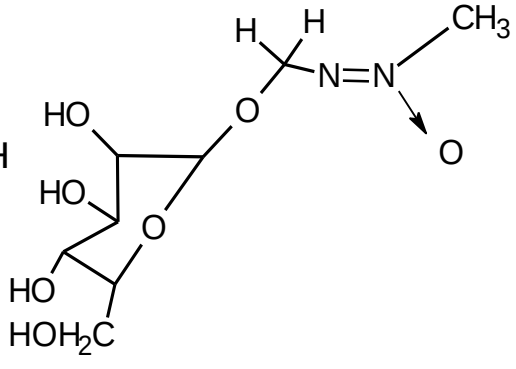
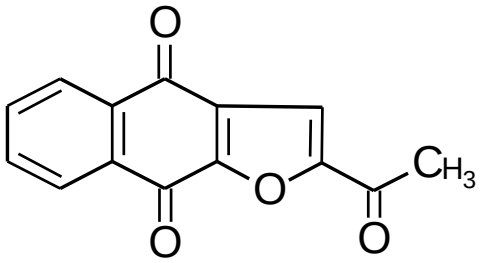


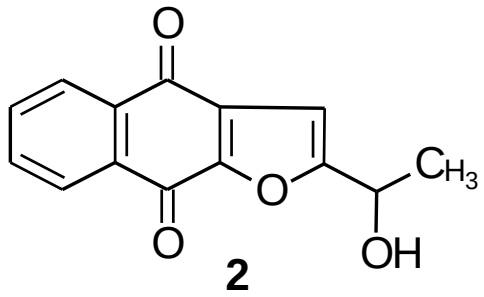
Ursolic acid



Cycasin

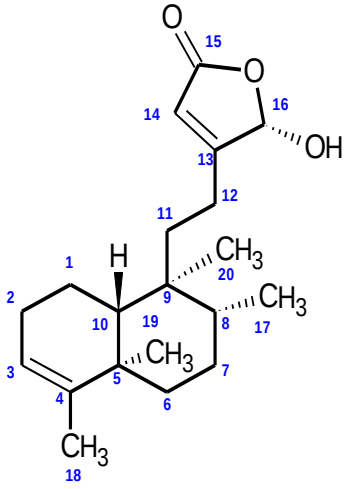


1

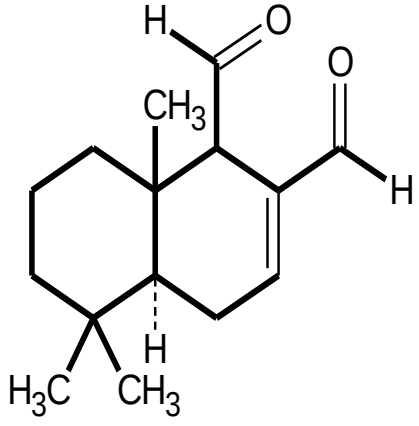


2

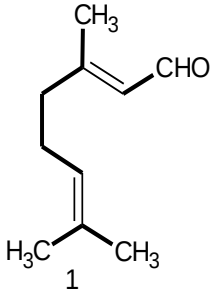
Napthoquinones (**1** and **2**)



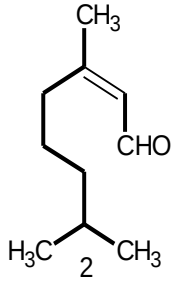
16a-hydroxycleroda-3,13 (14)Z-dien-15,16- olide



polygodial

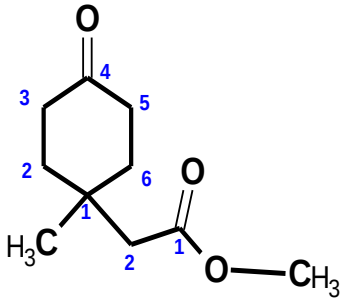


Geranial (citral a)



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
Tridax procumbens	Asteraceae	Whole plant	Methanol	Sánchez *et al*., 2007; Zelmy*et al*., 2009).
Urechites andrieuxii	Apocynaceae	Leaves and roots	Methanol	Pulido and Serralta, 1993; Argüeta*et al*., 1994; Manuel *et al*., 2003
Desmodiumgangeticum	Fabaceae	Whole plant	*n*-butanol	Iwu*et al*., 1992; Nasib*et al*., 2005
Pseudelephantopus spicatus	Asteraceae	Leaves, aerial parts	Ethanol	Odonne*et al*., 2011;
Himatanthussucuuba	Apocynaceae	Stem bark,	Ethanol	Villegas *et al*., 1997; Castillo *et al*., 2007
Azadirchtaindica	Meliaceae	Stem bark	Methanol	Ahmed *et al*., 1998;
Maytenussenegalensis	Celasteraceae	Stem bark	Methanol	Ahmed et al., 1998;
Pseudocedrelakotscifye	Meliaceae	Stem bark	Methanol	Ahmed *et al*., 1998;
Balanitesaegyptiaca	Balanitaceae	Seeds, stem bark	Methanol	Ahmed *et al*., 1998;
Eucalyptus globulus	Myrtaceae	Seeds	Methanol	Ahmed *et al*., 1998;
Acanthospermumhispidum	Asteraceae	Aerial parts	Dichlorometha ne	Joanne *et al*., 2011
Cymbopogoncitratus	Poaceae	Leaves	Fresh leaves were steam distilled using Clevenger's apparatus	Santin*et al*., 2001
Peschieraaustralis	Apocynaceae	Stem	Ethanol	Delorenzi*et al*., 2000
Lantana ukambensis	Verbenaceae	Stem, leaves	Methanol	Sawadogo et al., 2012
Chondodendrontomentosum	Menispermacea e	Bark and leaves	Ethanol	González-Coloma et al., 2011
Cedrelaodorata L	Meliaceae	Bark	Chloroform, hexane	González-Coloma et al., 2011
Pentacaliadesiderabilis	Asteraceae	Leaves	Methanol	Thiago et al., 2012
Drimysbrasiliensis Miers	Winteraceae	Stem barks	Hexane	Daniela et al., 2011).
Polyalthialongifolia	Annonaceae,	Leaves	Ethanol	Pragya et al., 2010
Valerianawallichii	Valerianaceae	Roots	Chloroform, methanol	Ghosh et al., 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 *Pseudelephantopusspicatus* (Odonne *et al.*, 2011) and *Keetialeucantha* (K. Krause) Bridson (syn. Plectronialeucantha 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 diterpenoidsand triterpenoids (Tan *et al.*, 2002), saponins (Ridoux *et al.*, 2001), and polyphenols (Kolodziej, 2001) are phytochemical compounds with antileishmanial effect.

REFERENCES

Ahmed, E., M. Adil, M. Gwiria, G. Thor, K. Arsalam and A. Sami, 1998. The potential antileishmanial activity of some sudanese medicinal plants. Phytotherapy Research, 12: 576–579.

Akbar, E., A. Malik, N. Afza and S. Hai, 2002. Flavone glycosides and bergenin derivatives from tridax procumbens. Heterocycles, 57: 733–739.

Ali, M., E. Ravinder and R. Ramachandram, 2001. A new flavonoid from the aerial parts of tridax procumbens. Fitoterapia, 72: 313–315.

Andre, L., J. Sirol, C. Le Vourch, J. Lebegorre and D. Cochevelou, 1978. Sudanese kala-azar in west africa. Med Trop (Mars), 38(4): 435-442.

Arfan, U. and B. Simeen, 2008. Cutaneous eishmaniasis: An overview of parasitology and host-parasite-vector inter relationship. Journal of Pakistan Association of Dermatologists, 18(42-48).

Argueta, V., 1994. Atlas de las plantas de la medicina tradicional mexicana. Instituto Nacional Indigenista, Mexico City, 2: 784.

Boakye, D., M. Wilson and M. Kweku, 2005. A review of leishmaniasis in west africa. Ghana Medical Journal 39(3): 94-97.

Bryceson, A., 1996. Leishmaniasis.

Buskuhl, H., F. de Oliveira, L. Blind, R. de Freitas, A. Barison, F. Capompas, Y. Corilo, M. Eberlin, G. Caramori and M. Biavatti, 2010. Sesquiterpene lactones from vernonia scorpioides and their in vitro cytotoxicity. Phytochemistry 71: 1539–1544.

Castillo, D., J. Arevalo, F. Herrera, C. Ruiz, R. Rojas, E. Rengifo, A. Vaisberg, J. Lock O. Lemesre, H. Gornitzka and M. Sauvain, 2007. Spirolactone iridoids might be responsible for the antileishmanial activity of a peruvian traditional remedy made

with himatanthus sucuuba (apocynaceae). Journal of Ethnopharmacology, 112: 410–414.

Chang, K., D. Fong and R. Bray, 1985. Biology of leishmania and leishmaniasis. In: Chang kp, bray rs, eds. Leishmaniasis: Human parasitic diseases. Philadelphia: Elsevier, 1: 1-30.

Chawla, B. and R. Madhubala, 2010. Drug targets in leishmania. J Parasit Dis, 34(1): 1-13.

Conteh, S. and P. Desjeux, 1983. Leishmaniasis in the gambia: A case of cutaneous leishmaniasis and a case of visceral leishmaniasis. Trans Roy Soc Trop med Hyg 77: 298-302.

Daniela, S., G. Andre, Q. Juliana, N. Noemi, A.P. Oriana, P. Murilo and H.C. Joao, 2011. Anti-leishmanial and anti-trypanosomal potentialof polygodial isolated from stem barks of drimys brasiliensismiers (winteraceae). Parasitology Research 109: 231–236.

de Campos, E., A. Amedome and K. Kpodzro, 1979. Kala-azar in togo, west africa. Presentation of a clinical case. Rev Inst Med Trop Sao Paulo, 21: 29-32.

Delorenzi, J.C., C.R. M. Attias, M. Gattass, C. Andrade, A.C. Rezende, A.T. Pinto, D.C. Henriques, E.M.B. Bou-Habib and Saraiva, 2001. Antileishmanial activity of indol alkaloid from peschiera australis antimicrob. Agents Chemother., Bethesda, 45: 1349-1354.

Desjeux, P., L. Waroquy and J. Dedet, 1981. La leishmaniose cutaneé humaine en afrique de l'ouest. Bull Soc Path Exot, 4: 414-425.

Dyce, S., 1924. Oriental sore in nigeria. Trans Roy Soc Trop Med Hyg 18: 336.

Gadre, A. and S. Gabhe, 1988. Saturated and unsaturated fatty acids from tridax procumbens. Indian Journal of Pharmaceutical Sciences 50: 168.

Ghosh, S., D. Sukalyani, H. Sudipta, H. Andreas, T. Katja, S. Martina, K. Petra, S. Uta, M. Heidrun, H. Ulrike and H. Banasri, 2011. Valeriana wallichii root extracts and fractions with activityagainst leishmania spp. Parasitology Research 108: 861–871.

Gnoatto, S., V. Dalla, L. , C. Lencina, K. Dassonville, A, , S. Da Nascimento, D. Mossalayi, J. Guillon, G. Gosmann and P. Sonnet, 2008. Synthesis and preliminary evaluation of new ursolic and oleanolic acids derivatives as antileishmanial agents. Journal of Enzyme Inhibition and Medicinal Chemistry, 23: 604–610.

González, C., A. , R. Matías, S. Claudia, L. Rodney, R. Lastenia, J. Vicente, S. Jesus and A.M. Rafael, 2011. Antileishmanial, antitrypanosomal, and cytotoxic screening of ethnopharmacologically selected peruvian plants. Parasitology Research, 110: 1381–1392.

Greenwood, B., A. Adjukiewicz, S. Conteh, P. Hagan, D. Mabey and L. Panton, 1984. Leishmaniasis in the gambia. Is its incidence increasing? . Trans Roy Soc Trop Med Hyg, 78: 407-409.

Iwu, M., J. Jackson, J. Tally and D. Klayman, 1992. Evaluation of plant extracts for antileishmanial activity using a mechanism-based radio respirometric microtechnique (ram). Planta Medica 58: 436–441.

Jiu, J., 1966. A survey of some medicinal plants of mexico for selected biological activities. Lloydia, 29: 250–259.

Joanne, B., H. Veronique, C. Gabrielle, F. Marie, H. and Q. Joelle, 2011. In vitro antitrypanosomal and antileishmanial activity of plants used in benin in traditional medicine and bio-guided fractionation of the most active extract. Journal of Ethnopharmacology, 137: 998– 1002.

Kendrick, R., 1986. Preliminary field observations on the flight speed of a phelbotomine sandfly. Trans R Soc Trop Med Hyg, 80: 138-142.

Kolodziej, H., 2001. Proanthocyanidins and related compounds: Antileishamanial activity and modulatory effects on nitric oxide and tumor necrosis factor-a-release in the murine macrophage like cell line rae 264.7. Biol Pharm Bull 24: 1016–1021.

Lefrou, G., 1948. La leishmaniose cutanée au soudan français. Fréquence de la forme sèche a papulo-tuberculeuse. Bull Soc Path Exot 41: 622-627.

Luciana, I., M. Felipe, d.M. Eliane, Teixeira., , S.d.S. Bruna, Lima., , V. Verônica and R. Ana, 2012. Validation of quantitative real-time pcr for the in vitro assessment of antileishmanial drug activity. Experimental Parasitology 131: 175–179.

Manuel, J., B. Elfride, D. Eric, M. Victoria, D. Rafael and M. Luis, 2003. Variation of leishmanicidal activity in four populations of urechites andrieuxii. Journal of Ethnopharmacology 86: 243–247.

Morsy, T., 1996. Cutaneous leishmaniasis in egypt (review and comment). J Egypt Soc Parasitol 26 105-130.

Moulisha, B., G.A. Kumar and H.P. Kanti, 2010. Anti-leishmanial and anti-cancer activities of a pentacyclic triterpenoid isolated from the leaves of terminalia arjuna combretaceae. Tropical Journal of Pharmaceutical Research, 9 135–140.

Nasib, S., K. Pushpesh, K. Aruna, R. Kamal, M. Rakesh and D. Anuradha, 2005. Efficacy of desmodium gangeticum extract and its fractions against experimental visceral leishmaniasis. Journal of Ethnopharmacology 98: 83–88.

Odonne, G., G. Herbette, V. Eparviera, G. Bourdye, R. Rojas, M. Sauvaine and D. Stiena, 2011. Antileishmanial sesquiterpene lactones from pseudelephantopus spicatus, a traditional remedy from the chayahuita amerindians (peru). Part III Journal of Ethnopharmacology 137: 875– 879.

Peraza-Sanchez, S., F. Cen-Pacheco, A. Noh-Chimal, F. May-Pat, P. Sima-Polanco, E. Dumonteil, M. Garcia-Miss and M. Mut-Martín, 2007. Leishmanicidal evaluation of extracts from native plants of the yucatan peninsula. Fitoterapia, 78: 315–318.

Pragya, M., V. Koneni, P. Suriya, K. Awanish, G. Reema, S. Shailendra, S. Souvik, H. Majumder, l.K. Ani and D. Anuradha, 2010. 16a-hydroxycleroda-3,13 (14)z-dien-15,16-olidefrom polyalthia longifolia: A safe and orally activeantileishmanial agent. British Journal of Pharmacology 159: 1143–1150.

Pulido, M. and L. Serralta, 1993. Lista anotada de las plantas medicinales de uso actual en el estado de quintana roo, méxico. Centro de Investigaciones de Quintana Roo, Chetumal, Quintana Roo, México: 6.

Rageu, J., 1951. Phlébotomes du cameroon. Bull Soc Path Exot, 44: 793-800.

Raju, T.S. and E.A. Davidson, 1994. Structural features of water-soluble novel polysaccharide components from the leaves of tridax procumbens linn. Carbohydrate Res, 258: 243-254.

Richard, R., C. Jean, D. , L. Hechmi, P. Claude, A. Bruce and B. Simon, 2007. Cutaneous leishmaniasis. Lancet Infectious Diseases, 7: 581–596.

Ridoux, O., C. Di Giorigi and D. F., 2001. In vitro antileishmanial activity of three saponins isolated from ivy, α-hederin, β-hederin and hederacolchiside a1, in association with pentamidine and amphotericin. Phytotherapy Research 15: 298-301.

Riou, M. and M. Advier, 1993. Leishmaniose cutanée cantractée au senegal. Bull Soc Path Exot 26: 254-256.

Santin, M., A. dos Santos, C. Nakamura, F. Dias, I. Ferreira and N. Ueda, T. , 2009. In vitro activity of the essential oil of cymbopogon citratus and its major component (citral) on leishmania amazonensis. Parasitology Research 105(6): 1489–1496.

Sawadogo, W., G. Le Douaron, A. Maciuk, C. Bories, P. Loiseau, B. Figadere, I. Guissou and O.G. Nacoulma, 2012. In vitro antileishmanial and antitrypanosomal activities of five medicinal plants from burkina faso. Parasitology Research 110 1779–1783.

Sawadogo, W., A. Maciuk, J. Banzouzi, P. Champy, B. Figadere and I. Guissou, 2011. Mutagenic effect, antioxidant and anticancer activities of six medicinal plants from burkina faso. Natural ProductResearch, 26: 575-579.

Sewice, M., 1980. Phlebotomine sandflies (order diptera: Family psychodidae). A Guide to Medical Entomology: 78-82.

Sheik-Mohamed, A. and J. Velema, 1999. Where health care has no access: The nomadic populations of sub-saharan africa. Trop Med Int Hlth, 4: 695-707.

Simon, L.K., S. and Y. Vanessa, 2006. Current scenario of drug development for leishmaniasis. Indian J Med Res, 123: 399-410.

Sirol, J., P. Delpy, M. Lefevre and J. Vedy, 1972. Kala-azar in tchad republic. Does an endemic exist in central and west africa? . Bull Acad Natl Med 156: 395-407.

Strobel, M., B.N. Diaye, J. Marchand and J. Dedet, 1978. Cas de leishmaniose cu-tanee avec atteinte muqueuse ay senegal. Bull Soc Path Exot Filiales, 71: 423-429.

Tan, N., M. Kaloga, O. Radtke, A. Kiderlen, S. Öksüz, A. Ulubelen and H. Kolodziej, 2002. Abietane diterpenoids and triterpenoic acids from salvia cilicicaand their antileishmanial activity. Phytochemistry, 61: 881–884.

The Center for Food Security & Public Health., 2009. Leishmaniasis (cutaneous and visceral). Available from http://www.cfsph.iastate.edu/Factsheets/pdfs/leishmaniasis.pdf.

The Centre for Food Security & Public Health., 2006. Leishmaniasis (fast facts). Available from http://www.cfsph.iastate.edu/FastFacts/pdfs/leishmaniasis_F.pdf.

Thiago, R., R. Paulete, A. Oriana, Q. Juliana, C. Walkyria, G. Andre, D. Angelica, M. Silvia, H. Joao, S. Patricia and J. Marcelo, 2012. Anti-malarial, anti-trypanosomal, and anti-leishmanial activities of jacaranone isolated from pentacalia desiderabilis (vell.) cuatrec. (asteraceae). Parasitology Research 110: 95–101.

Torres-Santos, E., D. Lopes, R. Oliveira, J. Carauta, C. Falcao, A. Kaplan and B. Rossi-Bergmann, 2004. Antileishmanial activity of isolated triterpenoids from pourouma guianensis. Phytomedicine, 11 114–120.

Vanhalen, M., J. Lejoly, M. Hanocq and L. Molle, 1991. The medicinal plant industry. CRC Press, Boca Raton, FL.

Verma, R. and M. Gupta, 1988. Lipid constituents of tridax procumbens. Phytochemistry 27: 459-463.

Villegas, L., I. Fernandez, H. Maldonado, R. Torres, A. Zavaleta, A. Vaisberg and G. Hammond, 1997. Evaluation of the wound-healing activity of selected traditional medicinal plants from peru. Journal of Ethnopharmacology, 55: 193–200.

Viscencio, d.l.R., G. , S. Tamay, P. , M. Issac, AP. and D. Lezama, CM. , 1995. Toxicidad in vitro de extractos de urechitesandrieuxii muell.-arg. En contra de l. Mexicana. Memorias de la III Reunión de Investigacion Qu´ımica en el Sureste de Mexico, Merida, Yucatán: 93.

World Health Organistion, W., 2010. Control of the leishmaniasis: Report of a meeting of the who expert committee on the control of leishmaniases, geneva.

Yadava, R. and K. Saurabh, 1998. A new flavone glycoside: 5,7,4′-trihydroxy-6,3′-dimethoxyflavone-5-o-α-l-rhamnopyranoside from the leaves of tridaxprocumbens linn. Journal of Asian Natural Products Research 1: 147–152.

Zhelmy, M., M. Rosa, G. Francisco, J. Manuel, W. Luis and R. Sergio, 2009. In vitro activity of tridax procumbens against promastigotes of leishmania mexicana. Journal of Ethnopharmacology 122: 463–467.