Are Medicinal Plants the Future of Loa loa Treatment?

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ABSTRACT
Loa loa filarial worm affects humans living in rural areas, urban slums, or conflict zones. This parasite is responsible for neglected tropical diseases, endemic in rainforest areas of the West and Central African. L. loa has also been diagnosed among travelers and migrants. In areas that are co-endemic of L. loa filarial with other filariasis such as onchocerciasis, lymphatic filariasis, or mansoniﬁasis, the treatment by diethylcarbamazine or ivermectin increases the risk of severe adverse effects. To remedy to this, it would be interesting to explore other tracks such medicinal plants. Nearly 80% of worldwide seed traditional practitioners are the first choice, and a large number of medicinal plants were claimed to possess antifilarial activities. This review relates about medicinal plants used to treat L. loa filarial disease.

Key words: Alternative treatment, Loa loa filarial, medicinal plants

INTRODUCTION
Loa loa filarial worm is transmitted to the host by the Tabanid females flies of the genus Chrysops (Chrysops silacea, Chrysops dimidiata, or Chrysops distinctipennis).[1,2] This filarial is extended from the West, Central, and South-East African.[3] L. loa filarial has native origins in Ethiopia.[4] Occasionally, L. loa can be found among travelers and migrants at risk areas.[5,6] Nearly 200 million persons are at risk; more than 13 million are infected.[7] L. loa filarial is the third reason of medical consultation in endemic areas after malaria and lung disease.[7,8] It is characterized by pruritus, subconjunctival migration of adult worm, and Calabar swellings’ acute allergic reaction due to the excretion of antigenic substances by migration of adult filarial.[1,11,12] The disease is particularly well known in rural communities in Africa where local symptom-based names exist: (“Nâa ziis” [Nâa = worm; ziis = eye] [Fang], Igolas [Mpongwe], Mehombi [Kota], Gabon). Loaïasis belongs to the group of filariasis including onchocerciasis, lymphatic filariasis, and mansoniﬁasis [Table 1].[13,14] L. loa infection affects economic peoples who contribute to agricultural productivity.[15,16] In areas co‑endemic by onchocerciasis, lymphatic filariasis, and L. loa filarial, global programs have elevated the risk of severe adverse effects when diethylcarbamazine (DEC) or ivermectin (IVM) treatment are used.[17,18] This is not the case with Mansonella perstans.[19] Although both are very active on microﬁlariae, these drugs can have severe adverse effects for peoples having >8000 L. loa microﬁlariae/milliliter in blood.[17,19] Adverse effects are less common in areas endemic for Wuchereria bancrofti, Brugia malayi, or single Onchocerca volvulus infection.[20,21] The treatment of loaïasis is not a priority because the impact is restricted some land of Central and West Africa.

Alternative treatments are urgently required. A high number of plants were claimed to treat L. loa filarial and its health-associated discords.[14,22] Since long-time ago, medicinal plants have been used and most people (60% of the world’s people) rely on traditional plants for their primary health-care needs.[23] On the basis of a survey of plant-derived, pure, or synthesis compounds used in many countries, WHO-traditional Medicine Centers indicated that, from 122 compounds identiﬁed, 80% were used for the same or related ethnomedical purposes, but they were derived from only 94 plants species.[24] This review focuses on medicinal plants used in traditional medicine against L. loa filarial and mentions the natural products or extracts that have been tested.

LITERATURE METHODS
Literature was collected by searching the English and French databases including PubMed, ScienceDirect, Mendeley Desktop, ResearchGate, and Google Scholar. Articles founded through tracking citation for other publications or by directly accessing the journals website. For traditional uses, all publications that could be accessed with any information on the ethnomedical management of L. loa with natural products, and extracts were considered useful. In vitro studies of medicinal plants and bioactive compounds isolated from plants were also reviewed carefully. The International Plant Name Index[25] and the Kew Botanic Garden Plant name database were used to validate the scientiﬁc name of each plant.

BIOLOGY OF THE PARASITe
L. loa is a small white worm, opaline, and cuticle dent; this worm can survive about 17 years.[12,27] The larvae develop into adult worms in...
approximate 1 year but can take up to 4 years to mature.[28] The male is about 3–4 cm long with 0.35–0.43 mm in diameter and the female 4–7 cm long with 0.5 mm diameter.[27,30] L. loa worms are sheathed, their body nuclei are continuous to the tip of the tail, and they have a hooked tail at one end. In difference, Onchocerca volvulus is unsheathed and has body nuclei that do not extend into the tail, and they leave a "shepherd's crook."[14,15]

### USUAL DIAGNOSTICS (STRATEGY)

The presence of microfilariae was determined by examining thin and thick blood smears obtained at non and stained with Giemsa.[2,27,32,33] Other possibilities for examining such as amplification performed[44] and indirect immunofluorescence using homolog antigens of L. loa.[31] The filariasis that could be visible in the eye may be tested as a macrofilariasis.[32] L. loa load is usually highest at midday, and the accuracy will be the greatest when blood samples are collected between 10:00 h and 14:00 h.[31] Eosinophilia and high immunoglobulin E (IgE) levels are also indicative of active infection since eosinophil, and IgE levels usually increase in response to helminthiasis.[11]

### CURRENT DRUGS FOR THE TREATMENT OF LOAISIS

Antifilarial drugs such as IVM, DEC, albendazole (ALB), and mebendazole (MEB) are currently used for the treatment of loiasis, but each of them is characterized by several restrictions.[11] Indeed, regions where loiasis, onchocerciasis, or lymphatic filariasis are co-endemic, individuals with >8000 L. loa microfilarial/milliliter of blood are at risk of developing severe adverse reactions and even encephalopathies after IVM treatment.[17,19,21]

Antifilarial drugs target primarily the microfilaria stage of the parasites. Several adverse effects are less common in endemic areas for W. bancrofti, B. malayi, or single O. volvulus infection.[2,22] In addition, long-term treatment of loiasis may result in parasite resistance.[38]

IVM has been asserted to have a manifest microfilaricidal effect against L. loa long term for at least 1 year after a single dose of 150 μg.[14,27] However, it showed no macrofilaricidal effect and has been recognized that individual coinfection can show serious neurological side effects including coma, encephalitis, retinal hemorrhage, and membrane glomerulonephritis.[27] This occurs especially when L. loa load is high (>8000 microfilaria/ml).[38] It is also of importance to note that IVM is incompatible with pregnant and lactating women, but several studies have suggested that the risk of congenital malformation or abortion is not higher.[39]

DEC has been asserted to have at the same time micro- and macrofilaricidal effect against L. loa, making this drug of choice to treat loiasis.[40] Although individuals with a high microfilaremia are at similar risk reactions as IVM.[41] Moreover, DEC required multiple courses of therapy to achieve a clinical and parasitological cure.[40] DEC is no longer marketed in Europe and is available in the USA only through the Centers for Disease Control and Prevention (CDC).[2]

ALB has been shown to reduce microfilarial masses progressively and slowly as a consequence of primary embryotoxic activity.[42] This reduces the risk of serious adverse effects in patients with high microfilarial loads.[43]

MEB has also been shown to be effective in slowly reducing microfilarial load.[44]

Treatments of nematodes and of L. loa filarial especially are no longer to demonstrated. However, in coinfection areas were L. loa lives with onchocerciasis or lymphatic filariasis, it was observed the limits of treating. However, social-cultural practices may be conducted to reject the mass program or non-cooperation at the treatments may constitute a risk because these people establish a reservoir. In endemic areas of loiasis, checkup of microfilariae is not regular in blood banks. Investigations were performed to assess how the dose and frequency of administration of the natural infective stage (L3) affect events in the peripheral blood of an infected host (Mandrillus sphinx). These results suggest that the regimen of L3 administration may have an effect on the level of humoral immune response and to some extent on the density of microfilaria.[45]

Strategies to detect these people and using alternative treatments such as medicinal plants should be considered.

### ARE PLANTS THE FUTURE?

As mentioned in this review, medicinal plants represent a valuable and relevant source of anti-infectious molecules. Indeed, we and others reported a series of in vitro and in vivo assays with obvious antifilarial effects.[7,46,47] In these assays, motility and viability were evaluated in one hand, and the selectivity index (SI) which compared the cytotoxicity of a drug against a parasite and a library of human cells was determined in the other hand.[7,48,51]

Recently, in vitro activities for two compounds (voacamine and voacamine) isolated from the stem bark of Voacanga. Africana inhibits

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**Table 1: Summarize of different types human filariosis**

<table>
<thead>
<tr>
<th>Filariasis</th>
<th>Parasites</th>
<th>Diseases (estimated number of infections)</th>
<th>Vector</th>
<th>Region</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loaasis</td>
<td>Loa loa</td>
<td>33 million</td>
<td>Chrysops</td>
<td>Central, West Africa</td>
<td>Diurnal female worms migrate through tissues and the eyes; Calabar, swelling</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Onchocerca volvulus</td>
<td>&gt;17 million skin filariases; onchocerciasis river blindness</td>
<td>Flies (Simulium spp.)</td>
<td>Mostly tropical Africa and America</td>
<td>Formation of large nodules under skin or in eyes (causing blindness)</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Wuchereria bancrofti and Brugia malayi</td>
<td>120 million</td>
<td>Mosquitoes (Aedes, Anopheles, Culex, and Mansonia)</td>
<td>Tropical Africa, Asia, America</td>
<td>Nocturnal microfilariae; elephantiasis; infection of lymphatic system, enlargement of lymph nodes</td>
</tr>
<tr>
<td>Mansonelliasis</td>
<td>Mansonella ozzardi, Mansonella persians, and Mansonella streptocerca</td>
<td>114 million</td>
<td>Midges (Calicoides) and black flies (Simulium)</td>
<td>South America and West Indies, Sub-Saharan Africa</td>
<td>Angioedema, recurrent pruritic subcutaneous lesions, fever, headaches, arthralgia, neurologic manifestations</td>
</tr>
</tbody>
</table>

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the motility of the *L. loa* microfilarial and adult male worms of *Onchocerca ochengi* at 30 µm drug concentration.\(^1\) The half maximal inhibition concentration (IC\(_{50}\)) for voacangine was 5.49 µM for *L. loa* and 9.07 µM for *O. ochengi*, while for voacamine, IC\(_{50}\) was 2.49 µM and 3.45 µM.\(^4\)

In another study, 50% lethal concentration (LC\(_{50}\)) of methanolic extracts from *Erythrophleum ivorense* A. Chev., *Erythrophleum Suaveolens* Guill. and Perr.) Brenan, and *Erythrophleum guineense* Chev. and *Dichrocephala integrifolia* (L.F.) Kuntze, to 3.78 for *L. loa*, and 9.07 for *O. ochengi* was 5.49 µM.\(^4\)

Many researchers showed that the plants used in traditional medicine could efficient for treatment of *L. loa* [Table 2].

### GENERAL CONCLUSION

Traditional medicinal plant applications vary significantly across countries. As far as, it depends on culture part, history, and philosophy. Obviously, theories and practices are very different from conventional medicine. The fact that many practices passed from generation to generation can be viewed as a proof of the safety and efficacy of these drugs. Nowadays, several researches are carried out on the medicinal plants for the research of new compounds on the different resistant pathologies.\(^3,4\)

The complications caused by the use of pharmaceutical worming drugs and mass treatment with reference drugs on co-endemic areas of onchocerciasis and lymphatic filariasis are a high argument. Research and evaluation of antifilarial biomolecules extracted from medicinal plants is an alternative sight which should not be neglected. In another way, in rural areas, pharmaceuticals drugs are inaccessible, and people have recourse to alternatives medicines to treat themselves. The discovery of new lead molecules might hopefully bring advancement in the safe and effective treatment of filariasis.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES


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**Table 2: Plants list indicated to treat *Loa loa* in traditional medicine**

<table>
<thead>
<tr>
<th>Family</th>
<th>Scientific name</th>
<th>Part used</th>
<th>Indication</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apocynaceae</td>
<td><em>Alstonia boonei</em> De Wild</td>
<td>Bark, fresh latex, fresh stem-bark</td>
<td>Loiasis, filarial swellings</td>
<td>[46,52,53]</td>
</tr>
<tr>
<td></td>
<td><em>Alstonia congensis</em> Engl.</td>
<td>Latex</td>
<td>Loiasis, filarial swellings (bandaged along with crushed bark of <em>Erythrophleum guineense</em>)</td>
<td>[46,54]</td>
</tr>
<tr>
<td>Compositae</td>
<td><em>Dichrocephala integrifolia</em> (L.F.) Kuntze</td>
<td>Stalk, leaves</td>
<td>Eyes worm diseases, conjunctivitis</td>
<td>[55,56]</td>
</tr>
<tr>
<td></td>
<td><em>Bidens pilosa</em> L.</td>
<td></td>
<td>The juice extracted from the stalk and the leaves is used against the eye filaria</td>
<td>[57]</td>
</tr>
<tr>
<td>Costaceae</td>
<td><em>Costus lucasanusius J. Braun and K. Schum</em></td>
<td>Stalk</td>
<td>The juice of stalk is used against the eye filaria</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td><em>Costus afer Ker-Gawl.</em></td>
<td>Stem</td>
<td>The juice of leaves is used against the eye filaria</td>
<td>[57]</td>
</tr>
<tr>
<td>Lamiaceae Leguminosae</td>
<td><em>Ocimum basilicum</em> L.</td>
<td>Leaves</td>
<td>Stem juice used from eye worm pain</td>
<td>[58]</td>
</tr>
<tr>
<td>Caesalpinoideae</td>
<td><em>Senna alata</em> L. Roxb.</td>
<td>Leaves, roots</td>
<td>Expels worms, eyes worm diseases, fever, fast delivery, yellow fever, hemorrhoids</td>
<td>[55,56]</td>
</tr>
<tr>
<td></td>
<td><em>Senna occidentalis</em> (L.) Link</td>
<td>Leafy stem, seeds</td>
<td>Leafy stem and seed decoction have drunk against eye worm</td>
<td>[58]</td>
</tr>
<tr>
<td>Meliaceae</td>
<td><em>Erythrophleum ivorense</em> A. Chev.</td>
<td>Dried stem-bark</td>
<td>Loiasis (filarial swellings) used on <em>Onchocera volvulus</em></td>
<td>[46,59]</td>
</tr>
<tr>
<td></td>
<td><em>Erythrophleum Suaveolens</em> Guil. and Perr.) Brenan</td>
<td>Crushed bark</td>
<td>Loiasis (filarial swellings), used with <em>Alstonia congensis</em></td>
<td>[46]</td>
</tr>
<tr>
<td>Portulacaceae</td>
<td><em>Turrea vogelii</em> Hook. f.</td>
<td>Fruits</td>
<td>The juice of fruits is used against the eye filaria</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td><em>Portulaca oleracea</em> L.</td>
<td>Whole plant</td>
<td>Intestinal worms, <em>Loa loa</em>, fever, skin disease, disorders of bladder, kidney and lungs, abscess, antispasmodic, astringent, diuretic</td>
<td>[60]</td>
</tr>
<tr>
<td>Proteaceae</td>
<td><em>Protea madakensis</em> Oliv.</td>
<td>Bark</td>
<td>Bark decoction is drunk against eye worms</td>
<td>[56]</td>
</tr>
<tr>
<td>Rubiaceae</td>
<td><em>Crossopteryx febrifuga</em> (Afzel. ex. G. Don) Benth.</td>
<td>Fresh fruit juice</td>
<td>Eye filaria</td>
<td>[46,61]</td>
</tr>
<tr>
<td>Solanaceae</td>
<td><em>Nicotiana tabacum</em> L.</td>
<td>Smoke, fresh-leaves</td>
<td>The smoke and the juice of green tobacco are used against the eye filaria</td>
<td>[57]</td>
</tr>
<tr>
<td>Vitaceae</td>
<td><em>Cissus quadrangularis</em> L.</td>
<td>Bark, sap</td>
<td>Bark serves as vulnerary, and the sap is used for the eye filaria</td>
<td>[57]</td>
</tr>
</tbody>
</table>
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In vitro, the extracts and chromatographic fractions of *Alstonia boonei* demonstrated activities against *Loa loa* microfilariae in eukaryotic cell lines. Parasitol Res 2010;107:643-50.


