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SHORT REVIEW

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 mansonelliasis, 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.[7-10] 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 [Mpongwé], Mehombi [Kota], Gabon). Loiasis belongs to the group of filariasis including onchocerciasis, lymphatic filariasis, and mansonelliasis [Table 1].[13,14]

L. loa infection affects economic peoples who contribute to agricultural productivity.[10,15] 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) were distributed,[16-19] this is not the case with *Mansonella perstans*.[20] Although both are very active on microfilariae, these drugs can have severe adverse effects for peoples having >8000 L. *loa* microfilariae/milliliter in blood.[7,17,21] Adverse effects are less common in areas endemic for *Wuchereria bancrofti*, *Brugia malayi,* or single *Onchocerca volvulus* infection.[7,22] The treatment of loiasis 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.[14,23] 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.[24] On the basic 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.[25]

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 ethnomedicinal 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[26] 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 dented; this worm can survive about 17 years.[1,27] The larvae develop into adult worms in

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Table 1: Summarize of different types human filarisis

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

approximately 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.[27,29,30] *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, at last, *Mansonella streptocerca* is unsheathed and has a tail that ends in partial coil known as a "shepherd's crook."[14,31]

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[34] and indirect immunofluorescence using homolog antigens of *L. loa*.[35] The filariasis that could be visible in the eye may be tested as a macrofilariasis.[2] *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 helminthiases.[1]

CURRENT DRUGS FOR THE TREATMENT OF LOASIS

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.[1] 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 microfilariae stage of the parasites. Several adverse effects are less common in endemic areas for *W. bancrofti*, *B. malayi*, or single *O. vulvulus* infection.[7,22] In addition, long-term treatment of loiasis may result in parasite resistance.[36]

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.[16,27] However, it showed no macrofilaricidal effect and has been recognized that individual coinfected can show serious neurological side effects including coma, encephalitis, retinal hemorrhage, and membrane glomerulonephritis.[37] 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 (voacangine and voacamine) isolated from the stem bark of *Voacanga. Africana* inhibits

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

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

the motility of the *L. loa* microfilarial and adult male worms of *Onchocerca ochengi* at 30 μm drug concentration.[47] 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.[47]

In another study, 50% lethal concentration (LC_{50}) of methanolic extracts on *L. loa* microfilarial equal to 0.22 for *Petersianthus macrocarpus* bark, to 1.082 for *Piptadeniastrum africanum*, to 3.78 for *vernonia conferta* bark, and to 5.29 for *Lophira alata* bark, and to 5.29 for *Lophira alata* bark compared to standard drug such as diethylcarbamazine citrate and IVM (0.385 μg/ml and 32.74 μg/mL, respectively) and none cytotoxicity from Eukaryotic cells.[7]

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.[62-66]

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.

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