A review of Phytochemical Constituents and Pharmacological Activities of Ethnomedicinal *Warburgia ugandensis* Sprague ssp. *ugandensis* in East Africa

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Abstract

Use of indigenous medicinal plants has been practiced in East Africa for centuries and is still being widely used to-date. The genus *Warburgia* belongs to family *Canellaceae*. The species *Warburgia ugandensis* Sprague ssp. *Ugandensis* (commonly known as East African greenheart, Pepper-bark tree) is an evergreen tree distributed throughout East Africa, including in the Democratic Republic of Congo, Ethiopia, Kenya, Malawi, Tanzania, and Uganda. The plant has been used for centuries by various local communities and several traditional healers in East Africa to treat many diseases including Malaria, constipation, tooth-ache, stomach-ache, diarrhoea, coughs and colds and general muscular and other body pains. The species, very well known to local communities by its local names, grows in natural habitats and also on farmlands where it has been domesticated. The present review describes the existing data on the botany and ecology, plant parts used, phytochemical constituents, traditional uses and pharmacological activities of *W. ugandensis*. The review established that during the last few decades, numerous folk medicine and scientific reports on the anti-plasmodial activitiy, antimicrobial activity and antifungal activity of this species have been cited in the literature. The chemical composition of the bark and leaves is relatively well studied. Literature review confirmed several chemical constituents isolated particularly from stem bark and leaves of this species. Drimane sesquiterpenes, including muzigadial, salutariolide, warburganal, polygodial and isopolygodial and mukaadial among several others have been reported in stem bark of *W. ugandensis*. The sesquiterpenes of *Warburgia* species are known to possess insect anti-feedant, anti-microbial, anti-plasmodial, anti-fungal anti-ulcer and molluscicidal properties. Further research by pharmaceutical companies and research institution needs to be carried out on *W. ugandensis* species for its potential in curing and treating diseases, particularly stem bark and leaves in regard to its antiplasmodial and antimicrobial activities. Therefore, pre-clinical and clinical trials need to be done to further validate the traditional medicine applications of *W. ugandensis* for possible antimalarial and antibacterial drug discovery.

Key words: *Warburgia ugandensis, Medicinal uses, Phytochemistry, Antiplasmodial activities, Antimicrobial activities.*

Introduction

The use of plants and plant derivatives for preventing and treating human diseases and afflictions is as old as civilization itself. History shows that every culture on Earth has benefited from medicinal virtues of plants. Indeed, plants are still the backbone of most medicinal and healthcare systems in many places around the world [1]. Use of indigenous medicinal plants has been practiced by sub-Saharan African communities for centuries and is still being widely used to-date. Medicinal plants and use of ethnomedicine is an integral part of the daily lives and the cultural heritage of many local East African communities [2]. Estimates put the number of plant taxa in everyday medicinal use around the world at between 50,000 and 75,000. In sub-Saharan Africa alone, about 10,000 medicinal plant species are in everyday use as ethnomedicine for curing and treating human and livestock diseases by traditional healers and herbalists [1].

The Genus *Warburgia*, belonging to the family Canellaceae, is widely distributed in Democratic Republic of Congo (DRC), Ethiopia, Kenya, Malawi, Mozambique, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe. The species *Warburgia ugandensis* Sprague ssp. *ugandensis* is an evergreen medicinal tree widely found growing in lowland rainforests, evergreen and swamp forests of DRC, Ethiopia, Kenya, Malawi, Tanzania, and Uganda [1, 2, 3]. It is used for timber, firewood, building poles, fodder, charcoal and carvings, food seasoning and spices, insecticide, mulch for soil conservation, ornamental, resin, shade, toothbrush and medicinal purposes [2, 4, 5, 6, 7]. Both stem bark and leaves of *W. ugandensis* have been widely used in primary health care systems throughout East Africa to cure and treat various ailments and diseases including Malaria, stomachache, fever, general muscle pain, cold and cough, toothache, bronchial infections, parasitic infections, constipation, and diarrhoea among others [1, 3, 8, 9, 10].

Phytochemical and pharmacological researchers have reported the presence of diverse secondary metabolites in the extracts of *W. ugandensis*. These metabolites are linked to the medicinal properties of this plant species [11, 12, 13]. Stem bark contains various sesquiterpenoids such as cinnamolide-3β-acetate; muzigadial and muzigadiolide and unsaturated fatty acids, including linoleic acid [9, 14]. Flavonol glycosides (e.g. Kaempferol-3,4',7-tri-O-β-D-glucoside) have been extracted from the leaves [9, 15].

The sesquiterpenes of Warburgia species are known to possess insect anti-feedant, antimicrobial, antiulcer, molluscicidal and antifungal properties [9, 14]. Extracts from stem bark and other parts of the plant have shown anti-plasmoidal activity [9, 16, 17]. Stem bark is used to treat Malaria, stomach problems and other ailments and is sold in a crude/raw form (Dry or fresh bark - Plates 1 & 2) in various local markets of different towns and villages throughout East African region [2, 18]. Due to high demand for its stem bark, *W. ugandensis* has been over-exploited in its natural habitats and hence its population has been declining over a period of time at an alarming rate, raising concerns about the conservation of the species [1, 9, 18, 19]. Clearly, there is an urgent need for programmes under which such species, propagated in special nurseries, can be cultivated in their natural habitats as well as domesticated on farmlands, managed and harvested commercially [1, 4].

Description and ecology of indigenous Warburgia ugandensis Sprague ssp. *ugandensis*

Common names: East African greenheart, Pepper-bark tree [1, 2, 4].

Local names: Muthiga (Kikuyu); Mukuzanume (Luganda); Osogonoi, Msokonoi (Maasai, Rangi); Omenyakige (Kisii); Apacha (Luhya); Balwegira (Lusoga); Musunui (Meru); Soget, Sorget (Nandi, Tugen); Sogoet (Kipsigis); Sagonai (Goro); Muhiya (Haya); Mdee, Mlifu (Sambaa); Mwiha (Runyankore); Musizambuzi (Runyoro); Muharami (Rutoro) [1, 2, 4].

Description and Ecology

This is a large evergreen tree (Plate. 3) growing to 25 m high with a dense leafy rounded canopy and whose parts have a hot, peppery taste; bark rough, black-brown, fissured, cracked in rectangular scales (Plate. 1); leaves alternate, shiny, dark green above with clear midribs, edges wavy (Plate. 5); flowers greenish-cream, inconspicuous, axibllary, less than 1 cm across (Plate. 4); fruit hard, round to egg or plum-shaped, 3–5 cm long, green to purple-black with a waxy white surface (Plate. 4). It is widely distributed throughout East Africa. In Kenya, it is widespread in lower montane forests, in drier highland forest and also in riverine forest. Sometimes also found growing in *Acacia xanthophloea* woodland [2, 5]. In Uganda, it grows in colonizing forest, forest edges and thickets, often in dry areas [2, 20]. While in Tanzania it is found in Lushoto, Babati and in Iringa in forest, forest edges and in drier areas [21]. This species grows at altitudes of 1000–2000 m [2].

Plate 1. Tree stem bark of *W. ugandensis*

Plate 2:.Dry stem bark of *W. ugandensis* sold in local market in Kenya

Plate 3. *W. ugandensis* - Young tree

Plate 4. Fruits of *W. ugandensis*

Plate 5. Leaves of *W. ugandensis*

(Plates ©: Najma Dharani)

Traditional medicinal uses

Plant parts of *Warburgia* species used in ethnomedicine include stem bark, leaves and roots [1, 3, 4, 6, 8, 9]. An infusion of dried bark is widely used for the treatment of malaria, stomachache, toothache, fever, common colds, coughs, chest complaints and general muscular pains [1, 4, 8, 9, 18]. It is also used to cure bronchial infections, oral thrush, cystitis and many other ailments [3, 18]. The roots feature in the treatment of diarrhoea [4, 8]. A decoction of the bark or leaves is administered as a cure for malaria (although it causes violent vomiting) [4, 8]. The stem barks of this plant are generally used in traditional medicine to treat rheumatism, gastro-intestinal disorders, odontological, backache, constipation, gastritis, sexually transmitted diseases, abdominal pains, snake bites and respiratory problems in African countries [16, 17, 18].

Phytochemical constituents and pharmacological activities

Phytochemical and pharmacological studies have been reported with the presence of diverse secondary metabolites in the extracts of *W. ugandensis*. These metabolites are linked to the medicinal properties of this plant species [1, 4, 11, 12, 13]. *Warburgia* species are known to be rich in sesquiterpenes with drimane and coloratane skeletons [14, 15]. Sesquiterpenes isolated from the bark or other parts of *W. ugandensis* include: mukaadial, muzigadial, muzigadiolide, warburganal, warbugin, warburgiadione, ugandensidial (cinnamodial), ugandenial A, isopolygodial (isotadeonal), polygodial cinnamolide, cinnamolide-3–acetat, salutarisolide, deacetylugandensolide, 11α-hydroxymuzigadiolide, mannitol, pereniporin B, drimenol, drimenin, and dendocarbins A, L and

M amongst others (Fig. 1) [9, 11, 12, 14, 22]. Stem bark reported with Coloratane sesquiterpenes such as 6α,9α-dihydroxy-4, 7-coloratadien-11,12-dial, 4,(13),7-coloratadien 12,11-olide and 7b-hydroxy-4(13),8-coloratadien-11,12-olide (Fig. 1) [9,14]. The sesquiterpenes of *Warburgia* species are known to possess insect antifeedant, antimicrobial, antibacterial, antimycobacterial, antiulcer, molluscicidal and antifungal properties [6, 14, 23]. Flavonol glycosides (e.g. Kaempferol-3,4,7-tri-O-β- D-glucoside) have been isolated from the leaves [6, 7, 33]. Analysis of active chemical compounds of this plant also showed the presence of alkaloids, flavonoids, phenolics, sugar alcohols, and unsaturated fatty acid including linoleic acid [11].

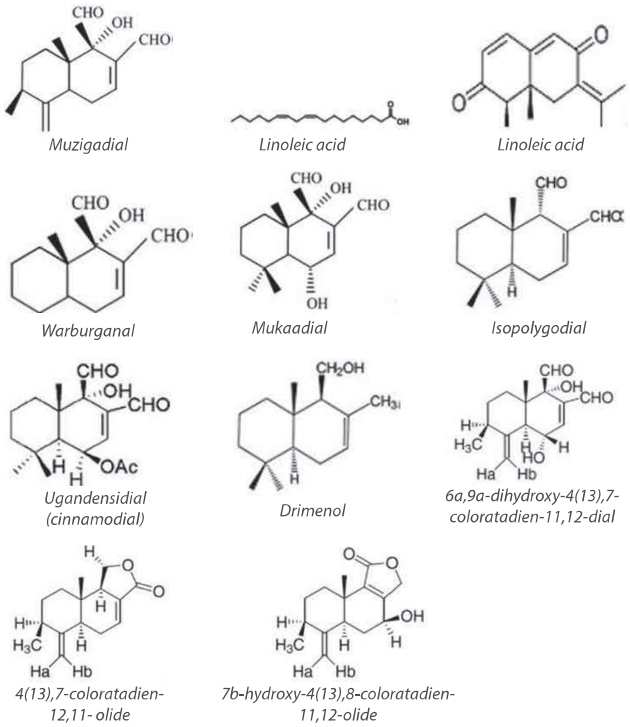

Figure 1. Chemical structures of some drimane, colorotane sesquiterpenoids and other compounds isolated from *Warburgia ugandensis* [1, 6, 9].

Methanol extracts from various parts of *W. ugandensis* have shown antiplasmodial activity with an IC50 value of less than 5 mg/ml against both chloroquine-sensitive (D6) and chloroquine resistant (W2) strains of *Plasmodium falciparum* and chloroquine resistant (W2) strains of *P. falciparum* [1, 4, 6, 9, 16]. Anti-plasmodial activity of its stem bark has also been demonstrated against *P. knowlesi* and P. berghei [24]. Extracts of W. ugandensis also showed moderate in vivo antiplasmodial activity in mice infested with *P. burghei* [6, 16]. Ethanol extract from the dried leaves showed antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Vibrio cholerae and Bacillus cereus* [25]. Stem bark extract also exhibited antibacterial activity with an MIC of 256 mg/ml against *Staphylococcus aureus* and 512 mg/ml against *Enterococcus faecalis* [6, 26].

In one of the studies, it was observed that the ethanolic extract from the dried leaves of *W. ugandensis* exhibited significant antifungal activity against *Candida albicans* and *Cryptococcus neoformans* [25] whereas the ethanol extract of stem bark exhibited antifungal activity against *Candida albicans* [9, 27]. It has been observed that extracts from stem bark of *W. ugandensis* showed strong antifungal activity with a MIC of 256 µg/ml against *C. albicans* due to the presence of the muzigadial compound in the plant [9, 26]. Furthermore, Warburganal which is one of the major phytochemicals contained in *W. ugandensis* reported with a broad-spectrum antifungal activity against yeasts and filamentous fungi especially against *Saccharomyces cerevisiae, C. utilis*, and *Sclerotinia libertiana* [9, 28].

Elsewhere a cytotoxic sesquiterpene characterized as muzigadial, isolated from *W. ugandensis*, showed in vitro trypanocidal activity against *Trypanosoma brucei* [6, 9, 27]. Stem bark demonstrated antimycobacterial activity against Mycobacterium aurum, *Mycobacterium fortuitum*, *Mycobacterium phlei* and *Mycobacterium smegmatis* [9, 14]. Muzigadial has been used to treat trypanosomiasis [29]. The methanol extract of the bark of *W. ugandensis* was found to exhibit potent insect antifeedant activity against the African armyworm *Spodoptera exempta* [28, 30]. Warburganal and muzigadial inhibited the feeding of larvae of two species of African armyworm, the monophagous *Spodoptera exempta* and the polyphagous *Spodoptera littoralis* at a concentration of 0.1 ppm in a regular leaf disk method [31]. Muzigadial also exhibited its activity against soil pathogens namely *Fusarium oxysporum, Alternaria passiflorae* and *Aspergillus niger* [32].

Conclusion

This review highlights *Warburgia ugandensis* Sprague ssp. *Ugandensis* as an important and highly valued medicinal plant species used by several local communities for centuries across East African region to treat various diseases and ailments. Literature review highlighted that numerous active chemical compounds have been isolated from stem bark, leaves and roots of this species. Several phytochemical and pharmacological studies have been carried out on *W. ugandensis* extracts leading to the identification and isolation of highly active medicinal compounds and pharmacological properties including antimicrobial, antifungal, antiplasmodial, antimycobacterial, insect antifeedant properties and others, backing up some of its documented traditional use in treatment of some diseases. However, there is no literature providing evidence on ethnomedicinal product development from *W. ugandensis* yet it has been proven through many studies of its potent therapeutic values. Therefore, further preclinical and clinical studies ought to be done to standardize the use of this plant in treatment and management of a number of disease conditions particularly malaria, fungal and bacterial diseases. Due to high demand for its stem bark, *W. ugandensis* has been over exploited in its natural habitats and hence its population is declining over a period of time at an alarming rate. Hence, there are concerns about the conservation of the species.

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