Review

A review on the botanical aspects, phytochemical contents and pharmacological activities of *Warburgia ugandensis*

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Received 15 June, 2018; Accepted 9 August, 2018

*Warburgia ugandensis* Sprague (Family Canellacea) commonly known as Ugandan greenheart or pepper bark tree, is a highly valued medicinal plant in traditional medicine with a broad spectrum of antimicrobial activity whose parts especially the leaves and stem bark have for long been used in the treatment and management of many diseases and health conditions such as stomachache, cough, toothache, fever, malaria, oral thrush, measles and diarrhea in African communities where the plant occurs. This review focused on the phytochemical contents, medicinal uses and antimicrobial activities of *W. ugandensis* based on published peer reviewed articles. This review established that the high therapeutic value of *W. ugandensis* is attributed to the abundance of drimane sesquiterpenes in its stem bark and leaves. These chemicals have also made the plant to have potent antibacterial and antifungal activities. However, more pre-clinical and clinical trials need to be done to further validate the traditional medicine applications of *W. ugandensis* for possible drug discovery. Due to its high demand, *W. ugandensis* has been over exploited and hence its population is in drastic decline. Consequently, there is need for development of advanced and more rapid propagation techniques to increase its population and distribution in its natural environment to meet the ever-increasing demand.

Key words: Antimicrobial, Canellaceae, medicinal uses, phytochemicals, *Warburgia ugandensis*.

INTRODUCTION

*Warburgia ugandensis* Sprague (Family Canellacea) is a plant with immense medicinal values with restricted distribution in tropical Africa (Muller et al., 2015). It is commonly known as the “Uganda Green Heart Tree”

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Figure 1. Morphology illustration of the main features of *W. ugandensis*: 
a) Whole plant of *W. ugandensis*; b) Stems of *W. ugandensis*; c) Fruits 
of *W. ugandensis*; d) Leaves of *W. ugandensis*. Source: Natural 
Chemotherapeutics Research Institute, Uganda.

or the “Pepper bark tree” with a unique characteristic bitter-peppery taste (Njire et al., 2014). Owing to its antimicrobial activities, *W. ugandensis* have been widely used throughout its distribution range to treat and manage myriad of diseases and disorders since time immemorial including cough, toothache, common cold, bronchial infections, parasitic infections, stomachache, fever, malaria, oral thrush, muscle pain, cystitis, constipation, weak joints, measles, and diarrhea among others (Lovett et al., 2006; Henke, 1994; Kiringe, 2006; Kokwaro, 2009; Wamalwa et al., 2006). Indeed, *W. ugandensis* is a highly valued plant species in African traditional health systems especially within the communities where it naturally grows (Were et al., 2015). In fact, due to the increasing demand for chemical diversity in screening programs, and seeking therapeutic drugs from natural products, interest particularly, in medicinal plants throughout the world has significantly grown (Were et al., 2015). This tree species has a high pharmaceutical value with potent antimicrobial activity (Olila et al., 2001).

Scientific studies showed that stem bark and leaves of *W. ugandensis* contain a number of essential phytochemicals such as drimane sesquiterpenes including ugandensidal, polygodial, warburganal, and isopolygodial (Were et al., 2015). Consequently, the medicinal efficacy of this plant could be due to the presence of some of these phytochemicals (Kuglerova et al., 2011). The stem bark of *W. ugandensis* accumulates higher amounts of the medicinally active phytochemical compounds explaining its preference for medicinal use compared to other plant parts (Grieb et al., 2011). Unfortunately, the stripping off of the tree bark injures or kills the tree (Botha et al., 2004). And with the increasing demand in the global market, the wild population of *W. ugandensis* has been greatly exploited raising concerns regarding conservation and the sustainability of utilization (WHO, 2002).

The nature of bioactive compounds in medicinal plants and their activities are influenced by genetic and environmental factors including geographical locations (Ullah et al., 2012; Soureshjan and Heidari, 2014; Arya et al., 2010; Muchugi et al., 2012). Abuto et al. (2016) observed that the antimicrobial activities varied among *W. ugandensis* populations across the Kenya rift valley due to possibly genetic diversity. This therefore, implies that the medicinal efficacy of the same species of plants from different populations may vary. The fruit is inedible, all plant parts have a hot peppery taste, leaves and seeds are used to add flavour to curries (Dharani, 2011). The wood of *W. ugandensis* produces fragrance that persists over 4 years of storage. The tree also produces resin that is used locally in Uganda as glue to fix tool handles (Orwa, 2009).

**Botany and distribution of *W. ugandensis***

*W. ugandensis* is an evergreen plant with a spreading rounded crown (Figure 1a). It grows to about 4.5 to 40 m
in height and diameter of about 70 cm at breast height (Figure 1a) with a smooth or scaly, pale green or brown stem bark (Orwa, 2009) (Figure 1b); leaves are simple, alternate, stalked, glossy, short, with a presence of dotted glands (Figure 1d); flowers are solitary or in small 3-4 flowered cymes, axillary, regular and bisexual (Leonard and Viljoen, 2015). The fruit is a berry, at first green and ellipsoidal, later sub-spherical and turning purplish on maturation (Figure 1c); seeds are compressed and more or less cordate, yellow-brown in colour (Beentje et al., 1994). In fact, *W. ugandensis* is a hermaphroditic plant.

Ecologically, *W. ugandensis* occurs in lowland rainforests, upland dry evergreen forests, secondary bush and grasslands and on termitaria in swamp forests (Orwa, 2009). *W. ugandensis* and other related species are native to Northeast Tropical Africa: Ethiopia; East Tropical Africa: Uganda, Tanzania and Kenya; Central Africa: Democratic republic of Congo and South Tropical Africa: Malawi, South Africa and Swaziland (Orwa, 2009) (Figure 2).

**Traditional medicinal uses of *W. ugandensis***

*W. ugandensis* has gained a lot of popularity due to the high demand for the medicinal extracts from its bark, roots and leaves for use by traditional healers (Wamalwa et al., 2006; Olila et al., 2001). *W. ugandensis* is one of the priority species for herbal medicine in Kenya (Hamilton, 2008). Herbal medicine extracted from bark, roots, young twigs, leaves and fruits are used by the traditional healers (Maroyi, 2013). *W. ugandensis* is actually considered an integral part of African traditional medicine by very many herbalists and traditional healers across the continent. All plant parts of *W. ugandensis* are used by herbalists and traditional healers to treat a wide range of diseases. Most herbalists/traditional healers use the bark of the herbal plant for various herbal formulations but the leaves and roots are as well highly medicinal. Various plant parts are used to cure or alleviate ailments such as stomachache, malaria, toothache, erectile dysfunction, measles, candidiasis, weak joints among others (Table 1). The mode of common use is by chewing and swallowing the juice from the bark of *W. ugandensis* (Kubo et al., 1976); powdered form is also known to be very effective in the treatment of the same diseases (Githinji et al., 2010). The skills and knowledge about the traditional herbal medicines are normally passed on orally from generation to generation.
The knowledge passed on include what each herbal plant treats, and how the plant part is harvested, which plant part to use and the mode of its administration.

Toxicity of *W. ugandensis*

Acute toxicity tests for extracts of *W. ugandensis* showed that the plant is not toxic at acute exposure to test organisms (Ahmad et al., 2017; Karani, 2013). Administration of single doses of varied concentrations of *W. ugandensis* to mice, no mortality was observed even at highest concentrations tested. *W. ugandensis* was classified as relatively harmless based on the scale of Loomis and Hayes (1996) with LD$_{50}>$5000 mg/kg body weight (Karani, 2013). In another study, *W. ugandensis* was showed to be non-toxic to *Drosophila melanogaster* at acute exposure but toxic at chronic exposure (Ahmad et al., 2017). *W. ugandensis* as well has been used as a medicinal plant whose bark extracts, leaves and young shoots have been used for ages with no adverse effects (Henke, 1994; Kokwaro, 1976; Mbuya et al., 1994). *W. ugandensis* stem bark extracts have been established to be non-toxic to BALB/c macrophages (Gitinjili et al., 2010). Consequently, it can be concluded that the use of *W. ugandensis* as a medicinal plant is indeed safe although further studies especially clinical studies on its safety still need to be conducted.

**Phytochemistry of *W. ugandensis***

The high therapeutic values of *W. ugandensis* is attributed to the abundance of phytochemical compounds in it including drimane sesquiterpenes (Haraguchi, 1998; Frum et al., 2005; Frum and Viljoen, 2006; Jansen and De Groot, 1991; Kiyo, 1990) and tannins and mannitol (Van Wyk and Gericke, 2000). Studies on this plant have indicated the presence of the following compounds (Figure 3) muzigadial (I), ugandensidial (II), muzigadiolide (III) (Mashimbye, 1999) drimenol (IV), drimenin (V) (Mohanlall and Odhav, 2009), pereniporin B (VI) and polygodial (VII) (Taniguchi and Kubo, 1993), mukaadial (VIII), warburganal (IX), cinnamolide (X), cinnamolide-3β-acetate (XI), deacetylugandensolide (XIII), 7α-hydroxy-8drimen-11,12-olide (XII), linoleic acid (XIV), and 11α-hydroxy muzigadiolide (XV) in the stem bark (Kiyo, 1990) and Ugandensolide (XVI), warburgin (XVII), warburgiadione (XVIII) (Mohanlall and Odhav, 2009). In addition, sesquiterpenes such as ugandenial A (XIX) (Xu et al., 2009), 9α-11α-dihydroxy,6β-acetyl-cinnamolide (XX), 9α-hydroxyccinnamolide (XXI) and dendocarbins A (XXII) (a), L (b) and M (c) were present (Wube et al., 2005). Coloratane sesquiterpenes 6α,9α-dihydroxy-4(13), 7-coloratadien-11,12-dial (XXIII), 4(13),7-coloratadien-
Table 1. Traditional medicinal uses of *W. ugandensis*.

<table>
<thead>
<tr>
<th>Disease/Ailment</th>
<th>Plant part</th>
<th>Mode of preparation/administration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kiringe, 2006; Kokwaro, 2009)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kokwaro, 2009)</td>
</tr>
<tr>
<td>Chest pains</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kiringe, 2006; Wamalwa et al., 2006)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Bark, roots</td>
<td>Dried chewed and swallowed; fresh roots boiled and mixed with soup.</td>
<td>(Lovett et al., 2006)</td>
</tr>
<tr>
<td>Malaria</td>
<td>Bark, leaves, roots</td>
<td>Boiled in water and decoction drunk</td>
<td>(Lovett et al., 2006; Kokwaro, 2009; Wamalwa et al., 2006)</td>
</tr>
<tr>
<td>Fever</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kokwaro, 2009; Lovett et al., 2006)</td>
</tr>
<tr>
<td>Stomachache</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Henke, 1994; Kiringe, 2006; Kokwaro, 2009)</td>
</tr>
<tr>
<td>Toothache</td>
<td>Bark</td>
<td>Dried chewed and swallowed, dried bark powder can be applied</td>
<td>(Kokwaro, 2009; Lovett et al., 2006)</td>
</tr>
<tr>
<td>Hernia</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Lovett et al., 2006)</td>
</tr>
<tr>
<td>General body pains</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kokwaro, 2009; Lovett et al., 2006)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Lovett et al., 2006)</td>
</tr>
<tr>
<td>HIV-related opportunistic</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Mbwambo et al., 2009)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kiringe, 2006)</td>
</tr>
<tr>
<td>Measles</td>
<td>Bark</td>
<td>Not specified.</td>
<td>(Olila, 1993)</td>
</tr>
<tr>
<td>Muscle pains</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kokwaro, 2009)</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>Leaves</td>
<td>Bath decoctions.</td>
<td>(Wamalwa et al., 2006)</td>
</tr>
<tr>
<td>Common cold</td>
<td>Bark</td>
<td>Not specified.</td>
<td>(Lovett et al., 2006)</td>
</tr>
<tr>
<td>Sinuses</td>
<td>Bark</td>
<td>Dried and ground to a snuff</td>
<td></td>
</tr>
<tr>
<td>Throat infections</td>
<td>Bark</td>
<td>Bark decoction or bark mixed with animal fat</td>
<td>(Kiringe, 2006)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bark</td>
<td>Not specified Ethiopia</td>
<td>(Wube et al., 2005)</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Bark</td>
<td>Dried chewed and swallowed.</td>
<td>(Kiringe, 2006)</td>
</tr>
<tr>
<td>Weak joints</td>
<td>Bark</td>
<td>Weak joints.</td>
<td>(Kokwaro, 2009)</td>
</tr>
<tr>
<td>Chest pain/Complaints</td>
<td>Bark</td>
<td>Dried chewed and swallowed Or Smoke from burning bark inhaled</td>
<td>(Kiringe, 2006; Wamalwa et al., 2006)</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Bark</td>
<td>Not specified.</td>
<td>(Kuglerova et al., 2011)</td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td>Bark</td>
<td>Bark boiled in water/soup and taken orally</td>
<td>(Ngure et al., 2009)</td>
</tr>
<tr>
<td>Emetic</td>
<td>Bark, leaves</td>
<td>Hot decoction of bark or leaves</td>
<td>(Nanyingi, 2008)</td>
</tr>
<tr>
<td>Lung problems</td>
<td>Bark</td>
<td>Bark decoction.</td>
<td>(Kiringe, 2006)</td>
</tr>
<tr>
<td>Snake bite</td>
<td>Bark</td>
<td>Not specified.</td>
<td>(Olila, 1993)</td>
</tr>
<tr>
<td>Intestinal Worms</td>
<td>Bark</td>
<td>Not specified.</td>
<td>(Lovett et al., 2006)</td>
</tr>
</tbody>
</table>
12,11-olide (XXIV), and 7b-hydroxy-4(13),8-coloratadien-11,12-olide (XXV) are present in stem bark of W. ugandensis (Wube et al., 2005) Monoterpenes (Kiy, 1990) and flavonol glycosides in the leaves (Manguro et al., 2003) (Figure 3).

Antimicrobial activities

Many pharmacological studies have confirmed antimicrobial activities of W. ugandensis extracts (Were et al., 2015; Kuglerova et al., 2011; Ahmed et al., 2013). The curative efficacy of extracts of W. ugandensis is attributed to the potent antifungal and antibacterial activities of the synergistic effects of the different bioactive phytochemical compounds in the plant (Olila et al., 2001; Haraguchi, 1998; Jansen and De Groot, 1991; Mashimbye, 1999; Taniguchi and Kubo, 1993). The pattern of antimicrobial inhibition of the various extracts of W. ugandensis varied with the solvents used for extraction and the part of the plant used as well as the regions where the samples were collected. It was observed that the DCM solvent extracts exhibited the highest antimicrobial activity than the MeOH solvent extracts regardless of the plant part analyzed.

Antibacterial and antimycobacterial activities

W. ugandensis showed antimicrobial activity against Staphylococcus aureus and Escherichia coli in the agar well diffusion assay (Olila et al., 2001). This effect, however, was not demonstrable in the paper disc assay. Kuglerova et al. (2011) also showed that W. ugandensis stem bark exhibited antibacterial activity with a minimum inhibitory concentration (MIC) of 256 µg/ml against S. aureus and 512 µg/ml against Enterococcus faecalis. Similarly in Kitale and Rumuruti in Kenya, dichloromethane stem bark extracts of W. ugandensis exhibited inhibitory activity against S. aureus and C. albicans with mean zones of inhibitions both of 19.75 mm (Abuto et al., 2016). The preliminary bioassay results showed that S. aureus and C. albicans were the most susceptible microorganisms while E. coli was resistant to W. ugandensis extracts (Abuto et al., 2016). S. aureus was more sensitive than E. coli to W. ugandensis extracts (agar well assay). Since S. aureus is more often associated with secondary bacterial infections in measles than E. coli it may explain the value of the plant in measles therapy (Olila et al., 2001). The compound muzigadiol has been found to be very active against S. aureus (Abuto et al., 2016). Antimycobacterial activity of W. ugandensis against Mycobacterium aurum, M. fortuitum, M. phlei and M. smegmatis were demonstrated using dichloromethane extract of the stem bark of W. ugandensis (Wube et al., 2005). Wube et al. (2005) further showed that the active constituents of W. ugandensis gave MIC values ranging from 4 to 128 mg/ml, compared to the antibiotic drugs ethambutol and isoniazid with MIC ranging from 0.5 to 8 mg/ml and 1 to 4 mg/ml respectively. Furthermore, muzigadiol and muzigadiolide were found to have antimycobacterial activities against M. fortuitum (MIC of 16 µg/ml) and M. phlei (MIC of 64 µg/ml) respectively (Wube et al., 2005).

Antifungal activity

In a study conducted by Olila et al. (2001), they observed that the ethanolic extracts of the stem bark of W. ugandensis showed significant antifungal activity against Candida albicans. Similarly, warburganal which is one of the major phytochemicals contained in W. ugandensis exhibited a broad-spectrum antifungal activity against yeasts and filamentous fungi especially against Saccharomyces cerevisiae, C. utilis, and Sclerotinia libertiana (Kubo, 1995). Kuglerova et al. (2011) also 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 muzigadiol compound in the plant. Furthermore, W. ugandensis stem bark and leaves extracts were found to exhibit antifungal activity against C. utilis (Mbwanmo et al., 2009; Ahmed et al., 2013; Taniguchi et al., 1983).

Antiplasmodial activity

W. ugandensis stem bark extract has shown potent activity against Plasmodium knowlesi and P. Berghei (Taniguchi et al., 1978). In fact, in an in vitro experiment, the methanol extracts from various parts of W. ugandensis exhibited antiplasmodial activity with an IC_{50} value of less than 5 mg/ml against both chloroquine-sensitive and chloroquine resistant strains of P. falciparum (Taniguchi et al., 1978). This result sets a basis upon which future antimalarial drugs could be developed and typically explained the continuous use of the plant in traditional medicine for the treatment and management of malaria throughout its distribution range.

Other activities

Beside the activities discussed above, the presence of drimane sesquiterpenoids in W. ugandensis makes the plant a vital insect pest controlling agent (Olila et al., 2001; Frum et al., 2005; Xu et al., 2009; Nanyingi et al., 2010; Kubo et al., 1977). Similarly, warburganal and muzigadiol showed strong inhibitory effects on the feeding of larvae of the monophagous Spodoptera exempta and the polyphagous Spodoptera littoralis at a concentration of 0.1 ppm in a regular leaf disk method (Nanyingi et al., 2010). W. ugandensis also exhibited...
antifeedant activity against S. frugiperda, Heliotis armigera and H. virescens (Kubo et al., 1977).

Drimane sesquiterpenoids in W. ugandensis are known to have cytotoxic activities that is, toxic effects at cellular level (Frum et al., 2005; Taniguchi and Kubo, 1993; Nanyingi et al., 2010; Meinwald et al., 1978). For example, ethanolic leaf extracts of W. ugandensis exhibited cytotoxic activity (95% CI), against brine shrimp larvae with reference to cyclophosphamide, a standard anticancer drug (Mbwambo et al., 2009). In an in vitro study, W. ugandensis bark exhibited potent cytotoxic activity on KB cell line with 99% and 64% inhibition at 10 and 1 mg/ml, respectively (Xu et al., 2009).

The hexane extract of W. ugandensis was strongly antileishmanial against Leishmania major and Leishmania donovani with IC₅₀ value of 9.95 and 8.65 respectively (Ngure et al., 2009). W. ugandensis demonstrated trypanocidal activity against Trypanosoma brucei in vitro (Oilla et al., 2001). A cytotoxic sesquiterpene characterized as muzigadial was isolated from W. ugandensis and used to treat trypanosomiasis and other parasitic diseases in animals (Meinwald et al., 1978; Kioy, 1990). Rugutt et al. (2006) in Kenya, showed W. ugandensis activity against soil pathogens namely Fusarium oxysporum, Alternaria passiflorae and Aspergillus niger. All these activities clearly justify the continued use of W. ugandensis in traditional medicine to treat and manage myriad of diseases and disorders.

CONCLUSION

In all the communities where W. ugandensis occurs and particularly across Africa, it is medicinally highly valued and used by the local populations to treat and manage wide range of ailments and health conditions indicating that the species is a very vital source of ethnomedicine. Besides, there have not been records of its toxicity in populations where its leaves and bark have been used as vital sources of medicine. Several pharmacological studies have been carried out on W. ugandensis extracts leading to the identification and isolation of highly medicinal compounds backing up some of its documented traditional use in treatment of disease across Africa. There is no much documentation providing evidence of proprietary medicinal product development from W. ugandensis yet it has been proven through many studies of its potent therapeutic values. The need for clinical research on the extracts of W. ugandensis could be the research gap needed to make these products attractive for further pharmaceutical product development. Further research is therefore important on W. ugandensis to develop products with highly valued medicinal contents. In all or most of the areas, the local people use the raw extracts directly in the treatment and management of various ailments without precise standardized dosage across the discipline. 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. It is also important to note that the ever-increasing use of W. ugandensis in the treatment and management of various ailments has led to over exploitation hence decreasing its population drastically. Consequently, there is need for advanced and rapid propagation techniques to increase the population and distribution of W. ugandensis.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

This work was supported under the framework of international cooperation program (Korea-South Africa Cooperative Research Project for Excavation of Candidate Resources of Complementary and Alternative Medicine) managed by National Research Foundation of Korea (Grant: 2017093655, KIOM: D17470). Additionally, this work was equally supported by Grants from Development of Foundational Techniques for the Domestic Production of Herbal Medicines (K18405) from the Korea Institute of Oriental Medicine (KIOM), through the Ministry of Science and ICT, Republic of Korea.

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