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EFFICACY OF *WARBURGIA UGANDENSIS* IN CHRONIC BRONCHIAL ASTHMA MANAGEMENT: A REVIEW OF THE EVIDENCE

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ABSTRACT

***Objectives*: The review was based on the botany, safety and efficacy of *W. ugandensis* in asthma management.**

***Data sources*: Search of original peer-reviewed articles on *W. ugandensis* from electronic database was done using key words.**

***Study selection*: Experimental researches were considered.**

***Data synthesis*: The obtained data was verified separately for reliability, any inconsistencies noted were settled through discussions amongst authors, the data was summarized, analyzed, compared and conclusions drawn accordingly.**

***Results*: *Warburgia ugandensis* reduced Nitric oxide in BALF, inflammatory cells in BALF and plasma ovalbumin specific immunoglobulin E (IgE) in BALB/c mice induced with asthma. It also demonstrated a protective effect to developing airway resistance proven by increase in pre convulsion time in Murine asthma model. With use of Vero E6 cell for cytotoxicity it was proven to be safe for use as its CC_{50} was >250 ug/ml and LD_{50} was > 5000mg/kg. There was insiginificant cytotoxicity in BALB/c peritonial cell macrophaged where 3 out of 100 cells died at the concentration of 1000 ug/ml when it was compared to Pentostam as a positive control. *Warburgia ugandensis* also was non-toxic to *Drosophila melanogaster* on acute exposure but toxic on chronic exposure.**

***Conclusion*: *Although Warburgia ugandensis* has anti-asthmatic properties there is need for further validation to augment the findings.**
***Recommendation*: More experimental studies should be done using specific isolated chemical compounds of *W. ugandensis* to demonstrate its' anti-asthmatic activity. The specific molecules be used in synthesis of potential drugs for asthma management. Other plant parts should be studied for their anti-asthmatic properties.**

INTRODUCTION

Across the world, traditional medicine (TM) is either the mainstay of health care delivery or serves as a complement to it. There is increasing resistance of disease agents to conventional medicine hence an upsurge in interest in complementary medicine by scientists (1). Integration of traditional medicine has been recommended by World Health Organization since 1978. Traditional medicine strategy 2014-2023 by World Health Organization aims to support member states in developing proactive policies and implementing action plans that will strengthen the role traditional medicine plays in keeping populations healthy (2). Henceforth knowledge on efficacy of *W. Ugandensis* in management of asthma will provide an insight into alternative management of asthma in line with the WHO recommendations. *Warburgia ugandensis* is an endangered indigenous species and has been rated as the second highest medicinal plant in Kenya after *Prunus Africana* (3).

Bronchial asthma is the most common chronic respiratory disorder. It is characterized by recurrent airway inflammation, hyper-responsiveness and reversible airway obstruction (4). The disease burden is approximately 8-10% of the world's population, with an increase of morbidity and mortality in the past 20 years (5). Uncontrolled asthma may be fatal and detrimental with enormous economic cost, poor social interaction, psychosocial trauma and often lead to symptoms that impair quality of life and lower self-esteem (6).

Plants are an important source of medicine both in modern and traditional systems (1). Indigenous knowledge on the use of medicinal plants and the effective plant part offers a wide range of cultural and subsistence benefit by providing affordable and sustainable means of primary health care especially for the developing countries due to impoverished condition (7). Current conventional asthma therapy lacks satisfactory success due to adverse effects, hence patients seek complementary and alternative medicine to treat asthma (7) . Conventional anti-asthmatic drugs currently being used for management of asthma such as beta 2 agonist, corticosteroids, mast cell stabilizers leukotriene inhibitors and methylxanthines are costly and have been shown to have a lot of side effects among them immune suppression, cardiac abnormalities hyperglycemia, hypokalemia and muscle tremors (5) .

Therefore, there is a high need to identify more safe, effective and affordable drugs to manage asthma.

LITERATURE REVIEW

Pathophysiology and pathogenesis of bronchial asthma

Asthma is a chronic airway inflammatory disease characterized by infiltration of the airway by T cells. T lymphocytes (Th 2) are activated in response to antigen stimulation.

This cause production of high levels of cytokines (IL4, IL5, IL-9, IL-13, TNF,) mediate recruitment of airway mast cells and eosinophils, cause switching of IgG to IgE, and increase mucus secretion. IL-13 stimulates airway hyperactivity and mucus production. IL-4 promotes differentiation and proliferation of more Th2 cells and switching of IgG to IgE (11). Immunoglobulin E antibodies attach to cell surface receptors of mast cells, basophils, dendritic cells and lymphocytes activating the cells. They release their granules containing histamine, prostaglandins D2 and leukotrienes that are potent broncho constrictors. Asthmatic patients have increased number of eosinophils along the airway. The number increases more during exacerbation of an asthmatic attack. The high number correlates with severity of the disease. Granules of eosinophil have pro-inflammatory mediators and leukotrienes that mediate inflammatory process in asthma (12).

METHODOLOGY

In the review, information on *W. ugandensis* from original peer-reviewed articles in English language published in scientific journals with a focus on its botany, safety and efficacy in asthma management was searched. Electronic literature databases, including but not limited to PubMed, Medline, Google Scholar, Hinari, Agora, Scinapse, EBSCOhost, AJOL and Science Direct for relevant information were carefully searched. The following words were used as key search terms "*Warburgia ugandensis*" OR "Pepper bark tree" OR "East African Greenheart" OR "East African Greenwood". "Ethnopharmacological uses" OR "Medicinal uses" OR "Diseases treated" OR asthma treatment" OR Antioxidant properties". "Toxicity" OR "safe dose". The obtained data was verified separately for the reliability, any inconsistencies noted were settled through discussions amongst authors, the data was summarized, analyzed, compared and conclusions were drawn accordingly.

RESULTS

Warburgia ugandensis common names, location and description

Warburgia ugandensis belongs to the family of Canellaceae. In English it's commonly known as East African green wood/East African greenheart/pepperbark tree/Kenya greenheart. *Warburgia* is a genus that includes several species, *W. salutaris Berto f. Chiov* found in north-eastern parts of South Africa, Swaziland, south-eastern Zimbabwe, southern Mozambique, Malawi and Zambia. *W. elongate Verd* and *W. stuhlmannii Engl*. found along East African coastline and *W. ugandensis Sprague* found within East African highland (8), lowland rainforest and upland dry evergreen forest (3).

Warburgia ugandensis is a spreading evergreen tree 4.5-30 m tall, 70 cm in diameter, bark smooth or scaly, pale green or brown (Figure 1A,1B). Leaves alternate, simple, dotted with glands, petiole 1-5mm long glossy dark green above, paler green and dull below (Figure 1C). It has berry fruits, at first, they are green and ellipsoidal, later sub spherical and turn purplish, 3-5 cm in diameter, skin leathery, glandular (Figure 1E). *Warburgia ugandensis* is hermaphroditic, flowering at the beginning of the rainy season (Figure 1D) and fruiting follows later in the rainy season. (9)

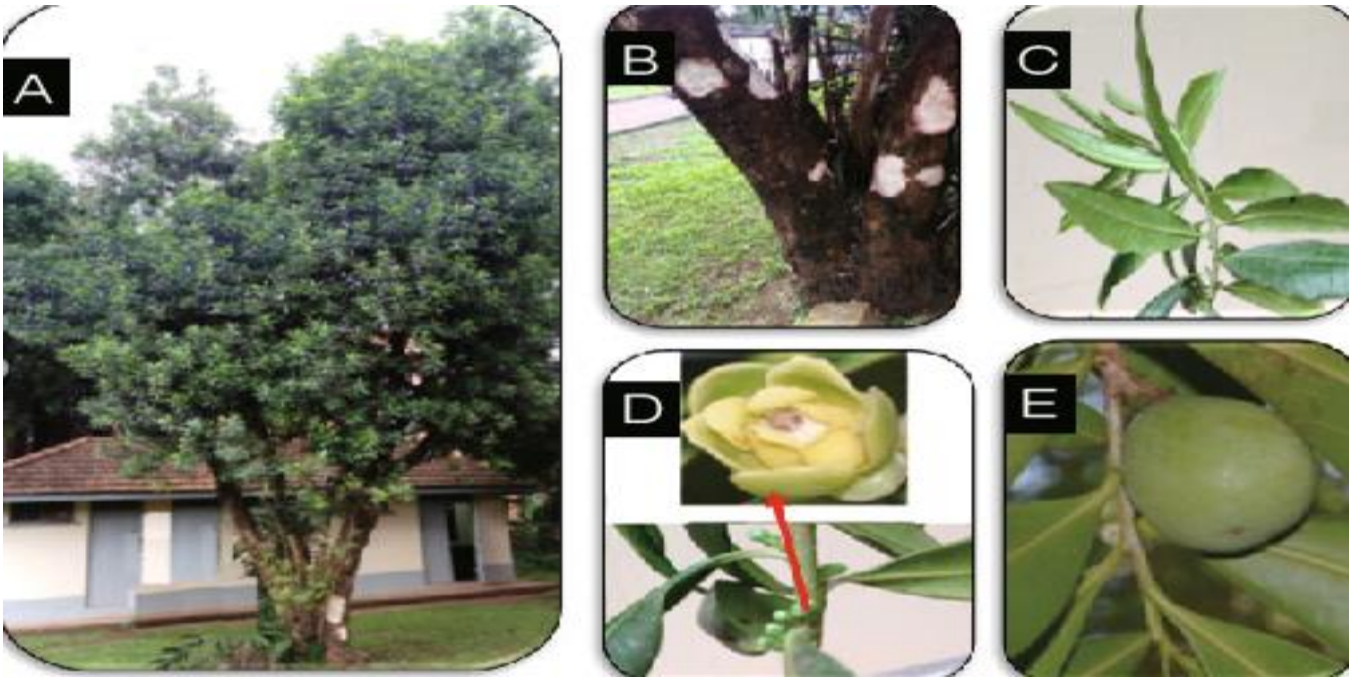

Figure 1 *Images of W. ugandensis tree and its parts adapted from Okello, D., & Kang, Y. (2019)(10).*

Ethnopharmacology of Warburgia ugandensis in management of asthma

Extract of *W. ugandensis* has diverse metabolites that are linked to its medicinal properties (13). Medicinal plants used for the treatment of asthma should have anti-inflammatory, immunomodulatory, anti-histaminic, smooth-muscle relaxation, anti-allergic activity and antioxidant effects. *Warburgia ugandensis* has been found to have antioxidant phytochemicals such as flavonoids and phenols (13). Anti-oxidants reduce bronchoconstriction severity by inhibiting pro-inflammatory events as a result of neutralizing the effects of excess reactive oxygen species and reactive nitrogen species (1). Phenolic phytochemicals also have anti-inflammatory effects and anti-mutagenic activity (14).

Warburgia ugandensis has been shown to have secondary metabolites such as alkaloids, terpenes, flavonoids, polyphenol, and terpenoids responsible for its anti-spasmodic activity (14). *Warburgia* species are known to be rich in sesquiterpenes with drimane and coloratane skeletons (13). Bark extract sampled from different populations across Kenyan Rift valley showed Sesquiterpenoids and fatty acid as the most abundant compounds (15). Sesquiterpenoids have anti- inflammatory and tumorigenesis activity (16).

Efficacy, dose and safety of W. ugandensis

Water extract of *W. ugandensis* given at a concentration of 500mg/kg body weight to BALB/c mice induced with asthma using ova albumin/alum significantlly reduced esinophil levels in BALF and ovalbumin specific immunoglobulin E (IgE) antibodies levels in blood hence proving to be effective in management of asthma (17).

Ngugi et al., (2019) determined anti-asthmatic activity of *W. ugandensis* using BALB/c mouse model for asthma with budesonide used as positive control. Several paramaters were examined; Pre-convulsion time (PCT), Nitric

oxide levels in BALF and differntial inflammatory cell count in BALF. There was a significant decrease in inflammatory cell that was dose dependent with 500mg/kg body weight of *W. ugandensis* decreasing the cells more than 250mg/kg body weight. Budesonide did not show any significant difference in BALF inflammatory cell reduction when it was compaired to 500mg/kg bdwt of *W. ugandensis* intervention. Warburgia ugandensis significantly reduced BALF NO levels in a dose dependent manner and 500mg/kg bdwgt of *W. ugandenis* was not significantlly different from positive contol budesonide. Pre convulsion time was used to determime the protecive effect of *W. ugandensis* to developing airway resisistance. There was a significant increase in PCT and percent inhibition to developing airway resistance when negative control was compaired to the intervention though was not dose dependent. There was no significant difference between positive control and the intervention groups (18).

Cytotoxicity study of *W. ugandensis* on Vero E6 cell using MTT assay by Karani et.al showed that it was safe for use as its CC_{50} was >250 ug/ml as per Rukunga and Simon classification of cytotocicity, and its LD_{50} was > 5000mg/kg using BALB/c mice for the toxicicity doses in vivo . This was in agreement with a study done by Githinji *et. al* (19) that showed insiginificant toxicity levels of crude extract of *W. ugandensis* that had a mean of 3 dead BALB/c peritonial cell macrophaged out of 100 at the concentration of 1000 ug/ml when it was compared to Pentostam as a positive control that had a mean of 45 BALB/c peritoneal cells dead in a 100 cells at same concentration. In another study, *W. ugandensis* was shown to be non-toxic to *Drosophila melanogaster* at acute exposure but toxic at chronic exposure (20).

CONCLUSION

Extract of *W. ugandensis* has diverse phytochemicals that are linked to its anti-asthmatic properties and have different mode of actions. It has been shown to be safe with a LD > 5000mg/kg using BALB/c mice. The bark is the most commonly used plant part in asthma management.

RECOMMENDATIONS

Clinical studies should be done to demonstrate the therapeutic efficacy seen in the murine models. All the studies included in the review were experimental that used crude extract. More experimental studies should be done using specific isolated chemical compounds of *W. ugandensis* to demonstrate its' anti-asthmatic activity and such compounds be used in synthesis of conventional anti-asthmatic drugs.

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