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WARBURGIA UGANDENSIS: A REVIEW OF COMPOUNDS AND BIOACTIVITY

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Abstract

Warburgia species (Canellaceae) are traditionally used to treat a wide range of illnesses including stomach ache, diarrhea, abdominal pains, toothache, oral thrush, venereal diseases, cold and cough, fever, muscle pains, weak joints, skin diseases, malaria, parasitic infections and snake bite. Therapeutic properties of medicinal plants have been linked to the secondary metabolites which are biosynthesized by the plants. The aim of this study was to review the bioactivities and chemical composition of *Warburgia ugandensis*. The findings from this study show that extracts from the plant have antifungal, antibacterial, antiulcer, insect antifeedant, molluscicidal, antimycobacterial, antileishmanial and anti-plasmoidal effects. The most investigated part of *W. ugandensis* is the stem bark (22 articles) followed by leaves (15), root bark (6), seeds (2) and fruits (2). All parts the plant have important bioactivities. Sixty nine compounds have been reported from the plant including sesquiterpenes (43), flavonoids (15), lignanamides, and macrocyclic glycosides (10) and fatty acid (1) some of which have demonstrated different bioactivities. The drimane sesquiterpenes are the main class of sesquiterpenes in the plant. The Further investigation of the not well studied parts of the plant such as the flowers and fruits is recommended to determine their chemical composition and efficacy in disease management.

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Introduction

Since many thousands of years ago, people have used plant extracts to treat illnesses. The majority of people in Africa's developing nations still rely on traditional medicines for their basic medical needs [1-4]. Secondary metabolites produced by plants have anti-disease properties that span a wide range of ailments [5-8]. Traditional remedies are preferred because they are readily accessible, effective and have no side effects [9-13]. In addition, chances of developing drug resistance is negligible. In recent years many researchers have concentrated on confirming the effectiveness of medicinal plant through *in-vivo* and *in-vitro* trials, as well as the identification of the bioactive components [14-18]. Such earlier research resulted in the discovery of a number of significant bioactive substances, including terpenoids, alkaloids, steroids, flavonoids and quinones [19-25]. Numerous secondary metabolites obtained from plants, with previously unknown pharmacological activities, have been extensively investigated as a source of medicinal agents [26-31]. In the process of creating novel medications, bioactive molecules originating from nature serve as a significant source of lead compounds [32-37].

The genus *Warburga* (Canellaceae) consists of three species namely, *W. ugandenss*, *W. salutars* and *W. stuhlmann*. The plants are widely distributed in Democratic Republic of Congo, Ethiopia, Kenya, Malawi, Mozambique, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe [38]. They are widely used in Eastern and Southern Africa for treatment of various ailments [2, 39]. *Warburgia ugandensis* is one of the most highly utilized medicinal plants in tropical and subtropical Africa and is now highly endangered in the wild [40]. It is rated as the second highest priority medicinal plant species in Kenya [41]. The plant 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 [42, 43]. Concoction from the stem roots, bark and leaves is used as a remedy for stomach ache, diarrhea, constipation, abdominal pains,

toothache, oral thrush, cystitis, venereal diseases, cold and cough, fever, muscle pains, weak joints, general body pains, skin diseases, malaria, bronchial infections, parasitic infections and snake bites [44, 45]. All parts of *W. ugandenss* are edible and leaves, bark, young shoots and fruits are used in curries while roots are used for soup suggesting that the plant is not toxic to human [2]. The aim of this study was to review the chemical compounds isolated from *W. ugandensis* and their biological activities.

Biological activities of *Warburgia ugandensis*

Due to the numerous traditional medicinal applications of the plant, several pharmacological studies have been conducted on the extracts (Table 1). Previous investigations have shown that the extracts have antifungal, antibacterial, antiulcer, insect antifeedant, molluscicidal, antimycobacterial, antileishmanial and anti-plasmoidal [46 -51]. Reports from previous studies indicated that the roots and stem barks are the most commonly used by traditional healers [43, 46]. The plants is becoming less available for medicinal application due to over harvesting of the roots and stem barks through uprooting and debarking [52]. Factors that affect the bioactivity and of medicinal plants include environmental conditions, climatic differences, seasonal variation, method of extraction and part of the plant used [53, 54].

Table 1: Some bioactivities of *Warburgia ugandensis* from different location

Bioactivity	Test organism/ model	Place of plant collection	Plant part	Ref.
Antiplasmodial	*Plasmodium knowlesi, P. berghei*	Oloolua Forests, Kajiado County, Kenya	Stem bark, root barks	[50]
	P. falciparum	Kampala, Uganda	Stem bark	[55]
	P. falciparum	Kibale National Park	Bark	[56]
	P. falciparum, P. burghei	Nairobi, Kenya	Stem bark	[57]
Antioxidant	DPPH, ABTS	Jomo Kenyatta University of agriculture and Technology, Kenya	Leaves, roots, stem, bark	[58]
	DPPH, ABTS	Narok, Kenya	Stem bark	[59, 60]
	DPPH	Kakamega, Kenya	Leaves	[61]
Anti-inflammatory	*COX-2 Inhibitory*	Narok, Kenya	Stem bark	[59, 60]
Antimicrobial	*Bacillus subtilis, Escherichia coli, Saccharomyces cerevisiae, Penicillium crustosum*	Rift Valley, Kenya	Leaf and stem bark	[62]
	Mycobacterium aurum, M. fortuitum, M. phlei, M. smegmatis		Bark	[39]
	Staphylococcus aureus, Candida albicans	Kitale, Kenya	Leaves, roots, fruits	[63]
	Pseudomonas aeruginosa, S. aureus, B. subtilis, E. coli C. albicans.	Nairobi, Kenya	Bark, roots, leaves, fruit	[47]
	Alternaria solani, Phytophthora infestans	Kiambu, Kenya	Stem bark	[64]
	S. aureus and C. albicans	Rift Valley, Kenya	Stem bark	[51]
	S. aureus, S. epidermidis, C. albicans, C. glabrata C. glabrata	Kakamega Forest,Kenya	Leaves	[65]
	Plasmopara viticola	Pakwach, Uganda	Bark, leaves	[66]
	Fusarium oxysporum, A. passiflorae, A. niger	Kenya	Bark, leaves	[67]
	S. cerevisiae, B. subtilis, Sclerotinia	Mabira Forest, Uganda	Stem bark	[43]

	libertiana.			
	S aureus, E. coli, Vibrio cholerae, B. cereus C. albicans and Cryptococcus neoformans.	Lushoto, Tanzania	leaves	[52]
	K. pneumoniae, E. coli, P. aeruginosa, S. boydii, S. aureus, S. pneumonia, B. albicans	Addis Ababa, Ethiopia	Leaves	[26]
	B. albicans, Cryptococcus neoformans, Microsporum gypseum, Trichophyton mentagrophytes	Ngong forest, Kenya	Stem bark	[68]
	Salmonella typhy, S. typhimirium, S. enterica	Nyamira, Kenya	Stem bark	[69]
	E. coli, B. albicans Proteus mirabilis, S. aureus	Tooro Botanical Center, Uganda	Stem bark	[70]
	M. tuberculosis	Mabira Forest, Uganda	Stem bark	[71]
	E. coli, Klebsiella pneumonia, P. aeruginosa, S. typhi	Jomo Kenyatta University of Agricultural and Technology, Kenya	Leaves, stem-barks and roots	[72]
Cytotoxicity/ antitumor	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in Vero cell lines	Natural Chemotherapeutics Research Institute, Uganda	Stem bark	[55]
	Human tumor cell line KB	Kibale National Park, Uganda	Bark	[73]
	Macrophage cells from BALB/c	Baringo, Kenya	Stem bark, leaves	[74]
	Leukemia and solid cancer cell lines and human primary cells *in vitro*	Sironko, Uganda	Stem bark	[75]
		Kibale National Park, Uganda	Bark	[56]
	HT-29, HCT116, and CT26 cell lines and colon tumors mouse model	Mount Kenya, Kenya	Root barks	[76]
Insecticidal	*Aedes agypti, Aedes africanus, Culex quinquefasciatus*	Ethiopia	Leaves	[77]
	Sitophilus zeamais	Kenyatta University, Kenya	Leaves	[78]
	S. zeamais, Prostephanus truncatus	Nakuru, Kenya	Stem bark	[10, 79] [80]
	Aedes aegyptica, Culex pipiens	Nakuru, Kenya	Seed	[81]
Anthelmintic	*Caenorhabditis elegans*	Kakamega Forest, Kenya	Leaves	[82]
Antileishmanial	Antipromastigote, anti-	Baringo, Kenya	Stem bark	[46, 49]

	amastigote assay			
	Anti-promastigote, anti-amastigote assay	Baringo, Kenya	Stem bark and leaves	[74]
Anti-asthmatic	BALB/c asthmatic mouse model	Meru Forest, Kenya	Stem bark	[48]

The most investigated part of *W. ugandensis* is the stem bark (22 articles) followed by leaves (15), root bark (6), seeds (2) and fruits (2). The results (Table 1) confirm that all parts the plant have important bioactivities. The use of the leaves is usually the most recommended as opposed to stem and roots because leaves grow faster and abundantly [52].

Compounds isolated from *Warburgia ugandensis*

Phytochemical studies on *W. ugandensis* have shown the plant to be rich in sesquiterpenes, flavonoid, lignanamides and macrocyclic glycoside (Figure 1) [83-84]. Drimane sesquiterpenes are the main class of sesquiterpenes found in the plant. However, some eudesmane-type sesquiterpenes were also reported [39].

Tricyclic drim-8(9)-ene sesquiterpenes namely 1,6,7-trihydroxy-8-drimen- 11,12-olide (**1**), 7α-hydroxy-8-drimen-11,12-olide (**2**), 6-hydroxy-8-drimen-11,12-olide (**3**), ugandensolide (**4**), deacetyl ugandensolide (**5**), 7α-acetylugandensolide (**6**), dendocarbin L (**7**), dendocarbin M (**8**) and 7-hydroxywinterin (**9**) have been reported [63, 67, 73, 83, 85, 86]. Tricyclic drim-7-ene sesquiterpenes reported from the plant include pereniporin A **(10),** isodrimeninol (**11**), drimenin (**12**), 3β-acetoxycinnamolide (**13**), pereniporin B (**14**), dendocarbin A (**15**), ugandenial A (**16**), 9α,11α-dihydroxy, 6β-acetylcinnamolide (**17**) and bemadienolide (**18**) [63, 65, 84, 87, 88]. Drim-7-ene sesquiterpenes including polygodial (**19**), warburganal (**20**), mukaadial (**21**), 1-hydroxymukaadial (**22**), ugandensidial (**23**), drimendiol (**24**), 12-hydroxy-epi-albrassitriol (**25**), 9,11,12-trihydroxy-7-drimene (**26**), 1,6,9,11,12-pentahydroxy-7-drimene (**27**) and the acid derivatives **28**-**34** were also reported [59, 63, 83, 88]. Coloratane type sesquiterpenes muzigadial (**35**), 6α-Hydroxymuzigadial (**36**), 9-deoxymuzigadial (**37**), muzigadiolide (**38**), 4(13),7-coloratadien-12,11-olide (**39**), 11α-hydroxymuzigadiolide (**40**) and 7β-hydroxy-4(13),8-coloratadien-11,12-olide (**41**) were reported [39, 67, 75, 83, 85, 86]. The eudesmane-type sesquiterpenes namely Warburgin (**42**) and warburgiadione (**43**) have also been reported from the plant [39, 73, 83].

Compounds **2**, **38** exhibited antimycobacterial [39] while compounds **4**-**6**, **12**, **13**, **18**, **21**, **28**, **32** exhibited antimicrobial activity [84, 86]. Compound **19** showed insecticidal, antimicrobial, cytotoxic, anticancer, anthelmintic and nematicidal activities [73, 75, 79, 82, 89, 90]. Compound **20** showed insecticidal, insect antifeedant, antimicrobial, molluscicidal, cytotoxic and anthelmintic activities [65, 75, 79, 80]. Compound **23** gave insecticidal, antimicrobial and antimalarial activities [86, 91].

Flavonoids from *Warburgia ugandensis*

Flavonoids reported from *Warburgia ugandensis* (Table 2) include kaempferol (**44**), kaempferol 3-glucoside (**45**), kaempferol 3,7,4'-tri-O-β-glucoside (**46**), kaempferol 3-arabinoside (**47**), kaempferide 3-O-β-xylosyl (1→2)-β–glucoside (**48**), kaempferol 3-O-α-rhamnoside-7,4'-di-O-β –galactoside (**49**), kaempferol 3-rhamnoside (**50**), kaempferol 3-rhamnoside-4'-galactoside (**51**), kaempferol 3-rutinoside (**52**), myricetin (**53**), myricetin 3-galactoside (54), quercetin (**55**), quercetin 3-glucoside (**56**), quercetin 3-O-[α-rhamnosyl (1→6)] [β-glucosyl (1→2)]-β-glucoside-7-O-α-rhamnoside (**57**), and quercetin 3-rhamnoside (**58**) [92].

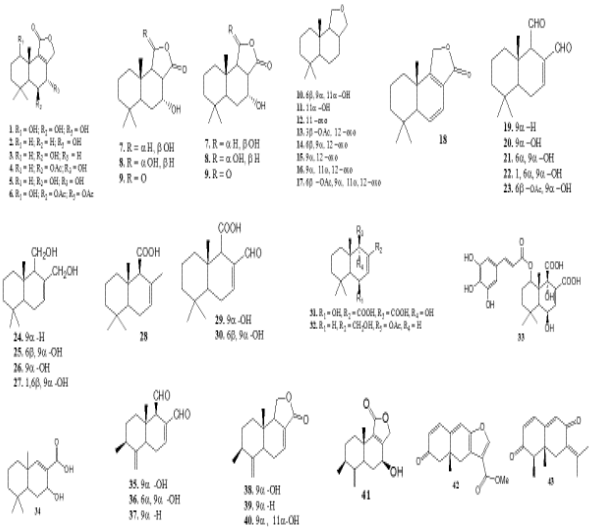

Figure 1: Some sesquiterpenes from *Warburgia ugandensis*

Table 2: Flavonoids from *Warburgia ugandensis*

Compound	Bioactivity	Ref.
Kaempferol (**44**)	Antimicrobial, antimalarial, anti-inflammatory, anti-oxidant	[22, 92-95]
Kaempferol 3-glucoside (**45**)	Antifungal, anti-inflammatory	[92, 96, 97]
Kaempferol 3,7,4'-tri-O-β–glucoside.(**46**)		[92[
kaempferol 3-arabinoside (**47**)	Antioxidant, cytotoxic	[92, 98]
Kaempferide 3-O-β-		[92[

xylosyl (1→2)- β – glucoside (**48**)		
Kaempferol 3-O-α-rhamnoside-7,4'-di-O- β-galactoside (**49**)		[92[
Kaempferol 3-rhamnoside (**50**)	Antitumor, antioxidant, antileishmanial	[92, 99, 100]
Kaempferol 3-rhamnoside-4'-galactoside (**51**)		[92]
Kaempferol 3-rutinoside (**52**)	Hepatoprotective, antioxidant anti-inflammatory, anti-tumor	[92, 101 - 103]
Myricetin (**53**)	Antimicrobial, antioxidant, anti-inflammatory, antioxidant, anticarcinogenic	[92, 104, 105]
Myricetin 3-galactoside (**54**)	Antioxidant, cytotoxicity, antigenotoxic, antinociceptive, anti-inflammatory	[92, 106]
Quercetin (**55**)	Antimicrobial, cytotoxic, antioxidant, anti-inflammatory, antiplasmodial	[73, 92, 110, 113, 114]
Quercetin 3-glucoside (**56**)	Cytotoxicity, antimicrobial, antioxidant, anti-inflammatory, antidiabetic, nephroprotective, anti-osteoporotic, anti-spasmodic, neuroprotective, anti-anxiety	[92, 111, 112]
Quercetin 3-O-[α-rhamnosyl (1→6)] [β-glucosyl (1→2)]-β-glucoside-7-O-α-rhamnoside (**57**)		[92]
Quercetin 3-rhamnoside (**58**)	Antimicrobial, wound healing, antioxidant	[92, 107, 108, 109]

Compound **44** showed antimicrobial, antimalarial, anti-inflammatory and antioxidant activities [93-95]. Compound **45** showed antifungal and anti-inflammatory activities [96, 97]. Compound **47** showed antioxidant and cytotoxic effects [98]. Compound **50** showed antitumor, antioxidant and antileishmanial effects [99, 100]. Compound **52** showed hepatoprotective, antioxidant, anti-inflammatory and antitumor effects [101-103]. Compound **53** showed antimicrobial, antioxidant, anti-inflammatory, anticarcinogenic and neuroprotective effects [22, 104, 105]. Compound **54** showed cytotoxicity, antioxidant, antigenotoxic, antinociceptive and anti-inflammatory effects [106]. Compounds **55** and **58** showed cytotoxicity, antimicrobial, antioxidant and wound healing effects [107-110]. Compound **56** showed cytotoxicity, antimicrobial, antioxidant, anti-inflammatory, antidiabetic, nephroprotective, anti-osteoporotic, antispasmodic, neuroprotective and anti-anxiety effects [111, 112].

Lignanamides, neolignanamides , and macrocyclic glycoside

Lignanamides and neolignanamides including 1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy-7,8-dihydroxy-*N*-[(3,4-dihydroxyphenyl)ethyl]-*N′* -[(4-hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3-dicarboxamide (**59**), 1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy-7,8-dihydroxy-*N*-[(4-hydroxyphenyl)ethyl]-*N′* -[(4-hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3-dicarboxamide (**60**), 1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy-7,8-dihydroxy-*N*,*N′* -bis-[2-(4-hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3-dicarboxamide (**61**), 1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy- 6,7-dihydroxy-*N*,*N′* -bis-[2-(4-hydroxyphenyl)ethyl]-8-methoxynaphthalene-2,3-dicarboxamide (**62**), *N-cis*-grossamide (**63**), *N-trans*-grossamide (**64**) and *N*-trans-caffeoyltyramine (**65**) have been reported [59] [60]. macrocyclic glycoside isolated from the plant include 2-[3-[2-*O*-(6-deoxy-*a*-L-mannopyranosyl)-*β*-D-glucopyranosyl]-4,5-dihydroxyphenyl]-5,7-dihydroxy-4*H*-1-benzopyran-4-one (**66**), 2-[3-[2-*O*-(6-deoxy-*a*-L-mannopyranosyl)-*β*-D-glucopyranosyl]-4-hydroxyphenyl]-5,7-dihydroxy-4*H*-1-benzopyran-4-one (**67**) and 4-[(6′-*O*-*β*-D-allopyranosyl)-oxy]-hydroxy-benzoic acid cyclic dimeric inner ester (**68**) [59, 60]. A fatty acid namely α-linolenic acid (ALA) was also reported from the plant [39, 65, 83, 85].

Compounds **59-68** showed antioxidant and anti-Inflammatory effects [59, 60] while compound **69** showed antimicrobial, Anthelmintic and cytotoxic effects (Table 3) [65, 82].

Conclusion

Findings from this study show that all parts of *Warburgia ugandensis* have important bioactivities including antifungal, antibacterial, antiulcer, insect antifeedant, molluscicidal, antimycobacterial, antileishmanial and antiplasmoidal activities. The high therapeutic values of *W. ugandensis* is attributed to the abundance of phytochemi-

cal compounds which are biosynthesized by the plant. Sixty nine compounds have been reported from the plant including sesquiterpenes (43), flavonoids (15), lignanamides, and macrocyclic glycosides (10) and fatty acid (1) some of which have demonstrated different bioactivities. The drimane sesquiterpenes are the main class of sesquiterpenes in the plant. Further investigation of the not well studied parts of the plant such as the flowers and fruits is recommended to determine their chemical composition and efficacy in disease management.

Table 3: Lignanamides, and macrocyclic glycoside from *Warburgia ugandensis*

Compound	Bioactivity	Ref.
1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy- 7,8-dihydroxy-*N*-[(3,4-dihydroxyphenyl)ethyl]-*N′* -[(4- hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3-dicarboxamide (**59**)	Antioxidant, anti-inflammatory	[60]
]1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy- 7,8-dihydroxy-*N*-[(4-hydroxyphenyl)ethyl]-*N′* -[(4- hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3- dicarboxamide (**60**)	Antioxidant, anti-inflammatory	[60]
1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy- 7,8-dihydroxy-*N,N′* -bis-[2-(4-hydroxyphenyl)ethyl]-6-methoxynaphthalene-2,3-dicarboxamide (**61**)	Antioxidant, anti-inflammatory	[60]
1-(3,4-dihydroxy-5-methoxyphenyl)-1,2-dihydroxy- 6,7-dihydroxy-*N,N′* -bis-[2-(4-hydroxyphenyl)ethyl]-8-methoxynaphthalene-2,3-dicarboxamide (**62**)	Antioxidant, anti-inflammatory	[60]
N-cis-grossamide (**63**)	Anti-inflammatory, anti-proliferative	[59]
N-trans-grossamide (**64**)	Anti-inflammatory, anti-proliferative	[60[
N-trans-caffeoyltyramine (**65**)	Antioxidant, anti-inflammatory	[60]
2-[3-[2-*O*-(6-deoxy-*a*-L-mannopyranosyl)-*β*-Dglucopyranosyl]-4,5-dihydroxyphenyl]-5,7-dihydroxy- 4*H*-1-benzopyran-4-one (**66**)	Antioxidant, anti-inflammatory	[60]
2-[3-[2-*O*-(6-deoxy-*a*-L-mannopyranosyl)- *β*-Dglucopyranosyl]-4-hydroxyphenyl]-5,7-dihydroxy-4*H*- 1-benzopyran-4-one (**67**)	Antioxidant, anti-inflammatory	[60]
4-[(6′ -*O*- *β*-D-allopyranosyl)-oxy]-hydroxy-benzoic acid cyclic dimeric inner ester (**68**)	Antioxidant, anti-inflammatory	[60]
α-Linolenic acid (ALA) (**69**)	Antimicrobial, anthelmintic, cytotoxic	[82, 83, 85]

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