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Phytochemicals of *Markhamia* Species (Bignoniaceae) and Their Therapeutic Value: A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SA and SE planned the review. Author SA wrote the first draft of the manuscript. Authors SE, NA and AS revised the written manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To present a compilation of data regarding the phytochemical content and pharmacological activities pertaining to genus *Markhamia* as one of 120 genera belonging to family Bignoniaceae.
Study Design: Literature was collected from various published textbooks and scientific papers then the required data was summarized and presented in both tabulated form and concise text.
Results: Phenyl propanoids, triterpenic acids and anthraquinones are the major phytochemicals reported in this genus. Traditional clinical practice demonstrated that the different species of *Markhamia* were used in curing anaemia and bloody diarrhoea in Africa as well as other ethnopharmacological uses. Many reports were published explaining the activity of the extracts of various species of *Markhamia* as potential anti-inflammatory, antiparasitic, anthelmintic, analgesic, anti-viral, antimicrobial and anti-fungal agents.
Conclusion: This review presents an overview on the reported phytochemicals isolated from different *Markhamia* species and the biological activities associated with various *Markhamia* extracts and isolated compounds.

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Keywords: Review; markhamia; bignoniaceae; phenyl propanoids; triterpenic acids; anthraquinones.

1. INTRODUCTION

Medicinal plants have been long used for their medicinal value, especially in developing countries where natural medicine is popular and widely used for maintaining better health. Nature is considered a vast source of therapeutic agents. Being safe and inexpensive, these natural agents are widely used in both prevention and treatment of numerous human diseases. Genus *Markhamia* is one of around120 genera belonging to family Bignoniaceae, mostly spread in the tropical and neotropical areas of Asia, America and Africa, although some species are cultivated in other areas as ornamentals [1]. Many species of this genus are traditionally used in the treatment of several diseases. In Tanzania, the aqueous extract of the root bark of *Markhamia lutea* is used to treat anaemia and diarrhoea however in Cameroon, M. lutea and M. tomentosa are both used to cure various microbial and parasitic diseases [2]. It was reported that the wood extract of *M. lutea* played a major role in the protection of wood against termite and fungal attack, hence its use as a wood preservative in Uganda [3]. The foliage of M. platycalyx are important food of the red colobus and the black-and-white colobus monkeys in Africa [4]. Plants belonging to genus *Markhamia* are either trees or shrubs. They are characterized by the presence of pseudostipules. The leaves are opposite, imparipinnate with terminal or axillary panicle or raceme. The corolla (cup shaped) is 2-lipped, composed of 5-lobes longer than the calyx. The ovary is bilocular and the seeds are winged. The name "Markhamia" is derived after Sir Clements Robert Markham an English geographer and traveler. The twelve species of *Markhamia* fall into three different categories (Table 1). The first category includes five different species: *M. stipulata*, *M. caudafelina*, *M. lutea*, *M. platycalyx* and *M. hildebrandtii*. The common characters of these species include yellow corollas and foliaceous and orbicular pseudostipules. The second category includes three species: *M. sessilis*, *M. tomentosa* and *M. obtusifolia*. They are characterized by yellow corollas and subulate pseudostipules. The third category includes four species: *M. puberula*, *M. stenocarpa*, *M. zanzibarica* and *M. acuminata*. They differ from the previously mentioned species in the presence of brownish purple corolla beside the foliaceous and orbicular pseudostipules [5].

2. PHYTOCHEMICAL CONSTITUENTS

The key classes of compounds isolated and identified from genus *Markhamia* vary widely. The genus constitutes phenylpropanoids, lignans, naphthoquinones, anthraquinones, sterols, cycloartane triterpenes and their glycoside derivatives, phenolic glycosides and triterpene acids. These compounds are isolated from different plant parts including roots, leaves, stem, root bark and heartwood (Table 2).

2.1 Phenylpropanoids

Phenylpropanoids are a large group of secondary plant metabolites, mainly produced in response to wound, infection, UV irradiation or any other stressful condition attributed to their free radical scavenging capability [6]. Phytochemical analysis of the roots of the medicinal plant *M. lutea* revealed the presence of different phenylpropanoid glycosides named verbascoside and its isomer isoverbascoside in addition to luteoside A, B and C [7]. From the leaves and the branches of *M. stipulata*, different verbascoside derivatives described as markhamiosides (A-E) were isolated [8].

2.2 Lignans

Lignans can be described as group of dimeric phenylpropanoids formed by attachment of two C6-C3 groups together. Coniferyl alcohol, p-coumaroyl alcohol and sinapoyl alcohol are considered the main precursors of lignans and lignins in plants [9]. D-sesamin and paulownin are lignans which were isolated from the heartwood of *M. lutea* [10].

2.3 Anthraquinones and Naphtho-quinones

Anthraquinones are class of natural products that have drawn attention for quite some time. Their bright colors allowed them to be used in the synthesis of numerous dyes where pigments of different colors have been now characterized as quinones. These compounds are also diversely used in both food and pharmaceutical industry. Many derivatives of anthraquinones exist in nature. The biosynthesis of the main 9, 10 dioxoanthracene skeleton originate from either the acetate or the isoprene units which act as the main building blocks used for the de-novo

synthesis of anthraquinones. Those, which originate from the acetate/malonate pathway are called polyketides (emodin-type) anthraquinones, however those, which originate from the isoprenoid pathway are called the isoprenoid anthraquinones [11]. It was reported that lapachol, Dehydro-α-lapachone, 2-isopropenylfurano-1,4-naphthoquinone were isolated from the heartwood of *M. lutea* [10], however tectoquinone and dehydrotectol were isolated from the stem bark of *M. stipulata* [12]. From the stem bark of *M. tomentosa*, 2-acetylnaphtho [2,3-β]furan-4,9-dione and 2-acetyl-6-methoxynaphtho[2,3-β]furan-4,9-dione were isolated [2]. Also, markhamioside F which was reported to be a hydroquinone derivative was isolated from the leaves and the branches of *M. stipulata* [8].

2.4 Sterols

The most abundant sterols in plants are β-sitosterol, Campesterol, and Stigmasterol. Plant sterols have a chemical structure very similar to that of cholesterol except for the presence of an extra methyl, ethyl group or double bond [13]. The main nucleus is a triterpene with a tetracyclic cyclopentane phenanthrene structure and a side chain at C17. They act by inhibiting intestinal absorption of cholesterol hence decreasing its serum concentration. Stigmasterol was isolated from the heartwood of *M. lutea* [10], however ɣ-sitosterol was isolated from the root extract of *M. zanzibarica* [14], while β-sitosterol was isolated from the stem bark of *M. tomentosa* [2].

2.5 Triterpene Acids

Triterpenes are a large class of plant secondary metabolites including sterols and steroids. Their carbon skeleton consists of 30 carbons and biosynthesized from squalene through cyclization, ring expansions or contractions and loss of small molecules. Sapogenin is the free triterpene aglycone however saponin is the triterpene glycoside. Triterpenes are divided into many subgroups depending on squalene cyclization as hopane, lupane, oleanane, ursane and gammacerane types. Triterpenes with cycloartane skeleton are common in many plants and they are formed by cyclization between C9 and C19. In the past few decades, a growing interest in natural triterpenes has evolved due to their wide pharmacological activities. They were reported to possess antiviral, antimicrobial, anti-inflammatory, cardiovascular and cytotoxic effects [15]. From the leaf extract of *M. lutea*, different hydroperoxy cycloartane triterpenes and their xylose glycosides were isolated together with 2-epitormentic acid. They exhibited significant in-vitro antiparasitic activity and low cytotoxicity against KB and MRC5 cells [16]. The leaf extract of *M. obtusifolia* showed the presence of different triterpenic acids namely pomolic (and its acetylated derivative), tormentic (and its epimer), oleanolic and ursolic acids [17]. The cuticular wax obtained from the chloroform leaf extract of *M. acuminata* was analyzed by GC-MS showing ursolic and oleanolic acids to be the major components forming the wax by 52 and 60% respectively [18].

2.6 Polyphenols

Polyphenolics are a diverse group of compounds widely spread among plants and include at least one aromatic ring bearing one or more hydroxyl groups. Hydroxy benzoic/cinnamic acid derivatives, stilbenes, lignans, flavonoids, anthocyanins, catechins and phenolic alcohols are different polyphenols biosynthesized in plants. Research on polyphenols showed their tremendous effect on degenerative diseases prevention. They are strong antioxidants with high free radical scavenging capacity. From the hydromethanolic leaf extract of *M. platycalyx*, various polyphenols were identified including cinaroside, luteolin, apigenin, cosmosiin, verbascoside, isoverbascoside and jacraninoside-I [19]. Different flavonoids have been isolated from the leaves of *M. acuminata*. Luteolin, apigenin and luteolinrutinoside are from the isolated flavones however naringenin, naringenin-7-rutinoside and eriocitrin are from the isolated flavanones [20].

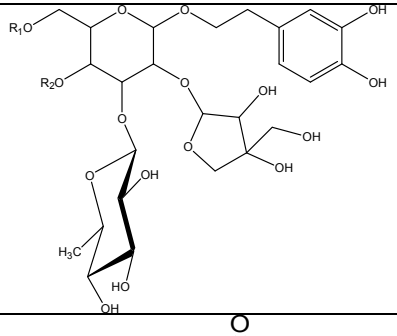
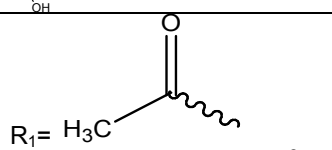
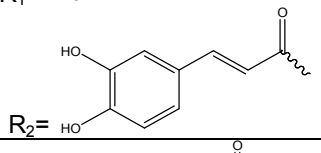
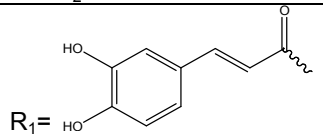
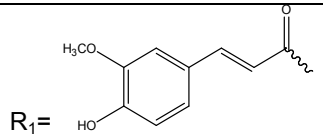
3. BIOLOGICAL ACTIVITIES

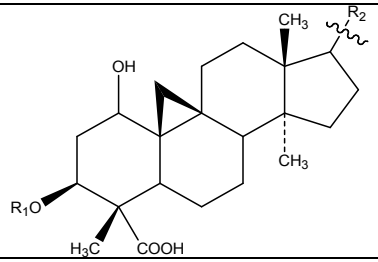
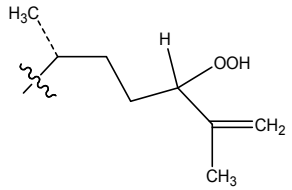
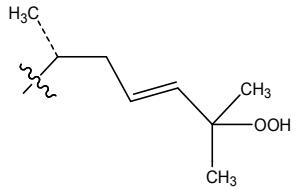
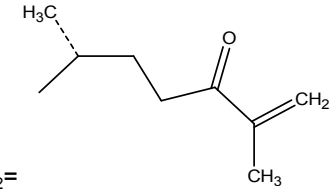
Extracts prepared from various *Markhamia* species showed a wide array of biological activities. Many of the reported pharmacological activities were aimed at verifying the traditional uses of *Markhamia* species in folk remedy.

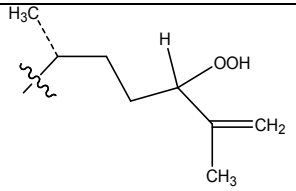
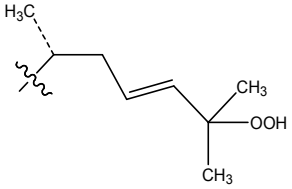
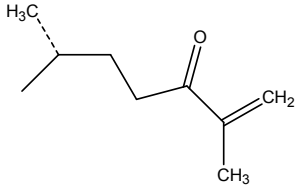
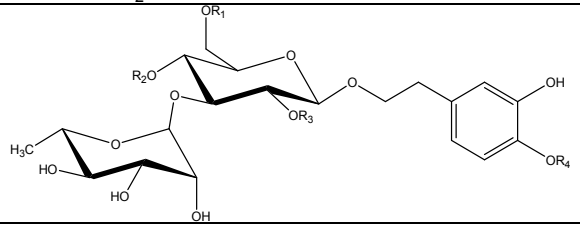
Table 1. The different synonyms and species of genus *Markhamia*

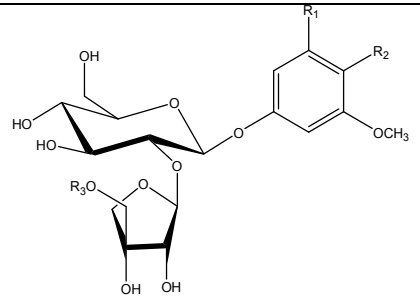
Species	Synonyms	Distribution	Varities
M. acuminata K. Schum.	*Spathodea acuminata* Klotzsch	East Africa	----------
M. caudafelina Craib	*Spathodea caudafelina* Hance. *Dolichandrone caudafelina* Benth. ex	China	----------
M. hildebrandtii Sprague	*Dolichandrone hildebrandtii* Baker	East Africa, Usambara	----------
M. lutea K. Schum.	*Spathodea lutea* Benth. *Muenteria lutea* Seem. *Dolichandrone lutea* Benth. ex	West Africa	----------
M. obtusifolia Sprague	*Markhamia lanata* K. Schum. *Dolichandrone obtusifolia* Baker	Congo, Central Africa East Africa	----------
M. platycalyx Sprague	*Dolichandrone platycalyx* Baker	Uganda, East Africa	----------
M. puberula K. Schum.	*Spathodea puberula* Klotzsch *Muenteria puberula* Seem.	East Africa	----------
M. sessilis Sprague	*Muenteria sessilis* Seem.	West Africa , Congo Angola	*Markhamia sessilis var. brachyrhyncha*
M. stenocarpa K. Schum.	*Muenteria stenocarpa* Seem. *Dolichandrone stenocarpa* Baker *Spathodea stenocarpa* Welw. ex.	Angola	----------
M. stipulata Seem.	*Bignonia stipulata* Roxb. Hort. Beng. *Bignonia campanulata* Ham. ex Wall. *Spathodea stipulata* Wall. *Spathodea campanulata* Ham. ex Wall. *Spathodea velutina* Kurz. *Dolichandrone stipulata* Benth. Ex	Upper and lower Burma Andaman Islands	*M. stipulata var. Kerrii*
M. tomentosa K. Schum.	*Spathodea tomentosa* Benth. *Muenteria tomentosa* Seem. *Dolichandrone tomentosa* Benth.	West Africa	*Markhamia tomentosa var. gracilis*
M. zanzibarica K. Schum.	*Muenteria zanzibarica* Seem. *Spathodea zanzibarica* Bojer	East Africa	----------

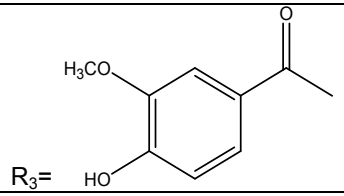
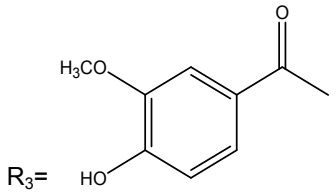
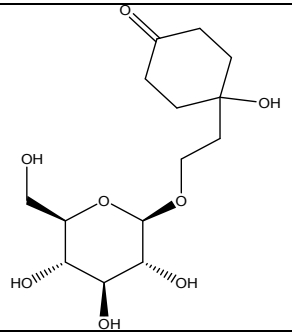
Table 2. List of reported compounds isolated from genus *Markhamia*

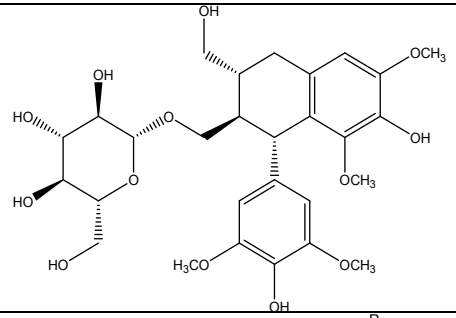
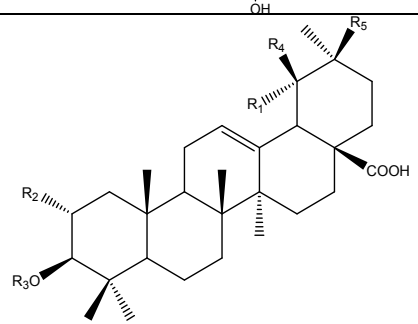
Compound name	Structure	Species	Organ used	Ref.
				
Luteoside A	 	*M. lutea*	Roots	[7]
Luteoside B	 R_2= H	*M. lutea*	Roots	[7]
Luteoside C	 R_2= H	*M. lutea*	Roots	[7]

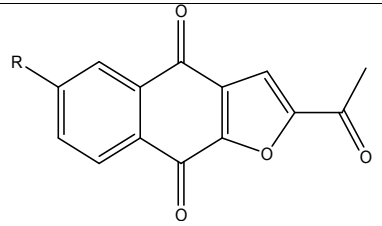
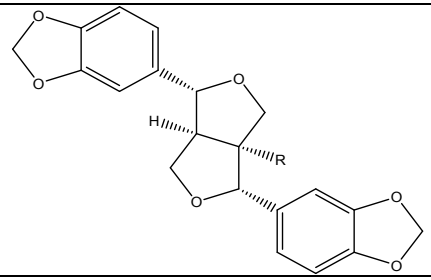
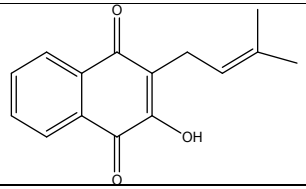
Compound name	Structure	Species	Organ used	Ref.
				
Musambin A	R_1= H R_2= 	*M. lutea*	Leaves	[16], [33]
Musambin B	R_1= H R_2= 	*M. lutea* *M. lutea*	Leave Leaves	[16], [33] [16], [33]
Musambin C	R_1= H R_2= 			
Musambioside A	R_1= Xylose	*M. lutea*	Leaves	[16], [33]

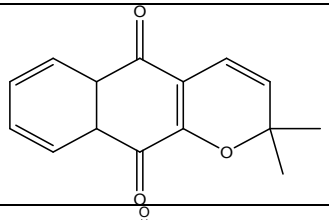
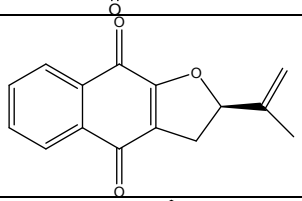
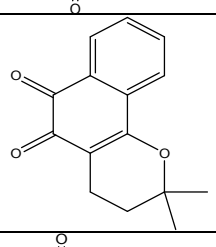
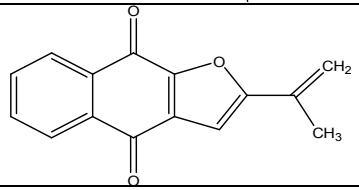
Compound name	Structure	Species	Organ used	Ref.
	 R_2=			
Musambioside B	R_1= Xylose  R_2=	*M. lutea*	Leaves	[16], [33]
Musambioside C	R_1= Xylose  R_2=	*M. lutea*	Leaves	[16], [33]
				
Decaffeoyl verbascoside	R_1=R_2=R_3=R_4=H	*M. stipulata*	Leaves and branches	[30]
Markhamioside A	R_1=R_2=R_4=H R_3= Apiosyl	*M. stipulata*	Leaves and branches	[30]
Verbascoside	R_1=R_3=R_4=H R_2= Caffeoyl	*M. stipulata*	Leaves and branches	[30]

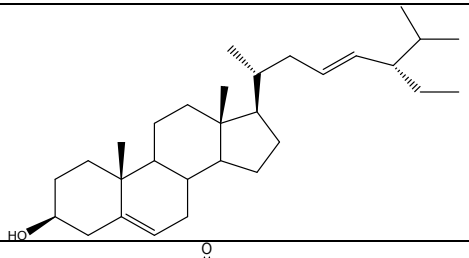
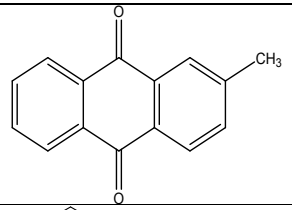
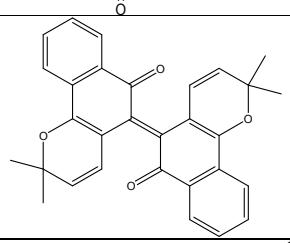
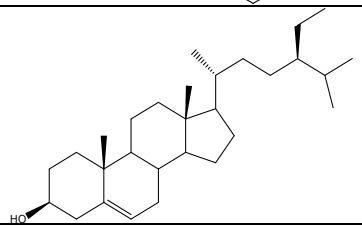
Compound name	Structure	Species	Organ used	Ref.
Isoverbascoside	R_2=R_3=R_4=H R_1= Caffeoyl	*M. stipulata*	Leaves and branches	[30]
2''-O-apiosylverbascoside	R_1= R_4=H R_2= Caffeoyl R_3= Apiosyl	*M. stipulata*	Leaves and branches	[30]
Markhamioside B	R_1= Feruloyl R_2=H R_3= Apiosyl R_4= Me	*M. stipulata*	Leaves and branches	[30]
Markhamioside C	R_2= R_4=H R_1= Caffeoyl R_3= Arabinosyl	*M. stipulata*	Leaves and branches	[30]
Markhamioside D	R_1= Acetyl R_2= Caffeoyl R_3= Arabinosyl R_4= H	*M. stipulata*	Leaves and branches	[30]
Markhamioside E	R_1= Acetyl R_2= Caffeoyl R_3= Galactosyl R_4= H	*M. stipulata*	Leaves and branches	[30]
				
Markhamioside F	R_1= R_3=H R_2= OH	*M. stipulata*	Leaves and branches	[30]
khaephuoside B	R_1= R_2= OMe	*M. stipulata*	Leaves and	[30]

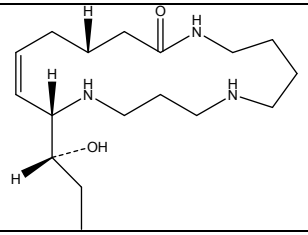
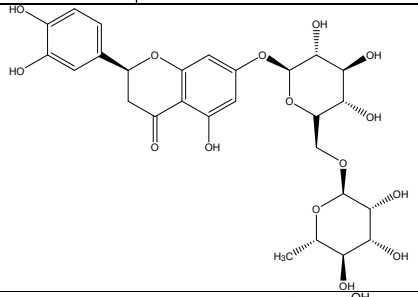
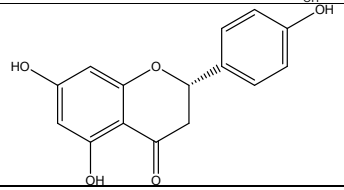
Compound name	Structure	Species	Organ used	Ref.
			branches	
Sequinoside K	R_1= H R_2= OH 	*M. stipulata*	Leaves and branches	[30]
Rengyoside B		*M. stipulata*	Leaves and branches	[30]

Compound name	Structure	Species	Organ used	Ref.
(+)-lyoniresinol 3α-O-β-glucopyranoside		*M. stipulata*	Leaves and branches	[30]
				
Pomolic Acid	R_1= OH R_2= R_3= R_5=H R_4=CH_3	*M. obtusifolia*	Leaves	[17]
Tormentic acid	R_1= R_2=OH R_3= R_5=H R_4=CH_3	*M. obtusifolia*	Leaves	[17]
Ursolic acid	R_1= R_2= R_3= R_5= H R_4=CH_3	*M. obtusifolia*	Leaves	[17]
3- acetyl pomolic acid	R_1= OH R_2= R_5=H R_3= $COCH_3$ R_4=CH_3	*M. obtusifolia*	Leaves	[17]

Compound name	Structure	Species	Organ used	Ref.
Oleanolic acid	R_1= R_2= R_3= R_4 =H R_5= CH_3	*M. obtusifolia*	Leaves	[17]
				
2-acetylnaphtho [2,3-β]furan-4,9-dione	R= H			
2-acetyl-6-methoxy naphtho[2,3- β] furan-4,9-dione	R= OCH_3	*M. obtusifolia*	Leaves	[17]
				
Sesamin	R= H	*M. lutea*	Heartwood	[10]
Paulownin	R= OH			
Lapachol		*M. lutea*	Heartwood	[10]

Compound name	Structure	Species	Organ used	Ref.
Dehydro-α-lapachone		*M. lutea*	Heartwood	[10]
Dehydroiso-α-lapachone		*M. tomentosa*	Stem bark	[10]
β-lapachone		*M. tomentosa*	Stem bark	[10]
2-isopropenyl furano -1,4-naphthoquinone		*M. lutea*	Heartwood	[10]

Compound name	Structure	Species	Organ used	Ref.
Stigmosterol		*M. lutea*	Heartwood	[10]
Tectoquinone		*M. stipulata*	Stem bark	[12]
Dehydrotectol		*M. stipulata*	Stem bark	[12]
β-sitosterol		*M. tomentosa*	Stem bark	[2]

Compound name	Structure	Species	Organ used	Ref.
Palustrine		*M. tomentosa*	Stem bark	[31]
Eriocitrin		*M. acuminata*	Leaves	[20]
Naringenin		*M. acuminata*	Leaves	[20]

3.1 Anti-protozoal Activity

Biological studies performed on the ethyl-acetate extract of the stem bark of *M. tomentosa*, showed promising in-vitro antimalarial activity. The isolated compounds were evaluated in-vitro for their anti-protozoal activities against two strains of *Plasmodium falciparum*, Leishmania donovani amastigotes, and the bloodstream trypomastigotes of *Trypanosoma brucei*. The ethyl-acetate extract showed potent antimalarial activity, with low IC_{50} recorded for the two tested strains of *P. falciparum* (K1 and W2 strains). The activity of the ethyl acetate extract was attributed to the presence of different classes of phytoconstituents classified as naphthofuranediones (lapachol derivatives). It was shown that the isolated naphthofuranediones exhibited very strong activity against both strains of *P. falciparum*, the leishmanial amastigotes and the tested trypanosomes with IC_{50} < 0.9 µg/ml however they showed strong cytotoxicity when tested on L-6 cell line with IC_{50} = 0.1 µg/ml. It was reported that naphtho- and anthraquinones (and their synthetic derivatives) isolated from various plants exhibit in-vitro antiprotozoal and antimalarial activity. One example is the naphthoquinone sterekunthal A which was isolated from the root bark of *Stereospermum kunthiamum* (another species of family Bignoniaceae) and exhibited in-vitro activity against P. falciparum with IC_{50} = 1.3 µg/ml. Even though naphtho-and anthraquinones and their derivatives posses high anti-protozoal activity but their high degree of cytotoxicity limits their medical use as potent anti-protozoals unless modulation in their structure is achieved for a higher degree of safety [2].

M. lutea ethyl acetate extract and isolated compounds were also evaluated for possible cytotoxicity against MRC5 and KB cells. The ethyl acetate leaf extract of *M. lutea* exhibited significant in-vitro anti-parasitic activity and low cytotoxicity. The extract was active against *T. brucei* with EC_{50} 1.9 µg/ml and against *P. falciparum* with IC_{50} 10.2 µg/ml however it showed weak activity against *L. donovani* with EC_{50} 42.0 µg/ml. The isolated compounds (musambin A, B and C) showed weak or no activity against *L. donovani* and *P. falciparum*, however musambin C showed the best activity against *P. falciparum* with IC_{50} 10.2 µg/ml. All the isolated compounds showed weak or no cytotoxicity against MRC5 and KB cells [16].

The triterpene acids (ursolic, pomolic and 2-*epi*-tormentic), isolated from the acetone leaf extract of *Markhamia obtusifolia*, were tested for their activity against three different strains of *C. albicans* isolated from dogs, cats and the standard strain ATCC 90028. The results showed that ursolic acid was the most active against the three strains, with minimum inhibitory concentration (MIC) = 12.5 µg/mL (for *C. albicans* strain isolated from dogs) and = 25 µg/mL (for standard ATCC 90028 and *C. albicans* strain isolated from cats) at 24 hours after incubation. However the MIC exceeds 400 µg/mL for all isolated triterpenes at 48 hours incubation. This showed that growth inhibition of *C. albicans* occurs only at the first 24 hours from the start of the experiment however no growth inhibition was observed at 48 hours either from the extract or from the pure isolated compounds [21].

The activity of different extracts of *M. lutea* was tested among other Rwandan plants against both chloroquine sensitive (3D7) and resistant (W2) forms of *plasmodium falciparum*. The dichloromethane extract of *M. lutea* showed weak antiplasmodial activity with IC_{50} of 29 µg/mL, however the ethyl acetate extract showed significant antiplasmodial activity with IC_{50} of 10.2 µg/mL. Although the methanolic extract showed 62.1% growth inhibition against *plasmodium bergheiin vivo*, the extract was inactive *in vitro* with IC_{50}>50 µg/ml [22]

3.2 Anthelmintic Activity

The anthelmintic activity of *M. obtusifolia* aqueous and acetone leaf extracts were evaluated against the gastrointestinal nematode *Trichostrongylus colubriformis* using the in-vitro egg hatch test. The effective concentration (EC50) for the aqueous leaf extract of *M. obtusifolia* (0.5 mg/mL) was significantly lower than the EC50 for the acetone extract (0.8 mg/mL). This proved that the aqueous extracts were twice as potent anthelmintic as the acetone extracts with an effect on the hatchability of the nematode eggs. These results supported the use of *M. obtusifolia* in traditional veterinary practices. In the cytotoxicity bioassay it was observed that the LD50 of the aqueous extract of *M. obtusifolia* was too high (relatively safe 0.476 mg/ml) when compared to standard toxic berberine which had an LD50 of 9.80 µg/ml [23].

3.3 Antibacterial and Antifungal Activity

The methanolic leaf extract of *M. tomentosa* was shown to possess strong antibacterial and antifungal activity. Five different concentrations of *M. tomentosa* leaf extract were tested for activity against different strains of bacteria (E.coli NCTC 10418, *P. aeruginosa* ATCC 10145, *S. aureus* NCTC 6571 and *B. subtilis* NCIB 3610) and fungi (*C. albicans*, *C. pseudotropicalis* NCYC 6 and *T. rubrum*). It was observed that at concentration 5 mg/ml and 10 mg/ml of *M. tomentosa* methanolic extract, there was neither activity against bacteria nor fungi however at concentration 20 mg/ml, the methanolic extract showed only antibacterial activity against *S. aureus* (the diameter of zone inhibition was 7 mm) without any antifungal activity. At concentration 40 mg/ml, the extract showed antibacterial activity against both *S. aureus* and *B. subtilis* (the diameter of zone inhibition was 10 and 5 mm respectively). Only at extract concentration of 225 mg/ml, was both antibacterial (against all bacterial strains tested, the diameter of zone inhibition for *E.coli* was 1 mm, *B. subtilis* 8 mm, *P. aeruginosa* 10 mm and *S. aureus* 16 mm) and antifungal (against only *C. pseudotropicalis* with 3 mm diameter of zone inhibition) activity achieved [24]. It was observed that the chloroformic leaf extract of *M. tomentosa* showed an MIC at 312 µg/ml for *B. subtilis* when compared to the standard chlorocresol which showed MIC at 125 µg/ml.

In another study, the acetone extract of *M. obtusifolia* showed the highest degree of activity against Candida when compared to other extracts (hexane, methanol and dichloromethane). Three triterpene acids (pomolic, ursolic and 2-epitormentic acid) were isolated from the leaf extract of *M. obtusifolia*. They inhibited the growth of three *Candida albicans* strains (two of them are clinical however the third is standard ATCC 90028). Pomolic acid was the most active with minimum inhibitory concentration of 12.5 µg/mL [17].

3.4 Antiviral Activity

Five phenylpropanoid glycosides isolated from the roots of *M. lutea*, exhibited potent in-vitro activity against the respiratory syncytial virus (RSV) according to the cytopathic effect assay (CPE) against standard ribavirin. The isolated compounds including verbascoside, isoverbascoside and luteoside A and B showed similar or even better in-vitro activity (EC50) against RSV than standard ribavirin as well as higher selectivity than ribavirin. It is likely that the mechanism by which phenylpropanoid glycosides inhibit RSV is through an intracellular antiviral mechanism similar to ribavirin since the *M. lutea* extract showed activity even when administered 3 hrs. after the infection with the cells with RSV. None of the isolated phenyl propanoid glycosides showed activity against herpes simplex virus, cytomegalovirus or varicella zoster virus [7].

3.5 Analgesic and Anti-inflammatory Activity

The analgesic and anti-inflammatory effect of different extracts of *M. tomentosa* (hexane, dichloromethane, ethyl acetate, methanolic, aqueous and aqueous residue) on rats and mice were investigated using thermal noxious stimuli (hot plate and tail immersion tests for evaluating analgesic activity) and carrageenan induced acute inflammation (for assessing anti-inflammatory activity). The aqueous, ethyl acetate, methanol and aqueous residue extracts showed significant inhibition on writhing response induced by acetic acid in a dose dependent manner ($p < 0.001$) however the methanol and aqueous extracts (200 mg/kg) demonstrated higher inhibition response with 60% and 53% inhibition, respectively. In the first phase of formalin test, it was observed that both the methanolic, aqueous and aqueous residue extracts at dose 200 mg/kg significantly reduced the licking time by 43%, 57% and 28% respectively when compared to morphine control which inhibited this first phase by 60% ($p < 0.001$). In formalin second phase, all extracts significantly ($p < 0.001$) reduced formalin induced pain however the methanolic extract (200 mg/kg) showed maximum inhibition by 80% when compared to morphine (10 mg/kg) which inhibited the inflammatory pain by 45.22%. The hot plate test showed that both *M. tomentosa* methanolic extract (50, 100 and 200 mg/kg) and morphine (10 mg/kg) decreased the reaction time of mice to the thermal stimuli significantly at $p < 0.001$ when compared to acetyl salicylic acid control (200 mg/kg) which showed no effect on the pain induced by the hot plate. In the tail immersion test, both the methanolic extract of *M. tomentosa* and morphine (10 mg/kg) increased significantly ($p < 0.01$) the latency time when compared to acetyl salicylic acid control (200 mg/kg) which failed to affect the reaction time. The anti-inflammatory activity of the *M. tomentosa* methanolic extract (50, 100 and 200

mg/kg) showed significant ($p < 0.001$) reduction in the edema induced by carrageenan in the rat hind paw after 2 hrs. of carrageenan injection with a maximum inhibition reached 43% after 5 hrs. of injection (for the dose 100 mg/kg) when compared to morphine (10 mg/kg) which inhibited rat paw edema by 37%. The acetyl salicylic acid control (200 mg/kg) showed 50% inhibition recorded after 2 hrs. of carrageenan injection [25]. This data was coherent to the reported folk medicinal use of *M. tomentosa* in Cameroon for treatment of pain and inflammatory related ailments.

The anti-ulcer activity of three per oral doses (50, 100 and 150 mg/kg) of the ethanol leaf extract of *M. tomentosa* was evaluated in both ethanol and indomethacin induced models. The extract in its different doses caused significant dose dependent ulcer inhibition ($p<0.05$). The ethyl acetate extract was the most potent among all fractions causing 72-92% inhibition of indomethacin and pylorus induced ulcers in dose 150 mg/kg. LC-MS profiling of this bioactive fraction revealed the presence of acteoside, ajugol, dilapachone, luteolin-7-rutinoside, Luteolin-3′,7-di-O-glucoside, carnosol, tormentic and oxo-pomolic acid [26].

In another study performed on the leaf extract of *M. tomentosa* to evaluate its anti-inflammatory activity, three different doses of the extract (50, 100 and 200 mg/kg) were enrolled in the study. The *in-vivo* anti-inflammatory activity was investigated using carrageenan, histamine, serotonin, xylene and formalin induced edema. In carrageenan induced edema, the extract exhibited significant ($p < 0.01$, 0.001, 0.0001) dose dependent activity with maximum effect obtained at 66.67% for the 200 mg/kg dose within the first 90 minutes (the first phase of inflammation). This possibly indicates the inhibiting effect of the extract on both histamine and serotonin release which mediate the first phase of inflammation. Xylene induced edema leads to acute inflammation which is mediated through phospholipase A_2. *M. tomentosa* produced significant ($p < 0.05$, 0.01) dose-dependent inhibition of ear edema induced by xylene with the highest effect produced by the highest dose 200 mg/kg. This result suggests the extract to act through inhibition of phospholipase A_2. The formalin induced edema is a model for sub chronic inflammation. The ethanolic extract of *M. tomentosa* showed significant ($p < 0.05$, 0.0001) reduction in edema which is also dose dependent. This suggests the use of the extract in treating sub-chronic inflammation [27].

3.6 Antioxidant Activity

The generation of reactive oxygen species and free radicals are the main precursors for oxidative stress which is implicated in the pathogenesis of numerous diseases. The antioxidant assay for *M. tomentosa* was performed using rapid radical scavenging screening test and DPPH photometric assay test. The results showed that the EC_{50} of the extract using DPPH photometric assay was 16.5 µg/ml for the *M. tomentosa* methanolic extract indicating high DPPH radical scavenging capacity and antioxidant activity [24].

3.7 Anti-tumor Activity

The reported cytotoxicity of the root wood of *M. zanzibarica* was attributed to the presence of Ɣ-sitosterol [14]. The naphthoquinone derivative, 2-isopropenylfurano-1,4-naphthoquinone, which was isolated from the benzene extract of *M. hildebrandtii* showed its powerful antitumor effect against Hela cells. The 50% growth inhibition concentration of Hela cells was 7.5 × 10-7 M [28]. The ethanolic leaf extract of *M. tomentosa* was evaluated for its cytotoxic activity using the brine shrimp lethality assay. Preliminary results showed cytotoxic activity of the extract towards brine shrimp larvae with LD_{50} 31.62 µg/ml. further cytotoxic assay was performed on the cancerous HeLa and MCF-7 cell lines and the non-cancerous Vero cell lines using MTT test. The extract showed significant cytotoxic activity against HeLa cells with IC_{50} of 189.1±1.76 µg/ml however no cytotoxicity was reported against either MCF-7 (IC_{50} greater than 2000 µg/ml) or the non-cancerous Vero cells (IC_{50} greater than 250 µg/ml) [29].

3.8 Plant Larvicidal Activity

The methanolic extracts of different Nigerian medicinal plants were tested for their larvicidal activity. The stem bark extract of *M. tomentosa* was one of the tested extracts for its activity against *Aedes aegypti* L., the main vector for transmission of dengue, yellow and chikungunya fevers. According to the egg hatch and larvicidal tests performed, the extract showed mild larvicidal activity lasted for 48 hours with LC_{50}> 4.2 mg/ml [32].

4. CONCLUSION

Phytochemical research is an ongoing process of discovery. The isolation and identification of the chemical components comprising the complicated make up of various organisms among which are plants and recognizing their biological activity seems endless. A significant part of this process relies on previous studies and discoveries upon which novel research is built. From the review at hand, *Markhamia* species are noticeably one of the understudied plant species with potential for further phytochemical and pharmacological investigation in an effort to find and reveal bioactive components with substantial weight in the field of medicinal plants.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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