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PLANT REVIEW

Review of the Phytochemical and Pharmacological Studies of the Genus *Markhamia*

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ABSTRACT

Natural product compounds obtained from medicinal plants have been great contributions in the discovery of numerous clinically useful drugs. *Markhamia* species have been reportedly used by many cultures in human and veterinary traditional medicines. The five identified species of *Markhamia*, that is, *Markhamia lutea*, *Markhamia obtusifolia*, *Markhamia stipulata*, *Markhamia tomentosa*, and *Markhamia zanzibarica* have been the subject of chemical investigations that have led to the characterization of their secondary metabolites. Plants of the genus with the identified phytoconstituents, including phenylpropanoid glycosides (PhGs), terpenoids, phytosterols, lignans, quinones, and flavonoids, have been claimed to possess antiviral, antifungal, antiprotozoal, analgesic, antiinflammatory, and cytotoxic activities. *In vitro* and *in vivo* pharmacological research studies have reported the validation of the medicinal properties of plants of this genus. The present review analyzes published data from the ethnomedicinal, phytochemical, and pharmacological studies of plants of the genus *Markhamia*.

Key words: Ethnomedicine, ethnopharmacology, *Markhamia*, phytochemistry

INTRODUCTION

Markhamia (Seemann ex K.Schum) is a genus of flowering plants in the family Bignoniaceae with about 100 genera and 800 species. *Markhamia* has been reported among other genera of the family in Nigeria and 10 species are widely distributed in tropical Africa and Asia.[1,2] The genus was named by Berthold Seemann, in honor of Sir Clements Robert Markham (1830–1916), who introduced the well-known quinine-yielding *Cinchona* into India.[3] Plants of this genus are trees or shrubs with opposite, compound imparipinnate leaves and yellow-green flowers grown mostly for social, agrihorticultural, and medicinal purposes.[4] They are mostly found in fringing forests and are drought-resistant. The roots, barks, stems, and leaves of *Markhamia* species have been used by traditional healers for the treatment of miscellaneous disease conditions such as microbial and parasitic diseases, anemia, diarrhea, backache, sore eyes, intercostal pain, pulmonary troubles, gout, scrotal elephantiasis, rheumatoid arthritis, and external skin diseases.[5-11] The plant has also been used in the treatment of diarrhea, dysentery, pain, and inflammation in veterinary patients.[12,13]

The therapeutic value of plants used in traditional medicine is due to the presence of phytochemical compounds that are found in parts of the plants; moreover, a medicinal plant is a plant whose biological activity has been ethnobotanically reported and scientifically established.[14,15] Preliminary phytochemical investigations of *Markhamia* species have shown the presence of biologically active substances such as flavonoids, saponins, steroids, terpenes and terpenoids, phytosterols, tannins, phenols, coumarins, and quinones.[2,16,17] In support of the significance of the genus *Markhamia*, diverse pharmacological investigations have been reported in the literature.[18-21] The isolation and identification of various chemical constituents from different plant parts of species including their pharmacological effects have been reported.

This review aims to provide a comprehensive and up-to-date report on species of the genus *Markhamia* with emphasis on the ethnomedicinal uses, the phytochemical and pharmacological studies, and highlights of research reports on the isolation, characterization, and identification of various active constituents present in the plant.

ETHNOMEDICINAL USES

The medicinal uses of plants range from administration of the various plant parts (alone or in combination with other plant parts) to the use of decoctions and extracts from the plants.[22,23] Plants of the genus *Markhamia* have been used by different tribes in various parts of African and Asian countries. Details of the uses of *Markhamia* species and the associated references are indicated in Table 1.

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Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/0973-7847.176547

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Cite this article as: Ibrahim MB, Kaushik N, Sowemimo AA, Odukoya OA. Review of the phytochemical and pharmacological studies of the *Genus Markhamia*. Phcog Rev 2016;10:50-9.

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Table 1: Ethnomedicinal data of plants of the genus *Markhamia*

Markhamia species	Synonym (s)	Distribution	Part used	Traditional uses	Reference
M. lutea (Benth.) K.Schum	*Dolichandrone lutea* Benth. ex Hook *Dolichandrone platycalyx* (Baker) Sprague *Markhamia hildebrandtii* Sprague *Markhamia platycalyx* Sprague *Spathodea lutea* Benth	Tanzania, Kenya, Uganda, Ethiopia and India	Root bark	The root barks are used in the treatment of anemia, diarrhea and backache The roots are soaked in cold water and the resulting tea is taken thrice daily to reduce symptoms of watery bloodless diarrhea. It is also used in treating difficult urination and as an analgesic	3,6,11,17,24
M. obtusifolia (Baker) Sprague	*Dolichandrone obtusifolia* Baker	Tanzania, Mozambique, Zimbabwe, Zambia, Angola, Namibia, Botswana, and South Africa	Root	Toothache and fever in children; treatment of hookworm infestation	17,30,37,45
M. stipulata Seem. ex K.Schum	*Dolichandrone stipulata* (Wall.) Clarke	India, China, Myanmar, Laos, Vietnam, Cambodia, and Thailand	Leaves and bark	External application on skin diseases; used internally for analgesic effect	7,47
M. tomentosa (Benth.) K.Schum. Ex Engl	*Dolichandrone tomentosa* (Benth.) Benth. ex B.D Jacks *Markhamia sessilis* Sprague *Muenteria tomentosa* (Benth.) Seem *Spathodea tomentosa* Benth	West African countries from Senegal, Ghana, and Nigeria to Cameroon, including Congo and Angola	Leaves, bud sap, bark, root, and stem bark	Leaves are used in the treatment of diarrhea and scrotal elephantiasis and against snake venom/bite. The leaf decoction and chewed leaves are also used for treating general body pains, backache, lumbago, and headache. The bud sap is used for eye treatment Decoction of the leaves and bark are used as mild laxative The stem bark is used as an antimalarial and in the treatment of intercostal pain In animals, the roots and leaves are used to treat diarrhea, dysentery, fever, pain, and inflammation	4,8-11,15,47,49
M. zanzibarica (Bojer ex DC.) K.Schum	*Markhamia stenocarpa* (Seem.) K.Schum *Muenteria stenocarpa* Seem *Spathodea zanzibarica* Bojer ex DC	South Africa, Botswana, Namibia, Zimbabwe, Malawi, Tanzania, Somali and recently reported in India	Roots	Roots are roasted and ground into powder which is rubbed into incised skin to relieve backache	3,45

PHYTOCHEMISTRY OF *MARKHAMIA* SPECIES

Chemical investigations of different plant parts of the *Markhamia* species *Markhamia lutea* (Benth.) K.Schum [Figure 1], *Markhamia obtusifolia* (Baker) Sprague [Figure 2], *Markhamia stipulata* (Wall.) Seem [Figure 3], *Markhamia tomentosa* (Benth.) K.Schum. ex Engl [Figure 4], and *Markhamia zanzibarica* (Bojer ex DC.) K.Schum [Figure 5] have led to the characterization of various secondary metabolites. These chemical constituents have been categorized as phenylpropanoid glycosides (PhGs), alkaloids, terpenoids, phytosterols, quinones, lignans, and flavonoids.[7,9,24-27] Table 2 shows the various chemical constituents isolated from the different plant parts of *Markhamia* species and the various chromatographic techniques used in the isolation and purification of the compounds.

CLASS OF SECONDARY METABOLITES COMMON TO *MARKHAMIA* SPECIES

Phenylpropanoid glycosides

PhGs are acylated glycoconjugates with the core structure [Figure 6] characterized by a hydroxyphenylethyl aglycone linked to a β-glucopyranose through glycosidic linkage. The glucose residue of the core structure is often encircled with substituents such as aromatic acids (cinnamic acid, ferulic acid, isoferulic acid, and caffeic acid) and various sugars (apiose, arabinose, rhamnose, galactose, and xylose) through ester and glycosidic linkages, respectively.[28] Isolation of PhGs from the genus *Markhamia* was reported for the first time by Kernan *et al*.[25] The known PhGs verbacoside (1) and isoverbacoside (2) and three new PhGs luteosides A–C (3–5) were isolated from the roots of *Markhamia lutea*. This was followed by the isolation of five new verbacoside derivatives: Markhamiosides A–E (6–10) and 13 known compounds from the leaves and branches of *Markhamia stipulata*.[7] The characterization and identification of acteoside, also known as verbacoside (1) and isoacteoside (2), in the ethyl-acetate fraction of the leaves of *Markhamia tomentosa* have been reported.[29]

Terpenoids and phytosterols

Terpenoids including their oxygenated, hydrogenated, and dehydrogenated derivatives are naturally occurring hydrocarbon molecules that are built up of isoprene units (C_5H_8) n joined in a head-to-tail fashion. Terpenoids are classified based on the number of isoprene units into monoterpenoids C_{10}, sesquiterpenoids C_{15}, diterpenoids C_{20}, sesterterpenoids C_{25}, triterpenoid C_{30}, and carotenoids C_{40}.[30] Phytosterols are among the subclass of terpenoids and are derived from tetracyclic triterpenes. Six cycloartane triterpenoids [Figure 7], that is, musambins A–C (19–21) and their 3-O-xyloside derivatives musambiosides A–C (22–24), along with other with pentacyclic triperpenes [Figure 8], that is, 2-epi-tormentic acid (25) and arjunic acid (26), were reportedly isolated from the ethylacetate leaf extract of

Figure 1: *Markhamia lutea* (Benth.) K.Schum

Figure 2: *Markhamia obtusifolia* (Baker) Sprague

Figure 3: *Markhamia stipulata* (Wall.) Seem

Figure 4: *Markhamia. tomentosa* (Benth.) K.Schum. ex Engl

Figure 5: *Markhamia zanzibarica* (Bojer ex DC.) K.Schum

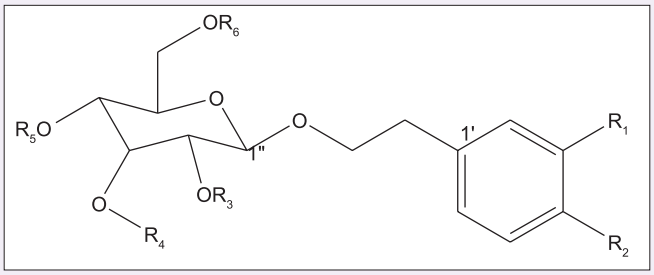


Figure 6: Phenylpropanoid glycosides

Markhamia lutea. Three bioactive pentacyclic triterpenoids [Figure 8], that is, epi-tormentic acid (25), ursolic acid (29), and pomolic acid (30) were isolated from the leaves of *Markhamia obtusifolia*.[31] Gamma-sitosterol (38), campesterol (39), and tritriacontane (40) were isolated from the root, stem bark, and leaves of *Markhamia zanzibarica*, respectively.[26] Additionally, the isolation of pentacyclic triterpenoids such as pomolic acid (30), oleanolic acid (33), tormentic acid (35), and β-sitosterol (28) and its derivatives has been reported from the stem bark of *Markhamia tomentosa*.[9] Ajugol (31), tormentic acid (35), carnasol (36), and oxopomolic acid (37) were identified in the leaves of *M. tomentosa*.[29] The structures of the compounds were established by proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR)—including one- and two- dimensional techniques—spectroscopy and mass spectrometry.

Table 2: Secondary metabolites isolated from plants of the genus *Markhamia* and their phytochemical analyses

Species/Part used	Extract type	Class of compounds	Isolation/Purification technique	Mobile phase	Reference
M. lutea roots	Aqueous extract	Phenylpropanoid glycosides:- Verbacoside (1) (3,4-dihydroxyphenylethyl alcohol 8-O-[(4"-O-caffeoyl)-3"-O-α-L-rhamnopyranosyl-(1"→3")]-β-D-glucopyranoside). Isoverbacoside (2); Luteoside A (3) (1-O-(3,4-dihydroxyphenyl) ethyl β-D apiofuranosyl (1""→2")-α-L-rhamnopyranosyl (1"→3")-4"-O-caffeoyl-6"-acetyl-β-D -glucopyranoside); Luteoside B (4) (1-O-(3,4-dihydroxyphenyl) ethyl β-D-apiofuranosyl (1""→2")-α-L-rhamnopyranosyl (1"→3")-6"-O-caff eoyl-β-D-glucopyranoside); Luteoside C (5) (1-O-(3,4-dihydroxyphenyl) ethyl β-D-apiofuranosyl (1""→2")-α-L-rhamnopyranosyl (1"→3")-6"-O-feruloyl-β-D-glucopyranoside)	Crude extract was subjected to successive reverse-phase HP-20 and C-18 column chromatography → Eluting fractions were monitored by thin-layer chromatography on C18 → Purification of fractions by preparative TLC on silica gel → Purification of fractions by centrifugal partition chromatography → Monitoring of eluent by TLC on C-18	Increasing amount of methanol in water; 40% methanol; SiO_2; dichloromethane-methanol-water (43:37:20) Dichloromethane-methanol-water (40:40:20 v/v). Dichloromethane-methanol-water (40:40:20 v/v) 20-100% aqueous methanol	24
M. lutea roots	Aqueous extract		Purification of fractions by preparative TLC on C-18 → Purification by preparative HPLC on C-18 column	40% aqueous methanol 20– 25% aqueous acetonitrile	24
M. lutea leaves	Ethylacetate extract	Terpenoids: Musambin A (19) (1α,3β-dihydroxy-24-hydro peroxy-cycloart-26-methylene-28-carboxylic acid); Musambin B (20) (1α,3β-dihydroxy-25-hydroperoxy-cycloart-23E-en-28-carboxylic acid); Musambin C (21) (1α,3β-dihydroxy-24-hydropero xy- cycloart-26-methylene-24-oxo-28-carboxylic acid); Musambioside A (22) (3β-D-xyloside of musambin A); Musambioside B (23) (3β-D-xyloside of musambin B); Musambioside C (24) (3β-D-xyloside of musambin C); 2-epi-tormentic acid (25), arjunic acid (26)	Repeated medium-pressure chromatography of crude extract on 60 H Merck silica gel column → Fractions were chromatographed on Sephadex LH-20 column → Further purification of fractions on silica gel column	Gradient elution with cyclohexane: dichloromethane; dichloromethane: Methanol; ethyl-acetate: methanol; cyclohexane: ethyl-acetate Methanol was used as the mobile phase. Cyclohexane: ethyl-acetate gradient elution	26
M. lutea leaves	Ethylacetate extract	Phaeophorbide A (27) and β-sitosterol (28)	Purification of subfractions by HPLC and semipreparative HPLC on RP-18 silica gel	Acetonitrile: water gradient elution	26
M. obtusifolia roots and leaves	Methanol root and acetone leaf extracts	Terpenoids: Ursolic acid (29) (3β-hydroxyurs-12-en-28-oic acid); Pomolic acid (30) (3β, 19α-dihydroxy-urs-12-en-28-oic acid); Epi-tormentic (25) (2β, 3β, 19α-trihydroxy-urs-12-en-28-oic acid) Hydroxynaphthoquinones	Fractionation of extract on silica gel column → Silica gel CC of fractions	Successive elution with chloroform (100%) followed by chloroform: methanol (95:5 v/v) Elution with 100% chloroform followed by increasing gradient of ethylacetate: methanol up to 50%	30,42
M. stipulata stem heartwood	Alcohol extract	Naphthoquinone:- Dehydro-α-lapachone (43); lapachol (44); dehydro-iso-α-lapachone (45); β-lapachone (46); tectol (47) Phytosterol: β-sitosterol (28) Lignans: Paulownin (41); Palmitone (42)	Successive CC on silica gel	Elution with light petroleum and benzene (3:1 and 1:4); pure benzene; benzene and ethylacetate (9:1; 3:1; 1:1; 1:3) and ratio 9:1 of ethylacetate: methanol	32

Contd...

Table 2: Contd...

Species/Part used	Extract type	Class of compounds	Isolation/Purification technique	Mobile phase	Reference
M. stipulata leaves and branches	Methanol extract	Phenylpropanoid glycosides:- Markhamioside A (6) (3,4-dihydroxy-β-phenylethoxy-O-[β-apiofuranosyl-(1""→2")-α-rhamnopyranosyl-(1"'→3")-O-β-glucopyranoside]); Markhamioside B (7) (3-hydroxy-4-methoxy-β-phenyethoxy-O-[β-apiofuranosyl-(1""→2")-α-rhamnopyranosy-(1"'→3")-6"-O-feruloyl-β-glucopyranoside]); Markhamioside C (8) (3,4-dihydroxy-β-phenylethoxy-O-[α-arabinopyranosyl-(1""→2")-α-rhamnopyranosyl-(1"'→3")-6"-O-caffeoyl-β-glucopyranoside]); Markhamioside D (9) (3,4-dihydroxy-β-phenylethoxy-O-[α-arabinopyranosyl-(1""→2")-α-rhamnopyranosyl-(1"'→3")-4-O-caffeoyl-6-O-acetyl-β-glucopyranoside]) Markhamioside E (10) (3,4-dihydroxy-β-phenylethoxy-O-[β- galactopyranosyl-(1""→2")-α-rhamnopyranosy-(1"'→3")-4-O-caffeoyl-6-O-acetyl-β-glucopyranoside])	Chromatography on column of highly porous copolymer of styrene and divinylbenzene → Methanol fraction subjected to silica gel CC → Subfractions were applied successively on RP-18 silica column → Purification of fractions by preparative HPLC → Successive purification of fractions by preparative HPLC-ODS (C-18 column) → Purification of fractions by preparative HPLC-Diol (normal phase column) →	Successive elution with methanol, water and acetone; Elution with ethyl-acetate: methanol: water (4:1:0.1; 7:3:0.3; 6:4:1); Successive elution with 40–70% aqueous methanol and 20–70% aqueous methanol; 40%–45% aqueous methanol used as eluting solvents; Successive elution with 5%, 8%, 10%, 15%, 20%, 25%, 28%, and 45% aqueous acetonitrile; Elution with 85% aqueous acetonitrile	
M. stipulata leaves and branches	Methanol extract	Phenethyl-0-β-glucopyranosyl-(1"'→2")-0-β- glucopyranoside (11); Decaffeoylverbacoside (12); Verbacoside (1); Isoverbacoside (2); Luteoside A (3); Luteoside B (4); 2"-O- apiosylverbacoside (13); Khaephuoside B (14); Sequinoside K (15); (6S,9R)-roscoside (16); Rengyoside B (17); (+)-lyoniresinol 3α-O-β-glucopyranoside (18) Terpene: Iridoid, ajugol (31) Hydroquinone: Markhamioside F (48) (deacyl-ester of sequinoside K);			7
M. tomentosa stem bark	Ethyl-acetate extract	Phytosterol:- β-sitosterol (28); β-sitosterol-3-O-β-D-glucopyranoside (32) Naphthoquinone:- 2-acetyl-naphtho[2,3-b] furan-4,9- dione (49); 2-acetyl-6-methoxynaphtho[2,3-b] furan-4,9-dione (50) Triterpenoid:- Oleanolic acid (33); Pomolic acid (31); 3- acetylpomolic acid (34); tormentic acid (35)	Fractionation of crude extract by silica CC → Purification of fractions and subfractions were performed by successive CC on silica gel →	Gradient elution with n-hexane-ethylacetate mixture of increasing polarity Successive gradient elution with hexane: ethyl-acetate and dichloromethane: methanol	9
M. tomentosa leaves	Ethyl-acetate fraction	Phenylpropanoid glycosides:- Acteoside, also known as verbacoside (1), isoacteoside (2) Terpenoids:- Iridiod, ajugol (31), tormentic acid (35), carnasol (36) and 2-oxo-pomolic acid (37) Naphthoquinone: Dilapachone (51) Flavonoids:- Luteolin (52), Luteolin-7-rutinoside (53), Luteolin-3',7-di-O-glucoside (54)	Ethyl-acetate fraction obtained from the ethanolic crude extract was characterized by electrospray ionization mass spectrometry →	Gradient elusion with acidified water and acetonitrile	28
M. zanzibarica root, stem bark, and leaves	Chloroform root and leaf extracts; petroleum stem bark extract	Phytosterol:- γ-sitosterol (38), campesterol (39), tritriacontane (40)	Crude extracts were subjected to silica gel CC to yield colorless and colored fractions →	Chloroform and petrol	25,42

CC: Column chromatography; TLC: Thin-layer chromatography; CPC: Centrifugal partition chromatography; MPLC: Medium-pressure chromatography; HPLC: High-performance liquid chromatography

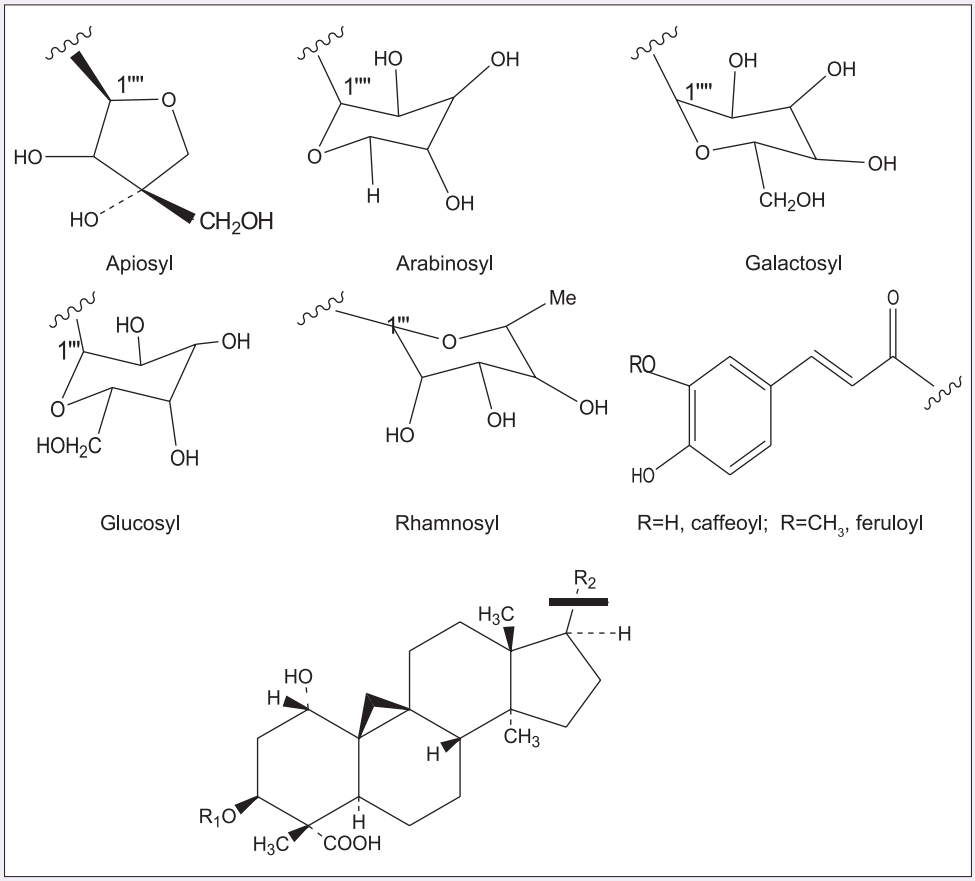


Figure 7: Cycloartane triterpenoids

Chemical constituent (structure number)	R_1	R_2	R_3	R_4	R_5	R_6
Verbacoside (1)	OH	OH	H	rhamnosyl	caffeoyl	H
Isoverbacoside (2)	OH	OH	H	rhamnosyl	H	caffeoyl
Luteoside A (3)	OH	OH	Apiosyl	rhamnosyl	caffeoyl	Ac
Luteoside B (4)	OH	OH	Apiosyl	rhamnosyl	H	caffeoyl
Luteoside C (5)	OH	OH	Apiosyl	rhamnosyl	H	feruloyl
Markhamioside A (6)	OH	OH	Apiosyl	rhamnosyl	H	H
Markhamioside B (7)	OH	OMe	Apiosyl	rhamnosyl	H	feruloyl
Markhamioside C (8)	OH	OH	arabinosyl	rhamnosyl	H	caffeoyl
Markhamioside D (9)	OH	OH	arabinosyl	rhamnosyl	caffeoyl	Ac
Markhamioside E (10)	OH	OH	galactosyl	rhamnosyl	caffeoyl	Ac
Phenethyl-0-β-glucopyranosyl-(1'''→2'')-0-β- glucopyranoside (11)	H	H	glucosyl	H	H	H
Decaffeoylverbacoside (12)	H	H	H	rhamnosyl	H	H
2''-O-apiosylverbacoside (13)	H	H	Apiosyl	rhamnosyl	caffeoyl	H

Lignans

Lignans are dimeric compounds formed by the union of two molecules of a phenylpropene derivative.[32] The lignans paulownin (41) and palmitone (42), as well as palustrine, have been isolated from the stem heartwood of *Markhamia stipulata*[33] and *Markhamia tomentosa*, respectively.[24]

Quinones

Quinones are derived from benzoquinone, naphthoquinone, or anthraquinone structural moieties. Four lapachol-type naphthoquinones (43–46) and markhamioside F (48) were isolated from the stem heartwood of *Markhamia stipulata*.[33] Two bioactive naphtho[2,3-b] furan-4,9-diones [Figure 9a], that is, 2-acetylnaphtho[2,3-b] furan-4,9-dione (49) and 2-acetyl-6- methoxy-naphtho[2,3-b] furan-4,9-dione (50) were reported to have been isolated from the stem bark of *Markhamia tomentosa*.[9] In addition, dilapachone (51) [Figure 9b] was identified in the ethyl-acetate fraction of the leaves of *Markhamia tomentosa*.[29]

Flavonoids

The identification of luteolin (52), luteolin-7-rutinoside (53), and luteolin-3',7-di-O-glucoside (54) [Figure 10] from the ethyl-acetate fraction of the leaves of *Markhamia tomentosa* has been reported.[29]

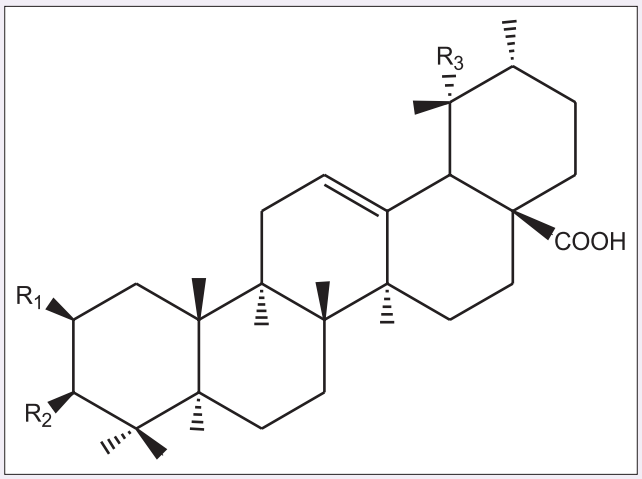
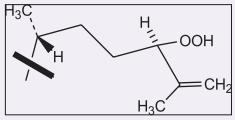
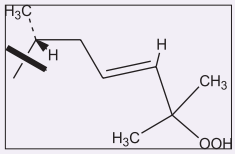
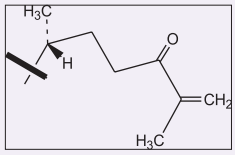


Figure 8: Pentacyclic triterpenoids

Chemical constituent (structure number)	R_2
Musambin A (19) R_1=H Musambioside A (22) R_1=xylose	
Musambin B (20) R_1=H Musambioside B (23) R_1=xylose	
Musambin C (21) R_1=H Musambioside C (24) R_1=xylose	

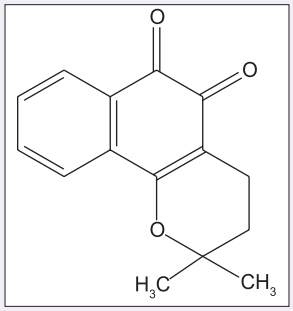


Figure 9b: Dilapachone

Chemical constituent (structure number)	R
2-acetylnaphtho[2,3-b] furan-4,9-dione (49)	H
2-acetyl-6-methoxylnaphtho[2,3-b] furan-4,9-dione (50)	OCH_3

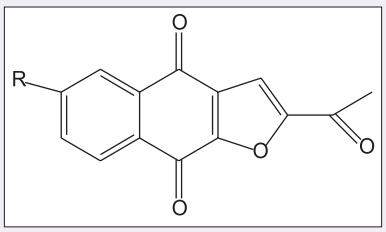


Figure 9a: Naphtho [2,3-b] furan-4,9 –dione

Chemical constituent (structure number)	R_1	R_2	R_3
Epi-tormentic acid (25)	OH	OH	OH
Ursolic acid (29)	H	OH	H
Pomolic acid (30)	H	OH	OH
3-acetylpomolic acid (34)	H	OAc	OH

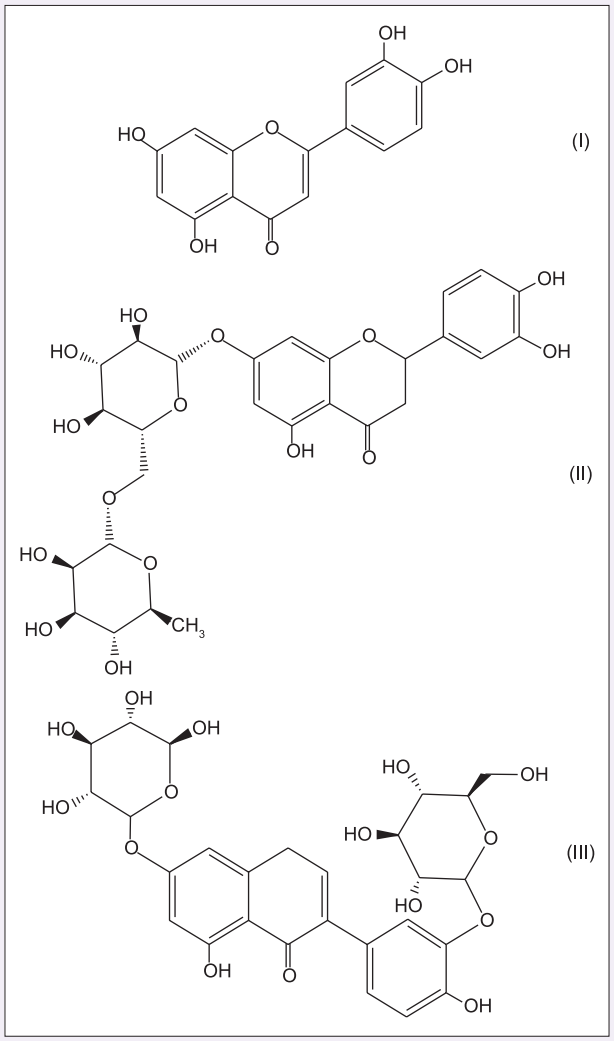


Figure 10: (I): Luteolin; (II): Luteolin-7-rutinoside; (III): Luteolin-3′,7-di -O-glucoside

ETHNOPHARMACOLOGICAL ACTIVITY

The primary metabolites are mainly important to the plants, while the secondary metabolites are of medicinal value for humans.[34] The medicinal plants of the genus *Markhamia* have emerged as a good source of medicines. Researchers have carried out various *in vitro* and *in vivo* screenings on the extracts and isolated compounds from members of the genus to authenticate their use in traditional medicine. Plants of this genus have demonstrated a wide spectrum of pharmacological profiles such as antiulcer, antioxidant, antimicrobial, antiinflammatory, analgesic, and antiviral activities. In our earlier work,[20] we reported the

cytotoxicity and the antiproliferative and apoptosis-inducing activity of one member of the genus *Markhamia* against brine shrimp larvae and HeLa cervical cancer cell lines. The following section presents a review of ethnopharmacological uses of *Markhamia* species. More details of the pharmacological properties of these species and the associated references are shown in Table 3.

M. lutea (Benth.) K.Schum

The roots of *Markhamia lutea* are soaked in cold water for 30 min and the resulting tea is used to reduce symptoms of watery and bloodless diarrhea.[25] The aqueous extract of the root bark is used in the treatment of anemia and diarrhea.[6] *Markhamia lutea* and *Markhamia tomentosa* are both used to cure various parasitic and microbial diseases.[11] In ethnoveterinary medicine, the plant is eaten by primates such as chimpanzees and red and black-and-white colobus monkeys.[17,35,36] The presence of phytoconstituents such as flavonoids, saponins, terpenoids, phytosterols, quinones, and coumarins in the different solvent extracts of *M. lutea* have been reported.[17] Several *in vitro* and *in vivo* studies have so far been carried out to validate the use of this plant. The commonly occurring PhGs including verbacoside (1) and isoverbacoside (2) and new PhGs such as luteosides A, B, and C (1–3) isolated from the root of *M. lutea* showed activity against respiratory syncytial virus.[24] The bioactive compounds musambins A, B, and C (19–21) isolated from the leaves of the plant

Table 3: Pharmacological Investigation of *Markhamia* species

Pharmacological properties	Markhamia species	Part Used	Application	Activity	Reference
Antiviral	*Markhamia lutea*	Roots	*In vitro*	Active against respiratory syncytial virus	24
Antiprotozoal	*Markhamia lutea*	Leaves	*In vivo*	Methanol extract showed active antiplasmodial effect	11
			In vitro	Ethylacetate extract was active against *Plasmodium falciparum* (IC_{50} 10.2 µg/mL), while dichloromethane extract showed weak activity (IC_{50} 29 µg/mL). The extract was poorly active against *Leishmania donovani*. Extract and isolated compound Musambin B were active against *Trypanosoma brucei brucei* (IC_{50} 1.9 µg/mL)	26,36
	Markhamia tomentosa	Stem bark	*In vitro*	Antimalarial activity against the ring stages of K1 and W2 chloroquine-resistant strains of *Plasmodium falciparum*. Extract showed leishmanicidal effect against *Leishmania donovani* and antitrypanosomal activity against *Trypanosoma brucei rhodesiense*	9
Antilarvacidal	*Markhamia tomentosa*	Stem bark	*In vivo*	Larvicidal activity against fourth-instar larvae of *Aedes aegypti*	49
Antimicrobial	*Markhamia obtusifolia*	Leaves	*In vitro*	Extracts and pure compounds inhibited growth of *Candida albicans* isolated from dogs and cats	30
	Markhamia tomentosa	Leaves and roots	*In vitro*	Extracts were active against clinical isolates of *Candida pseudotropicalis*, *Candida albicans*, and *Salmonella typhi*. Extracts and partitioned fractions were active against Gram-positive and Gram-negative bacteria	2,8
Antioxidant	*Markhamia tomentosa*	Leaves	*In vitro*	Methanol extracts showed strong radical scavenging ability (IC_{50}16.5 µg/mL)	8
Analgesic	*Markhamia tomentosa*	Leaves	*In vivo*	Alcoholic extract inhibited the writhing response induced by acetic acid; reduced the licking time induced by formalin; increased the reaction time to thermal stimulation in Swiss albino mice, and increased the latency time in Wistar rats	10
Antiinflammatory	*Markhamia tomentosa*	Leaves	*In vivo*	Extract reduced carrageenan-, histamine- and serotonin-induced edema in rats and xylene- and formalin-induced edema in mice	10,18
Cytotoxicity	*Markhamia lutea*	Roots	*In vitro*	Extracts and isolated compounds showed cytotoxic effect against respiratory syncytial virus cells	24
Cytotoxicity	*Markhamia lutea*	Leaves	*In vitro*	Extract and isolated compounds showed low cytotoxic effect against human mouth epidermoid carcinoma (KB) and human diploid embryonic lung (MRC5) cell lines	26
	Markhamia hildebrandtii Synonym: *M. lutea*	Leaves	*In vitro*	Extract showed <50% cell proliferation of one cancer cell line out of three tested cells	17
	Markhamia obtusifolia	Leaves	*In vitro*	Methanol extract exhibited cytotoxic effect against A431 human skin carcinoma cell lines	17
	Markhamia tomentosa	Stem bark	*In vitro*	Isolated compounds showed strong cytotoxic effect on rat skeletal-muscle myoblast (L-6) cells	9
		Leaves	*In vivo*	Cytotoxic effect against brine shrimp larvae	19
			In vitro	Alcoholic extract showed cytotoxic effect on HeLa cervical cancer cells but not on Vero cells	19
	Markhamia zanzibarica	Roots	*In vivo*	Cytotoxic effect against *Artemia salina*	42
Anti-Alzeheimer	*Markhamia platycalyx* Synonym: *M. lutea*	Leaves	*In vivo* and *ex vivo*	Alcoholic extract showed good discrimination ratio in object recognition and reduced amyloid beta 42 in mice	20
	Markhamia tomentosa	Root bark	*In vitro*	Methanol extract showed selective cholinesterase inhibitory activity toward butyrylcholinesterase enzyme	43
Antiulcer	*Markhamia tomentosa*	Leaves	*In vivo*	Ethanolic crude extract and the different solvent fractions (hexane, dichloromethane, ethyl-acetate, and butanol) exhibited a significant reduction of gastric leisions induced by ethanol and indomethacin in rats; the ethyl-acetate fraction was found to be the most active	28

exhibited mild antileishmanial and antitrypanosomal activities.[27] Dichloromethane leaf extract of the plant showed weak antiplasmodial activity with a half maximal inhibitory concentration (IC_{50}) value of 29 μg/mL.[37] The cytotoxic potential of the methanolic root extract of *Markhamia hildebrandtii* (synonym of *Markhamia lutea*) was investigated against cervical carcinoma, colon adenocarcinoma, and skin carcinoma.[18] *In vivo* pharmacological screening of the leaf extract of *Markhamia platycalyx* (synonym of *Markhamia lutea*) provided evidence that the plant has high potential as an anti-Alzheimer's disease drug lead due to its high phenolic content.[21]

M. obtusifolia (Baker) Sprague

The root of *Markhamia obtusifolia* is used in folk medicine to treat tuberculosis infection of lymph nodes in the neck,[38] convulsion in children,[18] and hookworm infestation.[39] The roots, barks, and leaves are boiled with other plants and used as an inhalant for the treatment of colds. In ethnoveterinary medicine, the leaves and fruits of this species are consumed as fodder by goats.[40] The methanolic root extract of *M. obtusifolia* exhibited minimal cytotoxic effect (<50% cell proliferation) against A431 skin carcinoma at 100 μg/mL.[18] The antifungal activity of three isolated triterpenoids (25, 29, and 30) from the acetone extract of *M. obtusifolia* has been reported.[31] The claimed anthelminthic activity of this plant species has been confirmed *in vitro*.[39] Further research is required to confirm the folk uses of the plant in treating other disease conditions.

M. stipulata Seem. ex K.Schum

The leaves and barks of *Markhamia stipulata* are used externally for the treatment of skin diseases and internally as an analgesic [Table 1]. Bioactive chemical compounds including quinones, phytosterols, lignans, and PhGs have been isolated from different parts of the plant.[7,33] Although the pharmacological activity of the compounds isolated from the plant has not been investigated, the pharmacological activities of verbacoside derivatives have been reported to have antifungal, antibacterial, antiviral, and analgesic effects.[25,41,42]

M. tomentosa (Benth.) K.Schum. ex Engl.

Of all the members of the *Markhamia* genus, the traditional use of the different plant parts of *Markhamia tomentosa* is the most reported [Table 1]. The species has found use in both human folk and ethnoveterinary medicines.[43,44] The plant is used in ethnoveterinary medicine to control gastrointestinal ailment and in pain management.[12,13] Preliminary phytochemical investigations of the leaves revealed the presence of major classes of bioactive compounds including saponins, flavonoids, terpenes, steroids, and phenolic nuclei.[2,16] A number of *in vitro* and *in vivo* studies have been carried out to validate the activity of the plant. Two naphthoquinone [Figure 9] compounds (49–50) isolated from the stem bark of *M. tomentosa* exhibited potent antiprotozoal activity against *Plasmodium falciparum*, *Leishmania donovani*, and *Trypanosoma brucei rhodesiense*.[9] The leaf extract of the plant was reported to possess strong antimicrobial and antioxidant effects.[8] The inhibition of *Escherichia coli* by the hexane and ethylacetate extracts of *M. tomentosa* justifies the traditional use of the plant in the management of dysentery and diarrhea.[2] Although hepatoprotective activity has not been reported for this plant, there has been a report on the prophylactic and therapeutic activities of a member of the family Bignoniaceae against paracetamol-induced liver damage in rats.[45] Alcoholic extracts of the leaves of *M. tomentosa* were shown to have potent analgesic and antiinflammatory effects[10,19] on rats and mice. The selective inhibition of butyrylcholinesterase enzymes by the root bark of this species in the management of Alzheimer'sdisease has also been reported.[46,47] Ethanol crude extract and the different solvent fractions of *M. tomentosa* leaves were reported to prevent gastric mucosal ulceration in the stomachs of rats.[29] In our earlier work,[20] we reported the cytotoxicity activity and underlying mechanisms of *Markhamia tomentosa* leaf extract on brine shrimp larvae, HeLa and MCF-7 cancer cell lines, and noncancerous Vero cell lines. In view of the wide application of this plant species and the tendency for prolonged intake, we are currently investigating the dose- and time-dependent chronic toxicity effects of *Markhamia tomentosa* in rodents (not published).

M. zanzibarica (Bojer ex DC.) K.Schum.

Markhamia zanzibarica is widely distributed in tropical Africa and Asia. In India, the plant is the second most reported *Markhamia* species after *Markhamia lutea*.[3,48] The plant is used to treat toothache, headache, and general pains[Table 1]. The cytotoxic effect of this species on *Artemia salina* has been investigated[49] and the activity was attributed to the bioactive gamma-sitosterol (38) compound isolated from the root of the species.[26]

CONCLUSION

This review summarizes information on the plants of the genus *Markhamia* with emphasis on their ethnomedicinal uses, isolated phytoconstituents, and ethnopharmacological studies on them. Species of this genus have been useful in the management of various disease conditions in both human and veterinary traditional medicines. Some of the claimed traditional uses have been validated through phytochemical and pharmacological studies of the genus. On preliminary phytochemical screening of plants of this genus, the presence of a wide range of secondary metabolites was reported. However, the major reported class of phytoconstituents, isolated through various separation and purification techniques from *M. lutea*, *M.obtusifolia*, *M. stipulata*, *M. tomentosa*, and *M. zanzibarica*, were PhGs, terpenoids, phytosterols, lignans, quinones, and flavonoids. The isolated compounds were identified on analysis of their spectroscopic and chemical data, which were consistent with values reported in the literature. A number of *in vitro* and *in vivo* pharmacological studies have confirmed that the plant extracts and isolated compounds possess significant antiviral, antiprotozoal, antimicrobial, antioxidant, analgesic, antiinflammatory, anti-Alzheimer, antiulcer, and cytotoxic activities. It may be concluded that plants of this genus hold great potential as a source of new drugs. Thus, further studies aimed at the proper documentation of folk uses, validation of the claimed bioactivities, and isolation and identification of the bioactive compounds of species of the genus are required.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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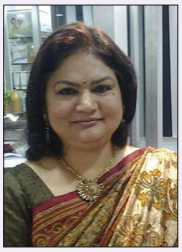
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