



Mini Review on Morphology, Traditional Uses, Phytochemical Pharmacological Potential of *Markhamialutea*



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Abstract

Markhamialutea (Benth) K. Schum is an evergreen tree, commonly known as the Bell Bean Tree or Nile Tulip. It is widely distributed throughout tropical regions of Africa, Malawi, Tanzania, and Namibia. *M. lutea* uses in folk medicine and the different extracts of leaves, stems, barks, and roots possess various pharmacological activities. The purpose of this review is providing a complete and updated review on morphology, the active constituents of different parts of *M. lutea* such as sterols, triterpenoids, phenylpropanoid glycosides and flavonoids and their antioxidant, antiprotozoal, antiviral, antimicrobial effects and anticancer activities. Cycloartanetriterpenoids were predicted to possess anti-dementia activity using the Pass Online Web Resource.

Keywords: Ethnopharmacological uses; *Markhamialutea*; Pharmacological activities; Phenylpropanoid glycosides; phytochemical compounds.

1. Introduction

Ethnopharmacology is a frontier tool in the search for bioactive constituents from medicinal plants of African origin[1]. Currently, natural resources containing phytoconstituents are being used as alternative remedies to cure several diseases[2]. *Bignoniaceae* is a family of trees, shrubs, and rarely herbs characterized by showy flowers, woody stem, opposite, and compound leaves, and zygomorphic flowers[3, 4]. The family is comprised of 100 genera and 800 species[5]. Family *Bignoniaceae* (Trumpet Creeper family) is also known as Jacaranda family, Bignonia family, or the Catalpa family[6]. The genus *Markhamia* is widely distributed throughout tropical regions of Africa, Malawi, Tanzania, Namibia, and India. Genus *Markhamia* was named after Sir Clement Markham who came with the famous quinine-yielding cinchona to India[7]. Genus *Markhamia* represent about 92% of *Bignoniaceae* family members[8]. All

Markhamia species were traditionally used in treatment of several diseases viz., *Markhamiazanzibarica* (Bojer ex DC) K. Schum as used in toothache, back pains, and headache while *Markhamiatomentosa* (Benth) K. Schum. Ex Engl's bark is used to treat worm infestation, migraine, and dysentery[9]. *Markhamialutea* (Benth) K. Schum is an evergreen tree that reaches 10-15 m in height; leaves are faint to dark green in color, and flowers are bright yellow in color and appear as showy terminal clusters[3]. *M. lutea* is commonly known as the Bell Bean Tree, Nile Tulip Tree, and Siala[7]. The leaves, stems, bark, and roots of *M. lutea* have been used to treat many diseases, such as microbial and parasitic diseases, diarrhea, anemia, and backache. Different extracts of the plant possess various pharmacological activities such as antiviral, anticancer, antiprotozoal, and antioxidant. A wide range of active constituents, including sterols, terpenoids, phenylpropanoid

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glycosides, and flavonoids, have been isolated from this species.

M. lutea is widely distributed in Egypt, but no detailed review has been conducted on it. For these reasons the purpose of this review is providing a complete and updated review on morphology, ethnomedical uses, phytochemical, and pharmacological studies of different parts of *M. lutea* to aid in further researching. To achieve the purpose of this study, a systematic search for literature was performed using the Google Scholar, Egyptian Knowledge Bank, Scopus, PubMed Web of Science, and Elsevier databases. This search was performed using all MeSH terms and covered all structures of isolated compounds, ethnopharmacological uses, biological activities, clinical investigations, and mechanisms for *M. lutea*. The review search period was from 1998 to 2022.

2. Taxonomy and macro morphology

Taxonomy

- Kingdom: Plantae.
- Family: *Bignoniaceae*.
- Genus: *Markhamia*.
- Species: *lutea*.
- Author: (BENTH.) K.SCHUM
- Synonyms: *Dolichandrone lutea* Benth. ex Hook, *Markhamia hildebrandtii* Spargue, *Markhamia platycalyx* Spargue, *Dolichandrone platycalyx* (Baker) Sprague [5].

Macro morphology

Plants in the genus *Markhamia* are either trees or shrubs. They are characterized by the presence of pseudo-stipules. The leaves are opposite, imparipinnate with terminal or axillary panicles or racemes. The corolla (cup-shaped) is 2-lipped, and composed of 5-lobes longer than the calyx. The ovary is bilocular, and the seeds are winged [10]. *M. lutea* is an upright evergreen tree that grows to reach 10-15 m in height. The bark is faint brown with an irregular edged crown [11]. Leaves are nearly opposite, and imparipinnate, with terminated panicles up to 20 cm in

length. Leaflets are long (to 10 cm), wavy, thin, elliptical to obovate, stipules are absent, acuminate at apex, cuneate to rounded at base; petiole 6 – 12 cm long [12] (Figure.1 (A)). The flowers are bright yellowish in color, and 6 cm in length. It has a trumpet-shape with five frilly lobes [12]. Calyx is 2.5 cm in the long, and bright yellow corolla limbs 5 cm across (Figure.1 (B)). Fruits with brown capsules up to 75 cm in length are thin, long, and hanging in clusters, forming a spiral shape. Yellow-whitish mature seeds are formed by splitting the fruits. Seed is 2.5 cm long with characteristic transparent wings [11].

3. Ethnopharmacological uses

M. lutea has been traditionally used for the treatment of snakebites, anemia, liver diseases, cataracts, inappetence, stomachache, headache, throat diseases, conjunctivitis, backache, and skin rash [13]. In Uganda, the leaves juice was mixed with water, and used to treat malaria, asthma, anemia, skin infection, stomach ache, syphilis, inappetence, and eye and ear infections [10, 14-16].

Herbalists in Uganda used *M. lutea* to treat HIV/AIDS to boost immunity by boiling it with other herbs, and drinking it [14]. Wood extract of *M. lutea* was reported to protect wood against both fungal, and termite attacks, and was therefore used as a wood preservative [10]. Moreover, in most communities *M. lutea* was used in crafts, and timber production [17]. In Kenya, stem bark is used alone or in combination with *Albizia gummifera* to treat throat, breast, and colorectal cancers [13]. Root tea of *M. lutea* was used to decrease the symptoms of watery diarrhea, and as an analgesic to treat the difficulty of urination at a dose of three times daily. In addition, root bark is used as a remedy for backache, anemia, and diarrhea [5].

4. Preliminary phytochemical screening of different organs of *M. lutea*

Based on the literature overview, the ethanolic extracts of leaves, stem bark, and flowers of *M. lutea* contain various constituents such as saponins, tannins, carbohydrates, alkaloids, quinones, phenols, and terpenes [7, 18, 19].

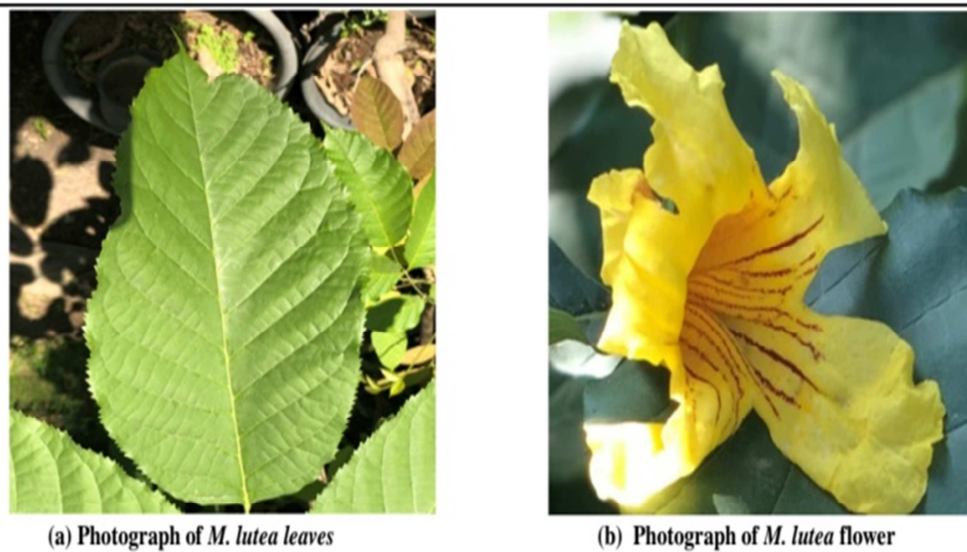


Figure 1: Photograph for different parts of *M. lutea*

1
2

5. Pharmacopeial constituents and phytochemical evaluation

Based on the literature, the physicochemical parameters of *M. lutea* leaves include the determination of different types of ash, extractive values, total phenols, flavonoids, tannins, saponins, and alkaloids content were evaluated. The total ash content of *M. lutea* leaf material was 3.65%, which consisted mostly of acid-insoluble ash (1.5%) as compared to water-soluble ash (0.833%). When considering the *M. lutea* extractive values, total alcohol (9.4%), and aqueous (4.6%) gave higher extractive values [7], followed by ethyl acetate (3.11%), chloroform (2.29%), and petroleum ether (1.88%)[20] Leaf material also showed high phenols content with value (407.83 mg /g sample) [3] followed by flavonoids (62.4 mg equivalent/g), tannins (27 mg equivalent /g), saponins (17 mg equivalent /g), and alkaloids (8 mg equivalent /g)[21] (table.1).

6. Metal and mineral composition of leaf powder

The leaves of *M. lutea* showed high levels of calcium (80.4%), potassium (10.79%), and iron

(1.5%) [20]. Calcium plays a critical role in tooth, and bone formation, muscle contraction and relaxation, normal blood clotting, heart function, and nerve function[22]. Iron is one of the most valuable components of haemoglobin, myoglobin, cytochromes, and many enzymes in muscle cells, all of which are involved in energy production during daily exercise[23]. Therefore, *M. lutea* leaf material is a public health concern, and is used for the treatment of anemia. Therefore, *M. lutea* leaves provide a nutritionally essential supplement[20]. All the metals and minerals are listed in Table (2).

7. Phytochemical constituents

Phytochemical constituents are believed to be responsible for the therapeutic properties of medicinal plants. Phytochemical analysis of *M. lutea* revealed the presence of different groups of active constituents such as flavonoids, phenylpropanoid glycosides, terpenoids, and their glycosides.

Phenylpropanoid glycosides

Phenylpropanoids are diverse groups of

pharmacologically active compounds. They are one of the end products of shikimate pathway[24]. Chemically, phenylpropanoids have six-carbon aromatic phenyl group and three-carbon propene tail of cinnamic acid and are considered the first product of the phenylpropanoid biosynthetic pathway [25]. Phenylpropanoids are widely distributed in plants and play a vital role in biological activity by carrying out important components of cell walls, high light protectants against UV radiation, phytoalexins against pathogens, herbivores, and floral pigments to facilitate plant-pollinator interactions. In addition, phenylpropanoids possess beneficial biological activities to human health, such as antioxidant, UV screening, anticancer, antiviral, anti-inflammatory, and antibacterial activities, and promote wound healing[26, 27]. *Markhamia* species are a good source of phenylpropanoids, which are known to have potent *in vitro* antiviral activity, especially against respiratory syncytial viruses[28]. Phytochemical analysis of the aqueous extract of *M. lutea* roots led to the isolation of five phenylpropanoid glycosides named verbascoside(**compound 1**), and its isomer isoverbascoside(**compound 2**) in addition to luteoside A, B and C (**compound 3,4,5**)[10, 29](Figure.2).

Terpenoids

Terpenoids and their derivatives are natural occurring compounds[30]. All terpenoids built up of isoprene units (C_5H_8)_n joined in an ahead to tail fashion. Depending on the number of isoprene units, terpenoids are classified as monoterpene (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterpenoids (C_{25}), triterpenoid (C_{30}), and carotenoids (C_{40}). Phytosterols are a subclass of terpenoids derived from triterpenes[5]. Hydroperoxycycloartanetriterpenes and their glycoside compounds were identified in the ethyl acetate fraction of the *M. lutea* leaf extract. Three new hydroperoxycycloartanetriterpenes were isolated from musambins A, B, and C (**compound 6,8,10**) as well as three glycoside derivatives, musambiosides A, B, and C (**compound 7, 9, 11**)(Figure.3). Other pentacyclitriterpenoids are identified such as arjunic acid, 2-epi-tormentic acid (**compound 14**) and Phaeophorbide A [5, 10]. Using LC/MS/MS on the ethanol extract of the stem bark of *M. lutea*, several triterpenoids were identified, such as oleanolic acid (**compound 15**), pomolic acid (**compound 13**) and

musambin A [18](Figure. 2).

Flavonoids

Flavonoids are various compounds found naturally in many medicinal plants. Flavonoids are rich in antioxidant activity and can help the body ward off toxins. LC-MS has been used to analyze six flavonoids from aqueous extract of *M. lutea* leaves which are kaempferol-3-glucoside-3-rhamnoside, 3-hydroxy-3,4-dimethoxy flavones, isorhamnetin-3-galactoside-6-rhamnoside, pectolinarin, chrysoeriol, and rutin[20].

8. Pharmacological activities:

Markhamia species are used in folk medicine to treat several diseases. *M. zanzibarica* used for treatment of toothache, headache, and back pains, while *M. tomentosa* bark used for treatment of dysentery, worm infestation, and migraine[9]. By reviewing genus *Markhamia*; many therapeutic activities were reported for *M. lutea* such as antimalarial, antileishmanial, antiprotozoal, antiviral, antitrypanosomal, antioxidant, anticancer, and antimicrobial[31]. Different parts of *M. lutea* contain a wide range of phytochemicals that impart medicinal value to plant. Several *in vitro* and *in vivo* studies have evaluated the pharmacological effects of *M. lutea* extract. These activities of *M. lutea* have been attributed to the crude extract, different fractions, and isolates from leaves, bark, and roots of the plant[32].

Antiprotozoal activity

Since long time antiparasitic agents have been used to overcome the problem of parasites, the emergence of resistance against industrial products has resulted in the search for natural alternative control strategies. The application of ethnoveterinary practices and harnessing plants as anthelmintic agents is gaining popularity worldwide[33]. Natural substances have safety profiles for humans, animals, and the environment. For these reasons, leaves extract fractions of *M. lutea* were tested for both *in vitro* and *in vivo* antiplasmodial activity. Methanolic extract of *M. lutea* leaves showed antiplasmodial activity *in vivo*. The ethyl acetate fraction showed strong *in vitro* activity against *Plasmodium falciparum* with an IC_{50} of 10.2 μ g/mL, and inhibition percentage of 71% [10,

16], whereas the dichloromethane extract showed weak *in vitro* activity (IC_{50} 29 μ g/mL). Among the isolated compound musambin B was active against *Trypanosomabrucei* (IC_{50} 1.9 μ g/mL) [5], while the ethyl acetate fraction was poorly active against *Leishmaniadonovani* (IC_{50} 42.0 μ g/ml)[15].

Antiviral activity

M. lutea has traditionally been used to treat viral diseases. The five phenylpropanoid glycosides from the root extract of *M. lutea* verbascoside and its isomer isoverbascoside, in addition to luteosides A, B, and C, are responsible for the antiviral activity of the extract[34]. *M. lutea* showed *in vitro* activity against respiratory syncytial virus (RSV) in cell culture owing to the isolation of five phenylpropanoid glycosides from its roots[5]. The isolated compounds, including verbascoside, isoverbascoside, and luteoside A,B (Figure.2) showed similar or better *in vitro* activity against RSV than ribavirin, as well as higher selectivity than ribavirin using a cytopathic effect assay (CPA). It seemed that phenylpropanoid glycosides act by a mechanism similar to that of ribavirin in the case of RSV. None of the isolated phenylpropanoid glycosides showed activity against herpes simplex virus, cytomegalovirus, or varicella-zoster virus[10].

Anti-trypanosomal activity

Loiseau *et al.*[35]assessed a method for describing and evaluating antiparasitic activity. One of the isolated cycloartanetriterpenoids “musambin B” (Figure.2) showed a potent anti-trypanosomal activity with IC_{50} 1.9 μ g/mL that was almost active as the reference drugs [1.0 g/mL for bis(aminoethylthio)-4-melaminophenarsine and 1.4 lg/mL for pentamidine[15].

Cytotoxicity and anticancer activity

All *M. lutea* leaf extracts (IC_{50} >10 μ g/ml) and different hydroperoxycycloartanetriterpenes, and their glycosides (IC_{50} >50 μ g/ml) showed no cytotoxicity against MRC5, and KB cells[10, 16]except for tormentic acid (IC_{50} 26.8 μ g/ml) against KB cells, and musambin A (IC_{50} 48.8 μ g/ml) against MRC5 showed a weak activity [15]. The ethanolic extract of *M. lutea* stem bark showed good anticancer activity against Ehrlich Ascites Carcinoma cells. The

anticancer activity of stem bark is due to the presence of pomolic acid, which has been reported to induce apoptosis in HL-60 cells (human promyelocytic leukemia cells) by activating caspases 3 and 9, and altering mitochondrial transmembrane energy. Pomolic acid also induced apoptosis in MCF7 breast cancer cells, activated cyclic AMPK, and inhibited cell proliferation. The stem bark of *M. lutea* also contains oleanolic acid, which arrests the cell cycle by inhibiting the tumor cell proliferation of the human colon cancer cell line HCT15. It has been shown to possess good angiogenic activity by inhibiting embryonic angiogenesis and capillary formation in the chorioallantoic membranes of chick embryo. An anticancer activity report of musambin A on (MRC-5) cells, which are human fetal lung fibroblasts, is also available, all of which indicate that the stem bark extract has good anticancer activity[18].

Antioxidant

The antioxidant activity of *M. lutea* was evaluated for both ethanol extract of the stem bark and aqueous extract of the leaves. The *M. lutea* leaf aqueous extract was evaluated for its antioxidant activity in terms of ferric reducing power, phosphomolybdate reducing power at doses of 1000 μ g/ml and 500 μ g/ml for both, and the obtained results (1.03%), (290 ascorbic acid equivalent), and (0.564%) (180 ascorbic acid equivalent), respectively, which means that there was dose-dependent antioxidant activity for leaf aqueous extract against ferric ion and phosphomolybdate. Moreover, DPPH radical scavenging activity (71.27%), hydrogen peroxide inhibition (55.08%), and superoxide radical scavenging activity (40%) have been reported [20].The free radical scavenging activity of the ethanolic extract of *M. lutea* stem bark was determined using a DPPH assay with an IC_{50} value of 169 μ g/mL, which revealed good antioxidant activity of the ethanolic extract of stem bark [18].

Antimicrobial

M. lutea ethanol and aqueous extracts showed antibacterial activity with inhibitory zone diameters ranging between 3-26 mm against food spoilage bacteria and food-borne pathogens. Both ethanol and aqueous extracts were resistant to *Sacharomycescerevisiae*, which plays a major role in the fermentation of African beers. Gram-negative bacteria (*Bacillus subtilis* and *Staphylococcus aureus*)

are resistant to *M. lutea* leaves extract [21]. Ethyl acetate extract of *M. lutea* showed also antimicrobial activity against *Xanthomonas axonopodis* sp. *Phaseoli* with inhibitory zone diameters 14 mm while there was no activity against *Pseudomonas syringae* sp. *Phaseolicola* [36].

Prediction of anti-dementia activity of *M. lutea* using Pass Online Web Resource

The PASS computer program predicts the probable activity of a drug, such as an organic compound (whose molecular mass ranges from 50 to 1250 Da), depending on the analysis of the structure-activity relationship. The PASS user obtains output information as a list of predicted types of activity with the estimated probability for each type of activity "to be active" Pa and "to be inactive" Pi, which varies from zero to one [37]. *M. lutea* reported to be used in treatment of dementia (Pa=0.709) by using PASS online program. Other biological activities were reported using PASS online program, such as apoptosis agonist (Pa=0.901), chemopreventive (Pa=0.871), antineoplastic (Pa=0.833), and antithrombotic (Pa= 0.728) activities. These activities were attributed to the presence of two cycloartanetriterpenoids, musambins A and B, and their corresponding glycosides, musambiosides A and B [38].

Anticonvulsant

A mixture of aqueous extracts of both *M. lutea* and *Drymaria cordata* was reported to have anticonvulsant activity against pentylenetetrazole-induced seizures and strychnine-induced seizures, and no effect against picrotoxin-induced seizures. Mixture of aqueous extracts of both *M. lutea* and *D. cordata* at dose (1554 mg/kg) protected 71.43% of subjects against pentylenetetrazole-induced seizures at dose 388.5 mg/kg protected 28.57% of subjects against strychnine-induced seizures. These results showed that the mixture of *M. lutea* and *D. cordata* have anticonvulsant properties that could contribute to improve the treatment of epilepsy [39].

9. Discussion and conclusion

Despite the widespread use of *M. lutea* in the

treatment of many diseases, there are a very limited number of published papers on *M. lutea*. As research process is an ongoing process, this review aims to provide a reference source for botanical, phytochemical, ethnopharmacological, and pharmacological research on *M. lutea* for future work. Most *M. lutea* literature has been based on the study of all its parts, as they have significant therapeutic activities. This plant has a variety of pharmacological activities, including antiprotozoal, antiviral, antitrypanosomal, anticancer, antioxidant, anti-dementia, and antimicrobial activities as confirmed by *in vivo* and *in vitro* studies. Chemically, *M. lutea* contains various biologically active constituents including terpenoids, triterpenoids, phenylpropanoid glycosides, fixed oils, and flavonoids (Table. 3)(Figure. 3). Taken together, the evidence presented in this work supports the fact that *M. lutea* has promising antiviral and anti-dementia therapeutic potential as a source of new drugs; however, further investigation is required to achieve this purpose, and estimating its mechanism of action will allow the development of successful anti-viral and anti-dementia drugs.

10. Conflicts of interest

The author declare no conflict of interest

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Phenyl propanoids

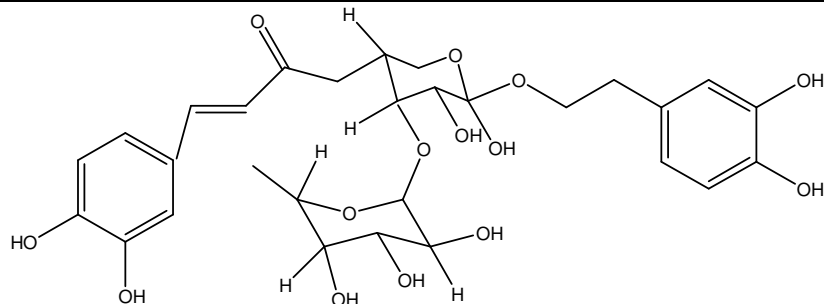
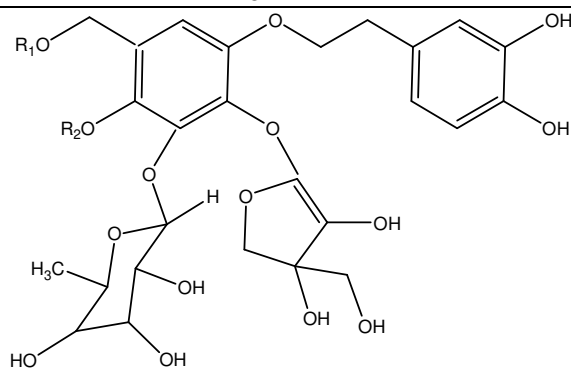
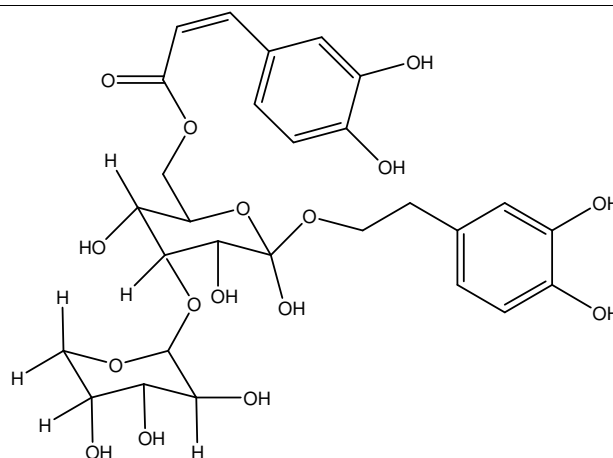
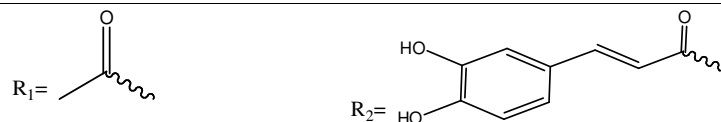
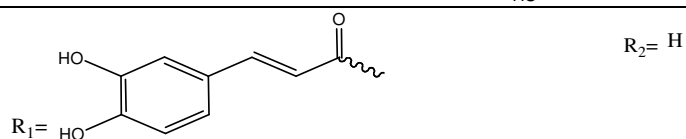
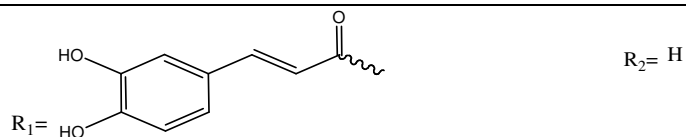
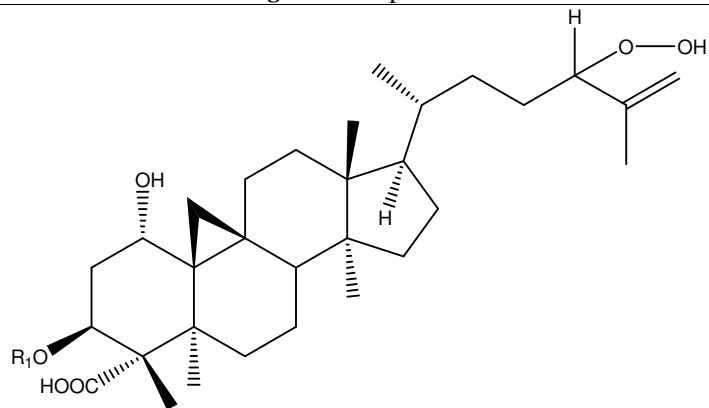
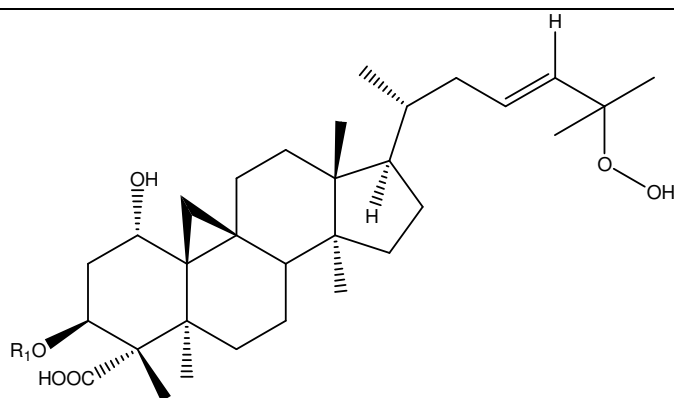
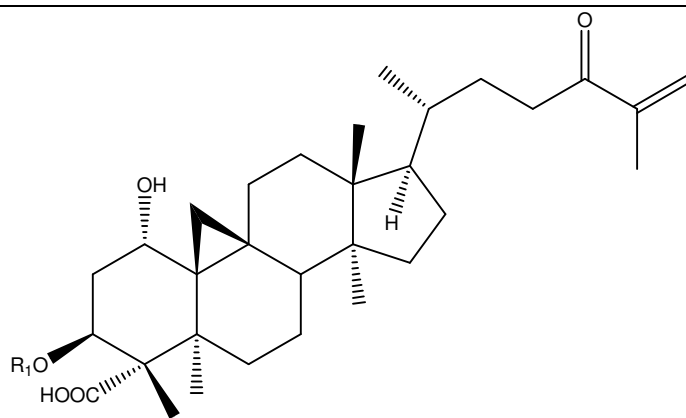
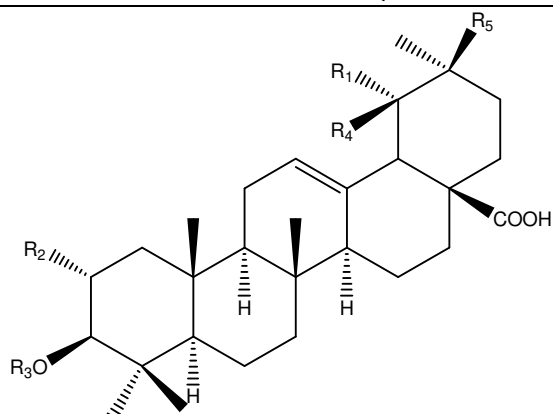
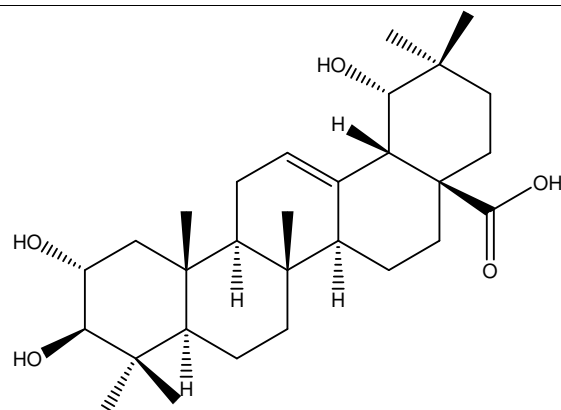
Compound.1: Verbascoside**Compound.2: Isoverbascoside****Compound.3: Luteoside A****Compound.4: Luteoside B****Compound.5: Luteoside C****Figure 2:** Structures of compounds identified from different parts of *M. lutea*

Figure.3: Terpenoids**Compound.6: Musambin A** $R_1 = H$ **Compound.7: Musambioside A** $R_1 = \text{xylose}$ **Compound.8: Musambin B** $R_1 = H$ **Compound.9: Musambioside B** $R_1 = \text{xylose}$ **Compound.10: Musambin C** $R_1 = H$ **Compound.11: Musambioside C** $R_1 = \text{xylose}$ **Figure 2:** Structures of compounds identified from different parts of *M. lutea*

Terpenoids continued

Compound.12: Arjunic acid



Compound.13: Pomolic acid

 $R_1=OH, R_2=R_3=R_5=H, R_4=CH_3$

Compound.14: 2-Epi-Tormentic acid

 $R_1=R_2=OH, R_3=R_5=H, R_4=CH_3$

Compound.15: Oleanolic acid

 $R_1=R_2=R_3=R_4=H, R_5=CH_3$
Figure 2: Structures of compounds identified from different parts of *M. lutea*Table 1: Extractive value and chemical content of *M. lutea*

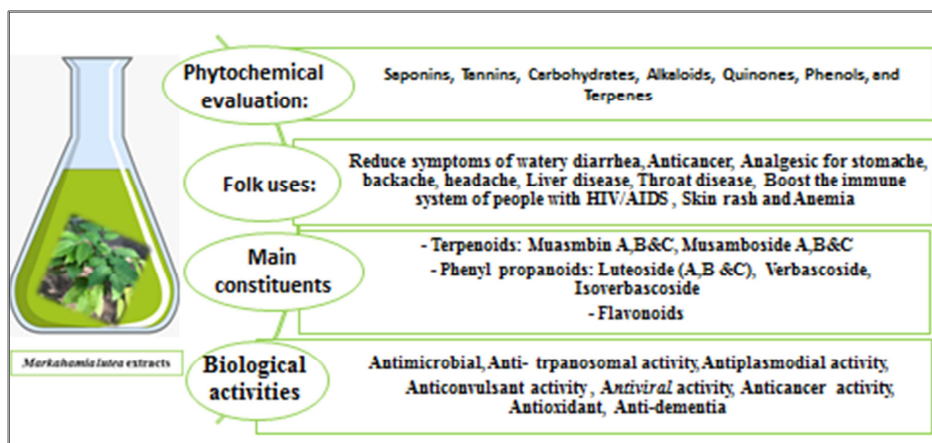
Ash value (%w/w)	Total ash	3.65 %w/w
	Acid soluble Ash	2.6 %w/w
	Water soluble ash	0.833 %w/w
	Acid insoluble ash	1.5 %w/w
Extractive values (%)	Alcohol	9.4 %w/w
	Aqueous	4.6 %w/w
	P. ether	1.88%
	Chloroform	2.29%
	Ethyl acetate	3.11%
Chemical values (mg/g)	Total phenols	407.83 mg/g
	Total flavonoids	62.4 mg/g
	Total saponins	27 mg/g
	Total tannis	17 mg/g
	Total alkaloids	8 mg/g

Table 2: Metals and minerals content of *M. lutea*

Metals and minerals (%)	Calcium (Ca)	80.48 ± 0.36
	Potassium (K)	10.79 ± 0.06
	Silicone (Si)	1.74 ± 0.03
	Chloride (Cl)	1.58 ± 0.02
	Iron (Fe)	1.50 ± 0.02
	Aluminium (Al)	0.97 ± 0.01
	Sulphur (S)	0.71 ± 0.04
	Magnesium (Mg)	0.60 ± 0.01
	Phosphorous (P)	0.58 ± 0.02
	Sodium (Na)	0.17 ± 0.01
	Zinc (Zn)	0.13 ± 0.01
	Strontium (Sr)	0.12 ± 0.00
	Molybdenum (Mo)	0.11 ± 0.01
	Titanium (Ti)	0.09 ± 0.01
	Tin (Sn)	0.09 ± 0.01
Copper (Cu)	0.07 ± 0.01	

Table 3: Compounds identified from different parts of *M. lutea* and their biological activities

Chemical class	Part used	Extract type	Biological activity	Reference
<ul style="list-style-type: none"> Terpenoid Musambins (A,B,C), Musambioside (A,B,C), 2-epi-tormentonic acid, Arjunic acid, Phaeophorbide A	Leaves	Ethyl acetate	Antiprotozoal, antitrypanosomal, dementia treatment, anticancer	[10] [15] [38]
<ul style="list-style-type: none"> Triterpenoids β -sitosterol, oleanolic acid, pomolic acid, β -sitosterol-3-O-b-D-glucopyranoside	Stem bark	Ethanol	Anticancer, Antioxidant	[10] [18]
<ul style="list-style-type: none"> Phenyl propanoid glycoside Luteoside (A,B,C), Verbascoside, Isoverbascoside	Roots	Aqueous	Antiviral	[10]
<ul style="list-style-type: none"> Flavonoids Rutin, Pectolarin, Chrysoeriol, Curcumin, kaempferol 3-glucoside 3-rhamnoside, 3-hydroxy3,4-dimethoxy flavones, Isorhamnetin-3-galactoside-6-rhamnoside	Leaves	Aqueous	Antioxidant	[20]

**Figure 3:** Diagram for Phytochemical evaluation, folk uses, main constituents and biological activities of *M. lutea* extracts