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Review article

Pharmacological activity of *Elephantopus mollis* Kunth: A review

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ABSTRACT

Elephantopus mollis Kunth., belongs to the family Asteraceae is a herbaceous perennial that originated from tropical America and was widely introduced to high rainfall tropical Africa, Asia and the Pacific. The whole plant and parts of this plant have been traditionally used and extensively studied for the treatment of various diseases, especially as cytotoxic agents. Other pharmacological activities such as anti-inflammatory, antioxidant, anti-leishmaniasis, antiprotozoal, antimicrobial, antidiabetic, bone stimulating regeneration and hepatoprotection activity have been reported in various research articles. This review intends to provide comprehensive investigations and findings of pharmacological activity from *Elephantopus mollis* Kunth., as well as the traditional uses, phytochemical constituents, and isolated compounds from *E. mollis* Kunth.

Keywords: *Elephantopus mollis* Kunth., pharmacological activity, traditional medicine, phytochemical constituent, sesquiterpene lactone

1. Introduction

The genus Elephantopus belongs to the family Asteraceae. The plant name derives from the Greek word *elephas* means elephant and 'pous' means foot. Thus, the genus Elephantopus is also called elephant's foot. *Elephantopus mollis* Kunth. is a herbaceous perennial and originated from tropical America. It has been widely introduced and becomes an invasive plantation in high rainfall tropical Africa, Asia and the Pacific since the beginning of the 20th century.[1,2]

E. mollis Kunth. is a perennial herb 0.5–2.0 m in height. Leaves are alternate and straightforward, 10–20 by 3–5 cm up to 30 cm long, rosette, elliptic or oblong. Leave and stem surfaces develop long-soft (filiform) hairs. Stem leaves are alternate, ovate to lanceolate, scabrid above, pilose below, 5–25 cm long, 3–10 cm wide, the margins shallowly to sharply toothed, lower surface gland-dotted and resinous. The leaf stalk is winged and decurrent. Flower heads are up to 2 cm across with small corolla white about 4 mm in length, surrounded by three leaf-like bracts about 1 cm long. Seeds black, about 3 mm long, densely covered in fine short hairs, apex with five white bristles

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3–4.5 mm long, each with a broad base; receptacle without scale[2,3] (Fig. 1).

Among the 32 species in this genus,[4] only two species are recorded in Indonesia, namely *E. scaber* Linn. and *E. mollis* Kunth.[5] Morphologically, they share relatively similar characteristics.[3] Hence, they are called as the same Indonesian traditional name, "Tapak Liman".

The extract and simplicia of *E. scaber* Linn. have been standardized, while the *E. mollis* Kunth. has not been standardized.[6] The traditional uses of *E. scaber* Linn and *E. mollis* Kunth. has been proven as treatment for asthma,[7] microbial infection,[8] wound-healing,[9] and hepatoprotection.[10] The leaves and roots are traditionally used as a tonic, antipyretic, expectorant, anti-catarrhal, emollient, healing, anti-rheumatic, astringent, and diuretic.[5]

Thirty-five compounds were isolated from *E. scaber* Linn., including four sesquiterpene lactones, five flavones, and nine triterpenes. Bioactivity studies on *E. scaber* Linn. demonstrated that the extracts or compounds from this species showed antibacterial, antiviral, and cytotoxicity activities.[11] The sesquiterpene lactones, in particular, have been explored for their anticancer, anti-inflammatory and hepatoprotective activities.[12] Previous bioactivity literatures have reported similar pharmacology activity of the extracts or isolated compounds of *E. mollis* Kunth. for anti-inflammatory, antioxidant, cytotoxic, apoptotic, and anti-α-glucosidase properties.[13,14]

E. scaber Linn. are the most widely explored plant in the genus Elephantopus, but the information about the traditional uses, pharmacological activity, phytochemical composition and the compounds isolated from *E. mollis* Kunth. have been limited. This review intends to provide comprehensive information on the pharmacological activities of *E. mollis* Kunth., as well as the traditional uses, phytochemical compositions, and isolated compounds.

Fig. 1. *Elephantopus mollis* Kunth.[5]

2. Material and methods

The literature search was conducted to gather all relevant information about botanical characterization, ethnopharmacology, secondary metabolites, and pharmacological activities of *E. mollis* Kunth. All available information was retrieved by Internet databases (PubMed, Web of Science, Wiley, Science Direct, Elsevier, Google Scholar, ACS publications, and Springer Link. All studies relating to *E. mollis* Kunth. reported up to October 2021 were included in this review.

3. Taxonomy

According to the Commonwealth Agricultural Bureaux International (CABI),[2] the taxonomy of *E. mollis* Kunth. is as follow.

Domain	: Eukaryota
Kingdom	: Plantae
Phylum	: Spermatophyta
Subphylum	: Angiospermae
Class	: Dicotyledonae
Order	: Asterales
Family	: Asteraceae
Genus	: Elephantopus
Species	: *E. mollis* Kunth.

4. Ethnomedical history

E. mollis Kunth. has been used as a folk medicine for various therapeutic properties. The herbs of *E. mollis* Kunth are used as Chinese traditional medicine for the treatment of hepatitis, tonsillitis, colds, and carbuncles.[10,15] In the Philippines, *E. mollis* Kunth. leaves are used as tonic, diuretic, febrifuge, and diaphoretic. The juice from manually macerated by hand is applied topically to reduce itching. In Myanmar, the decoction of aerial parts empirically is used to treat irregular menstruation. In Guam, the decoction of the whole plant is to treat asthenia fever.[16] In Ecuador, *E. mollis* Kunth. is traditionally used for Leishmaniasis.[17] It is also used in traditional Cameroonian medicine to treat fracture repair and bone diseases.[18] In Indonesia, leaves and roots are traditionally used as a tonic, antipyretic, expectorant, anti-catarrhal, emollient, wound-healing, anti-rheumatic, astringent, and diuretic. It is also used externally for the treatment of elephantiasis and bruises. The infusion of the leaves is believed to reduce kidney stones, whooping cough, and bronchitis.[5]

5. Phytochemical constituent

The chemical composition of methanol extract of *E. mollis* Kunth. includes flavonoids, polyphenols, triterpenes, and sterols.[19] The preliminary phytochemical screening of ethanol extract of *E. mollis* Kunth. are polyphenolics and terpenoids. There are no alkaloids, tannins, and saponins.[20] The study conducted by Bich Ngoc *et al*.[21] showed that the ethyl acetate extract contains carbohydrates, flavonoids, phenolics, steroids, terpenoids, saponins, and tannins. Interestingly, tannins and saponins are the first reported contents of *E. mollis* Kunth. only in Vietnam.

Several studies of *E. mollis* Kunth. reported several compounds including molephantin (1), molephantinin (2), and phantomolin (3), as well as the compounds that have previously been known as triterpene β–Amyrin acetate (4), lupeol acetate (5), epifriedelanol (6), and sigmasterol (7).[22] *E. mollis* cultivated in Peru and Brazil were reported to contain sesquiterpene lactones with antileishmaniasis activity, *i.e.*, 2,5-epoxy-2 β-hydroxy-8 α-(2-methylpropenoiloxy)-4 (15), 10 (14), 11 (13) -germakatrien-12.6 β-olide (8), (4 βH)-8 α-(2-methylpropenoiloxy)-2-oxo-1 (5), 10 (14), 11 (13) -guaiatrien-12-6 α-olide (9), (4 βH)-5 α-hidroksi-8 α-(2-methylpropenoiloxy)-1 (10), 11 (13) 12.6-guaiadien-α-olide (10), along with other sesquiterpene molephantin (1), elephantopin (11), isoelephantopin (12), and 2-de-etoxy-2 β-metoxyphantomolin (13).[23]

Methanol extract of *E. mollis* Kunth. root and leaves collected in Cameroon contains new compounds, elephanmollen (14) and 2,5-epoxy -2 β-hidroxy-8 α-(2-methylbut-2-enoiloxy)-4 (15), and 10 (14) 11 (13) -germakratrien-12.6 α-olide (15), as well as the compounds that have previously been identified, *i.e.*, molephantin (1), molephantinin (2), 2,5-epoxy-2 β-hidroxy-8 α-(2-metilpropenoiloxy)-4 (15), 10 (14) 11 (13) -germakratrien-12.6 α-olide (16), 2,5-epoxy-2 β-hidroxy-4 α methoxy-8 α-(2-methylpropenoiloxy)-10 (14), 11 (13), -germakradien-12.6 α-olide (17), 2,5-epoxy-2 β-metoxy-(2-methylpropenoiloxy), 1 (10), and 3 (4), 11 (13) -germakradien-12.6 α-olide (18).[24] The methanol extract of *E. mollis* Kunth. roots and stems contyain three new sesquiterpene lactones, *i.e.*, (4 βH)-5 α-hidroxy-8 α-(2-methybut-2-enoiloxy)-2-oxo-1 (10), 11 (13) -guaiadien-12.6 α-olide (19), (4 βH)-8 α-(2-methylbut-2-enoiloxy)-2-oxo-1 (5), 10 (14), 11 (13) -guaiatrien-12.6 α-olide (20) and 2,5-epoxy-2 α-hidroksi-4 α-methoxy-8 α-(2-methylbut-2-enoiloxy)-4 (15) and 10 (14) 11 (13) -germakratrien-12.6 α-olide (21), along with five other compounds that have previously been isolated, *i.e.*, 2 βmethoxy-2-deethoxyphantomolin (22), 2 β-methoxy-2-deethoxy-8-*O*-deacylphantolin-8-*O*-tiglinate (23), and molephantin (1), molephantinin (2).[25] The methanol extract of all parts of *E. mollis* Kunth. contains lupeol (24), lupeol acetate (5), epifriedelinol (6), molephantin (1), 2-deethoxy-2-hydroxyphantomolin (13), and 3, 4-di-o-cafeoylquinic acid (25).[13,26]

Hydroalcoholic extract collected in Guangdong province, China, contains seven new compounds of sesquiterpene lactone and ten compounds that have previously been reported. Petroleum ether fraction of hydroalcoholic extract *E. mollis* Kunth. Contains 8-O-methacryloylelephanpane (26) 2,4-bis-O-methyl-8-O-methacryloylelephanpane (27), 4-O-ethyl-8-O-methacryloylelephanpane (28), 8-O-methacryloylisoelephanpane (29), 2-O-demethyltomenphantopin C (30), tomenpantopin C (31), Molephantin A (32), Molephantin B (33), Scabertopin (34), and isodeoxyelephantophin (35)[14] (Fig. 2).

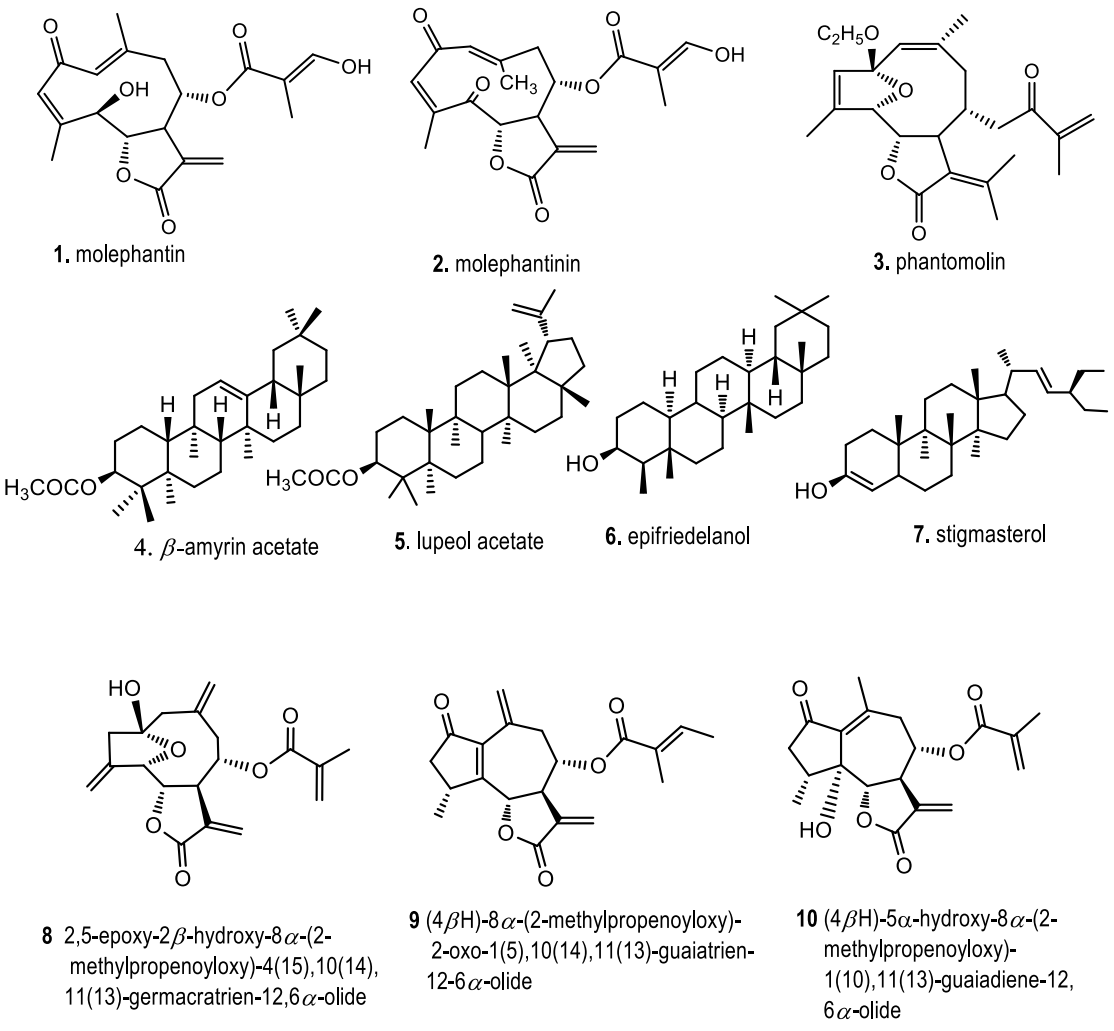
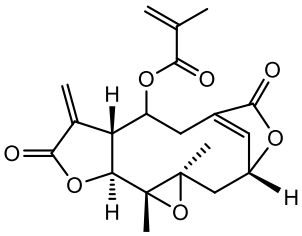
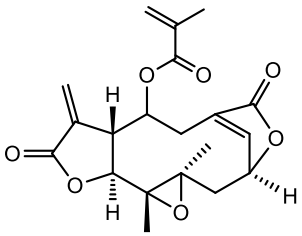


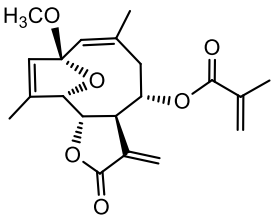
Fig. 2. Chemistry structure of isolated compounds of *E. Mollis* Kunth.



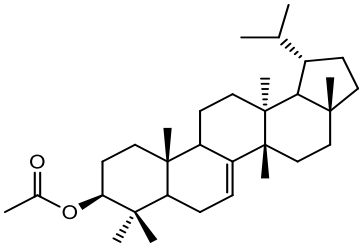
11. elephantopin



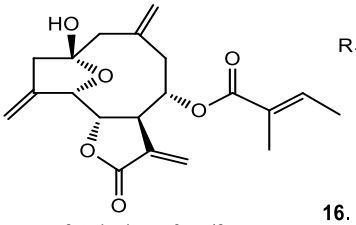
12. isoelephantopin



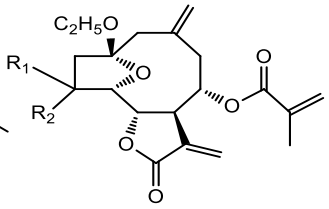
13. 2-deethoxy-2β-methoxyphantomolin



14. elephanmollen

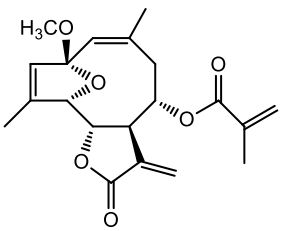


15. 2,5- epoxy-2β -hydroxy-8α -(2-methylbut-2-enoyloxy)-(15),10(14),11(13)-germacratrien-12,6a -olide

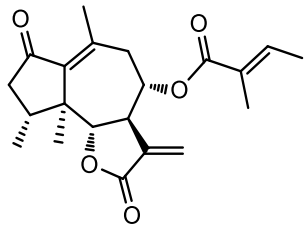


16. 2,5-epoxy-2β -hydroxy-8α-(2-methylpropenoyloxy)-4(15),10(14),11(13)-germacratrien-12,6 -olide. R_1. R_2=CH_2.

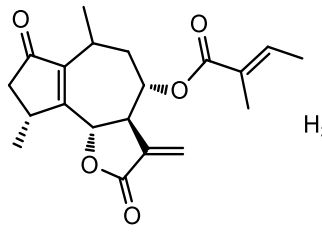
17. 2,5-epoxy-2β -hydroxy-4α-methoxy-8α -(2-methylpropenoyloxy)-10(14),11(13),11(13)-germacradien-12,6 -olide. R^1= CH_3 R^2=OCH_3



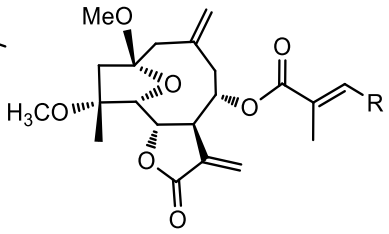
18. 2,5-epoxy-2β-methoxy-(2-methylpropenoyloxy),1(10),3(4),11(13)-germacra-dien-12,6α-olide)



19. (4βH)-5-hydroxy-8 -(2-methylbut-2-enoyloxy)-2-oxo-1(10),11(13)-guaiadien-12,6α-olide

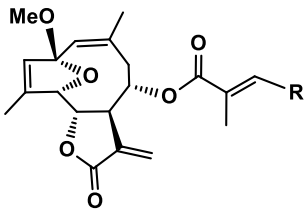


20. (4βH)-8α-(2-methylbut-2-enoyl-oxy)-2-oxo-1(5),10(14),11(13)-guaiatrien-12,6α-olide

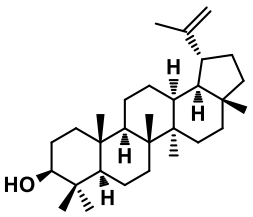


21. 2,5-epoxy-2β-hydroxy-4*a* -methoxy-8α-(2-methylbut-2-enoyloxy)-4(15),10(14),11(13)-germacratrien-12,6α-olide

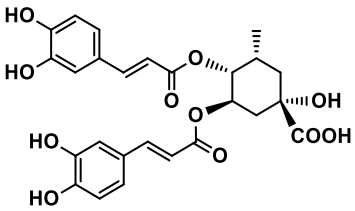
Fig. 2. Chemistry structure of isolated compounds of *E. Mollis* Kunth (cont.).



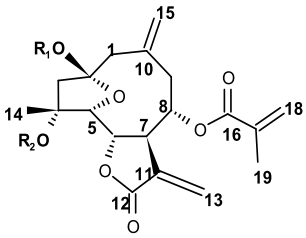
22. 2β-methoxy-2-deethoxyphantomolin, R=H
23. 2β-methoxy-2-deethoxy-8-*O*-deacylphantomolin-8-*O*-tiglinate, R=CH3



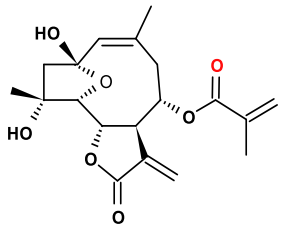
24. lupeol



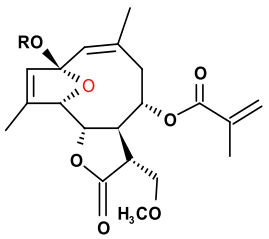
25. 3,4-di-*O*-caffeoyl quinic acid



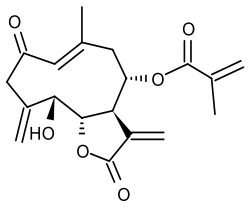
26. 8-O-methacryloylelephanpane R_1 =H; R_2 = H
27. 2,4-bis-O-methyl-8-O-methacryloylelephanpane R_1 = CH_3 ; R_2 = CH_3
28. 4-O-ethyl-8-O-methacryloylelephanpane R_1 = H; R_2 = CH_2CH_3



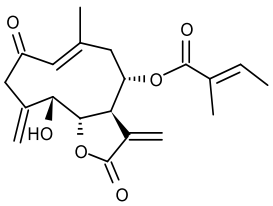
29.8-O-methacryloylisoelephanpane



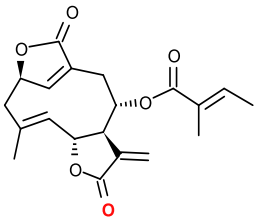
30.2-O-demethyltomenphantopin C R= H
31. Tomenpantopin C R= CH_3



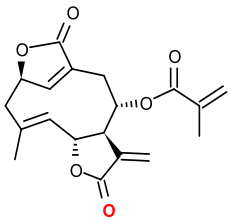
32. Molephantin A



33. Molephantin B



34. Scabertopin



35. Isodeoxyelephantopin

Fig. 2. Chemistry structure of isolated compounds of *E. Mollis* Kunth (cont.).

6. Pharmacological activity

6.1 Cytotoxic and antitumor activity

Cytotoxic activity of *E. mollis* Kunth. has been reported in various research. It was reported that both extracts and isolated compounds were effective as cytotoxic agents (Table 1). Ethanol extract from whole plant *E. mollis* Kunth. was effectively inhibited human liver carcinoma HepG2 cells by apoptosis mechanism in caspase-3-dependent pathway.[20] Bich Ngoc *et al.*[21] demonstrated that ethyl acetate extract of *E. mollis* Kunth. leaves caused proliferative inhibition and apoptotic induction towards A549 lung cancer cells (IC_{50} = 18.66 μg/mL, SI = 5.8) and HL60 leukemia cells (IC_{50} = 7.45 μg/mL, SI = 14.5), while petroleum ether extract of *E. mollis* Kunth. leaves showed high toxicity to HL60 cell line (IC_{50} = 11.14 μg/mL, SI = 6.7). Raji Burkitt lymphoma cells were also affected by these extracts (IC_{50} < 20 μg/mL, SI > 4). These extracts might restrain the cell proliferation due to PCNA-level down-regulating, contribute to the cell proliferation and effectively activate apoptosis in lung cancer cells through extrinsic and intrinsic signaling pathways. The extract might also cause a mitotic failure, leading to P53-dependent apoptotic deaths in leukemia cells.

Sesquiterpene lactones and triterpenes which contribute to the anticancer and antitumor activity of this species have also been isolated.[22,24-26,36] *In vivo* and *in vitro* experiments demonstrated that these compounds possess cytotoxicity against a variety of cancer cell lines. These compounds were potent inhibitors on mouse models of Ehrlich ascites carcinoma, Walker 256 ascites carcinosarcoma, P-388 lymphocytic leukemia, and B104 neuroblastoma cells.[22,25] In particular, *E.mollis* Kunth. extracts showed high toxicity to various human cancer cell lines, including T47-D (ethyl acetate extract, IC_{50} = 12.57 μg/mL), liver carcinoma HepG2 (methanol extract, IC_{50} = 3.74 μg/mL), A549 (methanol extract, IC_{50} = 24.38 μg/mL), and colorectal carcinoma DLD-1 (methanol extract, IC_{50} = 3.29 μg/mL), breast carcinoma MCF-7 (methanol extract, IC_{50} = 3.97 μg/mL), lung carcinoma NCI–H23 (ethyl acetate extract, IC_{50} = 13.17 μg/mL).[11,12,19] Recently, EM23 (a sesquiterpene lactone) were found.[15,18] EM23 was toxic to chronic and acute leukemia cells by activating apoptosis through thioredoxin- and ROS-mediated signaling pathways.[22] EM23 also triggered cell-cycle arrest and apoptosis in cervical cancer cell lines (CaSKi and SiHa) by generating ROS, inhibiting thioredoxin reductase (TrxR) activity, and activating ASK1/JNK signaling pathway.[28]

6.2 Antioxidant activity

Antioxidant activity of this species has been well investigated.[13,30,31] An active antiradical phenolic compound, 3,4-di-O-caffeoyl quinic acid was isolated from the methanolic extract of the whole plant. The isolated compound was more potent than its methanol extract with higher ferric reducing activity (EC_{50} = 2.18 ± 0.05 μg/mL), β-carotene bleaching activity (EC_{50} 23.85 ± 0.65 μg/mL) and DPPH scavenging activity (EC50 = 68.91 ± 5.44 μg/mL), while the methanol extract exhibited higher secondary antioxidant activity as a metal chelator with lower EC_{50} (49.39 ± 3.68 μg/mL) than the compound.[13] Aqueous extract of whole plant, stem, root, leaves and flower were investigated for antioxidant DPPH scavenging activity. The flowers were proven to possess more potent antioxidant activity (EC_{50} = 32.2051 μg/mL) compared with other parts ($p<0.05$).[22] Alian *et al.*[31] has also investigated antioxidant assay in ethanol-water extract of *E. mollis* Kunth. whole part, stem, and leaves. Both stems and leaves extracts exhibited significant antioxidant activity with IC_{50} = 2.53 and 4.13 μg/mL, respectively. The action of these antioxidants is believed to be due to their ability to donate hydrogen or electron atoms derived mainly from the flavonoid.[13,31]

6.3 Antibacterial and antifungal activity

The dichloromethane extract from leaves of *E. mollis* Kunth. has been evaluated for antibacterial potential against *Bacillus cereus, Bacillus subtilis, Staphylococcus aureus,* and *Listeria monocytogenes*. The result

Table 1. Review of pharmacological activity of *E. mollis* Kunth.

Plant Part	Type	Compound(s)	Test System (and Concentration/dose)	Bioactivity (s)	References
Whole plant	Ethyl acetate	-	*In vitro:* EC_{50}= 9.38 ± 0.43 μg/mL after 72 hours of exposure	Cytotoxic activity against human liver carcinoma HepG2 cells	Ooi *et al.*[20]
Whole plant	Ethyl acetate and petroleum ether	-	*In vitro:* ethyl acetate extract showed proliferative inhibition and apoptotic induction towards A549 lung cancer cells (IC_{50} = 18.66 µg/mL, SI = 5.8) and HL60 leukemia cells (IC_{50} = 7.45 µg/mL, SI = 14.5), while petroleum ether extract showed high toxicity to HL60 cell line (IC_{50} = 11.14 µg/mL, SI = 6.7) and Raji lymphoma cells (IC_{50} < 20 µg/mL, SI > 4)	Cytotoxic activity against A549 lung cancer cells, HL60 leukemia cells, and Raji lymphoma cells	Bich Ngoc *et al.*[21]
Whole plant	Methanol	-	*In vitro:* IC_{50} = 3.29 µg/mL for DLD-1 colorectal adenocarcinoma cells. IC_{50} 24.38 µg/mL for small lung cancer A549 cells.	Cytotoxic activity against DLD-1 colorectal adenocarcinoma cells and small lung cancer A549 cells	Kuete *et al.*[19]
Whole plant	Methanol	3,4-di-O-caffeoyl quinic acid (25)	*In vitro:* ferric reducing activity (EC_{50} = 2.18 ± 0.05 μg/mL), β-carotene bleaching activity (EC_{50}= 23.85±0.65 μg/mL), scavenging activity (EC_{50} = 68.91 ± 5.44 μg/mL) cytotoxic activity (EC_{50} =3.26±0.35 μg/mL), α-glucosidase activity (EC_{50} = 241.80 ± 14.29 μg/mL)	Antioxidant and cytotoxicity activities in NCI-H23 (human lung adenocarcinoma) and inhibitor of α -glucosidase	Ooi *et al.*[13]
Whole	Ethanol	(1) Molephantin; (2) Molephantinin;	*In vivo:* 2.5 mg/kg/day (2) and (3) were	Cytotoxic activity	Lee *et al.*[22]

Plant Part	Type	Compound(s)	Test System (and Concentration/dose)	Bioactivity (s)	References
plant		(3) Phantomolin;, (4) β-amyrin acetate, (5) Lupeol acetate; (6) Epifriedelanol; (7) stigmasterol.	potent inhibitors of Walker 256 ascites carcinosarcoma in Sprague-Dawley rats; 33.3mg/kg/day in Ehrlich ascites tumor; 25 mg/kg/day (1) also showed significant (T/C 2 125%) anti-leukemic activity in the P-388 lymphocytic leukemia (T/C = 146%)		
Root and stem	Methanol	(8) 2,5-epoxy-2 β -hydroxy-8α-(2-methylpropenoyloxy)-4 (15), 10 (14), 11 (13)-germacratrien-12,6α-olide; (9) (4βH)-8α-(2-methylpropenoyloxy)-2-oxo-1 (5),10 (14), 11 (13)-guaiatrien-12,6α-olide; (10) (4βH)-5α-hydroxy-8α-(2-methylpropenoyloxy)-1 (10), 11 (13)-guaiadiene-12,6α-olide; (22) 2β-methoxy-2-deethoxyphanto-molin; (23) 2β-methoxy-2-deethoxy-8-O-deacylphanto-molin-8-O-tiglinate	*In vitro:* IC_{50} = (8) 1.93 µM; (9) 2.13 µM; (10) 1.58 µM; (22) 2.57 µM; (23) 3.85 µM	Cytotoxic activity in neuroblastoma B104 cells	Tabopda *et al.*[25]
Root and leaves	Chloroform	(14) Elephanmollen; (15) 2,5-epoxy-2β-hydroxy-8α-[(E)-2-methylbut-2-enoyloxy]-4 (15), 10 (14), 11 (13)-germacratrien-12,6α-olide	*In vitro:* IC_{50} = (14) 25.2 ± 2.9 µM; (15) 3.6 ± 0.6 µM	Cytotoxic activity in neuroblastoma B104 cells	Tabopda *et al.*[24]
Whole plant	-	EM23 (Sesquiterpene lactone)	*In vitro:* IC_{50}= 6.3 μM and 1.4 μM in K562 and HL-60 cells, respectively after 72 hours of exposure	Cytotoxic activity in Human Myeloid Leukemia Cells HK562 and HL-60 cells	Liang *et al.*[15]; Li *et al.*[27]
Whole plant	-	EM23 (Sesquiterpene lactone)	*In vitro:* Cytotoxic activity (IC_{50} for CaSki cells= 5.8 µM and IC_{50} for SiHa cells = 6.6 µM)	Cytotoxic activity in cervical CaSki and SiHa cell lines	Shao *et al.*[28]
Leaves	1-3-butanediol	-	*In vitro:* extract (0.3%) significantly reduced the melanin content by 40%	Inhibititory activity against	Hasegawa *et al.*[29]

Plant Part	Type	Compound(s)	Test System (and Concentration/dose)	Bioactivity (s)	References
				melanogenesis in B16 Murine melanoma cells	
Whole plant	Dichloromethane	(8) 2,5-epoxy-2 β -hydroxy-8α-(2-methylpropenoyloxy)-4(15),10(14),11(13)-germacratrien-12,6α-olide;(9) (4βH)-8α-(2-methylpropenoyloxy)-2-oxo-1(5),10(14), 11(13)-guaiatrien-12,6α-olide; (10)(4βH)-5α-hydroxy-8α-(2-methylpropenoyloxy)-1(10),11(13)-guaiadiene-12,6α-olide; (1) molephantin; (11) elephantopin (12) isoelephantopin; (13) 2-deethoxy-2β-methoxyphantomolin	*In vitro:* IC_{50} = <0,1-1,0 mg/mL	Potent anti leishmaniasis activity (*Leishmania major)*	Fuchino *et al.*[23]
Leaves	Dichloromethane	-	*In vitro:* antiprotozoal activity (IC_{50} = 0.04 µg/Ml, *T. brucei. Rhodesiense;* IC_{50} = 0.6 (*L. donovanidon*); IC_{50} = 2.2 µg/mL (*P. falciparum)*; Antibacterial and antifungal activities: 2-3.9 mm inhibition zone against *B. cereus* ATCC11278 *and C. albicans*	Antiprotozoal, antibacterial and antifungal activities against *B. cereus* ATCC11278 and *C. albicans*	Gachet *et al.*[17]
Whole plant, stem, root, leaves and flower	Aqueous	-	*In vitro:* antioxidant (scavenging) activity (IC_{50} part and whole plant = 32.2-153.31 µg/mL); Antibacterial activity (inhibition zone 8.3±0.6 to 25.3±0.6 mm)	Antioxidant and antibacterial activities against *B. Cereus, B. subtilis, S. aureus, L. monocytogenes, E. coli, Salmonella*	Phuc *et al.*[30]
Whole plant, stem and	Ethanol	-	*In vitro:* antioxidant activity (IC_{50} = 0.117 ± 0.008 to 0.185 ± 0.002 µg/mL in DPPH assay); IC_{50} = 2.53±0.49 to 17.04±0.29	Antioxidant and potent antimicrobial against tested bacteria, except	Alain *et al.*[31]

Plant Part	Type	Compound(s)	Test System (and Concentration/dose)	Bioactivity (s)	References
leaves			µg/mL in ABTS assay; and IC_{50} = 16.00 ± 0.38 to 31.10 ± 0.035 µg/mL in FRAP assay; Antimicrobial activity (MIC/MBC ≤ 4 and MIC/MFC ≤4)	*S.enterica* and fungisidal in *C. albican.*	
Whole plant	Chloroform	(26) 8-O-methacryloylelephanpane, (27)2,4-bis-O-methyl-8-O-methacryloylelephanpane, (28) 4-O-ethyl-8-O-methacryloylelephanpane, (29) 8-O-methacryloylisoelephanpane, (30) 2-O-demethyltomenphantopin C, (31), Tomenpantopin C, (32) Molephantin A, (33) Molephantin B (8) 2,5-epoxy-2 β -hydroxy-8α-(2-methylpropenoyloxy)-4(15),10(14),11(13)-germacratrien-12,6α-olid; (9) (4βH)-8α-(2-methylpropenoyloxy)-2-oxo-1(5),10(14), 11(13)-guaiatrien-12,6α-olide; (10) (4βH)-5α-hydroxy-8α-(2-methylpropenoyloxy)-1(10),11(13)-guaiadiene-12,6α-olide; (34) Scabertopin; (1) Molephantin; (35) Isodeoxyelephantopin; (21) 2,5-epoxy2β-hydroxy-4α-methoxy-8α-[(E)-2-methylbut-2-enoyloxy]-4(15),10(14),11(13)-germacratrien-12,6α-olide; (15) 2,5-epoxy-2β-hydroxy-8α-[(E)-2-methylbut-2-enoyloxy]-4(15),10(14),11(13)-germacratrien-12,6α-olide; (22) deethoxy-2β-hydroxyphantomolin	*In vitro:* all tested compounds exhibited potent anti-inflammatory effects (IC_{50} values of 0.57 ± 0.17 to 14.34 ± 1.61 mM)	Anti-inflammatory activity	Wu *et al.*[14]

Plant Part	Type	Compound(s)	Test System (and Concentration/dose)	Bioactivity (s)	References
Whole plant	Aqueous	-	*In vivo:* anti-inflammatory activity (300 mg/kg significantly inhibited the development of joint swelling induced by carrageenan; 500 mg/kg showed promotion of inhibition rate)	Anti-inflammatory activity	Tsai *et al.*[32]
Leaves and twigs	Ethanol	-	*In vivo:* 250 and 750 mg/kg significantly increased mineral deposition	Stimulatory activity of bone regeneration	Ngueguim *et al*.[18]
Whole plant	Aqueous	-	*In vivo: h*epatoprotective activity: 400 mg/kg reduced AST and ALT by 71.43 ± 11.36% and 63.82 ± 19.43%, respectively, compared with the negative control group after 2 weeks of treatment	Hepatoprotective activity	Phan and Nguyen[33]
Whole plant	Aqueous	-	*In vivo:* hepatoprotective activity: 1g/kg significantly reduced AST and ALT ($p<0.01$) compared to a negative control. Improvement of hepatic fatty metamorphosis and necrosis of central lobule	Hepatoprotective activity	Lin *et al.*[34,35]

showed the extract had higher antibacterial activity than the other parts, with strongest activity at 200 mg/mL compared with ampicillin.[30]

The ethanol extract of *E. mollis* Kunth. was demonstrated to be significantly active against gram-negative strains (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Klebsiella pneumoniae* NR 41916, *Pseudomonas aeruginosa* HM 601, and *Salmonella typhi*); gram-positive strains (*Staphylococcus aureus* ATCC 43300, *Staphylococcus aureus* ATCC 49619, *Staphylococcus aureus* NR 46374, and *Shigella flexineri* NR 518) and yeasts (*Candida albicans* NR-29445, *Candida krusei* ATCC 6258, and *Candida parapsilosis* ATCC 22019), with highest antifungal activity found with *C. albicans*.[31]

6.4 Antiprotozoal activity

The dichloromethane extract of *E. mollis* Kunth. whole plant was isolated and screened for antiparasitic potential against *Leishmania major*.[23] The *in vitro* leishmanicidal activity of isolated compounds were significantly potent. Among them, elephantopin and 2-deethoxy-2b-methoxyphantomolin expressed a strong inhibitory effect on growth of *Leishmania major* promastigotes.[23] Gachet *et al*.[17] assessed *in vitro* antiprotozoal potential of plants traditionally used in Ecuador and found the dichloromethane extract of *E. mollis* Kunth. Whole plant effectively inhibited *Trypanosoma brucei rhodesiense* (IC_{50} = 0.04 µg/mL), *Leishmania donovani* (IC_{50} = 0.6 µg/mL), and *Plasmodium falciparum* (IC_{50} = 2.2 µg/mL).

6.5 Anti-inflammatory activity

Sesquiterpene lactones have been isolated from chloroform extract of *E. mollis* Kunth. whole plant and evaluated for anti-inflammatory activity on LPS-stimulated RAW 264.7 cells. All tested compounds exhibited potent anti-inflammatory activities (IC_{50} = 0.57 ± 0.17 to 14.34 ± 1.61 mM), except tomenphantopin C (IC_{50} = 59.97 ± 1.53 mM).[14] Tsai *et al*.[32] examined anti-inflammatory activity of the aqueous extract of *E. mollis* Kunth. whole plant and found the crude extract at 300 mg/kg significantly inhibited rat paw swelling induced by carrageenan injection. These results indicated *E. mollis* Kunth. has anti-inflammatory effects on acute experimental arthritis.

6.6 Antidiabetic activity

The isolated compound of *E. mollis* Kunth. whole plant, 3,4-di-O-caffeoyl quinic acid showed inhibitory activity against α-glucosidase. The α-glucosidase inhibitory activity is a preliminary study for the development of therapy for type-2 diabetes mellitus. In this assay, the 3,4-di-O-caffeoyl quinic acid exhibited α-glycosidase inhibitory effects in a dose-dependent manner and showed more than 80% of inhibition at higher final concentrations between 625 and 1250 µg/mL with EC_{50} = 241.80 ± 14.29µg/mL. Hence, *E. mollis* Kunth. is a promising agent in treating type- 2 diabetes mellitus.[13]

6.7 Hepatoprotective activity

Phan and Nguyen[22] investigated the pharmacological activities of the whole plant extract of *E. mollis* Kunth. that is traditionally used for remedy in various diseases in Vietnam. The plant extract at 400 mg/kg possessed hepatoprotective activity in reducing AST and ALT in tested mice (71.43 ± 11.36% and 63.82 ± 19.43%, respectively). The extract also improved mice liver morphology, histo-pathology, and decreased cells size significantly (28.02 ± 6.33 µm) compared to the negative control group (34.82 ± 6.36 µm).[28] The hepatoprotective activity of water extracts of *E. mollis* H.B.K. in 'Teng-Khia-U', the traditional medicine of Taiwan, has also been evaluated. A dose of 1g/kg significantly reduced AST and ALT (p<0.01) compared to the negative control. There was also improvement of hepatic fatty metamorphosis and necrosis of central lobule reported.[34]

6.8 Stimulatory activity of bone regeneration

Ngueguim *et al*.[18] evaluated plants that are used in traditional Cameroonian medicine for the treatment of bone diseases and

fracture repair and found that ethanol extract of the leaves and twigs of *E. mollis* Kunth. were dose-dependently stimulated bone regeneration at the drill hole site. The doses of 250 and 750 mg/kg significantly increased mineral deposition compared to controls. The doses of 500 and 750 mg/kg improve microarchitecture of the regenerating bone, evident from increased bone volume fraction, trabecular thickness, trabecular number, and decreased trabecular separation and structure model index. *E. mollis* Kunth. accelerates fracture repair in rats *via* stimulatory effects on osteoblast differentiation and mineralization, thereby justifying their traditional use.[18]

6.9 Skin-whitening agent

Leaves of 1,3-butanediol extracts was actively reduced melanogenesis by down-regulating Microphtalmia-associated Trans-cription Factor (MiTF) expression without cytotoxic effect, at least in B16 Murine melanoma cells. Given this significant effect, *E. mollis* Kunth could be potentially useful as skin-whitening agent.[29]

7. Conclusion

E. mollis Kunth., belonging to the family Asteraceae, is a herbaceous perennial that originated from tropical America and was widely introduced to high rainfall tropical Africa, Asia and the Pacific. Our comprehensive review of the scientific literatures indicated that *E. mollis* Kunth. Is a valuable herbal medicine with therapeutic potentials for various diseases. Numerous studies have shown that the extracts and secondary metabolites isolated from this plant have been used as folk medicine with diverse medicinal properties. The ethnomedical claims have been scientifically proved by conducting extensive research on this plant. Various pharmacological activities, such as cytotoxic activity, anti-inflammatory, anti-oxidant, anti-leishmaniasis, antiprotozoal, anti-microbial, antidiabetic, bone stimulating re-generation and hepatoprotective activity, have been evaluated.

To date, more than 25 secondary metabolites have been isolated and identified from plant of *E. mollis* Kunth. Among them, sesquiterpene lactones in the specific extracts such as methanol, petroleum ether, ethyl acetate, chloroform, ethanol and aqueous extracts contribute to most pharmacological activities. The major sesquiterpenoids of *E. mollis* Kunth. have been extensively studied to a variety of anticancer activity and highly significant results have been reported in a various cancer cell-line. These results indicated that *E. mollis* Kunth. and its sesquiterpene could be utilized as a renewable bioresource to develop a potential anticancer agent.

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