



MELASTOMA MALABATHRICUM L.: A REVIEW OF ITS TRADITIONAL USES, PHYTOCHEMICAL CONSTITUENTS AND BIOACTIVITIES

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ABSTRACT

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Melastoma malabathricum L. has been used as a traditional medicine in different parts of the world. The aim of this review is to summarize and critically analyze the literature on traditional uses, phytochemistry and bioactivities of *M. malabathricum*. The literature was retrieved from scientific databases. The leaves, flowers, stem and roots are being used for wound healing, treating stomachache, measles, low sperm count, jaundice, pain, leucorrhoea, diarrhea, dysentery, tooth decay, and fever. It contains 71 phytochemicals; flavonoids, terpenoids, tannins, sterols, amides, glycolipids and fatty acids. Extracts demonstrated antimicrobial, gastroprotective, hepatoprotective, anti-inflammatory, antioxidant, cytotoxic, anticancer, wound healing, antinociceptive, antihyperlipidemic, anti-infertile, antiarthritic and antidiabetic activities. This review provides insights on traditional uses, phytochemical constituents, and bioactivities of *M. malabathricum L.* Few papers in the literature were found to be lacking in scientific vigor. Further studies should be carried out on safe use of *M. malabathricum L.* and mechanisms underlying its bioactivities.

INTRODUCTION:

The shrub, *Melastoma malabathricum L.* belongs to the family, *Melastomataceae*, is found in tropical and subtropical regions of the world¹. It has many alternative names; *M. affine*, *M. candidum*, *M. cavaleriei*, *M. esquirolii*, *M. normale*, and *M. polyanthum* (www.theplantlist.org).

One of the major global health concerns is deaths due to infectious diseases and development of bacterial resistance. Plants are reported to have potential to treat infectious diseases and to overcome antimicrobial resistance and therefore many researchers across the world are being investigating the plants to explore their antimicrobial properties especially against

clinically relevant drug-resistant strains². In addition, it is pertinent to note that healing of wounds has always been a challenging task in the clinical practice and there is a growing research interest in exploring the potential of plants for their wound healing properties³. In traditional medicine, *M. malabathricum* L. is reported to be used for the treatment of infectious diseases and wounds. In addition, there are many reports in the literature investigating its antimicrobial and wound healing properties. Among phytochemicals, flavonoids and tannins are reported to possess many interesting biological activities⁴. Many published papers on *M. malabathricum* reported the presence of flavonoids and tannins. In this review, we provide an updated and critical analysis of the literature on *M. malabathricum* regarding phytochemical and biological investigations on extracts and isolated compounds.

Methods

For the collection of the information on reported bioactivities of *M. malabathricum* L., PICOS scheme⁵ was followed: the population are bacteria or cells or tissues or animals; the intervention is treatment with *M. malabathricum* extract or isolated compound; the comparator is no treatment or placebo or standard treatment; the outcome is the effect of *M. malabathricum* extract or isolated compound; the study design is either *in vivo* or *ex vivo* or *in vitro*. Its scientific name is confirmed via www.theplantlist.org. The eligible research papers published in English language found in databases (Scopus, PubMed, SpringerLink, EbscoHost, Google Scholar), as well as textbooks until February 2020 were referred. Specific search terms were used to gather information, such as “*Melastoma malabathricum*”, “*M. malabathricum*”, “ethnomedicinal uses”, “phytochemical constituents”, “pharmacological activities”, and “medicinal uses”. All authors independently screened the titles and abstracts for choosing the eligible papers. The chemical structures of reported phytochemicals were obtained either from the research articles or PubChem

or ChemSpider. The chemical structures were drawn using ChemDraw Professional 18.0.

Distribution

According to <http://www.theplantlist.org>, *Melastoma malabathricum* L. has three synonyms; *Melastoma malabathricum* subsp. *malabathricum*, *Melastoma malabathricum* var. *normale* (D. Don) R.C. Sirvast. and *Melastoma malabathricum* subsp. *normale* (D. Don) Karst. Mey.

M. malabathricum M. malabathricum Geographic distribution and traditional & ethnomedicinal uses

The plant *M. malabathricum* is widely distributed in Asian region and cultivated as an ornamental plant. Various communities and tribes have been using *M. malabathricum* as traditional medicine for protecting their health and treatment of ailments. It's geographic distribution, vernacular names and ethnomedicinal uses are listed in Table 1.

Phytochemical constituents

The major phytochemicals present in *M. malabathricum* L. are flavonoids and tannins. Many very recent literature reviews highlighted the biological activities and therapeutic potential of flavonoids, flavonoid glycosides and tannins^{6,7}. Therefore, the reported traditional uses of *M. malabathricum* L. could be attributed to the presence of flavonoids and tannins. The flavonoids and tannins are widely distributed in leaves compared to other parts which could explain why leaves are the most widely used part of the plant in traditional medicine. However, there were no studies on the amounts and percentage of these compounds in *M. malabathricum* L., a major research gap in the published literature. The chemical structures of important bioactive phytochemicals were shown in Table 2.

Many age-old-well-known phytochemical constituents have been well documented in the 80's and 90's. These include tannins such as Alienanin, Brevifolin-carboxylic acid, Casuarinin/Stachyurin, Dimethyl hexamethoxydiphenate, Malabathrin A, B, C, D, E, F, Nobotanin B, D, G, H, J, Pedunculagin, Procyanidin B2, B5, Pterocarbin C, Strictinin Stenophyllanin A, B;

flavonoids such as Isoquercetin 6''-O-gallate, Kaempferol-3-O- β -D-xyloside, Quercetin-3-O- α -L-rhamnosyl-(1 \rightarrow 2)- α -D-galactoside and Malvidin-3,5-diglucoside; Pentacyclic triterpenoids such as Ursolic acid; sterols such as β -Sitosterol; polyphenols such as (-)-Epicatechin, (-)-Epicatechin gallate, Gallic acid; organic acids such as Hexacosanoic acid, 2,5,6-Trihydroxynaphthoic carbonic acid, *p*-Hydroxybenzoic acid, 1-Octyl decanoate A; and 11-Methyl-1-triacontanol and 32-Methyl-1-triacontanol⁸⁻¹¹. The list detailing the bioactive phytochemical constituents documented in the past 20 years is concisely tabulated in Table 3. This includes information regarding their source of origin from part of plants, solvent used for extraction, isolation method as well as identification method.

Biological activities

Numerous researchers have elucidated a myriad of biological activities of *M. malabathricum*. The biological activities exhibited by *M. malabathricum* extract discussed in this paper include antimicrobial activity against gram positive & negative bacteria and fungi, gastroprotective activity, hepatoprotective activity, anti-inflammatory activity, antioxidant activity, anticancer activity, wound healing activity and antinociceptive activity. It is believed that the presence of various bioactive such as high flavonoids and tannin contents in the *M. malabathricum* extracts contribute to the synergistic effects in antioxidant, antimicrobial and anti-inflammatory activity. The biological activities of compounds studied between year 2015 to-date are summarized in Table 4.

Antimicrobial activity

The underlying issue with the surge of antibiotic resistance has become one of the main concerns shared among researchers. Apart from research focusing on small molecule organic synthesis, effort is also given to the natural products expertise in order to discover bioactive compound that these microbes can succumb to¹². Thus, extracts of *M. malabathricum* were

evaluated for their antibacterial activity. Most of the up-to date literature extensively investigated the extraction of different parts of *M. malabathricum* plant using methanol for their antimicrobial activity. It was reported in various research that some of the microbes succumbing to the extracts of leaves, flowers and fruit of *M. malabathricum* include *M. malabathricum* *C. capsica*¹³, *M. malabathricum* gram positive bacteria such as *Listeria monocytogenes*¹⁴, *Staphylococcus aureus* and *Bacillus subtilis*; and Gram-negative bacteria namely *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella typhi*, and *Shigella flexneri*¹⁵. Unfortunately, the extract fall short against as no activities were detected against gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium*¹⁴. With this, Che Omar *et al.* and Alwash *et al.* reported that Gram-positive bacteria were more susceptible to the plant extracts than that of the Gram-negative species^{14,16}. There were however no studies reported on antimicrobial activity of *M. malabathricum* roots, in which further studies could potentially be performed.

Gastroprotective activity

It was documented that *M. malabathricum* plant was traditionally used to relieve ulcers. It is interesting to note that *M. malabathricum* leaves showed dose-dependent gastroprotective activity in male adult Sprague-Dawley rats. Literature to date reported the investigation of *M. malabathricum* leaves chloroform extract¹⁷. It was previously reported that the gastroprotective effects of *M. malabathricum* extract was performed using established ethanol-induced gastric ulcer, and ethanol- and indomethacin-induced gastric ulcers¹⁸ models. *M. malabathricum* (500 mg/kg) exhibited equipotent activity of that of Omeprazole (reference drug;)¹⁹. In a different study, *M. malabathricum* (500 mg/kg) exhibited improved the inhibition of ulcer than that of Rantidine¹⁷ and carbenoxolone^{20,21}.

Hepatoprotective activity

Not much experimentation was performed to investigate the hepatoprotective properties of *M.*

malabathricum, thus, further research could be performed regarding its effectiveness. Thus far, only methanol extract of leaves was tested for their hepatoprotective activity in paracetamol-induced hepatotoxicity in male adult Sprague-Dawley rats. It was noted by Mamatet *al.* that the main contributors towards its hepatoprotective activity of *M. malabathricum* methanol extract could be due to the presence of flavonoids, tannins, and saponins²². Kamisanet *al.* also reported that *M. malabathricum* methanol extract was found to be effective for hepatoprotective activity where significant improvement in the levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) in both paracetamol-induced liver toxicity and carbon tetrachloride-induced liver toxicity compared to that of their respective control group²³.

Anti-inflammatory activity

Similarly, not many animal studies were performed to elucidate the mechanisms involved in reducing inflammation. Balamurugan *et al.* reported dose-dependent anti-inflammatory activity of leaves ethanol extract in carrageenan induced paw edema adult Wistar albino rats where ultimately, the percent inhibition was equipotent compared to that of the positive control group²⁴. Kumar *et al.* reported methanol extracts of leaves attenuated Complete Freund's adjuvant (CFA)-induced arthritis in a dose-dependent manner where *M. malabathricum* leaves extract at 500 mg/kg showed equipotent effect with that of the reference drug, Indomethacin (10 mg/kg) in modulating the proinflammatory mediators namely tumor necrosis factor- alpha (TNF- α), Interleukin (IL)-6, IL-1 β and COX-2²⁵.

Antioxidant

The antioxidant activity of *M. malabathricum* extracts from different extraction solvent including ethyl acetate²⁶ and ethanol²⁷ were previously reported to exhibit antioxidant activity in a β -carotene bleaching assay²⁶. Sari *et al.* reported that the leaves and fruit of the plant having antioxidant activity as potential herbal tea material where *M. malabathricum* leaves and flower extract respectively inhibited

90% and 88% of DPPH radical compared to that of commercial black tea and green tea (85-90%)²⁸. Danladi *et al.* reported that among leaves, fruits, flower and stem extracts, the flowers extract showed equipotent (IC₅₀: 48 μ g/mL) DPPH free radical scavenging activity to that of Quercetin (IC₅₀: 48 μ g/mL)²⁹. Verma *et al.* described that the *M. malabathricum* extract showed an inhibition of ABTS (99.7%; IC₅₀: 38 μ g/mL) and DPPH (98.8%; IC₅₀: 27 μ g/mL) free radicals³⁰; while Baruah *et al.* demonstrated that ABTS and DPPH values of *M. malabathricum* extract were found to be 55.58 ± 1.09 μ M/g and 0.9271 ± 0.22 μ M/g respectively³¹.

Antitumor activity: Numerous published articles had investigated both *in-vitro* and *in-vivo* for antitumor activities of different extracts from different parts of *M. malabathricum*. Roslenet *al.* reported that the leaves methanol extract showed the highest percentage of MCF-7 cells inhibition³². To date, the anticancer activity possessed by *M. malabathricum* extract was also tested on multiple cell lines, which includes human breast cancer (MCF-7)³³, Hepatoma G2 (HepG2)²⁹ and lung cancer (A549) cell lines³³. In summary, the leaves and the flowers of the plant possess higher antitumor activity compared to the stem bark, but the activity exhibited by the stem bark was still significant.

Wound healing activity

Very limited publications were reported on the wound healing activity of *M. malabathricum*. *In-vivo* wound healing studies were carried out in healthy male adult Sprague-Dawley rats demonstrated that *M. malabathricum* leaves extract was the better treatment for wound healing compared to the then reported conventional drugs, Povidone-Iodine and Acriflavine³⁴. While *in-vitro* studies were performed using human gingival fibroblasts by Ab Rahman *et al.* However, the effectiveness of wound healing activity reported by both publications was only subtle but was significant when compared to untreated groups regarding its wound closure activity³⁵.

Region	Vernacular name(s)	Part of plant	Mode of preparation	Traditional use(s)	Ref
Malaysia					
Shah Alam Kelantan Negeri sembilan Pahang	Senduduk, Sekedudok, Sikadudok, Kendudok, Kedudok, Sedudok, Lingangadi, Gosing-Gosing, Gagabang, Ngongodo, Gata-Gata	Leaves	Aqueous extract	Given to postpartum women for healing & womb strengthening.	40
		Fruit	Juice	Relieve dry lips.	
		Shoots	N/A	Puerperal infections, blood pressure, diabetes, toothache, leucorrhea.	41
		Roots	Decoction	Epilepsy, rheumatoid arthritis, tenderness in legs	42
				Diarrhea.	43
		Leaves & roots	Poultice	Aid healing process & reduce haemorrhoid discomfort.	44
Leaves & flowers	N/A	Cholera, diarrhea, prolonged fever, dysentery, leucorrhea, wounds, various skin diseases.			
India					
Assam, Manipur, Tripura, Mizoram, Odisha	Shapti, Bobuchunmei, Rongmei, Rindha, Palore, Nekkarike, Ankerki, Kinkerika, Gongoi, Koroti,	Leaves	Decoction, juice	Reduce smallpox scars, Dysentery, diarrhea, hemorrhoids	45
			Eaten raw	Dysentery.	46
			Paste	Cuts & wounds, stomach disorders, fever.	47
		Stem barks	N/A	Skin diseases.	47

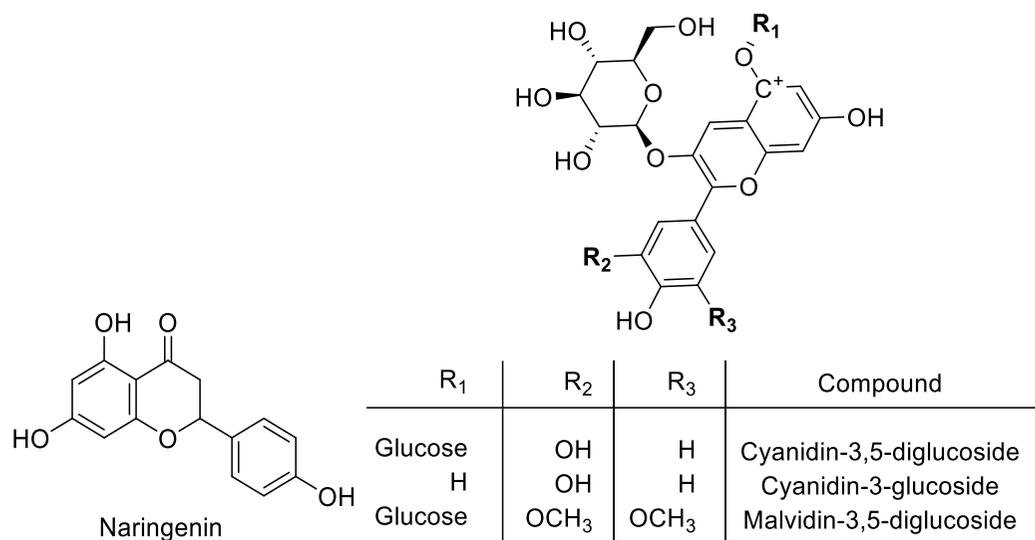
	Myetpyai, Phutki, Phutkala, Koroli, Karali	Bark, leaves and seeds	Decoction	Skin diseases, leucorrhea, diarrhea, dysentery.	48
Thailand					
N/A	Khlong Khlong, KheeNok, Mang Khre , Mang Re, Bre, Kadu-Da, Chuk Naaree	Roots	Decoction	Fever	49
Indonesia					
Sumatra West Java	Harendong, Senggani, Kemanden, Kluruk, Kendudu, Pucuk, Kendudu, DaunKhalendon g, Mua e bong, Sendudok	Leaves	N/A	Diarrhea, dysentery, gastric ulcers, haemorrhoids.	50
			Ingested raw	Toothache, Given to postpartum women for healing & womb strengthening	51
		Roots	N/A	Rheumatoid arthritis, toothache, epilepsy	50
		Flowers	Cold infusion	Anemia due to gastrointestinal bleeding, Epigastric pain.	52
Philippines					
N/A	Malatungau, Bubtoi, Yagomyum	Leaves	Powder	Dysentery	53
		Leaves, roots and flowers	Juice	Sedative, haemorrhoids, indigestion, leucorrhea, chronic diarrhoea	

Bangladesh					
Bandarban, Netrakona, Rangamati	Koiam-Pay-Bang, Kakkhu, Aksio, Koaim-pay-bang, Kakkhu	Roots	Juice	Jaundice, Leucorrhea	54
		Leaves	Juice	Diuretic, Urinary tract infections.	
Pacific Islands					
Tahiti	N/A	N/A	N/A	Diarrhoea, dysentery	53

Table 2. Chemical structures of isolated compounds from *M. malabathricum*

Flavonoids		
Name	R1	R2
Quercetin	OH	OH
Quercetrin	O-β-D-glu	OH
Kaempferol	OH	H
Kaempferol-3-O-β-D-glucopyranoside	O-β-D-glu	H
Kaempferol-3-O-(2'',6''-di-O-p-trans-courmaoyl)-β-glucoside	O-2,6-di-O-p-trans-courmaroyl)-β-D-glucoside	H
Quercetin-3-O-Dgalactoside	O-D-gal	OH
Kaempferol 3-O-α-L-rhamnopyranoside	O-α-L-rha	H
Kaempferol-3-O-β-D-galctopyarnoside	O-β-D-gal	H
Kaempferol 3-O-(2'',6''-di-O-E-p-	O-(2'',6''-di-O-E-p-coumaryl)-β-	H

coumaryl)- β -D-galactopyranoside	D-gal	
Kaempferol-3-O- β -D-xyloside	O- β -D-xylose	
Isoquercetin-6''-O-gallate	O- β -D-(6-O-gallyl)glu	OH
Quercetin-3-O- α -L-rhamnosyl-(1 \rightarrow 2)- α -D-galactoside	O- α -L-rha-(1 \rightarrow 2)- α -D-gal	OH
Rutin	O- β -D-(6-O- α -L-rhamnosyl)glucose	OH



Antinociceptive activity

Only a few published articles reported the investigation of antinociceptive activity of *M. malabathricum*. The reported literature only investigated methanol and ethanol extracts from the leaves and the stem bark in *in-vivo*, using male Balb/C mice³⁶ or male Sprague-Dawley rats^{37,38}. Sulaiman *et. al.* reported an inhibition of 84.4 % in acetic acid-induced abdominal writhing test with of *M. malabathricum* (300 mg/kg *i.p.*) ethanol extract³⁶. Zakaria *et. al.* reported that acetic-acid induced nociception was significantly ($p < 0.05$) attenuated by *M. malabathricum* petroleum ether (EC_{50} : 119.5 mg/kg) extract³⁷. Besides these methods latency of discomfort also showed positive results^{37,38}. Despite the different test animals and methods, it was reported that *M. malabathricum* exhibited antinociceptive activity.

Other pharmacological activities

There were also a few studies reporting interesting pharmacological activities of the plant. One such study is the study ethanolic extract of leaves increased the sperm density and motility in male albino rats³⁹. In this study, it was reported that male albino rats treated with *M. malabathricum* ethanol leaves extract (500mg/kg) daily for 14 resulted in a significant ($P < 0.01$) increase of sperm concentration ($486.30 \pm 14.83 \times 10^6$ mil) compared to that of the control group.

Concluding remarks and future perspectives

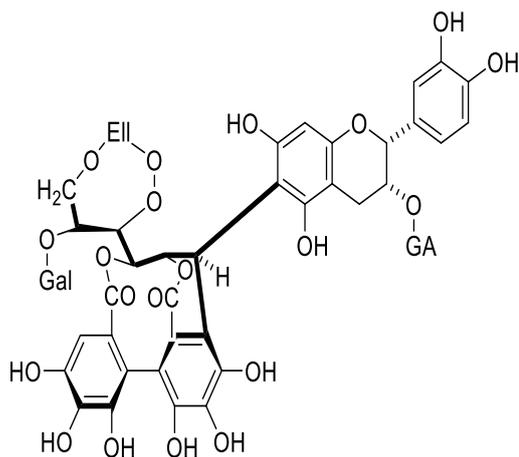
In this review we have presented the critical analysis of the reported literature on traditional uses, phytochemical constituents,

Tannins

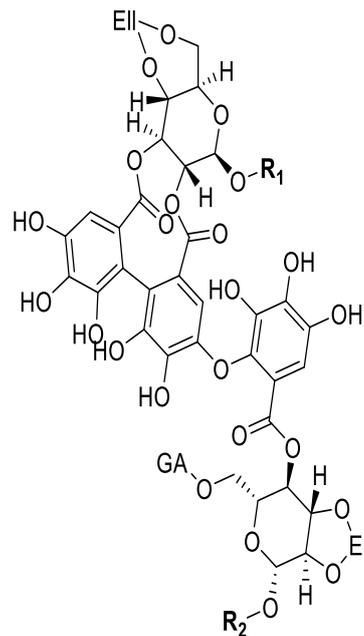
and biological activities of *M. malabathricum* L. Exhaustive literature has shown that, different parts of this plant *M. malabathricum* have been used in ethnomedicine - leaves being the most common one. Biological activity studies have been carried to provide scientific evidence for ethnomedicinal uses.

Studies have reported the phytochemical constituents and biological activities of this plant. The results have indicated the presence of tannins, flavonoids, pentacyclic triterpenoids, sterols, polyphenols, lactones, amides and glycolipids. The tannins and flavonoids are the major components. Studies also proved the biological activities; antimicrobial, antioxidant, gastroprotective, hepatoprotective, anti-inflammatory, antitumor, antinociceptive, antifertile and antidiabetic; of crude extracts.

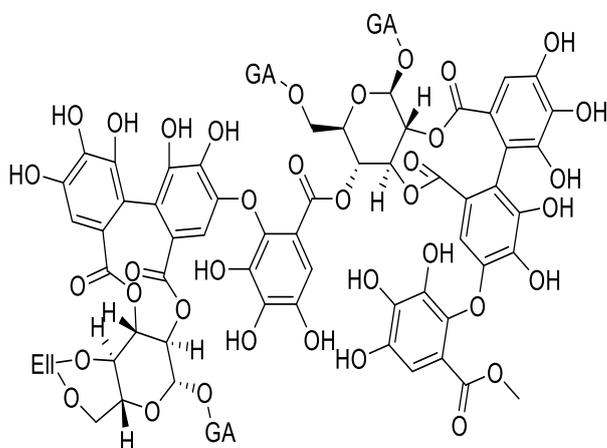
In many studies, the authors did not follow activity guided fractionation to isolate the bioactive compounds. Besides, a few studies did not report the use of adequate spectroscopic techniques to characterize the compounds. Other than few antimicrobial studies, no other studies directly compared the bioactivity of crude extracts and the isolated compounds in addition to the lack of mechanism of activity studies. No reports on quality control, toxicity and safety of crude extracts were found in the literature. The use of disease-relevant animal experiment models was scarce. The published *in vivo* assays did not follow the international standards in terms of the adequate number of animals, dose-range, use of appropriate positive & negative controls and dose-response studies.



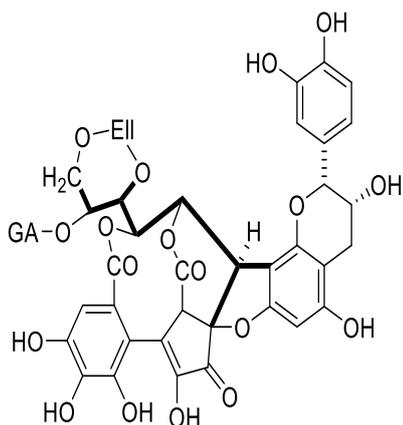
Malabathrin A



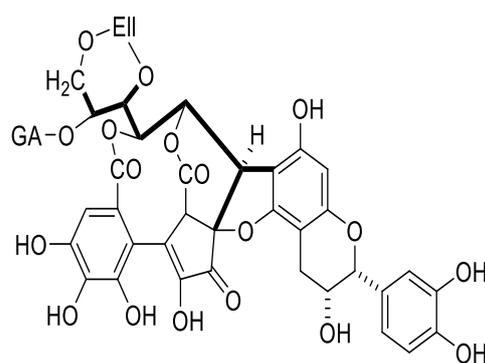
R ₁	R ₂	Compound
Gal	H	Malabathrin B
H	Gal	Malabathrin C



Malabathrin D

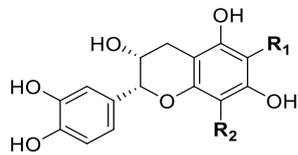
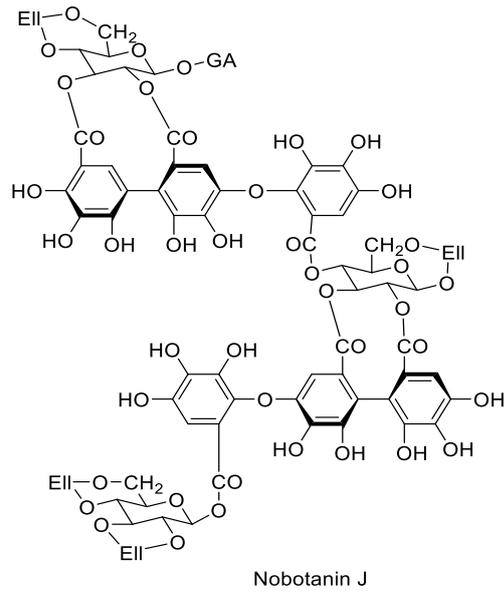
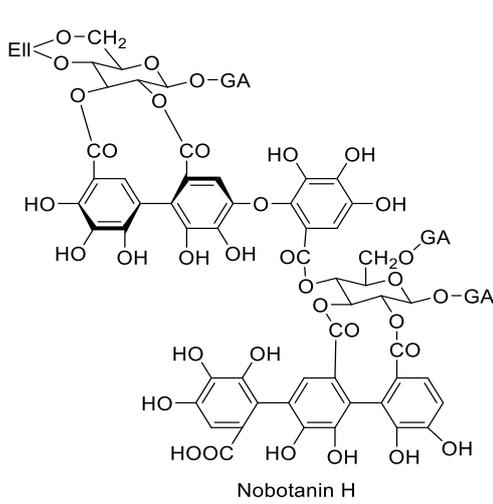


Malabathrin E

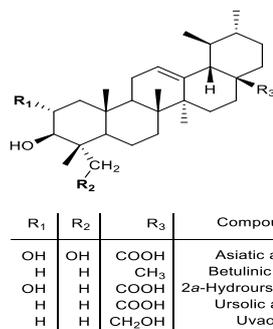
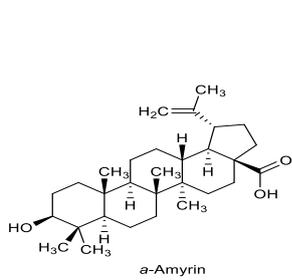
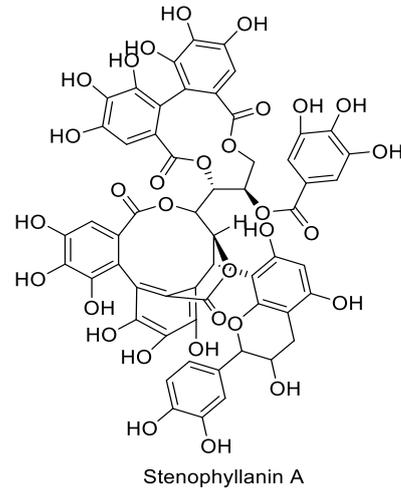
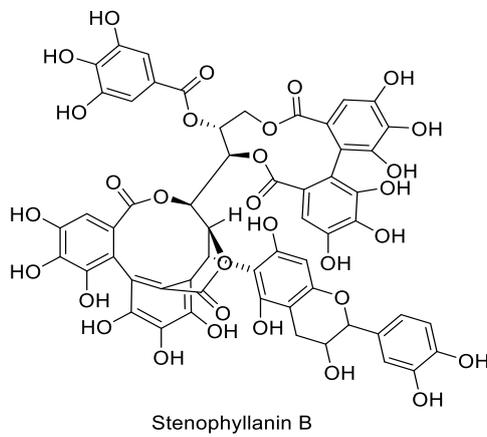


Malabathrin F

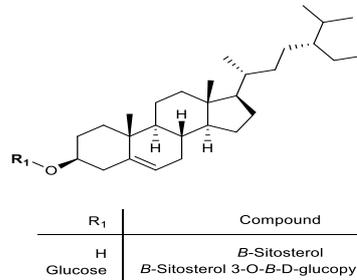
Tannins (continued)



R ₁	R ₂	Compound
H	(-)-Epicatechin	Procyanidin B2
(-)-Epicatechin	H	Procyanidin B5



R ₁	R ₂	R ₃	Compound
OH	OH	COOH	Asiatic acid
H	H	CH ₃	Betulinic acid
OH	H	COOH	2 α -Hydroursolic acid
H	H	COOH	Ursolic acid
H	H	CH ₂ OH	Uvaol

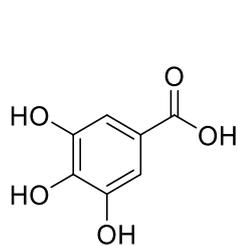


R ₁	Compound
H	<i>B</i> -Sitosterol
Glucose	<i>B</i> -Sitosterol 3-O- <i>B</i> -D-glucopyranoside

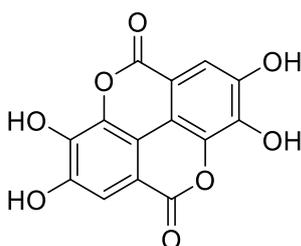
ic triterpenoids

Pentacycl

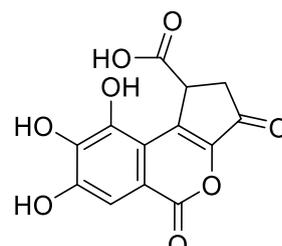
Polyphenols



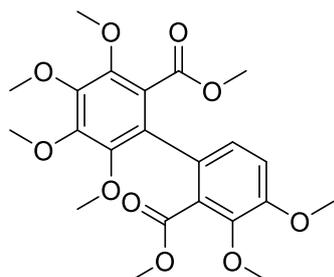
Gallic acid



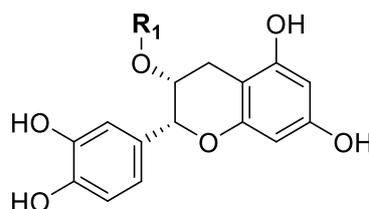
Ellagic acid



Brevifolincarboxylic acid

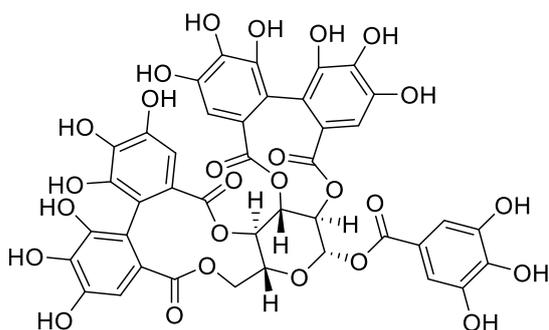


Dimethyl hexamethoxydiphenate



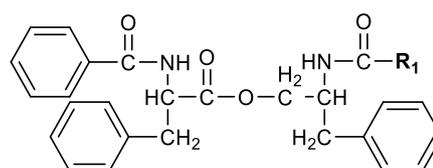
R ₁	Compound
H	(-)-Epicatechin
Gal	(-)-Epicatechin gallate

Lactone



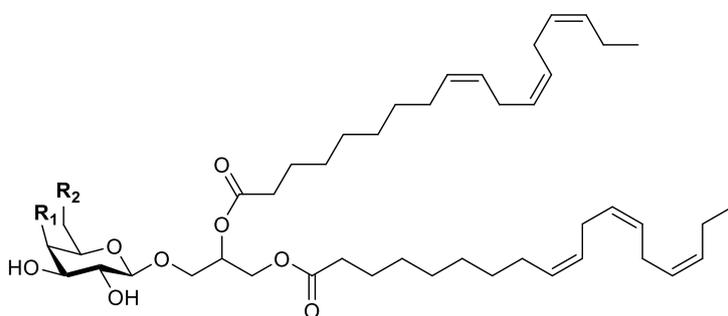
Casuarictin

Amides

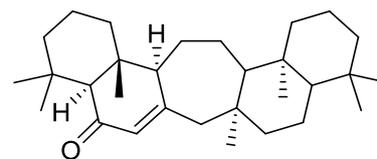
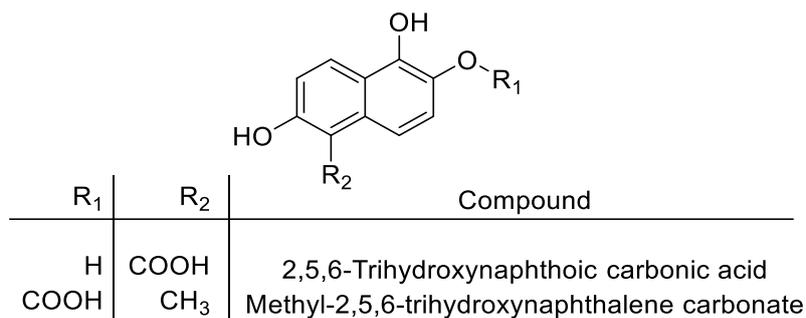


R ₁	Compound
Phe	Auranamide
CH ₃	Patriscabratine

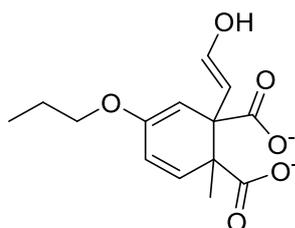
Miscellaneous compounds



R ₁	R ₂	Compound
OH	OH	Glycerol-1,2-dilinolenyl-3-O- <i>b</i> -D-galactopyranoside
2,2-dimethyl-dioxane		Glycerol-1,2-dilinolenyl-3-O-(4,6-di-O-isopropylidene)- <i>b</i> -D-galactopyranoside



Serrat-14-en-16-one



2-(2'-Hydroxyvinyl)-1-methyl-4-propoxyphthalate

Neither pharmacokinetic nor metabolic profiling of phytochemicals present in the extracts were found in the literature. The rationale of the preparing the extract in relation to how it is being prepared in traditional medicine is not reported elsewhere. None of the published reports indicated the recommended human dose. The above-said findings exposed the research gaps in the existing knowledge of *M. malabathricum L.* Therefore, this review recommends few future scientific studies to be considered for providing an evidence to support traditional uses and safe-use of *M. malabathricum L.* So far, the antimicrobial and antioxidant efficacy of the extracts were proven only using *in vitro* models, therefore further studies should be warranted to test the safety & efficacy in physiologically relevant animal modes. Since the extracts showed promising antimicrobial activities against standards strains the studies could be extended further to test their activity against clinical and drug-resistant strains. Only preliminary studies on gastroprotective, hepatoprotective, anti-inflammatory, antitumor, antinociceptive, antifertile and antidiabetic activities of the extracts were reported suggesting plenty of opportunities for future studies to elucidate the mechanisms of action and safety, metabolic & pharmacokinetic profile of the extracts. In addition, many reported traditional uses of

M. malabathricum L. such as rheumatoid arthritis, epilepsy, leucorrhoea, diarrhoea, dysentery, skin diseases, haemorrhoid and as a diuretic; were not investigated thus providing an opportunity to design future studies to prove these claims. A special attention should be paid in future studies to mimic the preparation of extracts to that of traditional preparation (decoction or juice). Lastly, all the good practices in phytopharmacology research; such as identification & authentication of the plant material, identification & characterisation of bioactive compounds, use of physiological & disease relevant experimental models, ethical standards in animal experiments and etc., must be followed in future studies.

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Conflict of interest:

The authors declare that they have no conflict of interest.

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