Trop J Nat Prod Res, September 2025; 9(9): 4066 - 4083

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Micromelum minutum: A Review of Its Traditional Uses, Chemical Constituents and Pharmacological Activities

Rollando Rollando[1,2]*

[1]*Pharmacy Study Program, Faculty of Health Sciences, Ma Chung University, Malang, East Java, Indonesia*
[2]*Drug Discovery and Design Group Research, Faculty of Health Sciences, Ma Chung University, Malang, East Java, Indonesia*

ARTICLE INFO

Article history:
Received 11 July 2025
Revised 31 July 2025
Accepted 23 September 2025
Published online 01 October 2025

ABSTRACT

Micromelum minutum, a shrub from the Rutaceae family, is extensively distributed in tropical and subtropical regions across Asia and the Pacific. Traditionally utilized in folk medicine for treating ailments such as fever, inflammation, infections, and digestive disorders, the plant has garnered scientific interest due to its therapeutic potential. Despite widespread traditional use and identification of various bioactive compounds, comprehensive scientific evaluations remain limited. This review systematically synthesizes peer-reviewed publications on *M. minutum*, critically examining its ethnomedicinal uses, phytochemical constituents, and pharmacological properties. Findings indicate the presence of numerous bioactive compounds, including coumarins, flavonoids, alkaloids, terpenoids, and essential oils. These constituents exhibit significant biological activities, such as antimicrobial, antioxidant, anti-inflammatory, cytotoxic, hepatoprotective, and antidiabetic effects in both in vitro and in vivo studies. Extracts from leaves, bark, fruits, and roots demonstrate pharmacological profiles aligning with traditional medicinal claims. Thus, accumulated evidence highlights the pharmacological potential of *M. minutum*, validating its traditional applications. However, additional pharmacokinetic, toxicological, and clinical studies are essential to confirm its safety and therapeutic efficacy. This comprehensive review provides a foundational scientific basis for future research directions and the development of novel therapeutic agents derived from this underutilized medicinal plant.

Keywords: *Micromelum minutum*, Traditional Medicine, Phytochemicals, Pharmacological Activity, Drug Discovery.

Introduction

Medicinal plants have been used in healthcare since ancient times and continue to play a crucial role today[1]. For example, about 10 % of all vascular plant species are estimated to have medicinal uses[2]. Many societies still rely on herbal remedies for primary care, and dozens of modern drugs (e.g. aspirin, artemisinin) were originally derived from traditional remedies[3]. This enduring importance of botanical medicines highlights the need to document and study individual species that are widely used or scientifically promising. *M. minutum* is one such species of growing interest. It is an evergreen tree native to tropical Asia and the Pacific-found throughout Southeast Asia (the Philippines, Malaysia, China, Indonesia, etc.) and on Pacific islands[4]. The species is common in its native range (not endangered). In many of these regions it is harvested from the wild as a medicinal plant. In fact, *M. minutum* appears as an ingredient in commercial herbal supplements (e.g. in Malaysia and the Middle East).

Corresponding author; Email: ro.llando@machung.ac.id
Tel: +6282220379864

Citation: Rollando R. *Micromelum minutum:* A Review of Its Traditional Uses, Chemical Constituents and Pharmacological Activities.Trop J Nat Prod Res. 2025; 9(9): 4066 – 4083 https://doi.org/10.26538/tjnpr/v9i9.1

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Locally it is known by various names (such as “Chemomar” or “Lunas kahoy” in parts of Southeast Asia), reflecting its long history in folk medicine[5]. *M. minutum* has a broad spectrum of traditional uses documented in ethnobotanical literature. It has been used to treat skin infections and irritations (for example, ringworm, scabies, sores) as well as respiratory problems (such as sore throat or cough)[6]. Leaf infusions are taken for toothache, bad breath or teething discomfort, and poultices made from leaves or bark are applied to soothe rashes and skin swellings. The bark and roots have been used as antipyretics (fever reducers) and to treat malaria (locally called ague)[7]. Other traditional applications include remedies for digestive upset and headache, a general tonic or menstrual stimulant, and even treatments for infant convulsions[8]. Together these reports show *M. minutum* was regarded as a multipurpose medicinal plant in many cultures. The interest in *M. minutum* is also reflected in its chemical profile. Phytochemical studies have isolated a variety of biologically active compounds from this species.

In particular, *M. minutum* is rich in coumarins (a class of naturally occurring aromatic compounds) and also contains alkaloids[9]. For example, researchers have isolated numerous unique coumarin derivatives (often given names like micromarin A, B, etc.) from the stem and leaves[10]. One known alkaloid (furoquinoline flindersine) has also been identified[11]. Coumarins are common in the citrus family (Rutaceae) and are linked to many medicinal effects (e.g. anti-inflammatory or anticancer activities). These diverse phytochemicals provide a scientific basis that may help explain many of the plant’s traditional uses[12]. Modern pharmacological tests have begun to probe the bioactivity of *M. minutum* extracts. Some early studies have focused on its potential anticancer properties. For instance, two coumarins from *M. minutum* (micromelin and microminutin) showed toxicity to leukemia cells in mouse models[13,14]. Leaf and stem extracts have also demonstrated inhibition of tumor growth in laboratory

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

assays. In broader terms, the plant's isolated compounds have been associated with anticoagulant, anticancer and antibacterial effects. Other reports suggest possible antimicrobial or anti-inflammatory actions, but these remain less thoroughly documented[7]. Indeed, a recent review noted that most existing research has emphasized cytotoxic or antitumor activity[15,16].

In summary, the available pharmacological data hint at *M. minutum*'s therapeutic potential but are still incomplete and scattered across different studies. In the context of growing global interest in medicinal plants, a comprehensive review of *M. minutum* is timely. While many traditional uses and several novel compounds have been reported, the information is spread over ethnobotanical records and isolated laboratory studies. For example, one recent study pointed out that although *M. minutum* from some countries has been chemically characterized, Indonesian populations had not been studied pharmacologically, indicating knowledge gaps[17]. A review of this kind can help integrate what is known, highlight unanswered questions, and guide future research. Therefore, this article presents a systematic review of *M. minutum*, summarizing its documented traditional uses, identified chemical constituents, and reported pharmacological activities. By bringing these elements together, we aim to provide a clear and up-to-date picture of this medicinal species and suggest directions for further investigation.

Materials and Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency in identifying, screening, and evaluating relevant literature[18]. The primary aim was to comprehensively summarize the traditional uses, chemical constituents, and pharmacological activities of *M. minutum*.

Literature search strategy

A systematic electronic search was performed using international databases, including PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and relevant local and regional databases. The search was conducted using combinations of the following keywords: "*Micromelum minutum*", "traditional uses," "ethnomedicine," "phytochemistry," "chemical constituents," "bioactive compounds," "pharmacological activity," "biological activity," "antimicrobial," "anticancer," "anti-inflammatory," "antioxidant," and related terms. The search was limited to studies published in English-language journals and included articles up to May 2025.

Eligibility criteria

Studies eligible for inclusion were original research articles, reviews, book chapters, theses, and conference proceedings providing detailed information on traditional uses, phytochemical investigations, or pharmacological studies of *M. minutum.* Studies were excluded if they were not published in English, focused on unrelated plant species, provided insufficient methodological detail, or lacked relevant outcomes[17,18].

Study selection

Iniially, the titles and abstracts of retrieved records were independently screened by two reviewers to identify potential articles meeting inclusion criteria. Full-text articles were then retrieved and independently assessed by the reviewers for eligibility. Disagreements were resolved through discussion or consultation with a third reviewer[20].

Data extraction and analysis

Data extraction was independently conducted by two reviewers, capturing the following information: authors, publication year, geographical origin of the plant material, plant parts investigated, traditional uses documented, methodologies employed, chemical constituents isolated, and reported pharmacological activities. A standardized form was used to record and organize data, facilitating comparative analyses. The extracted data were systematically categorized into three sections: traditional uses, chemical constituents, and pharmacological activities[19,20].

PRISMA flow diagram

The article selection process is illustrated in a PRISMA 2020 flow diagram, detailing the number of records identified, screened, excluded, and included in the final review (Figure 1).

Quality assessment

The methodological quality of included studies was evaluated using established criteria tailored for systematic reviews of ethnobotanical and pharmacological research. Particular attention was paid to the clarity of methods, validity of findings, reproducibility, and completeness of reported data. Studies were classified as high, moderate, or low quality based on these parameters[19].

Synthesis of results

Data synthesis involved a descriptive and narrative approach due to anticipated heterogeneity in methodologies and outcomes across studies. Given the broad scope of the review encompassing traditional medicinal uses, phytochemical composition, and diverse pharmacological activities of *M. minutum*, a meta-analysis was deemed impractical. Consequently, findings were systematically categorized and summarized narratively. Structured tables were used extensively to present the detailed data clearly, facilitating comparison and interpretation across different studies and thematic areas, including ethnobotanical applications, chemical constituents, and pharmacological evaluations[22].

Results and Discussion

Vernacular names

M. minutum is known by diverse vernacular names across the various regions where it naturally occurs. In Australia, it is commonly referred to as "Lime berry" in English, "Dilminyin" among the Yolngu Matha-speaking Aboriginal people of Arnhem Land, and "Kohiar margibur" in the Meriam Mir language of Murray Island. In Indonesia, different regions use distinct names: it is called "Sesi" by the Lampungese people in Lampung province, "Ki mangkok" by the Sundanese community in West Java, and "Mentanen" by the Javanese in Central and East Java. Similarly, in Malaysia, particularly in Peninsular Malaysia, the plant is widely recognized as "Chememar," "Cherek," or "Kematu"[23]. In the Philippines, numerous local names reflect its widespread use: the Tagalog-speaking populations commonly know it as "Piris" or "Tulibas tilos," the Bikol region refers to it as "Makabangon," while the Iloko communities of the Ilocos region name it "Basar basar." Among the Agusan Manobo of Mindanao, it is specifically called "Lunas kahoy," highlighting its medicinal significance. In Thailand, the plant is known by names such as "Samui" (southern regions), "Saam sok" (northern regions), and "Sabaek" (eastern regions), indicating regional linguistic variations. In Vietnam, the common local names are "Cam nui" and "Kim sung." Additionally, in Sri Lanka, two primary vernacular names are used: "Wal-karapincha" in Sinhala and "Kakaipalai" in Tamil[24]. These varied local names underscore the cultural significance and traditional utilization of *M. minutum* across its geographic distribution**.**

Morphology

M. minutum (G. Forst.) Wight & Arn., belonging to the Rutaceae family, is an evergreen shrub or small tree typically ranging from 1-10 meters in height, though it can occasionally grow taller under optimal conditions. The plant exhibits smooth to slightly rough, pale gray to brown bark, sometimes becoming fissured with age[25]. Young branches are slender and often densely covered with fine hairs, becoming glabrous (hairless) as they mature. Leaves are alternate, pinnately compound, measuring approximately 10-30 cm in length, composed of 5-13 leaflets arranged oppositely along the rachis with a single terminal leaflet. Each leaflet is ovate to elliptical in shape, usually 2-10 cm long and 1-4 cm wide, with entire or slightly crenulate margins[26]. Leaflets possess a glossy dark-green upper surface, lighter green underneath, and are often aromatic when crushed. The base of each leaflet is cuneate or rounded, and the apex tapers into an acute to acuminate tip. Leaf veins are prominent, pinnately arranged, and clearly visible on both surfaces[27]. The plant produces small, fragrant,

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

bisexual flowers, typically arranged in dense terminal or axillary panicles. Individual flowers measure around 3-5 mm in diameter, characterized by a greenish-white to pale-yellow color. Each flower consists of five sepals, five petals, and ten stamens arranged in two distinct whorls. The petals are elliptic to oblong, spreading outward, contributing to the overall star-like appearance of the flower[28]. The ovary is superior, spherical, and usually has 2-5 locules. Fruits of *M. minutum* are fleshy berries, spherical to oval, measuring approximately 6-10 mm in diameter. Initially green, the fruits turn bright orange to red upon maturity and contain one to several seeds embedded within the pulpy interior[29]. Seeds are elliptical, slightly compressed, and glossy brown to black when fully mature. This morphological description provides key identification traits and supports accurate recognition and differentiation of *M. minutum* from similar species within the Rutaceae family[30].

Traditional uses

M. minutum has a long-standing ethnomedicinal history across diverse cultures, especially in Asia and the Pacific regions. Traditionally, various plant parts, including leaves, bark, roots, and fruits, are utilized in local healthcare practices. Topically, fresh leaves or bark are frequently crushed and applied as poultices for treating skin disorders such as ringworm, scabies, fungal infections, insect bites, sores, wounds, boils, and general skin irritation[31]. In traditional Malaysian medicine, such leaf preparations have been commonly used to reduce swelling and promote wound healing. Additionally, leaf and bark infusions or decoctions are consumed orally to address respiratory ailments, including cough, bronchitis, asthma, and sore throat. In the southern Philippines, particularly among the Manobo tribe, leaf infusions are highly valued for relieving respiratory distress[32]. Oral health benefits of *M. minutum* are also traditionally recognized; chewing fresh leaves or rinsing the mouth with leaf infusions is practiced to alleviate toothache, gum pain, halitosis, and discomfort during teething in children, notably in Malaysia and Indonesia. The plant's use extends to treating digestive disorders, where decoctions from bark and roots are administered orally to manage diarrhea, dysentery, stomach pain, indigestion, and flatulence, especially in rural areas across Southeast Asia[5]. Furthermore, extracts of the plant's roots and bark have been traditionally used as antipyretics to reduce fever, as well as herbal remedies for malaria symptoms, illustrating its significance in local antimalarial practices. *M. minutum* preparations are also traditionally consumed as general health tonics, valued for their perceived benefits in enhancing vitality and well-being[33]. In addition, bark and leaf preparations have been reportedly utilized to regulate menstrual cycles and ease menstrual discomfort, reflecting their particular relevance in women's traditional healthcare in Indonesia, Malaysia, and the Philippines[34]. Lastly, the plant is documented in folk practices for addressing neurological conditions, such as infantile convulsions, where roots or bark preparations are administered either orally or externally applied. Collectively, these traditional medicinal uses underscore the plant's broad therapeutic potential, validating the importance of further scientific research into its pharmacological activities and potential biomedical applications[35] (Table 1).

Table 1: Ethno-Traditional Uses of Several *M. Minutum*

Countries	Plant part(s) used	Preparation method	Traditional medicinal use	References
Malaysia	Leaves; roots	Leaves pounded (poultice); roots boiled (poultice)	Skin irritation; fever (ague); ringworm	[23]
Indonesia	Roots	Chewed with betel	Cough	[23]
Philippines	Young shoots; leaves; roots	Shoots heated in oil; leaves/roots decoction (infusion)	Infantile convulsions; fever; children's diarrhea; stomachache; headache; toothache	[23]
Vietnam	Leaves	Rubbed on skin	Scabies (skin irritations)	[23]
Fiji	Leaves; inner bark	Various (infusions, poultices)	Headache; stomachache; cough; sore tongue; profuse menstruation; gonorrhea; thrush; general tonic	[23]
Thailand	Leaves	Infusion	Tumors (cancer)	[32]

Phytochemistry

Phytochemical investigations of *M. minutum* have consistently shown that the plant is particularly rich in coumarins, along with smaller amounts of alkaloids, lignans and other phenolics[11,23]. The dominant class of metabolites is prenylated 7-methoxycoumarins. For example, acetone extracts of the bark have yielded at least a dozen coumarins, micromarin A-H, micromelin, murrangatin, murralonginol isovalerate, microminutinin, 6-methoxymicrominutinin and microminutin, isolated by silica gel chromatography[15] (Figure 2). Other nonpolar bark extracts furnished the coumarin phebalosin[35]. Detailed phytochemical surveys of leaves, fruits and roots also report similar compounds. *M. minutum* leaves, for example, contain two unique monoterpenoid coumarins (minutin A and B) along with related capnoolide coumarins, isolated from methanol extracts by bioassay-guided fractionation on silica gel[16]. The fruit chemistry includes a novel 7-oxygenated coumarin (7-demethylmurralonginol isovalerate) and a new product murralonginol, plus known coumarins (murralonginol isovalerate, murralongin, micromelin, scopoletin, microminutin, murrangatin and minumicrolin)[15]. Similarly, an alkaloid-rich root extract yielded a new coumarin (minutuminolate) along with eleven known coumarins[14]. All of these compounds were characterized by spectroscopic methods (NMR, MS) after extraction with solvents (acetone or methanol) and separation by chromatographic techniques (silica-gel columns, preparative TLC)[17]. In addition to coumarins, *M. minutum* contains a few other bioactive metabolite classes: notably, the carbazole alkaloid mahanine-a pyranocarbazole-is a major constituent of the edible parts of the plant, and a furoquinoline alkaloid (flindersine) has been reported from the bark[11]. Phenolic constituents include the lignan sesamin, which was isolated from methanol bark extract, as well as coumarin glycosides (e.g. a glycoside of the furanocoumarin marmesin). Polyoxygenated flavonoids have also been described from leaves, although these are minor compared to the coumarins[17] (Table 2). The diverse phytochemicals of *M. minutum* have been associated with a range of

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

biological activities. Many of the isolated coumarins show cytotoxic effects: for instance, micromelin and microminutin produced in vivo antileukemic activity (P-388 assay) and the coumarin phebalosin exhibited brine shrimp toxicity (LC_{50} ~47 ppm) and inhibited crown-gall tumor growth. The newly discovered coumarins from fruits and

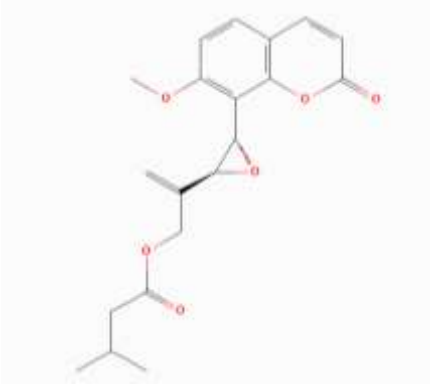
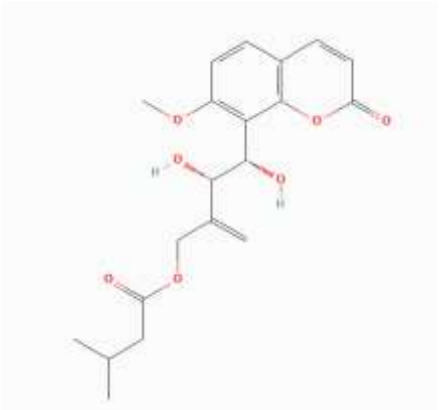
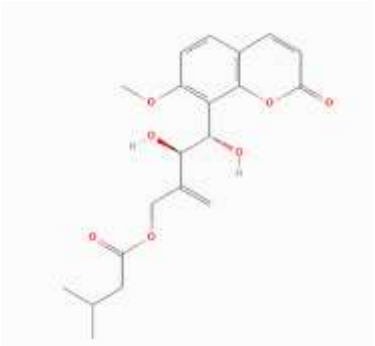
Table 2: Phytocompounds isolated from multiple parts of *M. minutum*

Classification	Compound name	Plant part /Source	Extraction & isolation methods	References
Coumarin	Minutin A Minutin B 8,4″-Dihydroxy-3″,4″-dihydrocapnolactone-2′,3′-diol 8-Hydroxyisocapnolactone-2′,3′-diol 8-Hydroxy-3″,4″-dihydrocapnolactone-2′,3′-diol Clauslactone E	Leaves	Ethanol/EtOAc extract of leaves; silica gel chromatography; preparative HPLC; structure by NMR/MS.	[16,87,87]
Alkaloid	Mahanine *(3,11-dihydro-3,5-dimethyl-3-(4-methyl-3-pentenyl)pyrano[3,2-a]carbazol-9-ol)*	Leaves	70% EtOH extract of leaves; acid-base extraction; silica gel CC; preparative RP-HPLC; NMR/MS.	[9,43,88,89]
Coumarin	8-Methoxycapnolactone	Leaves	MeOH extract of leaves; silica gel chromatography; structure by NMR/MS.	[16]
Sterol	Stigmasterol	Leaves	MeOH extract; column chromatography; NMR/MS.	[90–92]
Coumarin	Micromarin A Micromarin B Micromarin C Micromarin F Micromarin G Micromarin H	Stem (bark)	Acetone extract of stems; silica-gel CC (hexane–acetone gradients); preparative TLC; NMR/MS.	[5,93–95]
Coumarin	Micromelin Murralonginol isovalerate Microminutinin 6-Methoxymicrominutinin Microminutin Murrangatin	Stem (bark)	(as above: acetone extract, silica gel CC/TLC)	[15,31,96,97]
Coumarin	Phebalosin	Stem (bark)	Hexane/Et_2O extract of bark; silica gel CC; NMR/MS.	[35,98–103]
Coumarin	7-Demethylmurralonginol isovalerate Murralonginol Murralonginol isovalerate Murralongin Micromelin Scopoletin Microminutin Murrangatin Minumicrolin	Fruit	MeOH/EtOAc extract of fruits; silica gel CC; structure by NMR/MS.	[15,15,93,104–106]
Coumarin	Minutuminolate *(7-methoxy-8-(3-methyl-2-O-isovaleryl-1-oxo-butenyl)coumarin)* Murralonginol isovalerate Osthol	Roots	MeOH extract of roots; silica gel CC; HPLC; NMR.	[15,100,107–114]

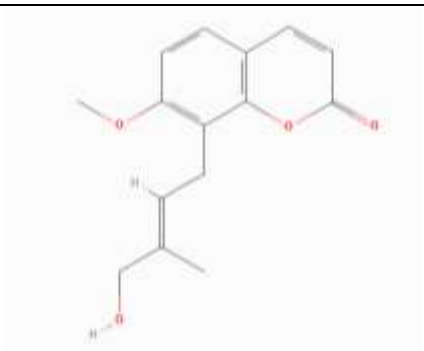
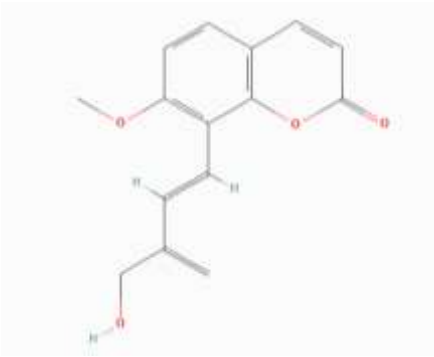
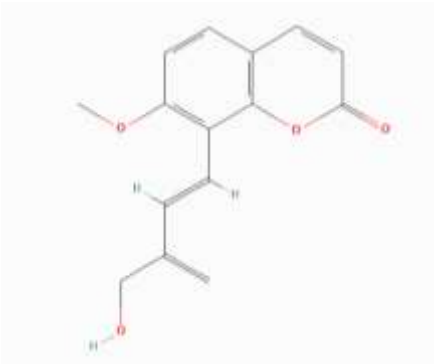
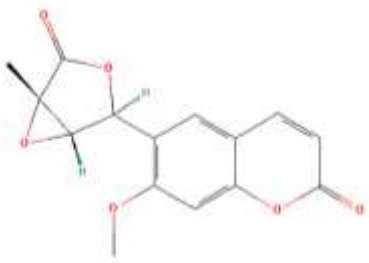
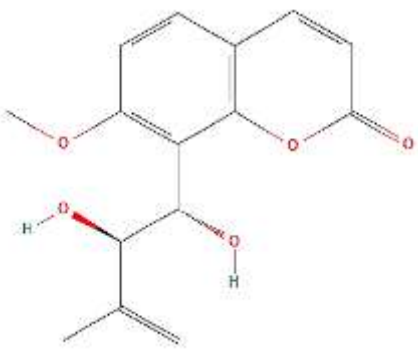
ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

	Phebalosin
	Micromelin
	Murrangatin acetate
	Osthenon
	Murrangatin
	Minumicrolin
	Murralongin

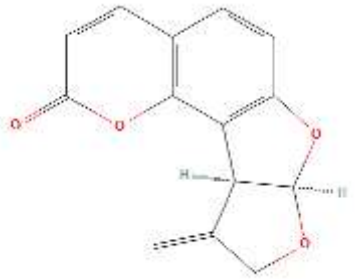
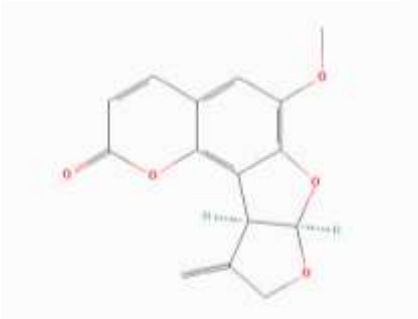
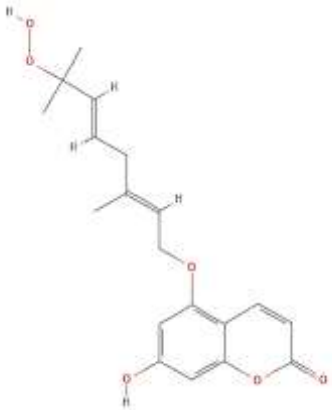
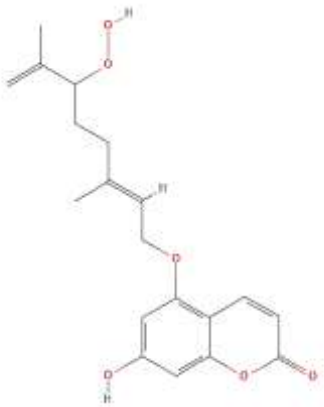
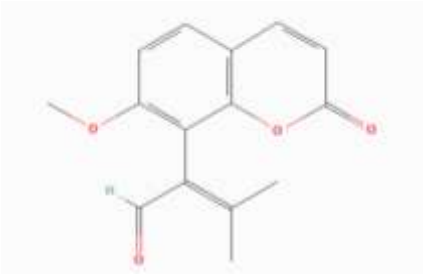
Table 3: Phytochemicals and bioactive compounds isolated from *M. minutum*

No.	Compound name	Structure	Pharmacological activity	References
1	Micromarin A		Antileukemic (in vivo)	[15]
2	Micromarin B		Antileukemic (in vivo)	[15]
3	Micromarin C		Antileukemic (in vivo)	[15]

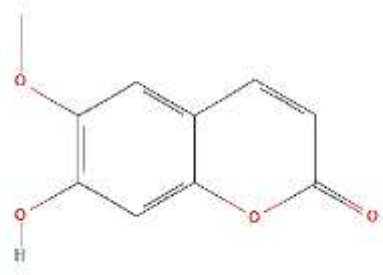
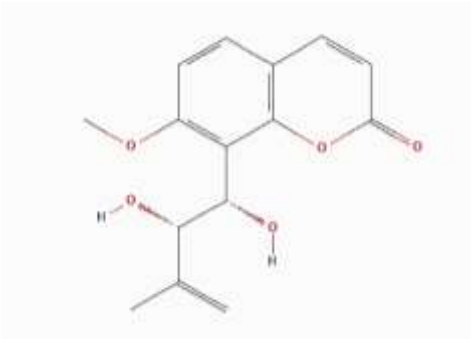
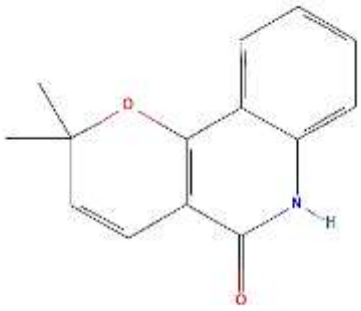
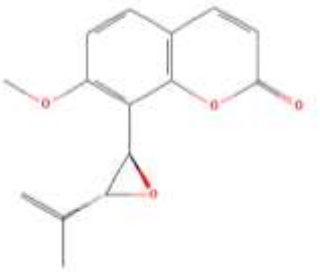
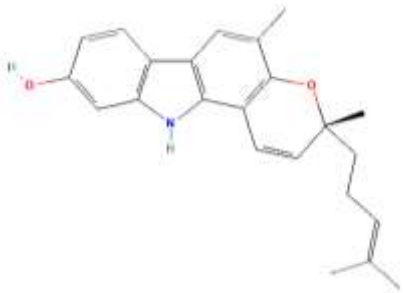
ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

4	Micromarin F		Antileukemic (in vivo)	[15]
5	Micromarin G		Antileukemic (in vivo)	[15]
6	Micromarin H		Antileukemic (in vivo)	[15]
7	Micromelin		Antileukemic (in vivo)	[15]
8	Murrangatin		Antitumor (preliminary)	[15]

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

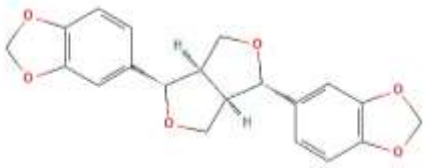
9	Microminutinin		Antileukemic, Cytotoxic	[15]
10	6-methoxymicrominutinin		Cytotoxic	[15]
11	Minutin A		Antileishmanial, Cytotoxic	[16]
12	Minutin B		Antileishmanial, Cytotoxic	[16]
13	Murralongin		Antileishmanial, Cytotoxic	[15]

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

14	Scopoletin		Anti-inflammatory, Antioxidant	117
15	Minumicrolin		Cytotoxic	15
16	Flindersine		Cytotoxic	118
17	Phebalosin		Cytotoxic, Antitumor	35
18	Mahanine		Apoptosis induction (leukemia cells)	115

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

19	Sesamin	Antioxidant, Antimicrobial	[116]



roots also displayed cytotoxicity against cancer cell lines[14]. The monoterpenoid coumarins from leaves (minutin A and B) showed significant activity against *Leishmania major* and various cancer cell lines[16]. Mahanine, the carbazole alkaloid from *M. minutum*, is notable for its pro-apoptotic effects: it induces mitochondrial-mediated apoptosis in leukemia cells[11]. Likewise, sesamin and the prenylated phenolics isolated from bark demonstrated strong antioxidant and antimicrobial activity in bioassay-guided studies[17]. These findings correlate with the plant's traditional uses and suggest that the rich phytochemistry of *M. minutum*-encompassing prenylated coumarins, alkaloids, lignans and volatile terpenes-underlies its pharmacological potential (Table 3).

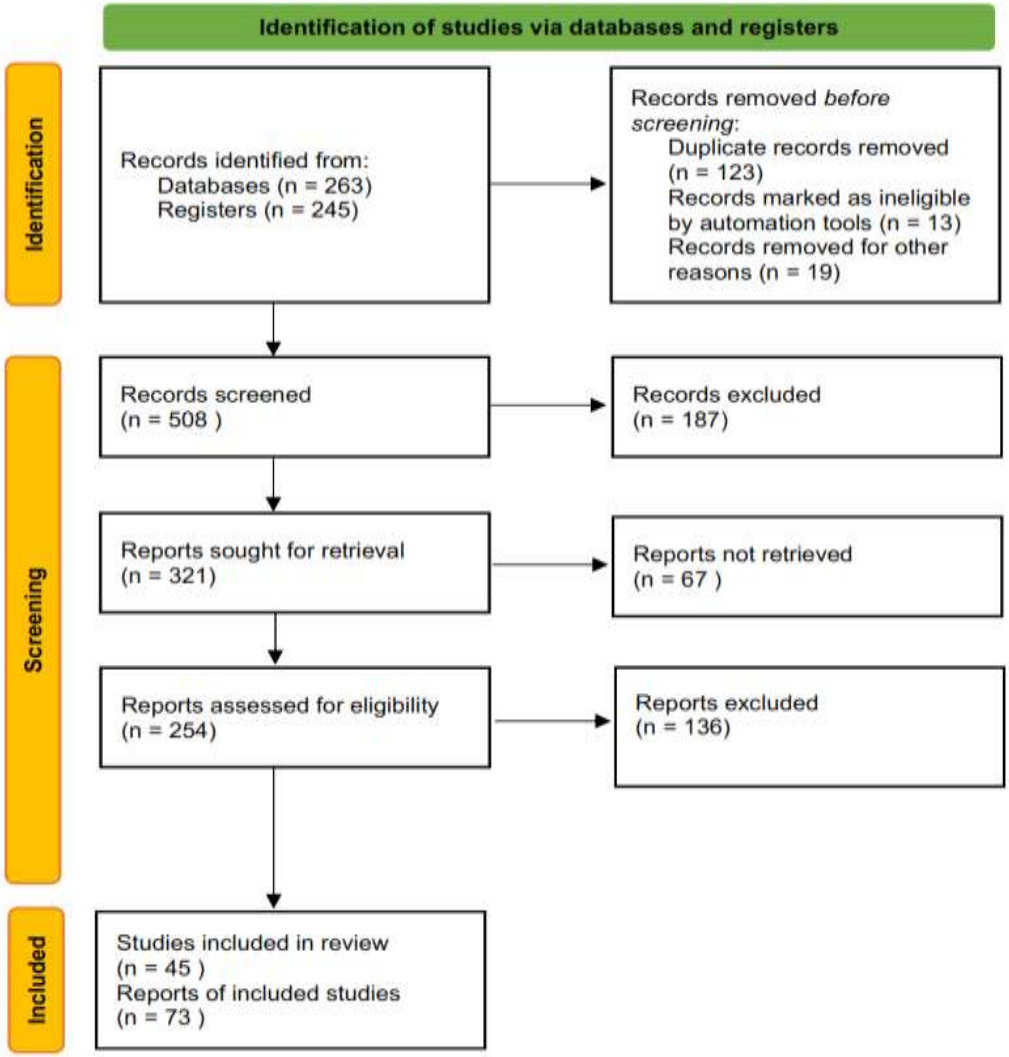


Figure 1: Diagram of search strategy

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

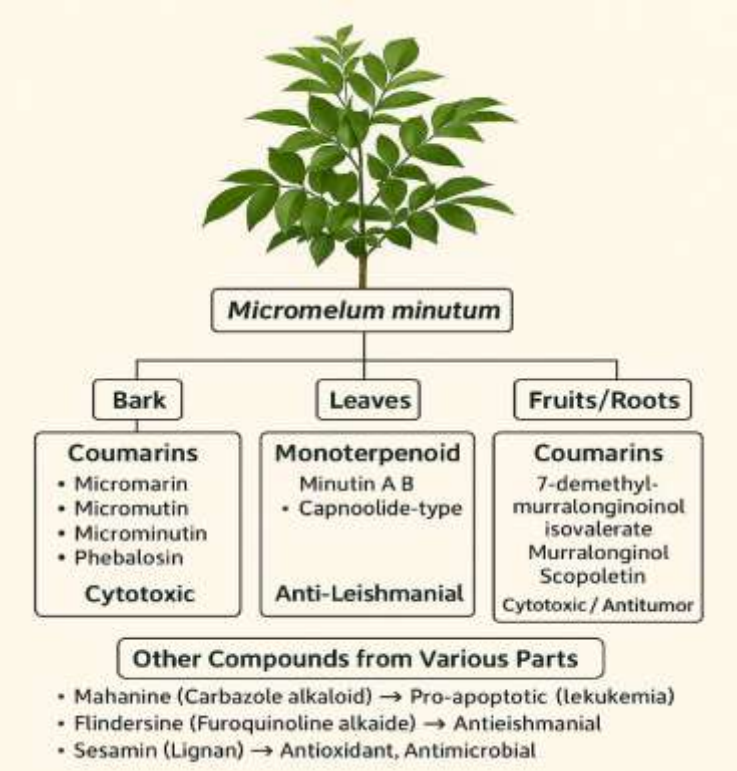


Figure 2: Overview of the principal bioactive constituents and their associated pharmacological effects identified in *M. minutum*

Biological activities

Antibacterial activity

Several studies have evaluated the antibacterial properties of *M. minutum*, focusing primarily on leaf and stem extracts. Leaves and stem bark are the most frequently tested parts, although roots and seeds have also been investigated. Extracts have been prepared with various solvents: ethanol and methanol extracts of leaves, stem bark, and root bark have been studied, as have aqueous extracts and essential oils obtained by hydrodistillation. Standard microbiological assays are used, typically agar diffusion to measure inhibition zones and broth microdilution to determine minimum inhibitory concentrations (MICs). For example, Abeysinghe et al.[6] tested ethanolic leaf extracts of *M. minutum* (as well as *M. koenigii*) and assessed antibacterial activity at concentrations up to 1.0 mg/mL. In other work, ethanolic extracts of *M. minutum* leaves, stem bark, and root bark were tested against

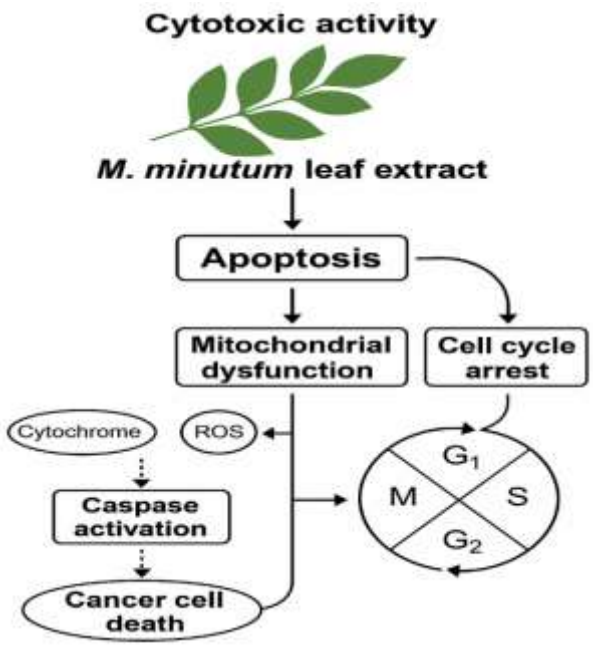


Figure 3: Schematic diagram of *M. minutum* leaf extract-induced cell cycle arrest in U937 cell lines

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

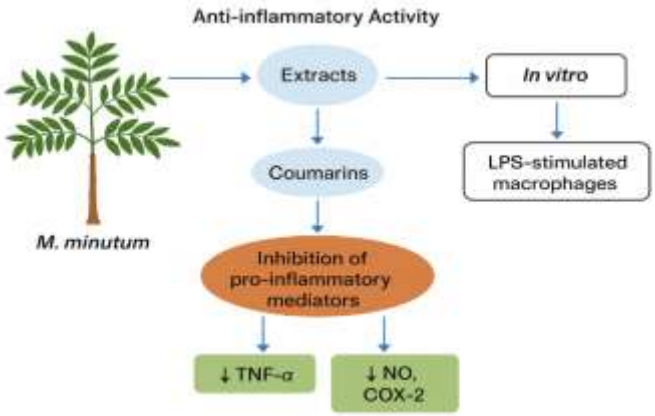
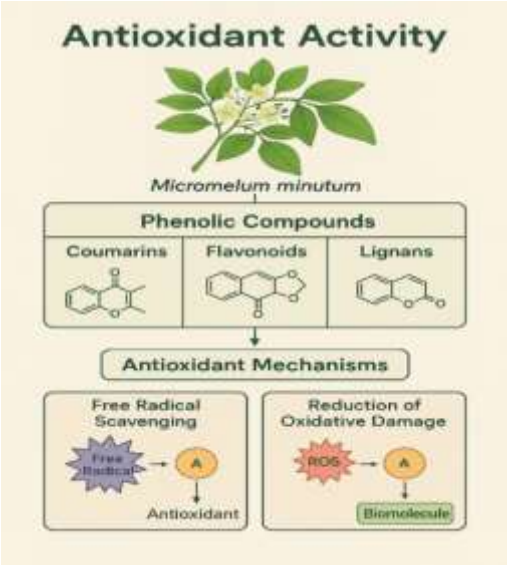


Figure 4: Schematic diagram of *M. minutum* anti-inflammatory activity

Staphylococcus aureus and *Escherichia coli*[4]. In all cases, gentamicin, tetracycline or ciprofloxacin were used as positive controls for comparison. These studies report that *M. minutum* exhibits modest activity against a range of bacterial pathogens. Gram-positive cocci tend to be more susceptible than Gram-negative rods. For instance, Abeysinghe et al.[6] found that *M. minutum* leaf extract showed its strongest activity against *E. coli* at 1.0 mg/mL, whereas *M. koenigii* leaf extract was most active against *S. aureus*. In the Abeysinghe review, all three ethanolic extracts of *M. minutum* (leaf, stem, root) produced measurable zones of inhibition against S. aureus, with leaf extract showing the largest zone against both *S. aureus* and *E. coli*[6]. By contrast, stem bark and root bark extracts were only weakly active against *S. aureus* and showed no inhibition of *E. coli* in that study[6]. In another report, the pure carbazole alkaloid mahanine (isolated from *M. minutum* leaves) had very low MICs of 6.25-12.5 µg/mL against *Bacillus cereus* and *S. aureus*[9]. This suggests that highly active constituents are present, even if crude extracts are less potent. Other common test organisms include *Salmonella* spp., *Bacillus subtilis*, and *Klebsiella pneumoniae*, against which related coumarin-containing Rutaceae often show MICs in the 5-125 µg/mL range[36]. (*M. minutum* activity against *Pseudomonas aeruginosa* appears limited or unreported). In these assays, by comparison the antibiotic ciprofloxacin (100 µg/disc) typically produces much larger inhibition zones - e.g. ~29 mm for *E. coli* and ~18 mm for *S. aureus*[6], underscoring that crude plant extracts are usually less active than standard drugs at the tested doses. In summary, *M. minutum* leaf and bark extracts show moderate antibacterial effects, generally more so against Gram-positive bacteria (e.g. *S. aureus*, *B. cereus*) than Gram-negatives (e.g. *E. coli*, *Salmonella*). Reported inhibition zones for crude extracts often range from 8-15 mm at 1000 µg/mL, and MICs (where measured) are in the hundreds of µg/mL. For example, Abeysinghe et al.[6] observed significant growth inhibition of *E. coli* only at the highest test concentration (1 mg/mL). These activities are weaker than those of conventional antibiotics but indicate that *M. minutum* contains bioactive compounds. Indeed, isolated components such as the alkaloid mahanine are quite potent (single-digit µg/mL MIC)[9]. The mechanisms of antibacterial action have not been directly studied in *M. minutum*, but insights can be inferred from known constituents. The plant is rich in coumarins (especially pyranocoumarins) and carbazole alkaloids, both classes with documented antimicrobial effects. For example, plant-derived coumarins can disrupt bacterial cell processes and inhibit quorum sensing and biofilm formation[36]. Subramoni et al.[36] note that simple coumarins often interfere with bacterial signaling and biofilms, contributing to anti-infective effects. Carbazole alkaloids like mahanine may perturb bacterial membranes or DNA, as suggested by their broad-
spectrum activity. It is also plausible that these phenolic compounds exert oxidative stress or enzyme inhibition in bacteria. In short, the antibacterial efficacy of *M. minutum* is attributed to its secondary metabolites (coumarins and alkaloids) acting through multiple targets (e.g. membrane integrity, signal pathways). Further mechanistic studies are needed, but the current evidence shows that *M. minutum* extracts can inhibit pathogens such as *S. aureus*, *E. coli*, *B. cereus* and others, albeit at relatively high doses[6].



ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Figure 5: Antioxidant activity of *M. minutum* via its phenolic constituents and proposed mechanisms.

Antifungal activity

Various parts of *Micromelum minutum* have been tested for antifungal activity. Studies have used leaves, stem bark, root bark, seeds, fruits and even roots, extracted with solvents ranging from polar (water, methanol, ethanol) to nonpolar (hexane, dichloromethane, petroleum ether) or as essential oils. For example, Abeysinghe et al.[6] examined ethanolic extracts of *M. minutum* leaves, stem bark and root bark. Essential oils obtained by hydrodistillation of fresh leaves have also been analyzed, these oils are rich in sesquiterpenes such as germacrene-D, δ-elemene and β-caryophyllene. Common fungal targets include both yeasts and filamentous fungi. In vitro assays have tested *Candida* species (especially *C. albicans*), *Aspergillus* species (e.g. *A. niger*, *A. fumigatus*), *Fusarium* spp., *Penicillium* spp., and dermatophytes (e.g. *Trichophyton* and *Microsporum* spp.), as well as other phytopathogens. Standard laboratory methods have included agar diffusion (disc or well diffusion) and broth dilution assays to determine zones of inhibition and MIC values. For example, a screening of 19 medicinal plant extracts (on PDA plates) found that *M. minutum* showed "moderate to strong" antifungal activity (≥65% mycelial inhibition) against a panel of five rice pathogens. Similarly, essential oils of *M. minutum* were evaluated by broth dilution and showed broad-spectrum activity: a 1% (v/v) concentration of the leaf oil significantly inhibited all tested microbes (including fungi). Key findings of these studies indicate that *M. minutum* extracts do inhibit fungal growth, though detailed quantitative data are limited. In one study the dichloromethane extract of a related plant produced MICs of 3.9-31.2 µg/mL against rice fungi (as a reference for potent plant extracts). In the case of *M. minutum*, reports typically describe "moderate" activity by crude extracts. For example, leaf ethanol extract showed the largest inhibition zones against *Staphylococcus aureus* in an antibacterial screen-by analogy, one might expect somewhat weaker zones against fungi. No published study has directly compared *M. minutum* extracts to standard antifungal drugs; however, extracts generally require much higher concentrations than clinical agents. (One can note that coumarin itself, a key class of compounds in *M. minutum*, has been shown to prolong survival in *Candida* infections in mice[37], indicating in vivo efficacy.) The phytochemical basis of the antifungal effect likely involves the plant's coumarins and alkaloids. *M. minutum* is rich in prenylated coumarins (such as osthol, murrangatin, and related C-7 oxygenated coumarins) and carbazole alkaloids (notably mahanine)[11]. Coumarins are well-known antimicrobial scaffolds, and coumarin (1,2-benzopyrone) itself has documented activity against *C. albicans*[37]. Mechanistic studies of pure coumarin show that it induces apoptosis in *C. albicans* by generating reactive oxygen species (ROS), disrupting mitochondrial membrane potential, releasing cytochrome c, and triggering calcium influx[37]. Similarly, the carbazole alkaloid mahanine (isolated from *M. minutum* leaves) has broad antimicrobial and cytotoxic effects through mitochondrial disruption: Roy et al.[11] showed that mahanine causes loss of mitochondrial membrane permeability and caspase-mediated apoptosis in human cells, a mechanism that could also impair fungal cells. Other compounds (e.g. phenolic glucosides or volatile terpenes) may contribute by membrane disruption or metabolic inhibition, but specific fungal targets have not been fully mapped. In summary, *M. minutum* extracts show antifungal inhibition in vitro against a range of yeasts and molds. Leaf and bark extracts (especially in ethanol or methanol) tend to be most active, and the essential oil is broadly antimicrobial at high doses. The potency is moderate, generally lower than standard drugs (though no direct comparisons are reported), but the activity is consistent with the traditional use of *M. minutum* preparations for skin fungal infections (ringworm)[32]. The likely bioactive constituents are coumarin derivatives and carbazole alkaloids, which are known to disrupt fungal cells via oxidative stress and apoptosis pathways[32]. These findings support further investigation of *M. minutum* as a source of antifungal leads, with the goal of isolating and optimizing its active compounds against pathogens like *Candida* and *Aspergillus*.

Cytotoxic activity

M. minutum (Rutaceae) contains numerous prenylated coumarins and a carbazole alkaloid (mahanine) in various parts of the plant[11]. Investigations have used leaves, stem/bark, roots and fruits. For example, Susidarti et al.[16] extracted *M. minutum* leaves and bark with nonpolar (petroleum ether/hexane, chloroform) solvents to yield coumarin-rich fractions. Similarly, an Indonesian study sequentially macerated dried leaves in n-hexane, ethyl acetate and methanol, followed by chromatographic purification[38]. These procedures typically yielded hexane (HEM), ethyl acetate (EEM) and methanol (MEM) extracts (e.g. 2.65%, 6.12%, 6.49% yield), as well as pure compounds. In summary, both lipophilic (hexane, chloroform) and polar (EtOAc, MeOH) extracts have been tested, and column chromatography was used to isolate individual constituents[38]. Cytotoxic effects of *M. minutum* have been evaluated in a range of human cancer cell models. Commonly tested lines include T-lymphoblastic leukemia (CEM-SS), promyelocytic leukemia (HL-60), cervical (HeLa), hepatocellular (HepG2), breast carcinoma (MCF-7, 4T1), lung carcinoma (A549) and leukemia (K562, U937) cells[39]. In vitro assays typically measure cell viability and apoptosis. The MTT colorimetric assay has been widely used to determine IC_{50} values[40], while trypan-blue exclusion and nuclear staining (e.g. Hoechst 33258) have been used to count live/dead cells and identify condensed apoptotic nuclei[41]. Flow cytometry with annexin V-FITC/propidium iodide staining is also employed to quantify apoptotic versus necrotic cells[42]. For example, Roy et al.[11] treated U937 leukemic cells with mahanine and used annexin V/PI FACS analysis to show ~35% apoptosis at 8 µM (6 h). In all cases, cell viability curves and IC_{50} values were derived from dose–response data. Many *M. minutum* constituents show low-micromolar (or low-µg/mL) IC_{50} values. For example, the prenylated coumarin 8-hydroxyisocapnolactone-2′,3′-diol was the most active in Susidarti et al.'s study, with IC_{50} = 2.9 µg/mL (CEM-SS), 2.5 µg/mL (HL-60), 6.9 µg/mL (HeLa) and 5.9 µg/mL (HepG2). Another coumarin (2′,3′-epoxyisocapnolactone) also showed strong activity, second only to the 8-hydroxy diol[39]. In crude extracts, the hexane (petroleum ether) leaf fraction was notably potent (IC_{50} ≈ 4.2 µg/mL against CEM-SS)[32]. By contrast, polar extracts (EtOAc, MeOH) were less potent (IC_{50} ~150-300 µg/mL against breast cancer lines). The flavonoid 5,7-dihydroxy-3,4′,8-trimethoxyflavone inhibited MCF-7 and 4T1 cell viability by 50% at ~369 µM and 227 µM, respectively. Mahanine's IC_{50} has been reported in the single-digit micromolar range: for example, ~10 µM mahanine completely blocked HL-60 proliferation[43], and ~8.7 µM induced ~50% apoptosis in U937 cells by 12 h[32]. *M. minutum* extracts and constituents induce cell death mainly through apoptosis. Treated leukemia and carcinoma cells exhibit nuclear condensation and DNA fragmentation (detected by Hoechst staining or DNA laddering)[43]. Mahanine, in particular, triggers the intrinsic (mitochondrial) apoptotic pathway. Roy et al.[43] showed that mahanine causes mitochondrial membrane permeabilization, cytochrome c release, and activation of caspase-9 and caspase-3. It also induces poly (ADP-ribose) polymerase (PARP) cleavage and generates reactive oxygen species. These pro-apoptotic effects were blocked by caspase inhibitors, confirming caspase dependence. Annexin-V/PI flow cytometry confirmed increased apoptotic fractions in treated cultures (e.g. annexin-positive cells rose dramatically with mahanine)[11]. Thus, both *M. minutum* coumarins and the alkaloid appear to kill cancer cells by activating caspase cascades, mitochondrial dysfunction and oxidative stress-mechanisms characteristic of cytotoxic anticancer agents. In summary, *M. minutum* yields bioactive coumarins and an alkaloid (mahanine) that are cytotoxic to a variety of cancer cell lines. Extraction methods (hexane, EtOAc, methanol maceration) have successfully isolated active fractions. The strongest effects have been seen in leukemia (CEM-SS, HL-60, U937) and carcinoma (HeLa, HepG2, A549, MCF-7) cell models. Reported IC_{50} values range from low µg/mL (for pure coumarins) to low µM (for mahanine), with apoptotic markers and caspase activation documenting their mode of action[43]. These in vitro results support the traditional use of *M. minutum* in medicine and highlight its potential as a source of anticancer compounds (Figure 3).

Anti-inflammatory activity

Studies of *M. minutum* often use extracts of various plant parts, especially stems, leaves, roots and bark. For example, Ito et al.[5] prepared an acetone extract of *M. minutum* stems and isolated six new 7-oxygenated coumarins. Similarly, methanolic extracts of bark yielded known and novel coumarins (including prenylated coumarins) and lignans[17]. In practice, extracts are made with organic solvents (methanol, ethanol or acetone) or water. These extracts (or isolated fractions) are then tested for bioactivity. In one report, a methanolic bark extract was used for antioxidant-guided fractionation[17]. In other work, pure coumarins were obtained and evaluated directly. In sum, *M. minutum* studies have employed multiple parts (stems, leaves, bark, fruits or seeds) and solvents (acetone, methanol, ethanol, etc.) to obtain coumarin-rich extracts[4,16]. In vitro models used to assess anti-inflammatory effects include lipopolysaccharide (LPS)-stimulated macrophages[44]. For instance, Choo et al.[45] treated RAW264.7 macrophages with LPS in the presence of isolated *M. minutum* coumarins and measured tumor necrosis factor-α (TNF-α) production. Such assays quantify how much the extract or compound reduces cytokine release from activated immune cells. Another common in vitro assay (not yet reported specifically for *M. minutum*) is LPS+IFN-γ stimulation of macrophages to induce nitric oxide (NO) via iNOS. In vivo, the classic test is carrageenan-induced paw edema in rodents, but published data on *M. minutum* in animal models are limited. One phytopharmacology report noted that an ethanolic seed extract of *M. minutum* inhibited carrageenan-induced rat paw swelling, implying anti-inflammatory activity (though detailed values were not given)[46]. In general, any reduction of edema or inflammatory markers in such models would indicate efficacy. Key outcomes from *M. minutum* studies involve inhibition of pro-inflammatory mediators. In the Choo et al. study, one coumarin (designated "coumarin 3" or muralatin I) showed a dose-dependent decrease in LPS-induced TNF-α production. In contrast, two related coumarins (minutuminolate and a 7-methoxy-8-acylcoumarin) were inactive in this assay[45]. Thus, muralatin I significantly attenuated TNF-α release in vitro. Numerical IC_{50} values were not reported for TNF-α inhibition. No data were given on other cytokines (e.g. IL-1β or IL-6) for these extracts. By analogy to related coumarins, we might expect suppression of inducible NO and COX-2. In fact, other reports show that natural coumarins can inhibit iNOS/NO and COX-2 in LPS-activated macrophages: for example, imperatorin (a *P. notoginseng* coumarin) markedly reduced NOS and COX-2 protein levels in RAW264.7 cells[47]. Thus, inhibition of NO production and cyclooxygenase activity is a plausible outcome for *M. minutum* compounds as well, although direct measurements (nitrite levels, iNOS/COX assays) have not yet been published for this species. Active anti-inflammatory constituents of *M. minutum* appear to be primarily coumarins. Ito et al.[5] identified six new 6-substituted, 7-oxygenated coumarins (micromarin A–H) from stem extracts. Kassim et al.[17] isolated several prenylated coumarins and a lignan (sesamin) from methanol bark extract. In the Choo et al. work, the active "coumarin 3" was structurally characterized as a C7-methoxy, C8-acyloxycoumarin (muralatin I), while "coumarin 1" was minutuminolate[45]. No other classes of compounds (e.g. flavonoids or alkaloids) have been reported with anti-inflammatory tests in *M. minutum*, although the carbazole alkaloid mahanine is known from the leaves. (Mahanine has broad bioactivities, but its anti-inflammatory effect was not evaluated in these studies.) Thus, prenylated and oxygenated coumarins are the main anti-inflammatory candidates identified so far. The proposed mechanisms of action are inferred from the effects on inflammatory mediators. The TNF-α inhibition by muralatin I suggests blockade of NF-κB or MAPK signaling in macrophages[48]. In general, coumarins often act by suppressing NF-κB activation and downstream genes. For example, imperatorin in RAW264.7 cells inhibited expression of inducible NOS (iNOS) and COX-2[47], enzymes that drive NO and prostaglandin synthesis. By analogy, *M. minutum* coumarins may downregulate iNOS and COX-2 as well, reducing NO and eicosanoid mediators. They may also activate antioxidant pathways (e.g. Nrf2/HO-1) that counter inflammation. While direct pathway studies in *M. minutum* are lacking, the observed cytokine suppression implies action at transcriptional level. Additional experiments (e.g. measuring phosphorylation of IκBα or MAPKs, or using reporter assays) would clarify whether these compounds prevent NF-κB nuclear translocation or alter kinase signaling. In summary, the limited data suggest that *M. minutum* extracts and coumarins mitigate inflammation by inhibiting pro-inflammatory cytokine production and possibly suppressing iNOS/COX-2, consistent with known mechanisms of coumarin phytochemicals[42,44] (Figure 4).

Antioxidant activity

M. minutum possesses strong antioxidant potential due to its rich content of phenolic compounds, particularly coumarins, flavonoids, and lignans. Phytochemical studies have shown that its leaf extracts contain approximately 80 mg gallic acid equivalents of total phenolics and 9.2 mg quercetin equivalents of flavonoids per gram[17]. These bioactive compounds are known for their ability to neutralize free radicals and prevent oxidative damage[50]. Extraction using solvents such as methanol, ethanol, and acetone has been optimized to maximize antioxidant yield, with 60% acetone identified as the most effective in extracting phenolics and enhancing radical-scavenging activity[6]. This antioxidant capacity supports the plant's traditional medicinal use and highlights its potential for further pharmacological development. Antioxidant capacity of *M. minutum* extracts has been evaluated by multiple in vitro assays. Common methods include DPPH and ABTS radical-scavenging assays (electron-transfer tests), ferric-reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), and β-carotene bleaching assays[51]. For instance, Kassim et al.[17,52] measured DPPH and ORAC of a methanol bark extract and its bioactive fractions. Likewise, Abeysinghe et al. determined DPPH IC_{50} for leaf extracts, and Krungkri & Areekul evaluated DPPH, ABTS and FRAP on leaf extracts across different pH and heat treatments[17]. In general, such assays have shown that *M. minutum* extracts can effectively quench free radicals. In the DPPH assay, for example, Sri Lankan *M. minutum* leaf extract had an IC_{50} ≈208 µg/mL (compared with 107 µg/mL for *Murraya koenigii* curry-leaf)[6]. In ORAC (Trolox-equivalent) assays, the *M. minutum* methanol bark extract gave values on the order of 5000-5500 µmol TE/g, reflecting high peroxyl-radical scavenging. These values are comparable to potent natural antioxidants: for example, Kassim et al.[17] reported ORAC values of 5123, 5539 and 4031 µmol TE/g for the bark extract and two isolated compounds, respectively. By contrast, the corresponding β-carotene bleaching inhibition was moderate (≈55% for the crude extract), underscoring that different assays probe distinct aspects of antioxidant action. Chemical analysis has identified several classes of antioxidants in *M. minutum*. Notably, Kassim et al.[17] used TLC-DPPH bioautography to isolate an antioxidant lignan (sesamin), two new prenylated coumarins and a glycosylated marmesin coumarin from the methanol bark extract. Sesamin is a well-known phenolic lignan (also found in sesame) with potent chain-breaking antioxidant activity[53,54]. Other studies have found a diversity of oxygenated coumarins and flavonoids in *M. minutum* leaves, roots and fruits[15]. For example, Thai *M. minutum* fruit yielded seven C-7 oxygenated coumarins (e.g. murralongin, scopoletin), many of which have been reported in other Rutaceae to scavenge radicals or inhibit lipid peroxidation[55,56]. In leaves, polyphenols such as kaempferol or quercetin glycosides (not yet fully characterized in this species) likely contribute to the measured total phenolics[15]. Overall, *M. minutum* appears rich in polyphenolic antioxidants, with coumarins and lignans being prominent representatives. The antioxidant mechanisms of these phytochemicals are typical of phenolic compounds[57,58]. In radical-scavenging assays like DPPH or ABTS (SET-based tests), antioxidants donate an electron (or hydrogen) to the radical, neutralizing it. In ORAC-type (HAT-based) assays, the antioxidant directly transfers a hydrogen atom to peroxyl radicals, breaking chain propagation[51]. Thus, *M. minutum* phenolics quench reactive oxygen species by hydrogen/electron donation and can also chelate metal ions to inhibit Fenton reactions. These actions prevent oxidative damage to lipids, proteins and DNA. For instance, sesamin and related lignans are known to inhibit lipid peroxidation and stabilize biological membranes (as documented in other systems)[59,60]. The net effect is to reduce oxidative stress, which is mechanistically linked to anti-inflammatory and cytoprotective outcomes [61]. These antioxidant

properties are highly relevant to the plant's pharmacology and traditional uses [62]. By scavenging free radicals and inhibiting oxidation, *M. minutum* extracts may mitigate inflammation and microbial infection, consistent with its use as an herbal febrifuge or anti-inflammatory remedy[63,64]. Moreover, oxidative stress is implicated in chronic diseases such as diabetes; indeed *M. minutum* has been reported to exhibit antidiabetic and antihyperlipidemic effects (e.g. from seed extract in animal studies), likely supported by its polyphenols[6]. In summary, phytochemicals such as sesamin and diverse coumarins endow *M. minutum* with strong free-radical scavenging and reducing activity[17]. These in vitro antioxidant findings provide a scientific basis for the plant's traditional roles in health, and suggest that *M. minutum* may be a valuable source of natural antioxidants for nutraceutical or pharmacological development (Figure 5).

Antidiabetic activity

Several studies have explored *M. minutum's* effects on glucose metabolism. Ethanolic extracts of the seeds (typically administered orally at ~100 mg/kg in rodent models) significantly lowered fasting blood glucose and corrected hyperlipidemia in alloxan or streptozotocin-induced diabetic rats[4]. For example, Koriem et al.[48,49] reported that 30-day treatment with seed extract (100 mg/kg) markedly reduced blood sugar and serum lipids in diabetic rats, accompanied by pancreatic islet regeneration (increased β-cell number) and modulation of apoptotic markers (upregulation of p53 with downregulation of Bcl-2). These effects are attributed to the plant's rich coumarin and flavonoid content. Identified compounds include coumarins such as microminutinin and related pyranocoumarins, which exhibit strong antioxidant activity. In vitro assays show that *M. minutum* extracts scavenge DPPH radicals and increase antioxidant enzymes (SOD, GSH), protecting β-cells from oxidative stress. This antioxidant protection likely underlies part of its antihyperglycemic action. In addition, some *M. minutum* coumarins may inhibit carbohydrate-digesting enzymes (α-glucosidase/α-amylase), delaying glucose absorption (a mechanism seen with other Rutaceae polyphenols). Overall, *M. minutum* exerts multi-factorial antidiabetic effects-enhancing insulin levels, preserving pancreatic tissue, and reducing oxidative stress[4].

Hepatoprotective activity

Direct hepatoprotective studies of *M. minutum* are scarce. However, the plant's phytochemical profile suggests potential liver-protective effects. The leaves and seeds contain potent antioxidants (coumarins, flavonoids and phenolics) known to quench free radicals[4,67]. In related Rutaceae (e.g. *Murraya koenigii*), such antioxidants have attenuated CCl_4 or acetaminophen-induced liver injury by reducing lipid peroxidation and inflammation[68]. By analogy, *M. minutum* extracts could normalize elevated liver enzymes (ALT/AST) and preserve hepatocyte integrity in toxin models, though formal studies are needed. Any hepatoprotection would likely stem from oxidative stress mitigation (increased SOD, catalase, GSH; reduced MDA) and anti-inflammatory cytokine modulation [69]. For example, quercetin (a common plant flavonoid) pretreatment is known to protect rat liver from ischemia–reperfusion damage[32,69]; *M. minutum's* own flavonoids might act similarly. Until in vivo data are reported, the proposed hepatoprotective mechanism for *M. minutum* remains enhancement of intrinsic antioxidant defense and inhibition of inflammatory pathways in the liver.

Analgesic and antipyretic activities

M. minutum is used traditionally as a febrifuge and for pain relief. Pharmacological evidence, although limited, supports an anti-inflammatory basis for these effects. A key finding is that 8-hydroxyisocapnolactone-2′,3′-diol (a coumarin isolated from *M. minutum*) strongly inhibited mast-cell degranulation in vitro. At concentrations of 10-100 µM, this compound reduced compound-48/80-induced histamine release by 25-50% (relative to control)[71]. Inhibiting mast cell histamine release suggests potent anti-inflammatory activity, which typically translates to analgesic and antipyretic effects[72,73]. Moreover, this coumarin has been reported to antagonize histamine H1 receptors (reducing vasodilation and edema) and stabilize mast cells[71,74]. These actions would decrease prostaglandin synthesis and lower fever and pain[75,76]. In animal models, such anti-inflammatory plant coumarins generally produce positive results in standard tests (e.g. reduced paw edema and acetic acid induced writhing)[77]. Although *M. minutum* itself has not been formally tested in analgesic assays, its H1-blocking, mast-cell-stabilizing activity and high antioxidant content suggest it can relieve fever and nociception by limiting inflammation[71].

Antimalarial activity

M. minutum has a history of use against malaria ("ague") in folk medicine[32]. Modern studies of related Rutaceae support this use. For instance, phytochemical investigation of *Clausena excavata* (a related genus) isolated an *M. minutum*-type coumarin (8-hydroxy-3″,4″-dihydrocapnolactone-2′,3′-diol) along with other pyranocoumarins[78,79]. Two of those compounds showed potent antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* (EC_{50} ≈0.6-1.1 µM)[78]. By extension, *M. minutum's* own coumarins (e.g. 8-hydroxy-3″,4″-dihydrocapnolactone-2′,3′-diol) likely inhibit Plasmodium in vitro. The proposed mechanism is interference with the parasite's redox metabolism and DNA synthesis: many plant phenolics reduce parasitic superoxide dismutase (SOD) activity and block hemozoin formation[80]. In vivo, *M. minutum* crude extracts might be expected to decrease parasitemia in *P. berghei*-infected mice, although specific animal studies are not yet published. One study on a related coumarin did report lower parasite loads in cultured parasites[81]. In summary, *M. minutum* exhibits antiplasmodial action via its coumarins (as evidenced by related plant studies)[78], supporting its traditional antimalarial use.

Anticoagulant activity

M. minutum contains multiple coumarins, a class famously associated with anticoagulant effects (e.g. warfarin-like vitamin K antagonism)[32]. In fact, a review notes that *M. minutum* "has revealed a range of physiologically active compounds including anticoagulants"[32]. Although no direct clotting assays have been reported for *M. minutum*, its coumarins (such as microminutin and related phenolics) could plausibly prolong prothrombin time by inhibiting vitamin K epoxide reductase[82,83]. Additionally, the plant's polyphenols might inhibit platelet aggregation[84–86]. In practice, an ethanolic extract given to animals would be expected to increase clotting time or bleeding time if active anticoagulants are present. Without published in vivo data, this remains speculative. Nonetheless, the presence of naturally occurring coumarins and warfarin-like compounds in *M. minutum* suggests potential anticoagulant action via the classic mechanism of vitamin K cycle inhibition and reduction of coagulation factor synthesis[32]. Future studies measuring PT, aPTT, and platelet function after extract administration would clarify this effect.

Conclusion

This comprehensive review underscores the significant pharmacological potential of *Micromelum minutum*, reflecting its diverse traditional uses across Southeast Asia and the Pacific regions. Scientific validation has revealed numerous bioactivities associated with different plant parts and extracts, particularly highlighting antioxidant, antibacterial, antifungal, cytotoxic (anticancer), anti-inflammatory, antidiabetic, hepatoprotective, analgesic, antipyretic, antimalarial, and anticoagulant activities. These effects are primarily attributed to its rich phytochemical profile, notably prenylated coumarins, flavonoids, lignans, and carbazole alkaloids such as mahanine. The plant's potent antioxidant properties, stemming from its high phenolic content, provide a foundation for its broad therapeutic efficacy, helping mitigate oxidative stress-related pathologies. Cytotoxic coumarins and alkaloids identified from *M. minutum* show promising anticancer activities, warranting further exploration as potential natural anticancer agents. Additionally, the observed anti-inflammatory and antimicrobial properties validate traditional medicinal claims for treating infections, inflammatory conditions, and skin ailments. The antidiabetic potential of *M. minutum* extracts, demonstrated by their ability to reduce blood glucose and enhance pancreatic function, offers valuable prospects for natural diabetes

management. While studies on hepatoprotective, analgesic, antipyretic, antimalarial, and anticoagulant activities are encouraging, further rigorous preclinical and clinical investigations are necessary to fully establish therapeutic safety, efficacy, and underlying mechanisms of action. Overall, *Micromelum minutum* presents a promising yet underutilized medicinal plant with diverse pharmacological applications, meriting continued scientific attention for the development of novel phytopharmaceuticals and nutraceuticals. Future research should focus on detailed mechanistic studies, isolation and standardization of active compounds, and clinical evaluations to translate traditional uses into evidence-based therapeutic solutions.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

The authors sincerely thank Prof. Subandi for his valuable corrections and insightful suggestions provided during the manuscript preparation prior to submission. No external funding was received for conducting this review.

References

1. Garima S, Ajit Kumar P, Marcy DM, Sakthivel R, Bhim Pratap S, Nachimuthu Senthil K. Ethnobotanical survey of medicinal plants used in the management of cancer and diabetes. J. Tradit. Chin. Med. 2020;40(6):1007–1017.
2. Sen T, Samanta SK. Medicinal plants, human health and biodiversity: a broad review. Adv. Biochem. Eng. Biotechnol. 2015;147:59–110.
3. Khan H, Pervaiz A, Kamal MA, Patel S. Antiplatelet Potential of Plant-Derived Glycosides as Possible Lead Compounds. Curr. Drug. Metab. 2018;19(10):856–862.
4. Abeysinghe DT, Alwis DDDH, Kumara K a. H, Chandrika UG. Nutritive Importance and Therapeutics Uses of Three Different Varieties (*Murraya koenigii*, *Micromelum minutum*, and *Clausena indica*) of Curry Leaves: An Updated Review. Evid-Based Comp. Altern. Med. 2021;2021:5523252.
5. Ito C, Otsuka T, Ruangrungsi N, Furukawa H. Chemical constituents of *Micromelum minutum*. Isolation and structural elucidation of new coumarins. Chem. Pharm. Bull. 2000;48(3):334–338.
6. Abeysinghe DT, Kumara K a. H, Kaushalya K a. D, Chandrika UG, Alwis DDDH. Phytochemical screening, total polyphenol, flavonoid content, in vitro antioxidant and antibacterial activities of Sri Lankan varieties of *Murraya koenigii* and *Micromelum minutum* leaves. Heliyon. 2021;7(7):e07449.
7. Hong X, Mat Isa N, Fakurazi S, Safinar Ismail I. Phytochemical and anti-inflammatory properties of *Scurrula ferruginea* (Jack) Danser parasitising on three different host plants elucidated by NMR-based metabolomics. Phytochem. Anal. 2020;31(1):15–27.
8. Kawami M, Yumoto R, Nagai J, Junyaprasert VB, Soonthornchareonnon N, Patanasethanont D, Sripanidkulchai B orn, Takano M. Effect of Thai plant extracts on P-glycoprotein function and viability in paclitaxel-resistant HepG2 cells. Drug Metab. Pharmacokinet. 2010;25(2):155–162.
9. Nakahara K, Trakoontivakorn G, Alzoreky NS, Ono H, Onishi-Kameyama M, Yoshida M. Antimutagenicity of some edible Thai plants, and a bioactive carbazole alkaloid, mahanine, isolated from *Micromelum minutum*. J. Agric. Food Chem. 2002;50(17):4796–4802.
10. Rahmani M, Hin TY, Ismail HB, Sukari MA, Manas AR. Microminutinin: A Novel Coumarin from *Micromelum minutum*. Planta Med. 1993;59(1):93–94.
11. Roy MK, Thalang VN, Trakoontivakorn G, Nakahara K. Mahanine, a carbazole alkaloid from *Micromelum minutum*, inhibits cell growth and induces apoptosis in U937 cells through a mitochondrial dependent pathway. Br. J. Pharmacol. 2005;145(2):145–155.
12. Rahmani M, Susidarti RA, Ismail HBM, Sukari MA, Hin TYY, Lian GEC, Ali AM, Kulip J, Waterman PG. Coumarins from Malaysian *Micromelum minutum*. Phytochemistry. 2003;64(4):873–877.
13. Bhattarai N, Kumbhar AA, Pokharel YR, Yadav PN. Anticancer Potential of Coumarin and its Derivatives. Mini Rev. Med. Chem. 2021;21(19):2996–3029.
14. Lekphrom R, Kanokmedhakul K, Sangsopha W, Kanokmedhakul S. A new coumarin from the roots of *Micromelum minutum*. Nat. Prod. Res. 2016;30(21):2383–2388.
15. Lekphrom R, Kanokmedhakul S, Kukongviriyapan V, Kanokmedhakul K. C-7 oxygenated coumarins from the fruits of *Micromelum minutum*. Arch. Pharm. Res. 2011 ;34(4):527–531.
16. Sakunpak A, Matsunami K, Otsuka H, Panichayupakaranant P. Isolation of new monoterpene coumarins from *Micromelum minutum* leaves and their cytotoxic activity against Leishmania major and cancer cells. Food Chem. 2013;139(1–4):458–463.
17. Kassim NK, Lim PC, Ismail A, Awang K. Isolation of antioxidative compounds from *Micromelum minutum* guided by preparative thin layer chromatography-2,2-diphenyl-1-picrylhydrazyl (PTLC-DPPH) bioautography method. Food Chem. 2019;272:185–191.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
21. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
22. Yao L, Zhang Y, Zhao C, Zhao F, Bai S. The PRISMA 2020 Statement: A System Review of Hospital Preparedness for Bioterrorism Events. Int J Environ Res Public Health. 2022 ;19(23):16257.
23. PROSEA - Plant Resources of South East Asia [Internet]. [cited 2025 May 9]. Available from: https://prosea.prota4u.org/view.aspx?id=1199
24. Dapar MLG, Alejandro GJD, Meve U, Liede-Schumann S. Quantitative ethnopharmacological documentation and molecular confirmation of medicinal plants used by the Manobo tribe of Agusan del Sur, Philippines. J. Ethnobiol. Ethnomedicine. 2020;16(1):9-14.
25. Ye H, Li C, Ye W, Zeng F. Common Chinese Materia Medica: Volume 5. Springer Nature Singapore; 2022. 622 p.
26. Mabberley DJ. Mabberley's Plant-book: A Portable Dictionary of Plants, their Classification and Uses [Internet]. 4th ed. Cambridge: Cambridge University Press; 2017 [cited 2025 May 9]. Available from: https://www.cambridge.org/core/books/mabberleys-plantbook/B1245736E70AF37DCB680659D5C981F7

27. Newman M, Ketphanh S, Svengsuksa B, Thomas P, Sengdala K, Lamxay V, Armstrong K. A checklist for the vascular plants of Lao PDR. Royal Botanic Garden Edinburgh, UK; 2007.
28. Castro IR. A Guide to Families of Common Flowering Plants in the Philippines. UP Press; 2006. 296 p.
29. Li S, Smith P, Stuart GA. Chinese Medicinal Herbs: A Modern Edition of a Classic Sixteenth-century Manual. Courier Corporation; 2003. 516 p.
30. The Angiosperm Phylogeny Group. An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG III: APG III. Bot. J. Linn. Soc. 2009;161(2):105–121.
31. Cassady JM, Ojima N, Chang C, McLaughlin JL. An investigation of the antitumor activity of *Micromelum integerrimum* (Rutaceae). J. Nat. Prod. 1979;42(3):274–278.
32. Zohora F, Hasan CM, Ahsan M. Chemical constituents, cytotoxic activities and traditional uses of *Micromelum minutum* (Rutaceae): a review. Pharm. Pharmacol. Int. J. 2019;23(3):17-35.
33. Boy HIA, Rutilla AJH, Santos KA, Ty AMT, Yu AI, Mahboob T, Tangpoong J, Nissapatorn V. Recommended Medicinal Plants as Source of Natural Products: A Review. Digit. Chin. Med. 2018 ;1(2):131–142.
34. Rahmani M, Hin Taufiq-Yap Y, Ismail HBM, Sukari A, Waterman PG. New coumarin and dihydrocinnamic acid derivatives from two malaysian populations of *Micromelum minutum*. Phytochemistry. 1994;37(2):561–564.
35. Tantishaiyakul V, Pummangura S, Chaichantipyuth C, Ma WW, McLaughlin JL. Phebalosin from the bark of *Micromelum minutum*. J Nat Prod. 1986;49(1):180–191.
36. Reen FJ, Gutiérrez-Barranquero JA, Parages ML, O´Gara F. Coumarin: a novel player in microbial quorum sensing and biofilm formation inhibition. Appl. Microbiol. Biotechnol. 2018;102(5):2063–2073.
37. Jia C, Zhang J, Yu L, Wang C, Yang Y, Rong X, Xu K, Chu M. Antifungal Activity of Coumarin Against *Candida albicans* Is Related to Apoptosis. Front. Cell. Infect. Microbiol. 2019;8(3):172-186.
38. Susidarti R, Meiyanto E, Ikawati M, Normaidah N, Sida N. Chemical Constituents of Indonesian *Micromelum minutum* Leaves and Their Cytotoxicity Against MCF-7 and 4T1 Breast Cancer Cells. J. Math. Fundam. Sci. 2021;53:97–108.
39. Asmah Susidarti R, Rahmani ,Mawardi, Ismail ,Hazar B.M., Sukari ,M. Aspollah, Yun Hin ,Taufiq-Yap, Ee Cheng Lian ,Gwendoline, and Manaf Ali A. Cytotoxic activity of coumarins from *Micromelum minutum*. Pharm. Biol. 2009;47(2):182–185.
40. Thant T, Aminah N, Kristanti A, Ramadhan R, Aung H, Takaya Y. Phytoconstituents of Genus Micromelum and Their Bioactivity—a Review. Nat. Prod. Commun. 2020 ;15:1934578X2092712.
41. Strober W. Trypan Blue Exclusion Test of Cell Viability. Curr. Protoc. Immunol. 2015;111:A3.B.1-A3.B.3.
42. Pozarowski P, Darzynkiewicz Z. Analysis of cell cycle by flow cytometry. Methods Mol Biol Clifton NJ. 2004;281:301–311.
43. Roy MK, Thalang VN, Trakoontivakorn G, Nakahara K. Mechanism of mahanine-induced apoptosis in human leukemia cells (HL-60). Biochem. Pharmacol. 2004;67(1):41–51.
44. da Silva AO, Damaceno Alves A, Almeida DAT de, Balogun SO, de Oliveira RG, Aires Aguiar A, Soares IM, Marson-Ascêncio PG, Ascêncio SD, de Oliveira Martins DT. Evaluation of anti-inflammatory and mechanism of action of extract of *Macrosiphonia longiflora* (Desf.) Müll. Arg. J Ethnopharmacol. 2014;154(2):319–329.
45. Choo MZY, Khaw LWT, Chai CLL. Syntheses of Minutuminolate and Related Coumarin Natural Products and Evaluation of Their TNF-α Inhibitory Activities. ACS Omega. 2023;8(44):41785–41791.
46. Koriem KMM, Arbid MS, El-Attar MA. Acute and subacute toxicity of Ammi visnaga on rats. Interdiscip. Toxicol. 2019;12(1):26–35.
47. Flores-Morales V, Villasana-Ruíz AP, Garza-Veloz I, González-Delgado S, Martinez-Fierro ML. Therapeutic Effects of Coumarins with Different Substitution Patterns. Molecules. 2023;28(5):2413.
48. Wei NN, Lv HN, Wu Y, Yang SL, Sun XY, Lai R, Jiang Y, Wang K. Selective Activation of Nociceptor TRPV1 Channel and Reversal of Inflammatory Pain in Mice by a Novel Coumarin Derivative Muralatin L from *Murraya alata*. J. Biol. Chem. 2016;291(2):640–651.
49. Lyu HN, Wei NN, Tu PF, Wang K, Jiang Y. A new coumarin from *Murraya alata* activates TRPV1 channel. Nat. Prod. Res. 2020;34(8):1068–1073.
50. Rumpf J, Burger R, Schulze M. Statistical evaluation of DPPH, ABTS, FRAP, and Folin-Ciocalteu assays to assess the antioxidant capacity of lignins. Int. J. Biol. Macromol. 2023 ;233:123470.
51. Platzer M, Kiese S, Tybussek T, Herfellner T, Schneider F, Schweiggert-Weisz U, Eisner P. Radical Scavenging Mechanisms of Phenolic Compounds: A Quantitative Structure-Property Relationship (QSPR) Study. Front. Nutr. 2022;9(22):128-144.
52. Kassim NK, Rahmani M, Ismail A, Sukari MA, Ee GCL, Nasir NM, Awang K. Antioxidant activity-guided separation of coumarins and lignan from *Melicope glabra* (Rutaceae). Food Chem. 2013;139(1–4):87–92.
53. Wei P, Zhao F, Wang Z, Wang Q, Chai X, Hou G, Meng Q. Sesame (*Sesamum indicum* L.): A Comprehensive Review of Nutritional Value, Phytochemical Composition, Health Benefits, Development of Food, and Industrial Applications. Nutrients. 2022;14(19):4079.
54. Altyar AE, Albadrani GM, Farouk SM, Alamoudi MK, Sayed AA, Mohammedsaleh ZM, Al-Ghadi MQ, Saleem RM, Sakr HI, Abdel-Daim MM. The antioxidant, anti-inflammatory, and anti-apoptotic effects of sesamin against cisplatin-induced renal and testicular toxicity in rats. Ren. Fail. 2024;46(2):2378212.
55. Kotali A, Nasiopoulou DA, Tsoleridis CA, Harris PA, Kontogiorgis CA, Hadjipavlou-Litina DJ. Antioxidant Activity of 3-[N-(Acylhydrazono)ethyl]-4-hydroxy-coumarins. Mol. Basel Switz. 2016;21(2):138-142.
56. Symeonidis T, Chamilos M, Hadjipavlou-Litina DJ, Kallitsakis M, Litinas KE. Synthesis of hydroxycoumarins and hydroxybenzo[f]- or [h]coumarins as lipid peroxidation inhibitors. Bioorg. Med. Chem. Lett. 2009;19(4):1139–1142.
57. Sawicki T, Jabłońska M, Danielewicz A, Przybyłowicz KE. Phenolic Compounds Profile and Antioxidant Capacity of Plant-Based Protein Supplements. Mol Basel Switz. 2024;29(9):2101.
58. Król-Grzymała A, Amarowicz R. Phenolic Compounds of Soybean Seeds from Two European Countries and Their Antioxidant Properties. Mol. Basel Switz. 2020;25(9):2075.
59. Dossou SSK, Xu F tao, Dossa K, Zhou R, Zhao Y zhong, Wang L hai. Antioxidant lignans sesamin and sesamolin in sesame (*Sesamum indicum* L.): A comprehensive review and future prospects. J. Integr. Agric. 2023;22(1):14–30.
60. Pham TH, Lee GH, Jin SW, Lee SY, Han EH, Kim ND, Choi CY, Jeong GS, Ki Lee S, Kim HS, Jeong HG. Sesamin ameliorates lipotoxicity and lipid accumulation through the activation of the estrogen receptor alpha signaling pathway. Biochem. Pharmacol. 2023;216:115768.
61. Yasuda K, Sakaki T. How is sesamin metabolised in the human liver to show its biological effects? Expert Opin Drug Metab Toxicol. 2012;8(1):93–102.
62. Akbari F, Mollaei M, Argani P, Daneshfard B, Derakhshan AR. Spinacia Oleracea: Exploring the Therapeutic Potential in Persian Medicine and Modern Pharmacology. Curr. Drug Discov. Technol. 2024;21(6):e150224227025.
63. Calella P, Di Dio M, Cerullo G, Di Onofrio V, Gallé F, Liguori G. Antioxidant, immunomodulatory, and anti-inflammatory effects of Spirulina in disease conditions: a systematic review. Int. J. Food Sci. Nutr. 2022;73(8):1047–1056.

64. Zhou N, Zhao Y, Yao Y, Wu N, Xu M, Du H, Wu J, Tu Y. Antioxidant Stress and Anti-Inflammatory Activities of Egg White Proteins and Their Derived Peptides: A Review. J Agric Food Chem. 2022;70(1):5–20.
65. Jachak SM, Thakur MS, Ahirrao P, Goyal A. Murraya koenigii (L.) Spreng. as a Natural Intervention for Diabesity: A Review. Curr. Pharm. Des. 2024;30(41):3255–3275.
66. Koriem K. Antihyperglycemic, Antihyperlipidemic and Antiapoptotic Activities of *Micromelum minutum* Seeds in Diabetic Rats. J. Mol. Genet. Med. 2014;17(12):123-134.
67. Machado IF, Miranda RG, Dorta DJ, Rolo AP, Palmeira CM. Targeting Oxidative Stress with Polyphenols to Fight Liver Diseases. Antioxid. Basel Switz. 2023;12(6):1212.
68. Nwaji AR. Antihyperlipidemic property of *Murraya koenigii* ethanolic leaf extract on lipid profile of rats fed with cholesterol-enriched diets. Niger. J. Physiol. Sci. 2022;37(2):215–218.
69. Husna F, Suyatna FD, Arozal W, Poerwaningsih EH. Anti-Diabetic Potential of *Murraya koenigii* (L.) and its Antioxidant Capacity in Nicotinamide-Streptozotocin Induced Diabetic Rats. Drug Res. 2018;68(11):631–636.
70. Lin J, Li F, Jiao J, Qian Y, Xu M, Wang F, Sun X, Zhou T, Wu H, Kong X. Quercetin, a natural flavonoid, protects against hepatic ischemia-reperfusion injury via inhibiting Caspase-8/ASC dependent macrophage pyroptosis. J. Adv. Res. 2025;70:555–569.
71. Novrizal Abdi Sahid M, Nugroho AE, Susidarti RA, Maeyama K. Effects of 8-Hydroxyisocapnolactone-2-3-diol and friedelin on mast cell degranulation. Asian Pac. J. Trop. Med. 2017;10(11):1043–1046.
72. Yang H, George SJ, Thompson D, Silverman HA, Tsaava T, Tynan A, Pavlov VA, Chang E, Andersson U, Brines M, Chavan SS, Tracey KJ. Famotidine activates the vagus nerve inflammatory reflex to attenuate cytokine storm. Res. Sq. 2022;rs.3.rs-1493296.
73. Chandrashekhar VM, Halagali KS, Nidavani RB, Shalavadi MH, Biradar BS, Biswas D, Muchchandi IS. Anti-allergic activity of German chamomile (*Matricaria recutita* L.) in mast cell mediated allergy model. J. Ethnopharmacol. 2011;137(1):336–340.
74. Huang W, Huang X, Xing Z, Qiu X, Wang Y, Fan R, Liu W, Ren P, Liu Z, Zhou H. Meranzin hydrate induces similar effect to *Fructus aurantii* on intestinal motility through activation of H1 histamine receptors. J. Gastrointest. Surg. Tract. 2011;15(1):87–96.
75. Okuyama E, Nishimura S, Ohmori S, Ozaki Y, Satake M, Yamazaki M. Analgesic component of *Notopterygium incisum* Ting. Chem. Pharm. Bull. 1993;41(5):926–929.
76. Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Nicolaides DN. Natural and synthetic coumarin derivatives with anti-inflammatory/ antioxidant activities. Curr. Pharm. Des. 2004;10(30):3813–3833.
77. Thomas V, Giles D, Basavarajaswamy GPM, Das AK, Patel A. Coumarin Derivatives as Anti-inflammatory and Anticancer Agents. Anticancer Agents Med. Chem. 2017;17(3):415–423.
78. Seephonkai P, Kaewtong C, Wangchuk P, Jearawuttanakul K, Kanjanasirirat P, Borwornpinyo S, Khulmanee T, Patrapuvich R. Bioassay-Guided Isolation and Identification of Antiplasmodial Compounds from the Stem Bark of *Clausena excavata*. Planta Med. 2023;89(12):1165–1169.
79. Sripisut T, Laphookhieo S. Carbazole alkaloids from the stems of *Clausena excavata*. J. Asian Nat. Prod. Res. 2010;12(7):614–617.
80. Adia MM, Emami SN, Byamukama R, Faye I, Borg-Karlson AK. Antiplasmodial activity and phytochemical analysis of extracts from selected Ugandan medicinal plants. J. Ethnopharmacol. 2016;186:14–19.
81. Hu XL, Gao C, Xu Z, Liu ML, Feng LS, Zhang GD. Recent Development of Coumarin Derivatives as Potential Antiplasmodial and Antimalarial Agents. Curr. Top. Med. Chem. 2018;18(2):114–123.
82. Suarez-Kurtz G, Botton MR. Pharmacogenetics of coumarin anticoagulants in Brazilians. Expert. Opin. Drug Metab. Toxicol. 2015;11(1):67–79.
83. MacLeod SM, Sellers EM. Pharmacodynamic and pharmacokinetic drug interactions with coumarin anticoagulants. Drugs. 1976;11(6):461–470.
84. Sugatani J, Fukazawa N, Ujihara K, Yoshinari K, Abe I, Noguchi H, Miwa M. Tea polyphenols inhibit acetyl-CoA:1-alkyl-sn-glycero-3-phosphocholine acetyltransferase (a key enzyme in platelet-activating factor biosynthesis) and platelet-activating factor-induced platelet aggregation. Int. Arch. Allergy Immunol. 2004;134(1):17–28.
85. Ludovici V, Barthelmes J, Nagele MP, Flammer AJ, Sudano I. Polyphenols: Anti-Platelet Nutraceutical? Curr Pharm Des. 2018;24(2):146–157.
86. Nardini M, Natella F, Scaccini C. Role of dietary polyphenols in platelet aggregation. A review of the supplementation studies. Platelets. 2007;18(3):224–243.
87. Ito C, Itoigawa M, Katsuno S, Omura M, Tokuda H, Nishino H, Furukawa H. Chemical constituents of Clausena excavata: isolation and structure elucidation of novel furanone-coumarins with inhibitory effects for tumor-promotion. J. Nat. Prod. 2000;63(9):1218–1224.
88. Bhattacharya K, Bag AK, Tripathi R, Samanta SK, Pal BC, Shaha C, Mandal C. Mahanine, a novel mitochondrial complex-III inhibitor induces G0/G1 arrest through redox alteration-mediated DNA damage response and regresses glioblastoma multiforme. Am. J. Cancer Res. 2014;4(6):629–647.
89. Agarwal S, Amin KS, Jagadeesh S, Baishay G, Rao PG, Barua NC, Bhattacharya S, Banerjee PP. Mahanine restores RASSF1A expression by down-regulating DNMT1 and DNMT3B in prostate cancer cells. Mol. Cancer. 2013;12(1):99.
90. Ali H, Dixit S, Ali D, Alqahtani SM, Alkahtani S, Alarifi S. Isolation and evaluation of anticancer efficacy of stigmasterol in a mouse model of DMBA-induced skin carcinoma. Drug Des. Devel. Ther. 2015;9:2793–2800.
91. Sianipar NF, Hadisaputri YE, Assidqi K, Salam S, Yusuf M, Destiarani W, Purnamaningsih R, So IG, Takara K, Asikin Y. In silico and in vitro Characterizations of Rodent Tuber (*Typhonium flagelliforme*) Mutant Plant Isolates against FXR Receptor on MCF-7 Cells. J. Oleo Sci. 2024;73(10):1349–1360.
92. El-Shanawany MA, Sayed HM, Ibrahim SRM, Fayed M a. A. Stigmasterol Tetracosanoate, a New Stigmasterol Ester from the Egyptian Blepharis ciliaris. Drug Res. 2015;65(7):347–353.
93. Suthiwong J, Sriphana U, Thongsri Y, Promsuwan P, Prariyachatigul C, Yenjai C. Coumarinoids from the fruits of *Micromelum falcatum*. Fitoterapia. 2014;94:134–141.
94. Wang ZC, Feng DQ, Ke CH. Coumarins from the Herb Cnidium monnieri and chemically modified derivatives as antifoulants against *Balanus albicostatus* and *Bugula neritina* larvae. Int. J. Mol. Sci. 2013;14(1):1197–1206.
95. Sarker SD, Nahar L. Progress in the Chemistry of Naturally Occurring Coumarins. Prog. Chem. Org. Nat. Prod. 2017;106:241–304.
96. Ma C, Case RJ, Wang Y, Zhang HJ, Tan GT, Van Hung N, Cuong NM, Franzblau SG, Soejarto DD, Fong HH, Pauli GF. Anti-tuberculosis constituents from the stem bark of *Micromelum hirsutum*. Planta Med. 2005;71(3):261–267.
97. Fun HK, Siridechakorn I, Laphookhieo S, Chantrapromma S. Absolute configuration of micromelin. Acta Crystallogr. Sect. E. 2011;67(Pt 7):o1706-1707.
98. Suthiphasilp V, Maneerat T, Andersen RJ, Patrick BO, Pyne SG, Laphookhieo S. α-Glucosidase inhibitory activity of compounds isolated from the twig and leaf extracts of *Desmos dumosus*. Heliyon. 2021;7(2):e06180.
99. Lapa F da R, Gadotti VM, Missau FC, Pizzolatti MG, Marques MCA, Dafré AL, Farina M, Rodrigues ALS, Santos ARS. Antinociceptive properties of the hydroalcoholic extract and

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

the flavonoid rutin obtained from Polygala paniculata L. in mice. Basic Clin. Pharmacol. Toxicol. 2009;104(4):306–315.
100. Arango V, Robledo S, Séon-Méniel B, Figadère B, Cardona W, Sáez J, Otálvaro F. Coumarins from Galipea panamensis and Their Activity against *Leishmania panamensis*. J. Nat. Prod. 2010;73(5):1012–1014.
101. Kawaii S, Tomono Y, Ogawa K, Sugiura M, Yano M, Yoshizawa Y, Ito C, Furukawa H. Antiproliferative effect of leaves of *Murraya exotica* L. using supercritical fluid extraction combined with consecutive high-speed countercurrent chromatography. J. Sep. Sci. 2018;41(9):2092–2101.
104. Ming LG, Zhou J, Cheng GZ, Ma HP, Chen KM. Osthol, a coumarin isolated from common cnidium fruit, enhances the conditions for osthol, a melanogenesis inhibitor from *Cnidium monnieri* fruits. Pharm. Biol. 2016;54(8):1373–1379.
106. Lv X, Wang CY, Hou J, Zhang BJ, Deng S, Tian Y, Huang SS, Zhang HL, Shu XH, Zhen YH, Liu KX, Yao JH, Ma XC. Isolation and identification of metabolites of osthole in rats. Compd. Biol. Syst. 2012;42(11):1120–1127.
107. Long W, Wang M, Luo X, Huang G, Chen J. Murrangatin suppresses angiogenesis induced by tumor cell-derived media and inhibits AKT activation in zebrafish and endothelial cells. Drug Des. Devel. Ther. 2018;12:3107–3115.
108. You CX, Yang K, Wang CF, Zhang WJ, Wang Y, Han J, Fan L, Du SS, Geng ZF, Deng ZW. Cytotoxic compounds isolated from *Murraya tetramera* Huang. Mol Basel Switz. 2014;19(9):13225–1334.
109. Teshima N, Yamada H, Ju-ichi M, Uji T, Kinoshita T, Ito C. Coumarins from *Murraya paniculata* var. zollingeri endemic to the Timor Islands. Nat. Prod. Commun. 2015;10(2):309–312.
110. Negi N, Abou-Dough AM, Kurosawa M, Kitaji Y, Saito K, Ochi A, Ushijima K, Kusakabe E, Kitaguchi Y, Jinguji Y, Teshima N, Ju-ichi M, Ito C. Coumarins from *Murraya exotica* collected in Egypt. Nat. Prod. Commun. 2015;10(4):617–620.
111. Ito C, Itoigawa M, Furukawa H, Tokuda H, Okuda Y, Mukainaka T, Okuda M, Nishino H. Anti-tumor-promoting effects of 8-substituted 7-methoxycoumarins on Epstein-Barr virus activation assay. Cancer Lett. 1999;138(1–2):87–92.
112. Rodanant P, Khetkam P, Suksamrarn A, Kuvatanasuchati J. Coumarins and flavonoid from *Murraya paniculata* (L.) Jack: isopentenylated coumarins on several cancer cell lines. Anticancer Res. 2001;21(3B):1905–1911.
102. Huang S, Luo XM, Wang JH. [Study on the chemical constituents from ethyl acetate extract of *Micromelum falcatum*]. J. Chin. Med. Mater. 2013;36(5):744–746.
103. Yan R, Shen J, Liu X, Zou Y, Xu X. Preparative isolation and purification of hainanmurpanin, meranzin, and phebalosin from
differentiation and maturation of osteoblasts in vitro. Pharmacology. 2011;88(1–2):33–43.
105. Beom Kim S, Kim C, Liu Q, Hee Jo Y, Joo Choi H, Hwang BY, Kyum Kim S, Kyeong Lee M. Optimization of extraction

Antibacterial and anti-inflammation activity. Pak J Pharm Sci. 2015;28(6):1947–1951.
113. Saied S, Nizami SS, Anis I. Two new coumarins from *Murraya paniculata*. J Asian Nat Prod Res. 2008;10(5–6):515–9.
114. Chen KS, Wu CC, Chang FR, Chia YC, Chiang MY, Wang WY, Wu YC. Bioactive coumarins from the leaves of *Murraya omphalocarpa*. Planta Med. 2003;69(7):654–657.
115. Maruthanila VL, Elancheran R, Kunnumakkar AB, Kabilan S, Kotoky J. Pleiotropic Effect of Mahanine and Girinimbine Analogs: Anticancer Mechanism and its Therapeutic Versatility. Anticancer Agents Med. Chem. 2018;18(14):1983–1990.
116. Ghaderi MA, Emami SA, Beirak Olia MD, Javadi B. The Role of Sesamin in Targeting Neurodegenerative Disorders: A Systematic Review. Mini Rev. Med. Chem. 2023;23(6):756–770.
117. Antika LD, Tasfiyati AN, Hikmat H, Septama AW. Scopoletin: a review of its source, biosynthesis, methods of extraction, and pharmacological activities. Z. Naturforschung. C. J. Biosci. 2022;77(7–8):303–316.
118. Varamini P, Javidnia K, Soltani M, Mehdipour AR, Ghaderi A. Cytotoxic activity and cell cycle analysis of quinoline alkaloids isolated from *Haplophyllum canaliculatum* Boiss. Planta Med. 2009;75(14):1509–1516.