Chemical characterization and enzyme inhibitory properties of *Calophyllum wallichianum* Planch. & Triana essential oil

Nur Nabilah Mohd Zaini[1]
Wan Mohd Nuzul Hakimi Wan Salleh[1,2] ✉
Faezatul Alwani Mohd Rahim[1]
Abubakar Siddiq Salihu[1,3]
Nurunajah Ab Ghani[4,5]
Noor Amira Muhammad[1,6]
Farkhod Eshboev[7]
Alfred Ngenge Tamfu[8]

[1] Department of Chemistry, Faculty of Science and Mathematics, Universiti Pendidikan Sultan Idris, Tanjong Malim, Perak, Malaysia

[2] Center of Biodiversity and Conservation, Faculty of Science and Mathematics, Universiti Pendidikan Sultan Idris, Tanjong Malim, Perak, Malaysia

[3] Department of Pure and Industrial Chemistry, Faculty of Natural and Applied Sciences, Umaru Musa Yar'adua University, Katsina, Nigeria

[4] Atta-ur-Rahman Institute for Natural Product Discovery (AuRIns), Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam, Selangor, Malaysia

[5] Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Selangor, Malaysia

[6] Faculty of Applied Sciences, Universiti Teknologi MARA, Perak Branch, Tapah Campus, Tapah Road, Perak, Malaysia

[7] Institute for Advanced Studies, New Uzbekistan University, Tashkent, Uzbekistan

[8] Department of Chemical Engineering, School of Chemical Engineering and Mineral Industries, University of Ngaoundere, Ngaoundere, Cameroon

✉ CORRESPONDING AUTHOR
wmnhakimi@fsmt.upsi.edu.my
Phone: +605-450 7123

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This work reports the first study on the chemical composition and enzyme inhibitory activities of the essential oil obtained from the leaves of *Calophyllum wallichianum*. The essential oil was extracted by hydrodistillation and subsequently analysed using GC and GC–MS techniques. A total of 29 constituents were identified, representing 98.8% of the total oil composition. The oil was dominated by sesquiterpenes, with α-cadinol (22.3%) as the major component, followed by δ-cadinene (11.2%), epi-α-cadinol (10.7%), α-muurolene (6.5%), γ-muurolene (5.6%), ledol (5.4%), β-selinene (4.6%), and α-copaene (4.0%). The enzyme inhibitory potential of the essential oil was assessed through acetylcholinesterase inhibition using the Ellman assay, tyrosinase inhibition employing mushroom tyrosinase, and lipoxygenase inhibition assays. The oil exhibited notable inhibitory activity against all three enzymes, with IC50 values of 168.2 µg/mL for acetylcholinesterase, 183.9 µg/mL for tyrosinase, and 123.5 µg/mL for lipoxygenase. These results demonstrate that the sesquiterpene-rich essential oil of *C. wallichianum* possesses broad-spectrum enzyme inhibitory properties, supporting its potential relevance in neuroprotective, dermatoprotective, anti-inflammatory, and functional food-related applications, and warranting further pharmacological and mechanistic investigations.

Keywords: *Calophyllum wallichianum*; acetylcholinesterase; antityrosinase; lipoxygenase; α-cadinol

1. INTRODUCTION

The genus *Calophyllum* (Calophyllaceae) comprises more than 180 species of evergreen trees widely distributed throughout tropical and subtropical regions, particularly in Southeast Asia, the Pacific Islands, Africa, and parts of South America [1]. Many *Calophyllum* species are ecologically and economically important, being valued for their durable timber, ornamental qualities, and traditional medicinal uses. In ethnomedicine, different parts of these plants, including leaves, bark, seeds, and resins, have been used to treat inflammation, skin infections, wounds, ulcers, and microbial diseases [2]. Phytochemical investigations of the genus have revealed a remarkable diversity of secondary metabolites, notably xanthones, coumarins, flavonoids, chromanones, triterpenoids, and various phenolic compounds, many of which exhibit significant biological activities such as antimicrobial, antioxidant, anticancer, anti-inflammatory, and enzyme inhibitory effects [3-5]. Despite the extensive studies on non-volatile constituents, research on essential oils from *Calophyllum* species remains relatively limited, creating a valuable opportunity to explore their volatile profiles and bioactivities.

Calophyllum wallichianum, locally known as *'bintangor tulang'*, is a tall evergreen tree that can reach heights of up to 36 m and is characterized by slightly

curved terminal buds at the ends of its twigs. The species is valued for its strong and durable timber, which is widely used in construction and furniture manufacturing, reflecting its economic importance. It is naturally distributed across several parts of Southeast Asia, including Malaysia, Thailand, as well as the islands of Sulawesi and Sumatra [6]. A previous study on *C. wallichianum* has resulted in the isolation of coumarins [7] and chromanone acids [8]. Previous studies have shown that *C. wallichianum* exhibits larvicidal activity against *Aedes aegypti* and possesses antioxidant, antibacterial, cytotoxic, and anticancer activities [9,10].

Acetylcholinesterase (AChE), tyrosinase, and lipoxygenase are key enzymes involved in distinct yet interconnected biological pathways associated with neurodegeneration, skin pigmentation, inflammation, and oxidative stress. Acetylcholinesterase regulates cholinergic neurotransmission by hydrolyzing acetylcholine, and its excessive activity is closely linked to cognitive decline and neurodegenerative disorders such as Alzheimer's disease, making its inhibition a major therapeutic strategy for neuroprotection [11,12]. Tyrosinase is responsible for the rate-limiting steps in melanin biosynthesis, and its overactivation leads to hyperpigmentation disorders and enzymatic browning in foods, highlighting the importance of antityrosinase agents in cosmetic, pharmaceutical, and food industries [13,14]. Lipoxygenase catalyzes the oxidation of polyunsaturated fatty acids into pro-inflammatory mediators, playing a central role in inflammatory responses and oxidative damage. Targeting these three enzymes simultaneously represents a multifunctional approach to managing neurological disorders, skin-related conditions, and inflammatory diseases [15]. In this context, natural products, particularly essential oils, have emerged as promising sources of multitarget enzyme inhibitors due to their chemical diversity, favorable safety profiles, and broad spectrum of biological activities.

Essential oils are complex mixtures of volatile secondary metabolites, predominantly composed of terpenoids and their oxygenated derivatives, which are biosynthesized by aromatic plants as part of their defense and communication systems [16]. They have long been valued for their broad spectrum of biological activities, including antimicrobial, antioxidant, anti-inflammatory, and enzyme inhibitory properties. Owing to their lipophilic nature and chemical diversity, essential oils can interact effectively with multiple biological targets, making them attractive candidates for multitarget therapeutic and functional applications. In recent years, increasing attention has been directed toward sesquiterpene-rich essential oils because of their pronounced bioactivities and relatively low toxicity profiles [17-19].

Therefore, studies on the essential oil composition and enzyme inhibitory activities of *C. wallichianum* are scientifically justified and may lead to the discovery of new natural lead compounds with multifunctional biological properties. To the best of our knowledge, this study is the first to report the chemical composition and the inhibitory activities of the essential oil of *C. wallichianum* against AChE, tyrosinase, and lipoxygenase.

2. EXPERIMENTAL

2.1. PLANT MATERIAL

The fresh leaves of *C. wallichianum* were collected from Behrang, Perak in September 2022, and identified by a botanist, Shamsul Khamis from Universiti Kebangsaan Malaysia (UKM). The voucher specimen (BB-16/22) was deposited at the Herbarium of the Universiti Kebangsaan Malaysia Bangi (Herbarium UKM).

2.2. ISOLATION OF ESSENTIAL OIL

The fresh leaves of *C. wallichianum* (300 g) were chopped and subjected to hydrodistillation using a Clevenger-type apparatus for 4 h, following the method described earlier [20]. The essential oil obtained was dried over anhydrous magnesium sulfate, filtered, and stored in sealed brown glass vials at 0 °C until analysis.

2.3. ANALYSIS OF ESSENTIAL OIL

Gas chromatography (GC) analysis was performed on a Hewlett Packard 6890 series II A gas chromatograph (Hewlett-Packard, Palo Alto, CA, USA) equipped with an HP-5 column (30 m × 0.25 mm × 0.25 µm film thickness) (Agilent, Santa Clara, CA, USA). Helium was used as a carrier gas at a flow rate of 0.7 mL/min. Injector and detector temperatures were set at 250 and 280°C, respectively. The oven temperature was kept at 50°C, then gradually raised to 280°C at 5°C/min and finally held isothermally for 15 min. Diluted samples (1/100 in diethyl ether, v/v) of 1.0 µL were injected manually (split ratio 50:1). The injection was repeated 3 times and the peak area percentages were reported as mean ± standard deviation (SD) of triplicate measurements. The calculation of peak area percentage was carried out by using the GC HP Chemstation software (Agilent Technologies, Santa Clara, CA, USA).

Gas chromatography-mass spectrometry (GC-MS) chromatograms were recorded using a Hewlett Packard Model 5890A gas chromatograph and a Hewlett Packard Model 5989A mass spectrometer (Hewlett-Packard, Palo Alto, CA, USA). The GC was equipped with an HP-5 column. Helium was used as a carrier gas at a flow rate of 1 mL/min.

The injector temperature was 250°C. The oven temperature was programmed from 50°C (5 min hold) to 250°C at 10°C/min and finally held isothermally for 15 min. For GC-MS detection, an electron ionization system with an ionization energy of 70 eV was used. A scan rate of 0.5 s (cycle time: 0.2 s) was applied, covering a mass range from 50 to 400 amu.

2.4. IDENTIFICATION OF CHEMICAL COMPONENTS

For identification of essential oil components, co-injection with the selected standards (major components) was used, together with comparison of retention indices (RIs) and mass spectra with those reported in libraries and literature [21]. RIs were calculated using a homologous series of n-alkanes (C_8–C_{30}) under the same chromatographic conditions, according to the Kovats index method. Semi-quantification of essential oil components was made by peak area normalization considering the same response factor for all volatile components.

2.5. ACETYLCHOLINESTERASE INHIBITORY ACTIVITY

The AChE inhibitory activity of the essential oil was initially measured by slightly modifying the spectrophotometric method [12]. Electric eel AChE was utilized, with acetylthiocholine iodide serving as the reaction substrate, and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) employed for measuring anticholinesterase activity. Briefly, 140 µL of sodium phosphate buffer (pH 8.0), 20 µL of DTNB, 20 µL of essential oil (conc. of 62.5-1,000 µg/mL in EtOH) and 20 µL of AChE (0.22 U/mL) solution were added to a 96-well microplate and incubated for 15 min at 25°C. The reaction was then initiated by adding 10 µL of acetylthiocholine iodide. Hydrolysis of acetylthiocholine iodide was monitored by the formation of the yellow 5-thio-2-nitrobenzoate (TNB) anion as a result of the reaction of DTNB with thiocholines at 412 nm utilising a 96-well microplate reader (Epoch Micro-Volume Spectrophotometer, USA).

The percentage inhibition (I%) of AChE was determined by comparing the reaction rate of the test sample with that of the blank (EtOH in phosphate buffer, pH 8.0) using the following equation:

$$I\% = [E - S / E] \times 100;$$

where E is the activity of the enzyme without the test sample and S is the activity of the enzyme with the test sample. Analyses were expressed as mean ± SD of triplicates and galantamine at the same concentration as the essential oil was used as a positive control.

2.6. ANTI-TYROSINASE INHIBITORY ACTIVITY

The tyrosinase inhibition assay was performed according to the previous method with slight modifications [13]. Briefly, essential oil and kojic acid were dissolved in dimethyl sulfoxide (concentration of 1000, 500, 250, 125, and 62.5 ug/mL in EtOH). The reaction was carried out using a 96-well microplate, and a microplate reader (Epoch Micro-Volume Spectrophotometer, USA) was used to measure the absorbance at 475 nm. 40 µL of sample dissolved in DMSO with 80 µL of phosphate buffer (pH 6.8), 40 µL of tyrosinase enzyme and 40µL of L-Dopa were placed in each well. Each sample was accompanied by a blank that had all of the components except L-Dopa. Kojic acid was used as the reference standard inhibitor for comparison. The percentage of tyrosinase inhibition (I%) was calculated as follows:

$$I\% = [A_{control} - A_{sample} / A_{control}] \times 100;$$

where $A_{control}$ is the absorbance of the control reaction and A_{sample} is the absorbance of the oil/reference. Analyses were expressed as mean ± SD of triplicates.

2.7. LIPOXYGENASE INHIBITORY ACTIVITY

Lipoxygenase inhibition was evaluated using a spectrophotometric method based on linoleic acid oxidation, with a slight modification [15]. Briefly, 5 µL of essential oil solution (conc. of 62.5-1,000 µg/mL in EtOH) was mixed with 1.74 mL of borate buffer (0.2 M, pH 9.2) before being mixed with 5 µL of enzyme solution (50,000 U/mL) in borate buffer. The reaction was initiated by adding 250 µL of linoleic acid solution (5 mg of linoleic acid was mixed with 15 µL of ethanol, and then 15 mL of borate buffer was added via vigorous shaking). The increase in absorbance at 234 nm was recorded for 5 min in a spectrophotometer (Genesys 10S ultraviolet-visible, Thermo Scientific). The reaction mixture containing 5 µL of DMSO instead of the essential oil solution was used as a negative control. The percentage inhibition (I%) was then calculated using the following:

$$I\% = [A_{initial\ activity} - A_{inhibitor}/A_{initial\ activity}] \times 100;$$

where $A_{initial\ activity}$ is the absorbance of the control without the test sample, and $A_{inhibitor}$ is the absorbance of the test sample. Analyses were expressed as mean ± SD of triplicates, and quercetin at the same concentration as the essential oil was used as a positive control.

2.8. STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation (SD) of three independent experiments (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Differences were considered statistically significant at $p < 0.05$. The IC_{50} values were calculated from dose–response curves using nonlinear regression analysis.

3. RESULTS AND DISCUSSION

The essential oil obtained from the fresh leaves of *C. wallichianum* was obtained in a yield of 0.29% (w/w), with the moisture content of the plant material ranging between 86 and 98%. The identified constituents of the oil, arranged according to their Kovats retention indices on an HP-5 column, are presented in Table I. GC-FID and GC-MS analyses led to the identification of 29 compounds, accounting for about 98.8% of the total oil composition. The oil was dominated by sesquiterpene hydrocarbons (51.0%), followed closely by oxygenated sesquiterpenes (47.8%). The major constituents were α-cadinol (22.3%), δ-cadinene (11.2%), epi-α-cadinol (10.7%), α-muurolene (6.5%), γ-muurolene (5.6%), ledol (5.4%), β-selinene (4.6%), and α-copaene (4.0%). Comparative analysis with other *Calophyllum* species shows that β-caryophyllene is a major constituent in the essential oils of *C. inophyllum* [22,23] and *C. soulattri* [24], whereas the oil of *C. coriaceum* is dominated by β-selinene [20]. Notably, the present work represents the first report of α-cadinol as a dominant compound in the leaf essential oil of *C. wallichianum*, suggesting its potential application as a chemotaxonomic marker for this species. The observed variation in chemical profiles among *Calophyllum* species is likely influenced by several factors, including extraction methods, seasonal variation, plant maturity, and ecological conditions at the collection site. These parameters can significantly affect secondary metabolite biosynthesis, resulting in differences in both the qualitative and quantitative composition of essential oils [25].

The essential oil was initially evaluated for its inhibitory potential against AChE, tyrosinase, and lipoxygenase, as presented in Table II. The cholinesterase inhibitory activity was assessed using the AChE enzyme and compared with galantamine, a clinically approved drug for the management of Alzheimer's disease. The essential oil exhibited AChE inhibition with an IC_{50} value of 168.2 µg/mL. In contrast, galantamine showed markedly higher potency, with an IC_{50} value of 18.3 µg/mL. These findings are consistent with previous reports indicating that essential oils rich in sesquiterpenes generally exhibit weak to moderate cholinesterase inhibitory effects [26]. Furthermore, Karakaya et al. [27] demonstrated that increasing the proportion of sesquiterpenoids in *Salvia* essential oil was associated with a reduction in AChE inhibitory activity, suggesting that sesquiterpene dominance may limit strong cholinesterase inhibition.

The tyrosinase inhibitory activity of the essential oil was evaluated using L-DOPA as the substrate, with kojic acid serving as the positive reference standard. The essential oil exhibited notable inhibitory potency, with an IC_{50} value of 183.9 µg/mL, whereas kojic acid demonstrated much stronger activity with an IC_{50} value of 10.5 µg/mL. These results indicate that, although less active than the standard inhibitor, the essential oil possesses appreciable antityrosinase potential. Previous studies have reported that sesquiterpenes can contribute to tyrosinase inhibition through hydrophobic interactions with the enzyme and by interfering with substrate binding at the active site. In particular, oxygenated sesquiterpenes such as cadinol- and ledol-type components have been associated with moderate enzyme inhibitory properties [28,29]. Similar observations have been reported for several sesquiterpene-rich essential oils. For example, the essential oils of *Hedychium longicornutum* and *Neolitsea villosa*, which are rich in oxygenated sesquiterpenes including eudesmol and cadinol derivatives, exhibited measurable tyrosinase inhibitory activity [30].

In the lipoxygenase inhibition assay, the essential oil exhibited moderate inhibitory activity with an IC_{50} value of 123.5 µg/mL, which was comparable to that of quercetin (an IC_{50} value of 84.2 µg/mL). This activity is in agreement with the sesquiterpene-dominated nature of the oil. Oxygenated sesquiterpenes, including α-cadinol, epi-α-cadinol, α-eudesmol, γ-eudesmol, ledol, and spathulenol have been reported to attenuate lipoxygenase-related pathways by modulating arachidonic acid metabolism [31,32]. Likewise, sesquiterpene-dominated essential oils from *Piper* species and several members of the Lauraceae family have demonstrated moderate to strong inhibition of lipoxygenase, suggesting that sesquiterpene hydrocarbons and oxygenated sesquiterpenes play an important role in modulating this enzyme [33-35]. Furthermore, research has indicated that the main compound of the essential oil may not always contribute to its activity, and in some cases, minor components are responsible for the observed effects. Essential oils are complex mixtures of many compounds, most of which have not been extensively studied for their AChE, tyrosinase or lipoxygenase inhibitory activities, nor for their synergistic or antagonistic effects [36].

4. CONCLUSIONS

In conclusion, this study provides the first report on the chemical composition and enzyme inhibitory activities of the essential oil derived from the leaves of *C. wallichianum*. The oil was found to be rich in sesquiterpenes, with α-cadinol, δ-cadinene, and *epi*-α-cadinol as the dominant constituents, highlighting a distinct chemotypic profile that may serve as a useful chemotaxonomic marker for this species. The essential oil exhibited moderate but consistent inhibitory activities against acetylcholinesterase, tyrosinase, and lipoxygenase. Overall, these findings support the relevance of *C. wallichianum* essential oil as a promising natural

TABLE I - Chemical components of the leaves oil of *C. wallichianum*

No.	Components	KI[a]	KI[b]	Percentage (%)	Identification[c]
1	α-Copaene	1376	1374	4.0 ± 0.12	RI, MS, Std
2	β-Elemene	1390	1389	1.8 ± 0.05	RI, MS
3	α-Gurjunene	1409	1410	0.5 ± 0.02	RI, MS
4	β-Caryophyllene	1415	1417	1.0 ± 0.01	RI, MS
5	Aromadendrene	1440	1439	1.5 ± 0.02	RI, MS
6	α-Humulene	1452	1452	1.2 ± 0.13	RI, MS
7	*trans*-Cadina-1,4-diene	1460	1462	2.6 ± 0.02	RI, MS
8	*allo*-Aromadendrene	1460	1458	0.8 ± 0.04	RI, MS
9	γ-Gurjunene	1475	1475	0.4 ± 0.10	RI, MS
10	γ-Muurolene	1478	1476	5.6 ± 0.02	RI, MS, Std
11	α-Amorphene	1484	1483	0.2 ± 0.13	RI, MS
12	β-Maaliene	1485	1485	3.6 ± 0.02	RI, MS
13	Germacrene D	1485	1484	1.0 ± 0.15	RI, MS
14	β-Selinene	1490	1489	4.6 ± 0.02	RI, MS, Std
15	α-Selinene	1498	1499	3.1 ± 0.02	RI, MS
16	α-Muurolene	1499	1500	6.5 ± 0.04	RI, MS, Std
17	Bicyclogermacrene	1500	1502	0.4 ± 0.05	RI, MS
18	δ-Cadinene	1522	1522	11.2 ± 0.12	RI, MS, Std
19	Elemol	1548	1548	0.4 ± 0.10	RI, MS
20	Germacrene B	1560	1559	1.0 ± 0.03	RI, MS
21	Spathulenol	1577	1578	2.0 ± 0.03	RI, MS
22	Caryophyllene oxide	1583	1585	1.2 ± 0.11	RI, MS
23	Viridiflorol	1592	1592	0.6 ± 0.02	RI, MS
24	Ledol	1600	1602	5.4 ± 0.03	RI, MS, Std
25	10-*epi*-γ-Eudesmol	1625	1622	0.5 ± 0.04	RI, MS
26	γ-Eudesmol	1630	1630	2.2 ± 0.12	RI, MS
27	*epi*-α-Cadinol	1640	1638	10.7 ± 0.05	RI, MS, Std
28	α-Cadinol	1650	1652	22.3 ± 0.04	RI, MS, Std
29	α-Eudesmol	1652	1652	2.5 ± 0.02	RI, MS
Group components					
	Sesquiterpene hydrocarbons			51.0	
	Oxygenated sesquiterpenes			47.8	
	Total identified (%)			98.8	

[a]Linear retention index experimentally determined using homologous series of C_6-C_{30} alkanes.
[b]Linear retention index taken from Adams, Wiley or NIST08 and literature.
[c]Quantification was done by the external standard method using calibration curves generated by running GC analysis of representative authentic compounds; RI, based on comparison of calculated RI with those reported in Adams; MS, based on comparison with Wiley, Adams, FFNSC2, and NIST08 MS databases; Std, based on comparison with standard compounds.

TABLE II - Comparative enzyme inhibition of the essential oil and reference inhibitors

Activity	Percentage inhibition (%)*					IC_{50} (µg/mL)
	62.5 µg/mL	125 µg/mL	250 µg/mL	500 µg/mL	1000 µg/mL	
AChE	32.5 ± 0.05	42.5 ± 0.12	65.3 ± 0.04	75.2 ± 0.02	79.8 ± 0.03	168.2
Tyrosinase	25.2 ± 0.08	40.6 ± 0.12	61.2 ± 0.10	69.4 ± 0.02	85.2 ± 0.05	183.9
Lipoxygenase	31.5 ± 0.11	50.8 ± 0.05	70.5 ± 0.04	75.6 ± 0.08	89.3 ± 0.07	123.5
Standard	**Percentage inhibition (%)***					**IC_{50} (µg/mL)**
Galantamine	70.8 ± 0.06	83.5 ± 0.04	92.0 ± 0.15	96.5 ± 0.02	98.2 ± 0.08	18.3
Kojic acid	55.4 ± 0.15	70.2 ± 0.12	85.6 ± 0.02	92.4 ± 0.05	95.5 ± 0.05	47.1
Quercetin	52.0 ± 0.13	68.2 ± 0.11	83.5 ± 0.12	90.6 ± 0.14	90.8 ± 0.06	52.5

*Data are presented as mean ± standard deviation (SD) of three independent experiments (n = 3)

source of multitarget enzyme inhibitors with potential applications in anti-inflammatory, neuroprotective, dermatoprotective, and functional food-related fields. Further studies focusing on bioactivity-guided fractionation, mechanistic investigations, and in silico and in vivo evaluations are warranted to better elucidate its pharmacological potential and therapeutic relevance.

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