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Research Article

Unveiling the Chemical Composition and Enzyme Inhibitory Activities of *Cratoxylum cochinchinense* (Lour.) Blume (Hypericaceae) Essential Oil from Malaysia

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ABSTRACT

Cratoxylum cochinchinense (Lour.) Blume, a member of the Hypericaceae family, is a lesser-studied tropical plant traditionally used in Southeast Asian ethnomedicine. Despite its known traditional applications, scientific evidence on the chemical and pharmacological properties of its essential oil remains scarce. This study presents the first analysis of the essential oil derived from the leaves of *C. cochinchinense* collected in Malaysia, focusing on its chemical composition and enzyme inhibitory activities. The essential oil was extracted via hydrodistillation and subsequently analyzed using gas chromatography (GC-FID) and gas chromatography-mass spectrometry (GC-MS) techniques. A total of 41 volatile components were identified, representing 98.8% of the total oil content. The predominant components detected in the essential oil were β-caryophyllene (28.5%), α-humulene (10.2%), germacrene D (9.8%), guaiol (5.8%), and globulol (5.2%). To explore its therapeutic potential, the essential oil was evaluated for its inhibitory effects on acetylcholinesterase (AChE) and lipoxygenase (LOX) enzymes. The AChE inhibitory activity was measured using the Ellman method, showing a moderate inhibition percentage of 72.8%, while LOX inhibition was recorded at 74.5%, indicating promising anti-inflammatory potential. These findings suggest that the essential oil of *C. cochinchinense* could be a useful natural source for developing anti-inflammatory and related neurodegenerative therapeutics.

Keywords: Hypericaceae, *Cratoxylum cochinchinense*, essential oil, β-caryophyllene, acetylcholinesterase, lipoxygenase

1. INTRODUCTION

Enzymes play a critical role in maintaining physiological and biochemical processes, making them important targets in the treatment of various diseases. Among these, acetylcholinesterase (AChE) and enzymes involved in inflammatory pathways, such as lipoxygenase (LOX), have attracted significant attention due to their implications in neurological disorders and inflammation-related diseases, respectively (Robinson, 2015). Acetylcholinesterase is a key enzyme responsible for breaking down acetylcholine in the synaptic cleft, thus regulating cholinergic neurotransmission. The inhibition of AChE has been extensively studied as a therapeutic approach for managing neurodegenerative diseases such as Alzheimer's disease, where acetylcholine levels are markedly reduced. AChE inhibitors help to prolong the action of acetylcholine, thereby improving cognitive function and slowing disease progression (Walczak-Nowicka and Herbet, 2021). Inflammation is a biological response to injury or infection, but chronic inflammation is associated with various pathological conditions, including arthritis, cardiovascular diseases, and cancer. Enzymes like lipoxygenase play a pivotal role in the biosynthesis of inflammatory mediators such as leukotrienes. Inhibiting LOX can reduce the production of these pro-inflammatory compounds, offering a potential strategy for anti-inflammatory therapy (Chen et al., 2017).

Natural products, particularly essential oils, have emerged as promising sources of bioactive compounds with enzyme-inhibitory properties. The rich phytochemical diversity found in essential oils provides a valuable reservoir of molecules capable of targeting key enzymes such as acetylcholinesterase (AChE) and lipoxygenase (LOX). Exploring these natural enzyme inhibitors not only deepens our understanding of their therapeutic potential but also supports the discovery of novel agents for the management of neurodegenerative and inflammatory disorders (Salihu et al., 2023; Shakri et al., 2020;).

Essential oils are composed of complex mixtures of terpenes, phenolics, and other secondary metabolites, many of which exhibit significant inhibitory activity against AChE and LOX. This chemical complexity and structural variety provide opportunities to develop selective, potent, and safe enzyme inhibitors, making essential oils attractive candidates for further pharmaceutical development (Salleh, 2021). Furthermore, the natural origin of these compounds aligns with the increasing demand for plant-based therapeutics that offer improved safety profiles and fewer side effects compared to synthetic drugs. Thus, continued investigation into the enzyme-inhibitory potential of essential oils not only contributes to understanding their mechanisms of action, but also paves the way for the development of effective alternative or complementary therapies for treating neurological and inflammatory diseases (Salihu et al., 2024; Yahaya et al., 2022).

The genus *Cratoxylum* is a small genus of deciduous shrubs in the family Hypericaceae. It is widely distributed in Southeast Asia (Indonesia, China, Vietnam, Malaysia and Thailand) and China (Bok et al., 2023). Plants of this genus were consumed as a vegetable side dish, a spice, an ingredient in soup, or a substitute for tea, being traditionally appropriate for various diseases such as fever, cough, flu and diarrhea (Huong et al., 2023). The plant extracts and their isolated compounds (anthraquinones, flavonoids, benzophenones and triterpenoids) have established a widespread panel of biomedical values such as anticancer, antioxidant, antibacterial, antidiabetic, neuroprotective and hepatoprotective actions (Juanda et al., 2019).

Cratoxylum cochinchinense (Lour.) Blume locally known as 'derum selunchor' in Peninsular Malaysia, is a deciduous shrub to tree growing between 5-30 m height. Among the seven species of *Cratoxylum* in Malaysia, *C. cochinchinense* can be distinguished by the faint appearance of the lateral veins on the underside of the leaves (Wong, 1995). The leaf, stem, bark, root and resin of this species were used in traditional Chinese medicine to treat a variety of ailments, including jaundice, oedema, cough, itching, fever, diarrhoea, hoarseness,

diuretics, flu, colic, ulcer and dental conditions. Furthermore, the young leaf has been utilized as a herbal tea alternative and the immature fruit as a cooking spice (Jia et al., 2019). Phytochemical studies of this species had yielded triterpenoids, xanthones and phenolic compounds, which have been reported to possess significant pharmacological properties, including antioxidants, cytotoxic, antimalarial, antibacterial and anti-HIV activities (Dai et al., 2014). Recently, the essential oil from *C. formosum* has been reported to have potential to be developed as an antibacterial and antioxidant essential oil product (Hidayat et al., 2023).

Therefore, this study is the first to report the essential oil composition of *C. cochinchinense* from Malaysia, along with its enzyme inhibitory activities against acetylcholinesterase and lipoxygenase.

2. MATERIALS AND METHODS

2.1. Plant material and extraction of essential oil

The leaves of *C. cochinchinense* were collected from Gambang, Pahang in September 2019, and identified by Shamsul Khamis from UKM. The voucher specimen (SK04/18) was deposited at the Herbarium of UKM. The essential oil was obtained by hydrodistillation (4 h) of fresh leaves (300 g) using a Clevenger-type apparatus. The oil was dried over anhydrous magnesium sulfate and stored at 4-6°C. The oil yield (w/w) was 0.15% based on fresh leaves weight.

2.2. Analysis of essential oil

Gas chromatography (GC) analysis was performed on an Agilent Technologies 7890B equipped with DB-5 capillary column (30 m long, 0.25 µm thickness and 0.25 mm inner diameter). Helium was used as a carrier gas at a flow rate of 0.7 mL/min. Injector and detector temperature 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). Calculation of peak area percentage was carried out by using the GC HP Chemstation software (Agilent Technologies). Gas chromatography-mass spectrometry (GC-MS) chromatograms were recorded using an Agilent Technologies 7890A/5975C MSD equipped with HP-5MS fused silica capillary column (30 m long, 0.25 µm thickness and 0.25 mm inner diameter). Helium was used as carrier gas at a flow rate of 1 mL/min. 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 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 50-400 amu (Azhar et al., 2020). For identification of essential oil components, co-injection with the standards (major components) were used, together with correspondence of retention indices and mass spectra with respect to those occurring in ADAMS, NIST 08 and FFNSC2 libraries (Adams, 2007). Semi-quantification of essential oil components was made by peak area normalization considering the same response factor for all volatile components. Percentages values were the mean of three chromatographic analyses.

2.3. Acetylcholinesterase (AChE) inhibitory activity

The AChE inhibitory activity of the essential oil was initially measured by slightly modifying the spectrophotometric method (Salleh and Khamis, 2020). Electric eel AChE was

used, while acetylthiocholine iodide was employed as a substrate of the reaction, and DTNB acid was used for the measurement of the anticholinesterase activity. In brief, 140 µL of sodium phosphate buffer (pH 8.0), 20 µL of DTNB, 20 µL of essential oil, and 20 µL of AChE (0.22 U/mL) solution were added into a 96-well microplate and incubated for 15 min at 25 °C. The reaction was then initiated by adding 10 µL of acetylthiocholine iodide. The hydrolysis of acetylthiocholine iodide was monitored by the formation of the yellow 5-thio2-nitrobenzoate anion as a result of the reaction of DTNB with thiocholines at 412 nm using a 96-well microplate reader (Epoch Micro-Volume Spectrophotometer, USA). The percentage of inhibition (I%) of AChE was determined by comparing the reaction rates of the relative to the blank sample (EtOH in phosphate buffer pH 8) using the formula: I% = [E – S/E] × 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 means ± SD of the triplicates, and galantamine at the same concentration as essential oil was used as a positive control.

2.4. Lipoxygenase (LOX) inhibitory activity

LOX inhibition was performed following the method developed by Ellman with slight modification (Ghani et al., 2024). Briefly, 5 µL of essential oil solution was mixed with 1.74 mL of borate buffer (0.2 M, pH 9.2) before being mixing 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 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 equation: $I\% = [A_{initial\ activity} - A_{inhibitor} / A_{initial\ activity}] \times 100$; where $A_{initial\ activity}$ is the absorbance of control without the test sample, and $A_{inhibitor}$ is the absorbance of the test sample. Analyses were expressed as means ± SD of the triplicates, and quercetin at the same concentration as essential oil was used as a positive control.

2.5. Statistical analysis

Data obtained from biological activities were expressed as means ±SD and compared using the Student's t-test. Statistical analyses were carried out employing one-way ANOVA ($p<0.05$). A statistical package (SPSS version 11.0) was used for the data analysis.

3. RESULTS AND DISCUSSION

The chemical composition of the essential oil extracted from *C. cochinchinense* was thoroughly analyzed using gas chromatography (GC-FIS) and gas chromatography–mass spectrometry (GC-MS), leading to the identification of 41 components, which together accounted for 98.8% of the total oil content (Table 1). The essential oil was found to be rich in sesquiterpenes, primarily composed of sesquiterpene hydrocarbons (66.3%) and oxygenated sesquiterpenes (24.5%), indicating a chemically diverse profile. Among the identified compounds, β-caryophyllene (28.5%) was the most abundant, followed by α-humulene (10.2%), germacrene D (9.8%), guaiol (5.8%), and globulol (5.2%). In addition to these major components, several minor components present in amounts greater than 2.0% including α-amorphene (3.2%), bicyclogermacrene (3.0%), aromadendrene (2.8%), spathulenol (2.5%), caryophyllene oxide (2.5%), (*E*)-nerolidol (2.0%), and α-bisabolol (2.0%).

Table 1. Chemical components identified from *C. cochinchinense* essential oil

No	Components	KI[a]	KI[b]	Percentage (%)	Identification
1	α-Pinene	940	942	1.2	RI, MS, Std
2	β-Pinene	980	985	1.2	RI, MS, Std
3	α-Phellandrene	1005	1005	0.4	RI, MS
4	α-Terpinene	1014	1012	0.2	RI, MS
5	o-Cymene	1022	1020	0.2	RI, MS
6	Limonene	1025	1025	1.5	RI, MS, Std
7	β-Phellandrene	1032	1030	1.8	RI, MS
8	γ-Terpinene	1062	1062	0.5	RI, MS
9	Linalool	1095	1095	0.6	RI, MS
10	Terpinen-4-ol	1174	1175	0.2	RI, MS
11	α-Copaene	1374	1375	0.5	RI, MS
12	β-Elemene	1380	1380	1.2	RI, MS, Std
13	β-Bourbonene	1384	1382	0.8	RI, MS
14	β-Cubebene	1385	1385	0.2	RI, MS
15	α-Gurjunene	1405	1405	1.3	RI, MS
16	α-Cedrene	1410	1412	0.2	RI, MS
17	**β-Caryophyllene**	1425	1420	**28.5**	RI, MS, Std
18	Aromadendrene	1442	1442	2.8	RI, MS
19	**α-Humulene**	1455	1456	**10.2**	RI, MS, Std
20	**Germacrene D**	1485	1482	**9.8**	RI, MS, Std
21	Cadina-1,4-diene	1486	1485	0.2	RI, MS
22	α-Amorphene	1487	1488	3.2	RI, MS
23	β-Selinene	1488	1490	0.5	RI, MS
24	Bicyclogermacrene	1502	1500	3.0	RI, MS
25	Germacrene A	1509	1510	0.5	RI, MS
26	δ-Cadinene	1524	1520	1.6	RI, MS
27	*cis*-Calamenene	1525	1526	0.3	RI, MS
28	α-Calacorene	1545	1545	0.4	RI, MS
29	Selina-3,7(11)-diene	1548	1550	0.2	RI, MS
30	Germacrene B	1560	1560	0.9	RI, MS
31	(*E*)-Nerolidol	1565	1568	2.0	RI, MS
32	Spathulenol	1575	1575	2.5	RI, MS, Std
33	Caryophyllene oxide	1580	1582	2.5	RI, MS
34	Aromadendrene epoxide	1582	1585	0.5	RI, MS
35	**Globulol**	1592	1590	**5.2**	RI, MS, Std
36	**Guaiol**	1595	1595	**5.8**	RI, MS, Std
37	Ledol	1598	1596	0.3	RI, MS
38	α-Cadinol	1649	1650	1.8	RI, MS
39	β-Eudesmol	1650	1652	1.9	RI, MS
40	α-Bisabolol	1685	1686	2.0	RI, MS
41	Phytol	1942	1945	0.2	RI, MS
	Monoterpene hydrocarbons			7.0	
	Oxygenated monoterpene			0.8	
	Sesquiterpene hydrocarbons			66.3	
	Oxygenated sesquiterpenes			24.5	
	Others			0.2	
Total identified				**98.8**	

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; [a]Linear retention index experimentally determined using homologous series of C6-C30 alkanes; [b]Linear retention index taken from Adams, Wiley or NIST08 and literature

The high content of β-caryophyllene is consistent with previous reports on *C. cochinchinense* from Vietnam (Dai et al., 2014), suggesting that this compound may serve as a potential chemotaxonomic marker for the *Cratoxylum* genus. Such consistency across species and regions reinforces the significance of β-caryophyllene in distinguishing essential oil profiles within this group of plants. Furthermore, variations observed in the essential oil composition due to factors such as geographical origin, climate, soil conditions, and harvesting period point to the critical role of environmental and genetic influences on the plant's secondary metabolism. These differences not only affect the yield and chemical diversity of the essential oil but also have implications for its biological activities and potential applications in medicine, aromatherapy, and natural product research (Kadir and Salleh, 2022; Azhar and Salleh, 2020).

The essential oil was evaluated for its inhibitory effects on two clinically significant enzymes acetylcholinesterase (AChE) and lipoxygenase (LOX) both of which are associated with the pathophysiology of neurodegenerative and inflammatory disorders, respectively. The dual inhibitory activity observed highlights the potential of the essential oil as a source of multifunctional bioactive compounds, offering therapeutic promise in managing complex diseases that involve oxidative stress and inflammation.

AChE plays a pivotal role in the regulation of cholinergic neurotransmission by hydrolyzing the neurotransmitter acetylcholine. In the context of Alzheimer's disease, characterized by cholinergic deficits, AChE inhibitors are employed to increase synaptic acetylcholine levels, thereby improving memory and cognitive functions (Salleh and Ahmad, 2016). In this study, the essential oil exhibited moderate AChE inhibitory activity, with 72.8% inhibition at 1,000 µg/mL, compared to 95.9% inhibition by galantamine, a standard therapeutic agent. While not as potent, the essential oil's significant activity suggests the presence of cholinesterase-inhibiting constituents. Previous research has indicated that β-caryophyllene, a sesquiterpene hydrocarbon commonly found in essential oils, possesses notable cholinesterase inhibitory properties (Orhan et al., 2004). The high content of β-caryophyllene in the tested oil may therefore contribute substantially to the observed AChE inhibition. However, it is important to consider that essential oils are complex mixtures of various volatile compounds, and their bioactivity often results from the synergistic or antagonistic interactions between these components. As highlighted by de Sousa et al. (2023), such interactions can either enhance or diminish the net pharmacological effects, thus emphasizing the need for further fractionation and mechanistic studies to identify the most active constituents and their interactions.

In parallel, the essential oil also demonstrated moderate inhibitory activity against LOX, a key enzyme in the biosynthesis of leukotrienes and reactive oxygen species (ROS) from arachidonic acid. These mediators play critical roles in initiating and sustaining inflammatory responses, as well as promoting oxidative damage associated with skin disorders, cancer progression, and chronic inflammation (Dey et al., 2022). The essential oil showed 74.5% LOX inhibition, relative to 90.8% inhibition by quercetin, a flavonoid with well-established anti-inflammatory and antioxidant properties. Similar to its role in AChE inhibition, β-caryophyllene may also be a major contributor to LOX inhibition. The compound has been documented for its anti-inflammatory potential, particularly through its interaction with cannabinoid receptor type-2 (CB2), which modulates immune responses without psychoactivity (Jha et al., 2021). The presence of β-caryophyllene, along with other sesquiterpenes commonly found in essential oils such as those from *Syzygium aromaticum*, *Cannabis sativa*, *Rosmarinus officinalis*, and *Tagetes minuta*, likely underpins the oil's LOX inhibitory effect (Baylac and Racine, 2003; Ghiasvand et al., 2011).

4. CONCLUSION

This study provides the first report on the essential oil composition and enzyme inhibition of *C. cochinchinense* grown in Malaysia. The analysis revealed that sesquiterpenes, particularly β-caryophyllene, dominate the essential oil's chemical profile. Given the reported enzyme inhibitory activities, the essential oil shows potential for use in aromatherapy for patients with Alzheimer's dementia or inflammatory diseases, either to enhance oxidative status or as an adjunct to conventional therapies. However, further research is needed to identify the specific distribution of aromatic compounds and their receptor interactions to better understand their mechanisms of action. Future studies should include in vivo experiments, pharmacokinetic, and bioavailability studies to establish a comprehensive understanding of the essential oil's pharmacological potential.

Conflict of Interest
The authors declare no conflicts of interest.

Author Contribution Statement
Nurunajah Ab Ghani, Noraini Kasim and Hazimin Safiq Mohd Mahsop: Conceptualization, investigation and writing original draft. Mohd Hafiz Arzmi, Mohd Shafiq Aazmi, Faezatul Alwani Mohd Rahim, Nur Nabilah Mohd Zaini, Syarifah Nadhirah Wan Idrus and Norazrina Md Ramin: Methodology and formal analysis. Nurunajah Ab Ghani: Review, editing, and supervision.

Data Availability Statement
The authors confirm that the data supporting the findings of this study are available within the article.

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