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***Special dedication of this grateful feeling to**;*

Whom I love and those who love me

This humble work is a sign of my love to all of you

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ABSTRACT

The purpose of this study was to investigate the essential oils, phytochemicals, and biological activities of *Lindera subumbellifora* and *Lindera caesia* (Lauraceae). The essential oils were obtained from the leaves part using hydrodistillation technique and their chemical compositions were determined using gas chromatography (GC-FID) and gas chromatography-mass spectrometry (GC-MS) methods. Cold extraction of the leaves and roots of *L. subumbellifora* was employed followed by isolation of phytochemicals using gravity column chromatography techniques. The chemical structures of phytochemicals were confirmed by comparison with literature and spectroscopic data. The antioxidant and antibiofilm activities were investigated using DPPH free radical scavenging and semi-quantitative static biofilm assay, respectively. A total of 28 components (99.6%) were successfully identified from the leaf oil of *L. subumbelliflora* which mainly consisted of β-eudesmol (14.6%), *cis*-α-bergamotene (11.0%), α-copaene (8.5%), dodecen-1-ol (8.5%), and (*E*)-nerolidol (8.3%). Meanwhile, the leaf oil of *L. caesia* constituted a total of 39 components (96.7%), dominated by terpinen-4-ol (26.3%), *neo*-intermedeol (23.2%), and eudesma-4,11-dien-3-one (10.4%). Isolation studies on the leaves and roots extracts of *L. subumbelliflora* had yielded 5,6-dehydrokawain, pinostrobin, β-sitosterol, pinocembrin, 4-hydroxy-3-methoxyacetophenone, ferulic acid, quercetin, and syringic acid. In antioxidant activity, the methanolic root extract of *L. subumbelliflora* and quercetin displayed significant activity with IC_{50} values of 77.4 and 55.2 µg/mL, respectively. In antibiofilm activity, the methanolic root extract of *L. subumbelliflora* displayed substantial inhibitory activity against *Streptococcus mutans* (99.2%) and *Candida albicans* (49.2%), while quercetin showed highly effective inhibitory activity against *Streptococcus mutans* (98.4%). In conclusion, the essential oils of *L. subumbellifora* and *L. caesia* contain sesquiterpene hydrocarbons and oxygenated sesquiterpenes as principal components, respectively. Meanwhile, the isolation study of *L. subumbellifora* extracts led to discovery of dihydrochalcones, steroid, phenolics, and flavonol. These findings suggest the potential applications of *Lindera* species in preventing oral biofilm formation and their therapeutic potential in drug development.

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FITOKIMIA DAN AKTIVITI BIOLOGI DARIPADA *Lindera subumbelliflora* Kosterm. DAN *Lindera caesia* Reinw. ex Fern.-Vill

ABSTRAK

Tujuan kajian ini adalah untuk mengkaji minyak pati, fitokimia, dan aktiviti biologi *Lindera subumbellifora* dan *Lindera caesia* (Lauraceae). Minyak pati diperolehi daripada bahagian daun menggunakan teknik penyulingan hidro dan komposisi kimianya ditentukan dengan menggunakan kaedah kromatografi gas (GC-FID) dan kromatografi gas-spektrometri jisim (GC-MS). Pengekstrakan sejuk daun dan akar *L. subumbellifora* digunakan diikuti dengan pengasingan fitokimia menggunakan teknik kromatografi lajur graviti. Struktur kimia fitokimia telah disahkan dengan perbandingan antara literatur dan data spektroskopi. Aktiviti antioksidan dan antibiofilem telah disiasat masing-masing menggunakan penghapusan radikal bebas (DPPH) dan ujian biofilem statik separa-kuantitatif. Sebanyak 28 komponen kimia (99.6%) berjaya dikenalpasti daripada minyak daun *L. subumbelliflora* yang kandungan utamanya terdiri daripada β-eudesmol (14.6%), *cis*-α-bergamoten (11.0%), α-kopaen (8.5%), dodecen-1-ol (8.5%), dan (*E*)-nerolidol (8.3%). Manakala minyak daun *L. caesia* terdiri daripada 39 komponen (96.7%), didominasi oleh terpinen-4-ol (26.3%), *neo*-intermedeol (23.2%), dan eudesma-4,11-dien-3-on (10.4%). Kajian pengasingan terhadap ekstrak daun dan akar *L. subumbelliflora* telah menghasilkan 5,6-dihidrokawain, pinostrobin, β-sitosterol, pinocembrin, 4-hidroksi-3-metoksiasetofenon, asid ferulik, kuersetin, dan asid siringik. Dalam aktiviti antioksidan, ekstrak akar metanol *L. subumbelliflora* dan kuersetin menunjukkan aktiviti ketara dengan nilai IC_{50} masing-masing 77.4 dan 55.2 µg/mL. Dalam aktiviti antibiofilm, ekstrak akar metanol *L. subumbelliflora* menunjukkan aktiviti perencatan yang besar terhadap *Streptococcus mutans* (99.2%) dan *Candida albicans* (49.2%), manakala kuersetin menunjukkan aktiviti perencatan yang berkesan terhadap *Streptococcus mutans* (98.4%). Kesimpulannya, minyak pati *L. subumbellifora* dan *L. caesia* masing-masing mengandungi hidrokarbon seskuiterpena dan seskuiterpena beroksigen sebagai komponen utama. Sementara itu, kajian pengasingan ekstrak *L. subumbellifora* membawa kepada penemuan dihidrokalkon, steroid, fenolik, dan flavonol. Penemuan ini mencadangkan potensi spesies *Lindera* dalam mencegah pembentukan biofilem oral dan terapeutik dalam pembangunan ubat.

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LIST OF ABBREVIATIONS

α	Alpha
Abs	Absorbance
β	Beta
^{13}C	Carbon-13
CC	Column Chromatography
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
cm^{-1}	Per centimetre
COSY	Correlation spectroscopy
1D	1 Dimension
2D	2 Dimension
δ	Chemical shift
d	doublet
DCM	Dichloromethane
dd	doublet of doublets
DEPT	Distortionless Enhancement by Polarization Transfer
EIMS	Electron Impact Mass Spectrometry
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry

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GC-FID	Gas Chromatography-Flame Ionisation Detector
^{1}H	Proton
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infrared
J	Coupling constant
KBr	Potassium bromide
KI	Kovats Index
L	Liter
m	multiplet
M^{+}	Molecular ion
MeOH	Methanol
MHz	Megahertz
min	Minute(s)
m/z	Mass to charge ion
mg	milligram
$MgSO_4$	Magnesium sulphate
mL	milliliter
mm	millimeter
MS	Mass Spectrometer
NaCl	Sodium chloride
NMR	Nuclear Magnetic Resonance

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nm	nanometer
s	singlet
SiO_2	Silica gel
t	triplet
TLC	Thin Layer Chromatography
PTLC	Preparative Thin Layer Chromatography

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

Since the beginning, ancient medical knowledge has been transferred and maintained in every corner of this civilised globe. Almost all early discoveries in medicine came from the field of herbs and natural remedies. Because at the time there was not sufficient information either concerning the reasons for the illnesses or concerning which plant and how it could be utilized as a cure, everything was based on experience. In time, the reasons for the usage of specific medicinal plants for the treatment of certain diseases were being discovered; thus, the medicinal plants' usage gradually abandoned the empiric framework and became founded on explicatory facts (Petrovska, 2012).

Natural products are produced by the living organism through biosynthesis mechanisms (Zhou et al., 2021). Certain illnesses are typically treated by medicinal

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plants, which also serve as a possible source for pharmaceuticals. In the past, natural compounds and their structural analogues have significantly influenced pharmacology, particularly for the treatment of cancer and infectious disorders. Nowadays, natural products have undergone a million years of evolution and chemical diversification, which has led to a variety of biological activities and drug-like qualities (Maria & Christoph, 2020).

Malaysia boasts a vast array of plant species and famed in the ancient medical tradition. There is a wide variety of medicinal plants in Malaysia that are used to create potent nutritional, folk medicine, and aesthetic preparations. The most common traditional Malaysian medicinal plants are *Aloe vera* (lidah buaya), *Andrographis paniculata* (hempedu bumi), *Eurycoma longifolia* (tongkat ali), *Labisia pumila* (kacip fatimah), *Ficus deltoidea* (mas cotek), *Cymbopogon nardus* (serai wangi), *Centella asiatica* (pegaga), *Melastoma malabathricum* (senduduk), *Morinda citrifolia* (mengkudu), *Phyllanthus niruri* (dukung anak), *Momordica charantia* (peria), *Orthosiphon stamineus* (misai kucing), and *Piper sarmentosum* (kaduk) (Abu Bakar et al., 2018).

According to earlier research, the presence of specific phytochemicals in a variety of Malaysian plants has proven to be an effective treatment for a better quality of life. For instance, eupatorin and sinensetin isolated from *Orthosiphon stamineus* have anti-inflammatory properties, which may be utilized in the development of novel anti-inflammatory treatments (Laavola et al., 2012). Besides, curcumin found in *Curcuma longa* roots can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia (Giordano & Tommonaro,

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2019). Meanwhile, the roots of *Panax ginseng* contain ginsenosides which show effects on diabetes, fatigue, pulmonary problems, dyspepsia, vomiting, and ulcers (Kang & Min, 2012). Furthermore, *Centella asiatica* leaf contains active ingredients, kaempferol and quercetin that are able to treat skin damage and improve blood circulation (Gray et al., 2018). In addition, *Marinda citrifolia* is having the active compounds, scopoletin and rutin, which can act as antioxidant, anticancer, and anti-inflammatory agents (Jamaludin et al., 2021).

Many species of ethnobotanical plants still need to be thoroughly studied in order to serve as a source for prospective pharmaceuticals. For now, many scientists are attempting to identify more plants which have medicinal values and have the potential to be commercialized as herbal medicines. Hence, additional research should be conducted on different plant species, particularly those that have medicinal value for usage as herbal treatments. Lauraceae is one of the plant families which are believed to have high medicinal value due to its wide use in many traditional medicines.

1.2 Problem Statement

Plants from the family Lauraceae showed potential medicinal applications due to their wide range of phytochemicals and biological characteristics that have been reported previously. *Lindera* is a genus of flowering plants in the family Lauraceae that have shown an extensive range of phytochemicals and biological features of Lauraceae plants, and they tend to be of great importance. Earlier, phytochemical studies of *Lindera* species had successfully yielded sesquiterpenoids, alkaloids, butanolides,

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lucidones, flavonoids, and phenylpropanoids. These phytochemicals have shown a variety of pharmacological and biological characteristics including anticancer, antihypertensive, anti-inflammatory, and analgesic properties. Nevertheless, several Malaysian *Lindera* species have not been properly investigated, both chemically and physiologically.

To the best of our knowledge, this is the first study reporting on the essential oils composition of *L. subumbelliflora* and *L. caesia*, as well as the phytochemistry and their biological activities. In view of the difficulty of treating infections caused by *Staphylococcus aureus* and *Candida albicans* which produces biofilms, the need for novel and effective therapies is urgent. For this reason, the development of novel therapeutic strategies, such as the use of medicinal plants with antioxidant or antimicrobial activity with a focus on inhibition or eradication of biofilm, is of great interest. This study aims to fill this gap by investigating the antioxidant and antibiofilm properties of *Lindera* species, thereby introducing a novel approach to combating dental biofilms and improving oral health. Hence, these efforts will enable a comprehensive exploration of its pharmacological importance and potential applications in drug discovery.

1.3 Objectives of Study

1. To investigate the chemical composition of the essential oil from the leaves of *L. subumbelliflora* and *L. caesia* using gas chromatography (GC-FID) and gas chromatography-mass spectrometry (GC-MS).

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2. To isolate the phytochemicals from the leaves and roots extracts of *L. subumbelliflora* using various chromatography techniques and characterized using spectroscopy methods (IR, MS, and NMR).
3. To determine the antioxidant and antibiofilm potential of the essential oils, crude extracts, and isolated phytochemicals.

1.4 Scopes of Study

The study was divided into three parts. The first part was the extraction of the essential oils by hydrodistillation method from the leaf part of *L. subumbelliflora* and *L. caesia.* The chemical compositions of the essential oils were analysed using GC-FID, GC-MS, and Kovats Indices. The second part was the isolation of the phytochemicals from the leaves and root extracts of *L. subumbelliflora* using various chromatographic methods such as column chromatography. The structures of the isolated phytochemicals were analysed spectroscopically using IR, NMR (1D and 2D), and MS. Finally, the antioxidant and antibiofilm activities of the essential oils, crude extracts, and selected phytochemicals were investigated using DPPH radical scavenging and semi-quantitative static biofilm, respectively.

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CHAPTER 2

LITERATURE REVIEW

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2.1 Botany of the Genus *Lindera*

Lauraceae, belongs to the Magnoliidae subclass, is a family of pantropical plants that includes trees and shrubs. It consists of about 45 genera and about 2500 species. The family is highly diversified in Southeast Asia, Madagascar, northern South America and the Eastern Brazil. In addition, it is also the most abundant in forests at intermediate altitudes in the Andes and Southeast Asia (Cao et al., 2016).

In Malaysia, it is known as '*medang'* and contributes about 213 species from 16 genera. Besides, there are 25 genera and 445 species in China altogether distributed over the low and moderate altitude ranges from the Southwest to the south. The genera *Sinosassafras* and *Sinopora* are two of them that are native to China, while *Laurus* and *Persea* are the genera that are commercially grown (Feng et al., 2022).

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The specific floral morphology of the Lauraceae family can be used to identify it. The bark has many lenticels and smooth leather. After being cut, the inner bark emits sap that ranges from pale yellow to pale brown. The leaves are plain, stipule-free, opposite, spiral, whorled, and alternate. The flowers are bisexual, actinomorphic, tiny, aromatic, and trimerous. Most of the flowers in greenish-white, or yellow colour that have six sepals arranged in two cycles. The fruits, usually in baccate or drupaceous and frequently seated or surrounded by a persistent and cup-shaped corolla. Many tropical species in the Lauraceae family have persistent leaves, which stay on the plant even when they are no longer useful (Feng et al., 2022).

The Lauraceae family holds significant economic value, providing essential sources of spices, perfume oils, and medicines. Many species within this family are widely used in traditional medicine such as the leaves of *Laurus nobilis* (bay laurel), have been used to treat digestive disorders (Alejo Armijo et al., 2017), while the bark of *Cinnamomum verum* (cinnamon tree) has been used to treat respiratory infections and digestive problems (Ranasinghe et al., 2013). Additionally, the essential oil extracted from the fruit of *Persea americana* (avocado tree), has been used topically to treat skin conditions (Nayak et al., 2008). In addition, the majority of Lauraceae family are used to make timber for export as they are suited for making plywood and decorative projects. Many species barks offer marketable qualities such as cinnamon (Chen et al., 2017).

Lindera is a genus of about 80-100 species of flowering plants in the family Lauraceae. According to Zhang et al. (2023), there are about 3 subgenera in the *Lindera* genus, which are *Lindera*, *Neolindera*, and *Parabenzoin*. Besides, there are over 100

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species in the genus *Lindera* which can be found all over the world in tropical, subtropical climates, and temperate zones of Asia and Midwestern America. The most widespread *Lindera* species are *L. aggregata*, *L. erythrocarpa*, *L. akoensis*, *L. umbellata, L. angustifolia*, *L. chunii merr*, *L. communis*, *L. fragrans*, *L. glauca*, *L. melissifolia*, *L. nacusua*, *L. neesiana*, *L. obtusiloba*, *L. pipericarpa*, *L. pulcherrima*, *L. radix*, and *L. strychnifolia*, and. They are native in China, Korea, Japan and India, United State, Nepal, Vietnam and Malaysia (Cao et al., 2016).

Lindera species possess a few similar traits in general. *Lindera* trees have aromatic leaves and bark, which are frequently used in traditional medicine and as a culinary spice. These aromatic leaves and bark are also frequently used in aromatherapy. Besides, *Lindera* species are dioecious, where the male and female flowers grow on separate plants. The flowers are small and inconspicuous, it also has six tepals arranged in a star configuration. The fruit is a tiny drupe that has just one seed (Nakamura et al., 2021).

Lindera species are great for ornamental and economical use, as well as for their medicinal and therapeutic benefits. Most of *Lindera* species have been used as medicine to treat a wide range of conditions, such as gastrointestinal disorders, respiratory infections, and menstrual cramps. For example, *L. radix* is a well-known species in Chinese culture, where the roots can be used to tonifying the kidneys by promoting qi circulation to lessen discomfort and relieve congestion (Cao et al., 2016). In addition, *L. aggregata* has been used in traditional Chinese medicine to treat several conditions, such as pain, inflammation, and gastrointestinal problems (Lai et al., 2021). Overall, the medicinal uses of various *Lindera* species are listed in Table 2.1.

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Table 2.1

Medicinal uses of several Lindera species

Species	Part	Medicinal Uses
L. aggregata	Leaves	Used as nutritional supplements to prevent liver damage and decrease cholesterol as well as effective to stop the infection caused by SARS-CoV (Lv et al., 2023)
	Roots	Used to treat rheumatic, cardiac, and renal illnesses, as well as to treat conditions affecting the digestive system, metabolism, inflammation, and urinary system (Cao et al., 2016)
L. akoensis	Aerial	Used in Taiwanese folk therapy for inflammation (Yang et al., 2019)
	Leaves	Used to treat stomach pain, fever, respiratory infections, headaches, migraines, and reduced inflammation or swelling (Yang et al., 2019)
L. angustifolia	Roots	Used in the south and middle of China to relieve swelling caused by contusions, rheumatic pain, and stomach aches (Zhao et al., 2006)
	Flower	Used to treat carminative diuretics and pain relievers especially in nervous headache and migraine (Leung & Foster 1996)
	Leaves	Used to treat diarrhea and other gastrointestinal issues (Zhao et al., 2006)

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Table 2.1 *(continue)*

Species	Part	Medicinal Uses
L. erythrocarpa	Fruit	To treat indigestion in folk medicine (Wang et al., 2007)
	Bark	Used to treat diabetic properties and breast cancer (Wang et al., 2007)
	Leaves	Used to treat multiple cardioprotective and cancerous disorders as well as for treating digestive disorders, thirst, pain, and neuralgia (Patel, 2021)
L. fragrans	Leaves	To treat the depressive-like behaviours that prolonged mild stress caused as well as acts as an effective barrier that prohibits mosquitoes (*A. stephensi* and *A. aegypti*) from biting (Du et al., 2020)
	Leaves	Used to treat bad breath (Du et al., 2020)
	Leaves	Used to treat rheumatic numbness and low back pain (Wang et al., 2023)
L. pulcherrima	Bark	Used as spice for the remedy of cold, fever, and cough (Joshi & Mathela, 2012)
	Flower	Used to treat intestinal worms and cure sores (Joshi & Mathela, 2012)
	Leaves	Used to treat fever as it may have purgative properties (Joshi & Mathela, 2012)
L. radix	Leaves	Used in pelvic inflammatory disease (Zou et al., 2021)

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Table 2.1 *(continue)*

Species	Part	Medicinal Uses
L. glauca	Leaves	Used for detoxification and hemostasis (Sun et al., 2023)
	Fruits	Used to treat rheumatoid arthritis, extravasation, and contusion (Sun et al., 2023)
	Fruits	Used to treat several kinds of stomach and heart discomfort problems (Sun et al., 2023)
L. neesiana	Roots	To treat indigestion, gastric disorders, constipation, and intestinal issues as well as diabetes mellitus and intestinal parasitic worms like round and tape worms (Khakurel et al., 2022)
L. obtusiloba	Leaves	Improve blood circulation, inflammation, fever, and abdominal pain (Haque et al., 2020)
	Branch	Used to treat anti-melanogenic (Haque et al., 2020)
	Stem	Treatment for type II diabetes by lowering blood glucose levels (Haque et al., 2020)
L. umbellata	Leaves	Effective treatment for pediculosis and efficient in biological herbicides as well as in relaxation properties (Maeda et al., 2013)
	Twigs	Treat stiff neck, and back pain (Maeda et al., 2013)

In this study, two *Lindera* species have been selected, which are *L. subumbelliflora* and *L. caesia*. The descriptions and details for each species are shown in Table 2.2.

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Table 2.2

The selected species of the genus Lindera

Species / Description
Lindera subumbelliflora

Distribution: Native to East Asia, particularly in Japan, Korea, and China. Medicinal uses: Used to treat digestive ailments such as diarrhea, abdominal pain, and nausea (Lv et al., 2023)
Lindera caesia

Distribution: Borneo, Jawa, Malaysia, Philippines Medicinal uses: Used to treat allergies, inflammation, hepatotoxicity, and cancer (Haque et al., 2020)

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2.2 Plant Derived Essential Oils

Essential oils have been utilised for thousands of years for their therapeutic and medical effects. Ancient civilizations like Egyption are known for essential oils throughout history in their religious rituals, in cosmetics as well in perfumes (McMullen & Dell'Acqua, 2023). Essential oils have been used by the Greeks and Romans in their bathhouses and for therapeutic and healing purposes. Over 2,500 years ago, Chinese physicians began to use essential oils in traditional medicine, to cure a variety of diseases. The usage of essential oils expanded in the 20th century as more individuals started looking into alternative and natural types of treatment (Bhavaniramya et al., 2019).

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Essential oils are composed of secondary metabolites commonly concentrated in the leaves, barks, or fruits of aromatic plants. Secondary metabolites are produces by living organism that are not necessary for growth, development, or reproduction. The mevalonate pathway is responsible for the biosynthesis of terpenes, which are the primary component of essential oils (Bergman et al., 2019). These volatile molecules consist of hydrocarbons and oxygenated monoterpenes as well as hydrocarbons and oxygenated sesquiterpenes. They also contain phenolic chemicals that are produced through the shikimate pathway (Dhifi et al., 2016).

Some of the most common medicinal uses of essential oils include in relieving pain in inflammation, boosting mood, fighting infections and boosting the immune system and promoting relaxation (Ali et al., 2015). For example, eucalyptus oil used to treat respiratory issues as this essential oil are rich in eucalyptol, 1,8-cineole, limonene,

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citronellal, and citral. Besides, lavender oil is believed to be responsible for many of its therapeutic properties as it contains camphor, geraniol, linalool, and linalyl acetate as an active component (Prashar et al., 2003). Studies show that, this oil is commonly used in aromatherapy to promote relaxation, reduce stress, and improve sleep, thus it may be helpful for people with insomnia (Ali et al., 2015). In addition, peppermint oil, commonly used in oral hygiene products as the main active compound, is menthone and menthol. Tea tree oil has been used to treat nail fungi as it promotes wound healing for minor cuts due to terpinen-4-ol is the main ingredient that acts as antimicrobial properties (Tighe et al., 2013).

There are a variety of ways to extract essential oils including solvent extraction, distillation, pressing, sublimation, supercritical CO_2 extraction, steam distillation, and hydrodistillation (Zhang et al., 2018). The common technique that is used is steam distillation and hydrodistillation procedure. Both methods are used in extraction of essential oils from plant. The volatile components in the plant material are vaporised by steam, which causes them to condense and accumulate. The extraction product's quantity, and composition can change depending on the environment, the soil composition, plant age, and the vegetative cycle stage (Raza et al., 2019). Furthermore, the modern extraction techniques like solid phase microextraction, supercritical fluid extraction and simultaneous distillation extraction are readily accessible (Wang et al., 2014).

Nowadays, the extensive method for determination the chemical components in essential oils was gas chromatography (GC) and combined with mass spectrometry (GC-MS) (Baharum et al., 2010). Other analysis techniques also have been applied,

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such as high-performance liquid chromatography (HPLC), which may provide an alternative method for volatile oil analysis due to its adaptability, sensitivity, and selectivity (Medeiros, 2018).

Essential oils are not only used in therapeutic properties, but also can be used in several industry. In food industries, essential oils can be used to provide various flavours, and aroma of food. Peppermint and lemon oil are frequently used as natural flavourings in candies, baked products, and beverages (Sharmeen et al., 2021). Besides, essential oils have been used in agriculture as natural alternatives of pesticides and herbicides (Raveau et al., 2020). Neem oil are examples to be useful in preventing pests and insects away, while clove and cinnamon oil have herbicidal characteristics to reduce the growth of weeds (Campiglia et al., 2007).

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Over the years, the market for products linked to essential oils has increased. In the upcoming years, it will be the demand for essential oils. The essential oils of the genus *Lindera* have been broadly studied and investigated. The available information on the *Lindera* essential oils were collected and the overview of all published reports were discussed. Fourteen *Lindera* species of chemical compositions in essential oils have been documented from 1999 to 2023 which are *L. aggregate, L. chunii*, *L. communis*, *L. erythrocarpa*, *L. fragrans*, *L. glauca*, *L. melissifolia*, *L. nacusua*, *L. neesiana*, *L. obtusiloba*, *L. pipericarpa*, *L. pulcherrima*, *L. strychnifolia*, and *L. umbellate*. Table 2.3 shows the details of several Lindera essential oil that have been identified from various regions in the world.

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Table 2.3

Major components identified from Lindera essential oils

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. chunii	China (Flower)	37, 95.4	0.59	SH, 59.1	Viridiflorene (14.6%) (1), β-cadinene (9.5%) (2), globulol (6.3%) (3), germacrene B (6.2%) (4), *t-cadinol* (5.4%) (5) (Liu et al., 2013b)
	China (Leaf)	34 , 96.2	0.46	SH, 59.1	Germacrene B (6.2%) (4), globulol (11.6%) (3), ledol (10.2%) (6), γ-muurolene (4.4%) (7) (Liu et al., 2013b)
	China (Stem)	37, 96.4	0.06	OS, 52.1	α-Cadinol (8.6%) (8), globulol (7.7%) (3), *t-cadinol* (7.3%) (5), δ-cadinene (6.5%) (9) (Liu et al., 2013b)
L. communis	China (Leaf)	23, NM	NM	NM	Spathulenol (22.5%) (10), endo-1,3,3-trimethyl-2-norbornanol (10.0%) (11), β-caryophyllene (6.7%) (12) (Yang et al., 1999a)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. erythrocarpa	Korea (Leaf)	15, 63.7	0.07	NM	Nerolidol (18.7%) (13), β-caryophyllene (14.4%) (12), α-humulene (7.7%) (14), germacrene D (4.8%) (15), α-pinene (4.47%) (16) (Ko et al., 2017)
	Korea (Leaf)	31	NM	NM	Nerolidol (26.9%) (13), β-caryophyllene (13.2%) (12), methyl cinnamate (8.5%) (17), α-humulene (8.4%) (14), geranyl acetate (7.8%) (18) (Kim et al., 2009)
L. fragrans	China (Leaf)	62, 76.4	NM	SH, 47.8	Spathulenol (27.6%) (10), ledol (6.8%) (6), β-caryophyllene (4.0%) (12) (Du et al., 2020)
L. glauca	China (Fruit)	48, 95.7	NM	MH, 56.9	(E)-β-Ocimene (41.5%) (19), α-copaene (13.1%) (20), δ-cadinene (6.2%) (9), 3-carene (5.9%) (21) (Sun et al., 2023)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. glauca	China (Fruit)	70, 98.6	1.9	MH, 56.6	(*E*)-β-Ocimene (30.5%) (19), β-caryophyllene (4.9%) (12), α-guaiene (4.7%) (22), δ-guaiene (4.7%) (23) (Chen et al., 2021)
		87, 73.9	0.6	SH, 40.0	*(E)*-β-Ocimene (12.9%) (19), α-pinene (4.0%) (16), cadina-1(10),4-diene (3.4%) (24), camphene (2.5%) (25) (Zhu et al., 2016)
		72, 88.6	1.2	MH, 57.7	*(E)*-β-Ocimene (37.4%) (19), β-caryophyllene (3.7%) (12), myrcene (3.5%) (26) (Zhu et al., 2016)
		74, 87.2	1.4	MH, 44.7	*(E)*-β-Ocimene (30.3%) (19), α-copaene (12.7%) (20) (Zhu et al., 2016)
		54	NM	NM	*N*-carproic acid (25.3%) (27), germacrene A (10.7%) (28), n-dodecanole acid (10.0%) (29), epishyobunol acetate (7.2%) (30) (Yang et al., 1999b)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. glauca	China (Fruit)	54	NM	NM	*N*-Carproic acid (25.3%) (27), germacrene A (10.7%) (28), n-dodecanole acid (10.0%) (29), epishyobunol acetate (7.2%) (30), β-caryophyllene (5.44%) (12). (Yang et al., 1999b)
	China (Leaf)	41, 87.5	0.32	MH, 46.5	β-Phellandrene (19.0%) (31), myrcene (17.9%) (26), aromadendrene (17.1%) (32), γ-cadinene (10.1%) (33), (*E*)-β-ocimene (9.1%) (19) (Niu et al., 2015)
	Vietnam (Leaf)	34, 90.0	0.21	SH, 54.1	β-Caryophyllene (29.2%) (12), α-humulene (18.0%) (14) (*E*)-β-caryophyllene (14.6%) (22), humulene epoxide II (5.3%) (34), spathulenol (4.6%) (10) (Chau et al., 2022)
	China (Fruit)	15 56.6	1.91	MH	(*E*)-β-Ocimene (30.5%) (19), (*E*)-β-caryophyllene (5.1) (22), δ-guaiene (5.0%) (23) (Chen et al., 2021)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. melissifolia	USA (Fruit)	35, 86.7	NM	NM	Sabinene (66.2%) (35), (E)-β-ocimene (12.9%) (19), α-phellandrene (4.1%) (36) (Oh et al., 2012)
L. nacusua	China (Leaf)	22, 64.4	NM	SH, 42.5	β-caryophyllene (8.7%) (12), hexahydrofarnesyl acetone (6.8%) (37), β-selinene (5.0%) (38), neophytadiene (4.5%) (39), palmitic acid (4.4%) (40) (Wei et al., 2016a)
L. neesiana	Nepal (Fruit)	40, 86.0	NM	NM	*Z*-citral (15.0%) (41), *E*-citral (11.8%) (42), α-copaene (8.7%) (20), citronellal (6.7%) (43) (Comai et al., 2010)
L. obtusiloba	Korea (Leaf)	25, 65.7	0.25	NM	δ-Cadinene (13.8%) (9), limonene (10.2%) (44), β-eudesmol (10.0%) (45), hedycaryol (6.7%) (46), α-pinene (5.7%) (16), bornyl acetate (5.6%) (47) (Yang et al., 2022a)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. obtusiloba	Korea (Leaf)	27, 67.8	4.23	NM	β-Caryophyllene (32.1%) (12), α-copaene (31.4%) (20), nerolidol (6.8%) (13), β-farnesene (4.1%) (48) (Chung & Moon, 2011)
	Korea (Fruit)	70, 83.7	NM	MH	Camphene (18.4%) (25), α-thujene (13.8%) (49), limonene (12.8%) (44), linalyl acetate (12.5%) (50), dihydromyrcene (11.1%) (51) (Hwang et al., 2013)
	Korea (Stem)	58, 87.3	NM	MH, 37.0	Limonene (11.7%) (44), β-phellandrene (7.7%) (31), *tert*-butylbenzene (5.4%) (52), santolina alcohol (5.0%) (53), 1(10)*E*,5*E*-germacradien-4-ol (4.0%) (54) (Hwang et al., 2013)
	Korea (Root)	70, 80.8	NM	MH, 27.4	Limonene (6.7%) (44), linalyl acetate (6.2) (50), camphene (5.1%) (25), β-phellandrene (5.0%) (31), 1-decyne (4.7%) (55) (Hwang et al., 2013)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. obtusiloba	Korea (Stem)	77, 89.1	NM	MH, 29.5	Linalyl acetate (12.5%) (50), limonene (11.4%) (44), dihydromyrcene (3.9%) (51), β-Phellandrene (3.8%) (31), elema-1,3,11(13)-trien-12-ol (3.6%) (56) (Hwang et al., 2013)
	Korea (Root)	78, 98.8	NM	MH, 31.8	Linalyl acetate (13.0%) (50), limonene (12.8%) (44), β-phellandrene (4.6%) (31), cyclododecanone (4.1%) (57) (Hwang et al., 2013)
	Korea (Fruit)	70, 93.1	NM	MH, 67.8	Camphene (18.4%) (25), α-thujene (13.8%) (49), limonene (13.4%) (44), β-myrcene (9.2%) (58), α-phellandrene (3.8%) (36) (Hwang et al., 2013)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. obtusiloba	Korea (Leaf)	78, 87.8	NM	MH, 37.4	Dihydromyrcene (11.1%) (51), germacrene B (7.5%) (4), limonene (5.5%) (44), α-eudesmol (4.3%) (59), 2,2-bis(prop-2-enoxy-methyl)-butan-1-ol (3.87%) (60) (Hwang et al., 2013)
L. pipericarpa	Malaysia (Leaf)	22, 98.3	1.0	SH, 60.0	β-Caryophyllene (32.1%) (12), α-copaene (31.4%) (20), nerolidol (6.1%) (13) (Ali & Jantan, 1993)
	Malaysia (Wood)	24, 97.5	0.04	MH, 89.9	Limonene (55.4%) (44), linalool (6.6%) (61), geranial (6.7%) (62), neral (5.1%) (63) (Ali & Jantan, 1993)
L. pulcherrima	India (Leaf)	26, 98.2	NM	OS, 75.3	Furanodienone (49.1%) (64), curzerenone (17.4%) (65), furanosesquiterpenoid (5.2%) (66), furanodiene (3.5%) (67) (Joshi & Mathela, 2012)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. pulcherrima	India (Leaf)	35, 97.5	1.12	OS, 89.1	Furanosesquiterpenoid(79.3%) (66), furanodienone (46.6%) (67), curzerenone (17.6%) (65) (Joshi et al., 2009)
	India (Leaf)	28, 83.2	NM	SH, 79.3	Furanodienone (46.6%) (64), germacrene D (26.0%) (15), curzerenone (17.6%) (65), β-caryophyllene (5.4%) (12), β-eudesmol (4.1%) (45) (Joshi et al., 2010)
L. strychnifolia	China (Leaf)	49, 94.9	0.36	OS, 65.9	Sesquithuriferol (35.9%) (68), 14-oxy-α-muurolene (16.5%) (69), 1,8-cineole (5.3%) (70), β-selinene (4.6%) (38) (Yan et al., 2014)
	China (Leaf)	51, 94.5	0.43	OS, 65.8	Sesquithuriferol (35.9%) (68), 14-oxy-muurolene (16.4%) (69), 1,8-cineole (5.3%) (70), β-selinene (4.5%) (38) (Yan et al., 2009)

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Table 2.3 *(continue)*

Species	Locality (Part)	Total, %	Yield, %	Group, %	Major components (%)
L. strychnifolia	China (Root)	58, 91.4	0.31	OS, 39.5	(*E*)-β-Ocimene (10.2%) (19), 1,8-cineole (8.4%) (70), isoterpinolene (4.7%) (71) (Yan & Hua 2014)
L. umbellate	Japan (Leaf)	27, 89.9	NM	NM	Linalool (42.8%) (61), 1,8-cineole (13.7%) (70), β-myrcene (7.6%) (58), limonene (7.6%) (44) (Nanashima et al., 2020)
L. umbellate	Japan (Twig)	14, 75.2	NM	NM	Linalool (65.7%) (61), geranyl acetate (17.5%) (18), limonene (5.2%) (44) (Maeda et al., 2013)
	Japan (Leaf)	20, 93.2	NM	OM, NM	Linalool (42.8%) (61), 1,8-cineole (13.7%) (70), β-myrcene (7.6%) (58), limonene (7.4%) (44) (Maeda et al., 2013)

NM-not mentioned; MH-monoterpene hydrocarbon; SH-sesquiterpene hydrocarbon; OS-oxygenated sesquiterpene; OM-oxygenated monoterpene

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Based on Table 2.3, most of *Lindera* species were reported mainly from China (11 studies), followed by Korea (5 studies), India (3 studies), Japan (2 studies), whereas Vietnam, USA, Nepal and Malaysia each were reported in one study. The extraction of essential oils is mostly from the leaves, roots, and flowers, along with fruit, bark, and twig parts. The essential oils of *L. glauca* and *L. obtusiloba* were recorded as the most with 9 studies. In addition, *L. chunii, L. pulcherrima, L. strychnifolia,* and *L. umbellata* with 3 studies.

Analysis of the chemical components identified in *Lindera* essential oils shows that the oil consists of several groups of components, which are monoterpene hydrocarbons, oxygenated monoterpenes, sesquiterpene hydrocarbons, and oxygenated sesquiterpenes. Moreover, the leaf oil of *L. obtusiloba* gave the highest yield among others with 4.23%, followed by the fruit oil of *L. glauca* with 1.91%. In addition, other components have been recorded several times in *Lindera* essential oils. β-Caryophyllene **(12)** was the most reported with 12 studies, followed by limonene **(44)** (12 studies), α-pinene **(16)**, α-copaene **(20)** and β-phellandrene **(31)** with 5 studies respectively. For globulol **(3)**, germacrene B **(4)**, nerolidol **(13)**, and 1,8-cineole **(70)** each were reported with 4 studies.

Monoterpenes were reported as major components in several *Lindera* species. *L. pipericarpa* wood oil showed the dominant of monoterpene hydrocarbons (89.8%), which constituted of limonene **(44)**, linalool **(61)**, geranial **(62)** and neral **(63)** (Ali & Jantan, 1993). Hwang et al. (2013) state that the major group of *L. obtusiloba* fruit oil is monoterpene hydrocarbons (67.8%) with the main components are camphene **(25)**, α-thujene **(49)**, β-myrcene **(58)** and α-phellandrene **(36)**. Meanwhile, other

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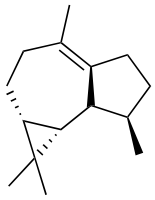
monoterpene hydrocarbons which were found as major components in *Lindera* essential oil were (*E*)-β-ocimene **(19)** (Sun et al., 2023; Zhu et al., 2016; Chen et al., 2021), β-phellandrene **(31)** (Niu et al., 2015), and dihydro-myrcene **(51)** (Hwang et al., 2013). Besides that, oxygenated monoterpenes were dominated in the leaf oil of *L. umbellate* with the foremost components being linalool **(61)**, 1,8-cineole **(70)**, β-myrcene **(58)**, and limonene **(44)** (Maeda et al., 2013).

Sesquiterpene hydrocarbons were found in several *Lindera* essential oils. The leaf oil of *L. pipericarpa* constituted about 60% of sesquiterpene hydrocarbons and was identified dominantly with β-caryophyllene **(12)** and α-copaene **(20)** (Ali & Jantan, 1993). Besides, other sesquiterpene hydrocarbons which were found as major components in *L. chunii* flower oil are viridiflorene **(1)**, β-cadinene **(2)** and germacrene B **(4)** (Liu et al., 2013). Meanwhile, *L. erythrocarpa* leaf oil presented α-humulene **(14)** (Chau et al., 2022), while *L. pulcherrima* leaf oil gave germacrene D as the principal component (Joshi et al., 2010). Currently, *L. glauca* fruit oil was successfully commanded to cadina-1(10),4-diene **(24)** (Zhu et al., 2016), and (*E*)-β-caryophyllene **(22)** (Chau et al., 2022).

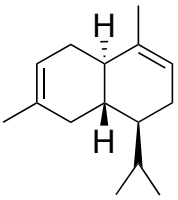
In the case of oxygenated sesquiterpene, the leaf oil of *L. pulcherrima* constituted about 89.1% of these groups and identified dominantly with curzerenone **(65)** and furanodienone **(67)** (Joshi et al., 2009). Another oxygenated sesquiterpene which were found as major components in *Lindera* leaf oil were spathulenol **(10)** (Du et al., 2021), α-cadinol **(8)**, and ledol **(6) (**Liu et al., 2013) which were reported from the stem and leaf oils of *L. chunii.*

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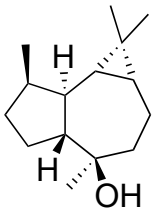
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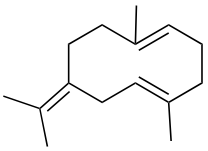
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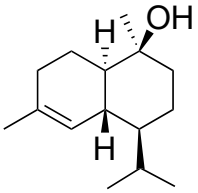
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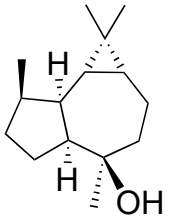
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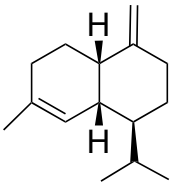
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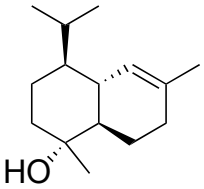
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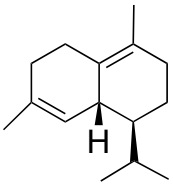
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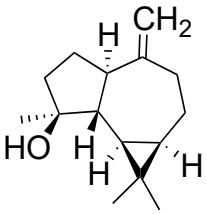
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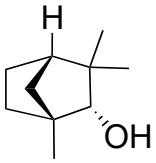
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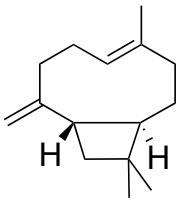
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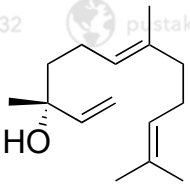
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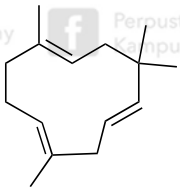
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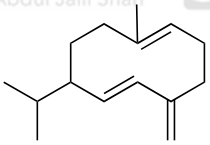
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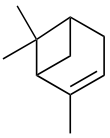
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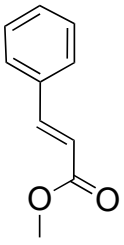
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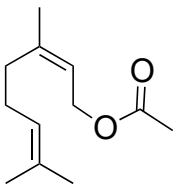
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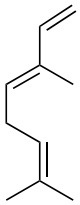
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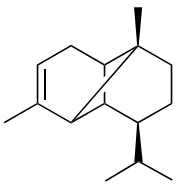
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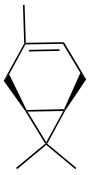
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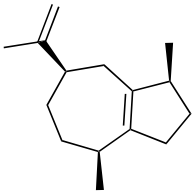
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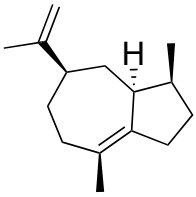
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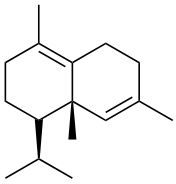
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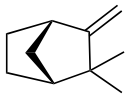
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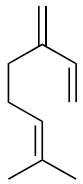
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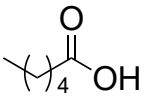
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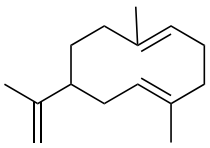
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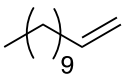
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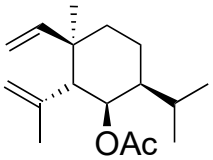
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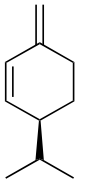
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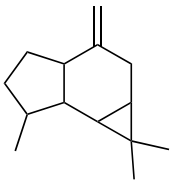
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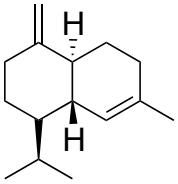
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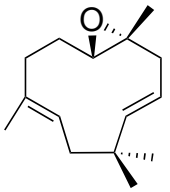
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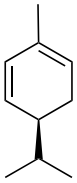
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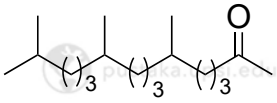
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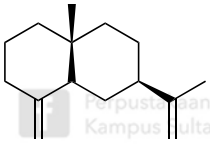
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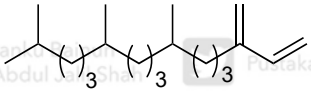
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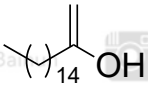
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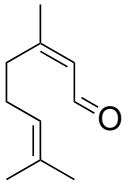
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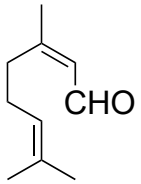
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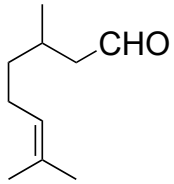
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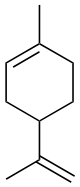
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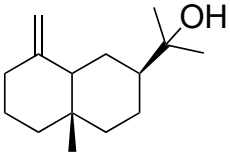
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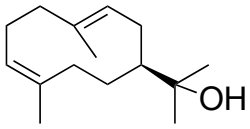
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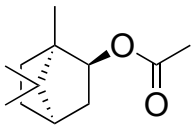
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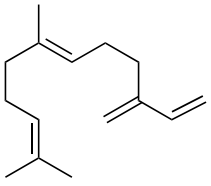
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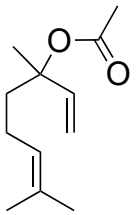
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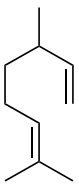
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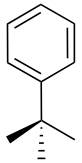
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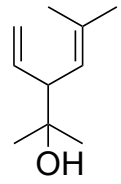
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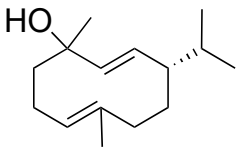
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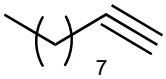
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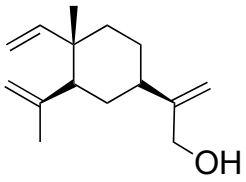
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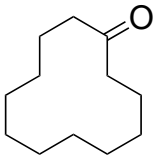
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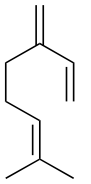
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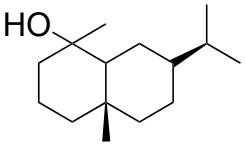
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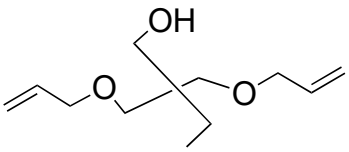
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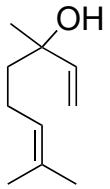
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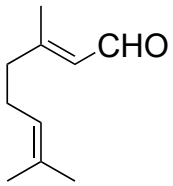
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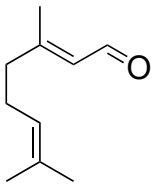
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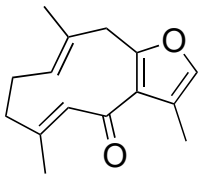
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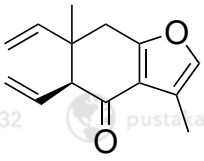
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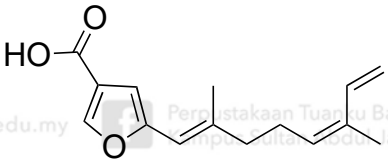
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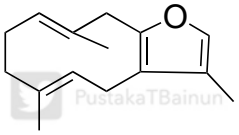
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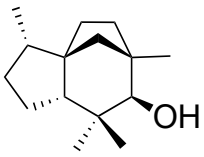
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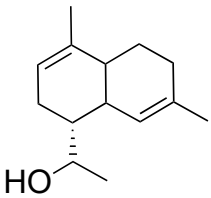
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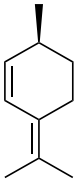
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2.3 Phytochemical Studies of *Lindera* Species

2.3.1 Sesquiterpenes

Sesquiterpenes are a class of terpenes that consist of three isoprene units, resulting in a molecular formula of $C_{15}H_{24}$. These compounds are synthesized via the mevalonate or methylerythritol phosphate pathways in plants, playing significant roles in plant defense and ecological interactions (Cheng et al., 2007). They are naturally occurring compounds found in plants and insects, often contributing to the scent, flavor, and bioactive properties of essential oils. Numerous plants, including fruits, vegetables, herbs, and spices, contain sesquiterpenes. They are frequently found in plants such as chamomile, ginger, and turmeric (Dhifi et al., 2016).

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Besides, sesquiterpenes are commonly found in fungi and some marine organisms and known for their diverse range of biological activities and therapeutic properties. Sesquiterpenes have diverse structures, including linear, cyclic, and bicyclic forms (Lv et al., 2023). Several different classes of sesquiterpenes can be identified depending upon the carbon skeleton as well as the presence of functional groups such as elemane-, eudesme-, germacrane-, guaianes-, bisabolane-type as illustrated in Figure 2.1 (Feng et al., 2022).

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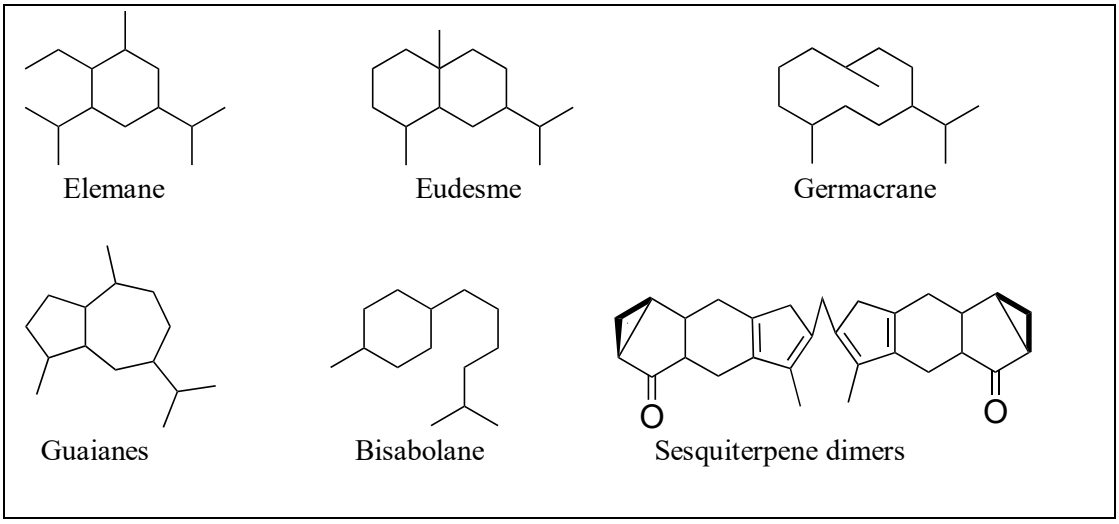


Figure 2.1. Classification of sesquiterpenes

According to Scopus, there are about 87 documents that relate to *Lindera* sesquiterpenes since 1964. To date, a total of 362 sesquiterpenes have been reported, mostly isolated from the roots, leaves, flowers, and a few obtained from whole plants. Among them, germacrane-, eudesmane- and lindenane-type sesquiterpenoids account for a fairly large proportion (Feng et al., 2022). Table 2.4 shows several sesquiterpenes that have been isolated and identified from various *Lindera* species. Most of the compounds are reported mainly from *L. aggregata* (102 compounds), *L. strychnifolia* (15 compounds), and *L. glauca* (9 compounds). Furthermore, there that were 157 compounds were classify as bisobolane (2 compounds), elemane (5 compounds), eudesme (28 compounds), gemacrane (21 compounds), guaiane (10 compounds), as well as 37 compounds from lindenane, sesquiterpenes dimer (42 compounds).

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Table 2.4

Sesquiterpenes isolated from several Lindera species

Compounds	Species	Part	References
BISABOLANE			
3-(Hydroxymethyl)-6-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)-4-oxocyclohex-2-en-1-yl acetate (72)	*L. blume*	Leaves	Ryen et al., 2020
6-(2-Hydroxy-6-methylhept-5-en-2-yl)-3-(hydroxymethyl)-4-oxocyclohex-2-en-1-yl acetate (73)	*L. blume*	Leaves	Ryen et al., 2020
ELEMANE			
β-Elemene (74)	*L. aggregata*	Roots	Chen, 2015
Hydroxyisogermafurenolide (75)	*L. aggregata*	Roots	Gan et al., 2009b
Isogermafurenolide (76)	*L. aggregata*	Roots	Chen, 2015
Isolinderalactone (77)	*L. strychnifolia*	Roots	Yen et al., 2016
Isogermafurene (78)	*L. strychinifolia*	Roots	Cao et al., 2016
EUDESME			
ent-4(15)-Eudesmene-1β,6,α-diol (79)	*L. aggregata*	Roots	Yang et al., 2020b
3-Oxo-4, 5αH, 8βH-eudesma-1,7(11)-dien-8, 12-olide (80)	*L. strychinofolia*	Roots	Ohno et al., 2005

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Table 2.4 *(continue)*

Compounds	Species	Part	References
3-Oxo-5αH, 8βH-eudesma-1,4(15), 7(11)-trien-8, 12-olide (81)	*L. strychinofolia*	Roots	Ohno et al., 2005
8-Hydroxylindestenolide (82)	*L. aggregata*	Roots	Cheng et al., 2007
Atractylenolide III (83)	*L. aggregata*	Roots	Gan et al., 2009b
Eudesma-4(14),11-diene (84)	*L. strychinifolia*	Roots	Cao et al., 2016
Dehydrolindestrenolide (85)	*L. aggregata*	Roots	Yang et al., 2020a
Hydroxylindestenolide (86)	*L. strychinifolia*	Roots	Jian et al., 2002
Lindestrene (87)	*L. strychinofolia*	Roots	Liu et al., 2013a
Lindenanolides B_2 (88)	*L. aggregata*	Roots	Chou et al., 2000
Lindenanolide H (89)	*L. chunii*	Roots	Zhang & Wang, 2000
Linderaggredin A (90)	*L. aggregata*	Aerial	Kuo et al., 2020
Linderolide A (91)	*L. strychinofolia*	Roots	Sumioka et al., 2011
Linderolide C (92)	*L. strychinofolia*	Roots	Sumioka et al., 2011
Linderolide B (93)	*L. strychinofolia*	Roots	Sumioka et al., 2011
Linderolide D (94)	*L. strychinofolia*	Roots	Sumioka et al., 2011
Linderolide E (95)	*L. strychinofolia*	Roots	Sumioka et al., 2011
Linderolide G (96)	*L. strychinofolia*	Roots	Liu et al., 2013a
Linderolide H (97)	*L. strychinofolia*	Roots	Liu et al., 2013a
Linderolide I (98)	*L. strychinofolia*	Roots	Liu et al., 2013a
Linderolide J (99)	*L. strychinofolia*	Roots	Liu et al., 2013a

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Table 2.4 *(continue)*

Compounds	Species	Part	References
Linderagalactone D (100)	*L. aggregata*	Roots	Gan et al., 2009b
Linderagalactone E (101)	*L. aggregata*	Roots	Gan et al., 2009b
Lindestrenolide (102)	*L. strychinifolia*	Roots	Liu et al., 2013a
Hydroxylindestrenolide (103)	*L. aggregata*	Roots	Gan et al., 2009b
Myrrhalindenane C (104)	*L. myrrha*	Roots	Nguyen et al., 2023
Linerenone (105)	*L. communis*	Fruits	Deng et al., 2011
Polydactin B (106)	*L. communis*	Fruits	Deng et al., 2011
GEMACRANE			
Neosericenyl acetate (107)	*L. aggreggata*	Roots	Lv et al., 2023
Linderalactone (108)	*L. strychnifolia*	Roots	Jian et al., 2002
Linderane (109)	*L. aggregata*	Roots	Wen et al., 2021
Linderanines A (110)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanines B (111)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanines C (112)	*L. aggregata*	Roots	Qiang et al., 2011
Linderadine (113)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide A (114)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide B (115)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide C (116)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide D (117)	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide E (118)	*L. aggregata*	Roots	Qiang et al., 2011
Linderoline (119)	*L. strychnifolia*	Roots	Sumioka et al., 2011
Lindeneol (120)	*L. chunii*	Roots	Zhang et al., 2002

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Table 2.4 *(continue)*

Compounds	Species	Part	References
Linderoxide (121)	*L. strychnifolia*	Roots	Cao et al., 2016
Eudeglaucone (122)	*L. glauca*	Twigs	Yu et al., 2016
Neolinderane (123)	*L. strychnifolia*	Roots	Cao et al., 2016
Neolinderalactone (124)	*L. strychnifolia*	Roots	Cao et al., 2016
Pseudoneolinderane (125)	*L. strychnifolia*	Roots	Jian et al., 2002
Parvigemone (126)	*L. strychnifolia*	Roots	Liu et al., 2016a
Neolindenenonelactone (127)	*L. aggregata*	Roots	Cheng et al., 2007
GUAIANE			
1,4-Dimethyl-7-ethylazulene (128)	*L. strychnifolia*	Roots	Cao et al., 2016
Aciphyllene (129)	*L. glauca*	Leaves	Nii et al., 1983
Glaucyl alcohol (130)	*L. glauca*	Roots	Nii et al., 1983
Aciphyllic acid (131)	*L. glauca*	Roots	Nii et al., 1983
Aciphyllyl alcohol (132)	*L. glauca*	Leaves	Nii et al., 1983
Dehydrocostuslactone (133)	*L. aggregata*	Roots	Qiang et al., 2011
Glaucic acid (134)	*L. glauca*	Roots	Nii et al., 1983
Lindenanolides C (135)	*L. aggregata*	Roots	Chou et al., 2000
Lindenanolides D (136)	*L. aggregata*	Roots	Chou et al., 2000
Linderazulene (137)	*L. strychnifolia*	Roots	Cao et al., 2016
LINDENANE			
Shizukanolide (138)	*L. strychinifolia*	Roots	Liu et al., 2013a
Chloranthalactone D (139)	*L. strychinifolia*	Roots	Liu et al., 2013a

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Table 2.4 *(continue)*

Compounds	Species	Part	References
(1*R*, 3*S*, 4*R*, 5*R*, 8*S*, 10*S*)-4,8-Dihydroxy-1,3-cycloeudesma-7(11)-en-12,8-olide (140)	*L. strychinifolia*	Roots	Liu et al., 2016a
(1*R*, 3*S*, 4*R*, 5*R*, 6*R*, 8*S*, 10*S*)-4,6,8-Trihydroxy- 1,3-cyclo-eudesma-7(11)-en-12,8-olide (141)	*L. strychinifolia*	Roots	Liu et al., 2016a
(1*R*, 3*S*, 4*R*, 5*R*, 6*R*, 8*S*, 10*S*)-4,8-Dihydroxy-6-acetoxy-1,3-cycloeudesma-7(11)-en-12,8-olide (142)	*L. strychinifolia*	Roots	Liu et al., 2016a
(1*R*, 3*S*, 4*S*, 5*S*, 8*R*, 10*R*)-4-Hydroxy-6-oxo-1,3-cycloeudesma-7(11)-en-12,8-olide (143)	*L. strychinifolia*	Roots	Liu et al., 2016a
(1*R*, 3*S*, 5*R*, 6*R*, 8*R*, 10*S*)-6-Methoxy-8-hydroxy-1,3-cyclo-eudesma-4(15),7(11)-dien-12,8-olide (144)	*L. strychinifolia*	Roots	Liu et al., 2016a
6α-Acetyl-lindenanolide B1 (145)	*L. aggregata*	Roots	Gui et al., 2000
6α-Acetyl-lindenanolide B2 (146)	*L. aggregata*	Roots	Gui et al., 2000
Lindenenyl acetate (147)	*L. strychifolia*	Roots	Li et al., 2009
Linderene (148)	*L. strychifolia*	Roots	Li et al., 2009
Lindenene (149)	*L. strychifolia*	Roots	Liu et al., 2016a

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Table 2.4 *(continue)*

Compounds	Species	Part	References
Lindenanolide A (150)	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolide B1 (151)	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolide B2 (152)	*L. aggregata*	Roots	Wen et al., 2021
Linderanlide F (153)	*L. aggregata*	Roots	Qiang et al., 2011
Linderolide K (154)	*L. strychifolia*	Roots	Liu et al., 2013a
Linderagalactone B (155)	*L. aggregata*	Roots	Gan et al., 2009b
Linderagalactone C (156)	*L. aggregata*	Roots	Gan et al., 2009b
Linderaggredin B (157)	*L. aggregata*	Aerial	Kuo et al., 2020
Linderolide L (158)	*L. strychnifolia*	Roots	Liu et al., 2013a
Linderolide M (159)	*L. strychnifolia*	Roots	Liu et al., 2013a
Linderolide N (160)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide O (161)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide P (162)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide Q (163)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide R (164)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide S (165)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide T (166)	*L. strychnifolia*	Roots	Liu et al., 2016a
Linderolide U (167)	*L. strychnifolia*	Roots	Kim et al., 2021
Linderolide V (168)	*L. strychnifolia*	Roots	Kim et al., 2021
Isolinderoxide (169)	*L. strychnifolia*	Roots	Liu et al., 2013a
Myrrhalindenane A (170)	*L. myrrha*	Roots	Duong et al., 2020
Myrrhalindenane B (171)	*L. myrrha*	Roots	Duong et al., 2020

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Table 2.4 *(continue)*

Compounds	Species	Part	References
Strychnilactone (172)	*L. aggregata*	Roots	Jian et al., 2002
Strychnistenolide (173)	*L. aggregata*	Roots	Jian et al., 2002
Strychnistenolide 6-O-acetate (174)	*L. strychnifolia*	Roots	Li et al., 2002
SESQUITERPENE DIMERS			
Aggreganoid A (175)	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid B (176)	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid C (177)	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid D (178)	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid E (179)	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid F (180)	*L. aggregata*	Roots	Liu et al., 2019a
Linderin A (181)	*L. aggregata*	Roots	Wen et al., 2021
Linderin B (182)	*L. aggregata*	Roots	Wen et al., 2021
Lindera aggrenolide A (183)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide B (184)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide C (185)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide D (186)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide E (187)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide F (188)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide G (189)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide H (190)	*L. aggregata*	Roots	Liu et al., 2021b
Lindera aggrenolide I (191)	*L. aggregata*	Roots	Liu et al., 2021b

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Table 2.4 *(continue)*

Compounds	Species	Part	References
Lindenaggrenolide J (192)	*L. aggregata*	Roots	Liu et al., 2021b
Lindenaggrenolide K (193)	*L. aggregata*	Roots	Liu et al., 2021b
Lindenaggrenolide L (194)	*L. aggregata*	Roots	Liu et al., 2021b
Lindenaggrenolide M (195)	*L. aggregata*	Roots	Liu et al., 2021b
Lindenaggrenolide N (196)	*L. aggregata*	Roots	Liu et al., 2021b
Lindenanoid A (197)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid B (198)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid C (199)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid D (200)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid E (201)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid F (202)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid G (203)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid H (204)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid I (205)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid J (206)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid K (207)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid L (208)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid M (209)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid N (210)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenanoid O (211)	*L. aggregata*	Roots	Liu et al., 2021a
Lindenaneolide F (212)	*L. aggregata*	Roots	Liu et al., 2021a
Linderalide A (213)	*L. aggregata*	Roots	Liu et al., 2019b

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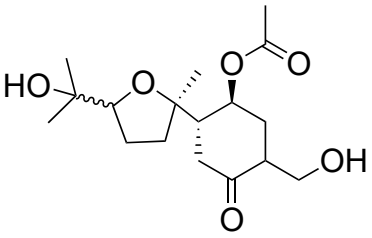
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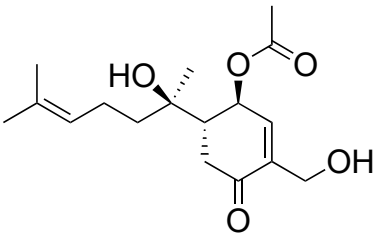
Compounds	Species	Part	References
Linderalide B (214)	*L. aggregata*	Roots	Liu et al., 2019b
Linderalide C (215)	*L. aggregata*	Roots	Liu et al., 2019b
Linderalide D (216)	*L. aggregata*	Roots	Liu et al., 2019b
OTHERS			
10,11-Dihydroxyeremophilan-3-one 11-O-β-D-glucopyranoside (217)	*L. strychinifolia*	Roots	Mimura et al., 2010
Alangioside L (218)	*L. umbellata*	Stems	Kuroda et al., 2011
Aristofone (219)	*L. communis*	Fruits	Deng et al., 2011
Cadinene (220)	*L. strychinifolia*	Seeds	Cao et al., 2016
Cadina-4,10 (15)-diene (221)	*L. strychinifolia*	Seeds	Cao et al., 2016
Dehydrocostuslactone (222)	*L. aggregata*	Root	Qiang et al., 2011
Epiglobulol (223)	*L. communis*	Fruits	Deng et al., 2011
Lindera aggredin C (224)	*L. aggregata*	Aerial	Kuo et al., 2020
Linderagalactone A (225)	*L. aggregata*	Aerial	Kuo et al., 2020
Pseudoguaianelactones A (226)	*L. glauca*	Roots	Ruan et al., 2020
Pseudoguaianelactones B (227)	*L. glauca*	Roots	Ruan et al., 2020
Pseudoguaianelactone C (228)	*L. glauca*	Roots	Ruan et al., 2020

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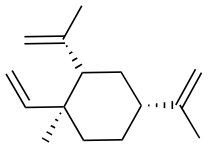
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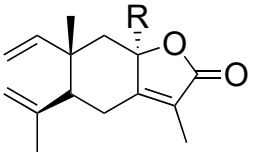
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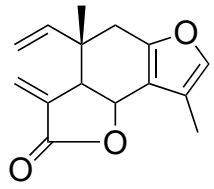
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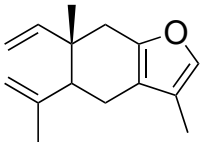
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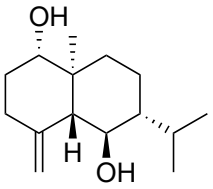
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(76) R = H



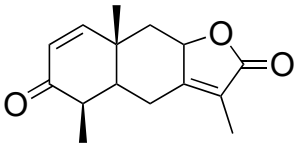
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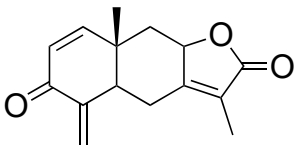
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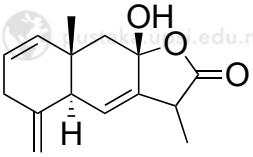
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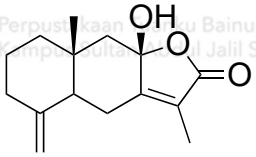
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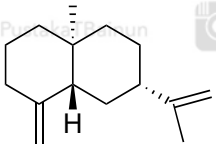
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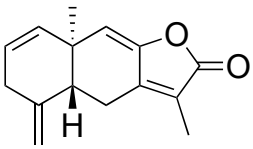
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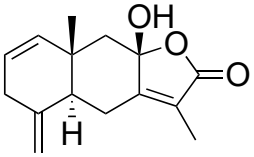
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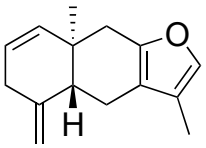
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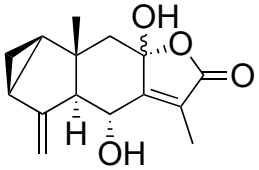
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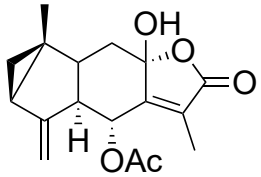
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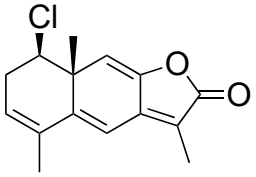
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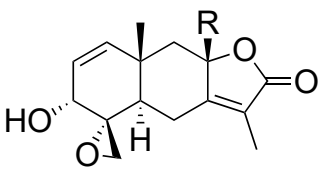
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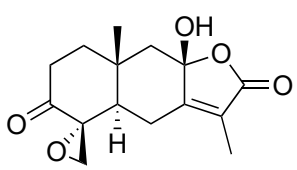
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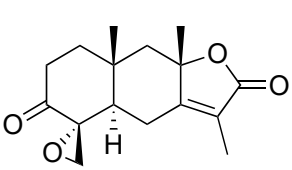
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(91) R = OH
(92) R = H



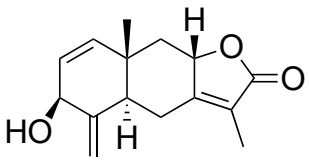
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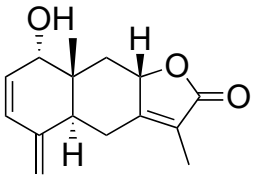
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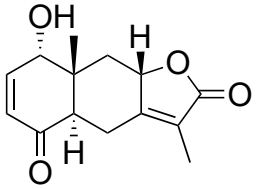
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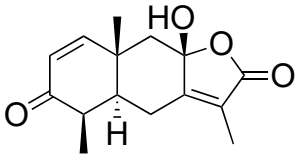
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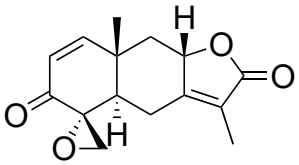
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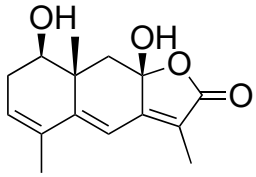
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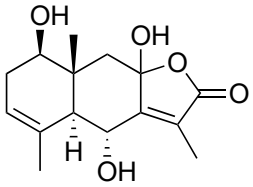
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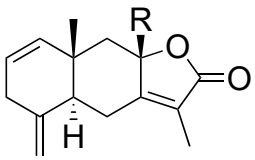
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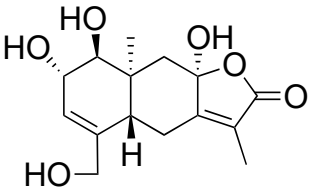
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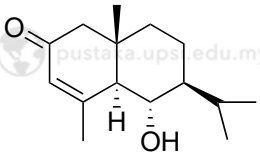
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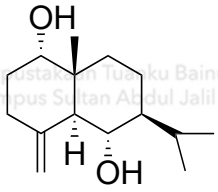
(102) R = H
(103) R = OH



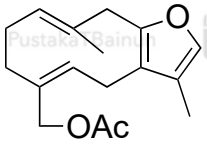
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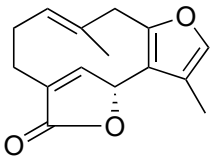
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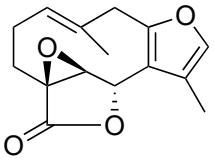
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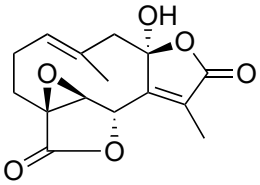
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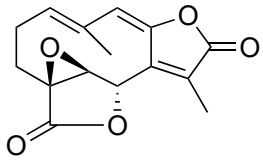
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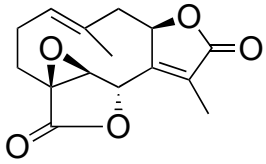
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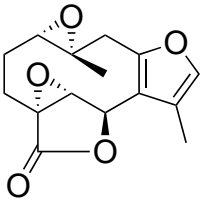
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(111)



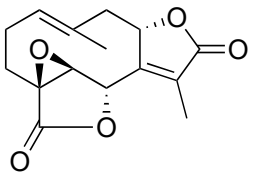
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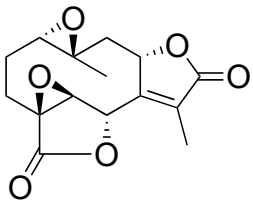
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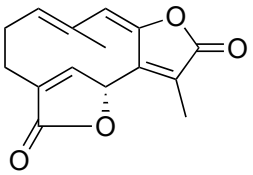
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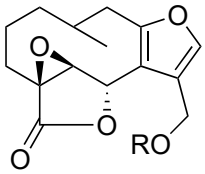
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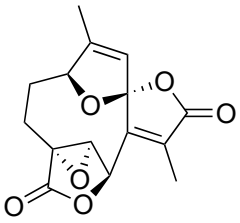
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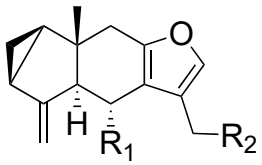
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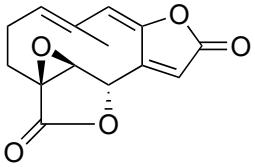
(117) R = CH_3
(118) R = Ac



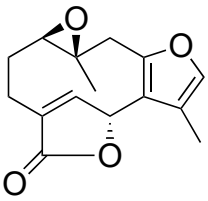
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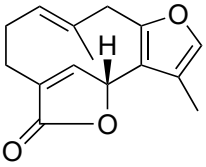
(120) R_1 = OH, R_2 = H
(121) R_1 = H, R_2 = OCH_3



(122)

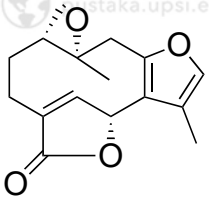


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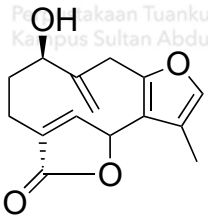


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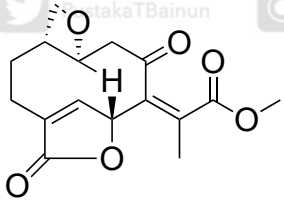
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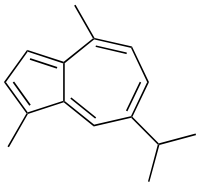
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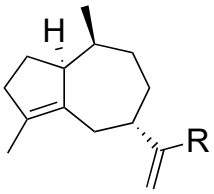
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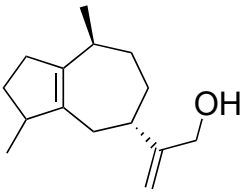
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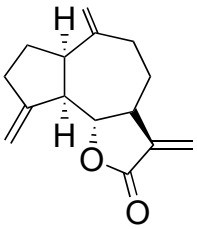
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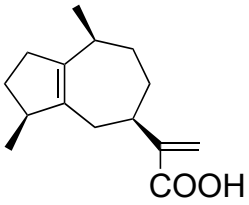
(129) R = CH_3
(130) R = CH_2OH
(131) R = COOH



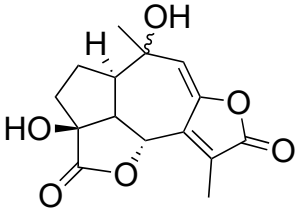
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(133)



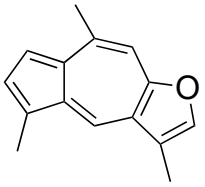
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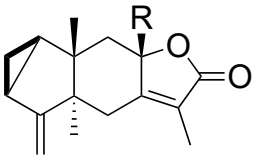
(135) R = α-OH
(136) R = β-OH

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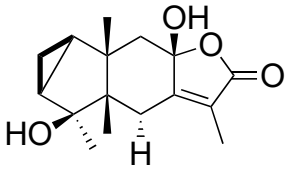
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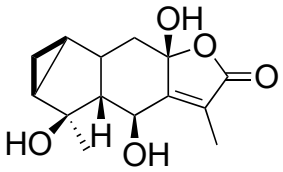
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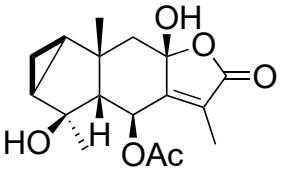
(138) R = H
(139) R = OH



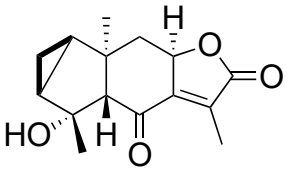
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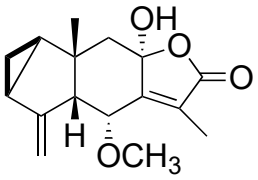
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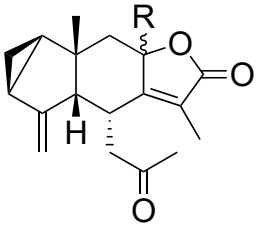
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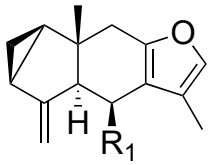
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(144)

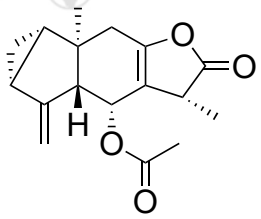


(145) R = α-OH
(146) R = β-OH

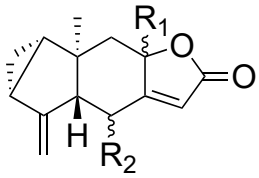


(147) R = OAc
(148) R = OH
(149) R = H

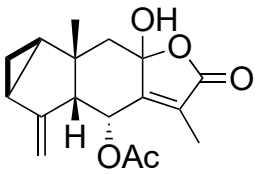
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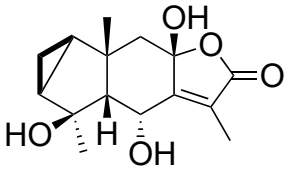
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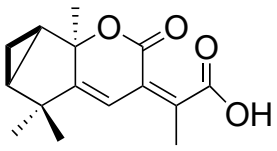
(151) R_1 = α-OH, R_2 = β-OH
(152) R_1 = β-OH, R_2 = α-OH



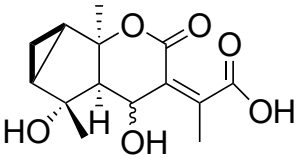
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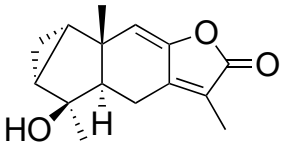
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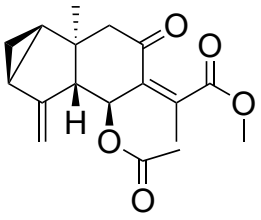
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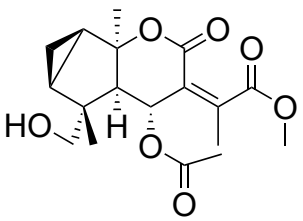
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(157)



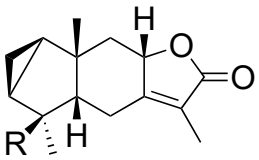
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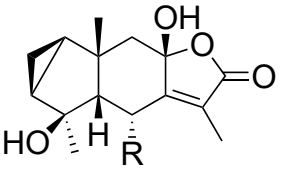
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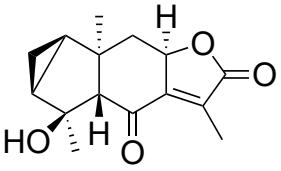
05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi



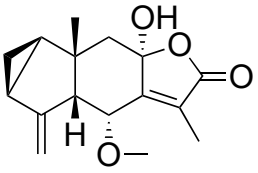
(160) R = OH
(161) R = OCH_3



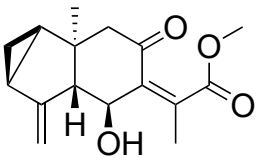
(162) R =H
(163) R = OH
(164) R = OAc



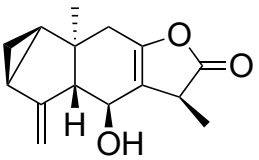
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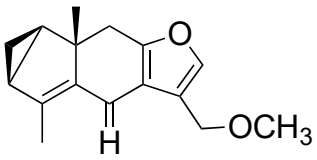
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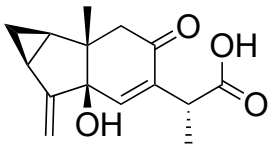
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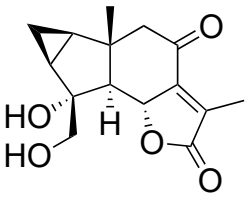
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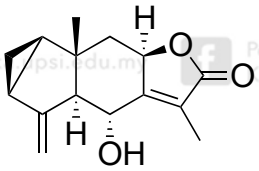
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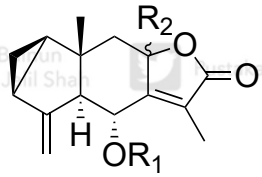
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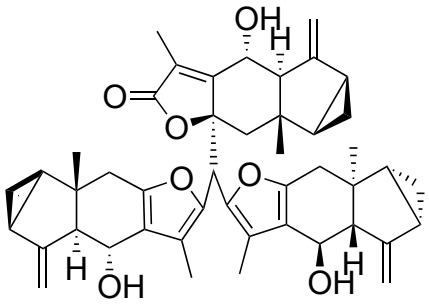
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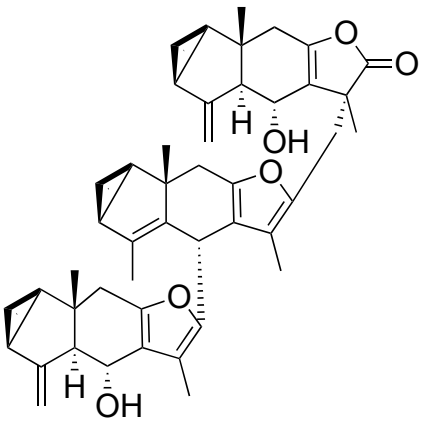
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(173) R_1 = H, R_2 = α-OH
(174) R_1 = $COCH_3$, R_2 = β-OH



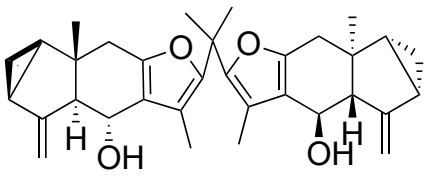
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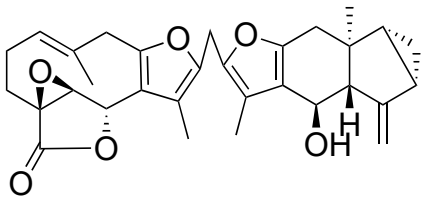
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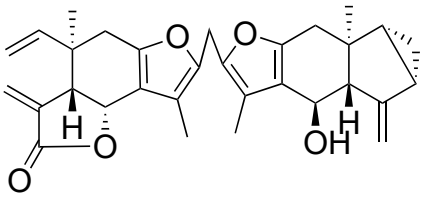
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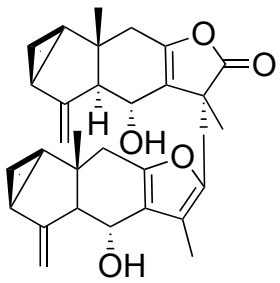
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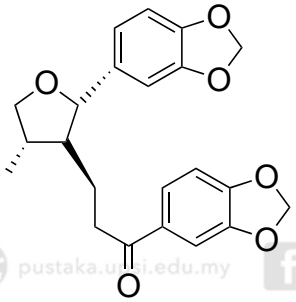
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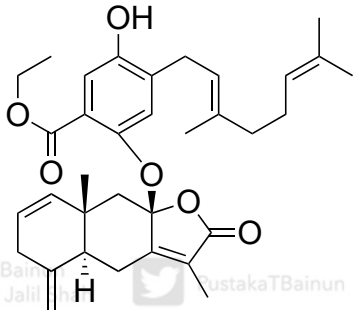
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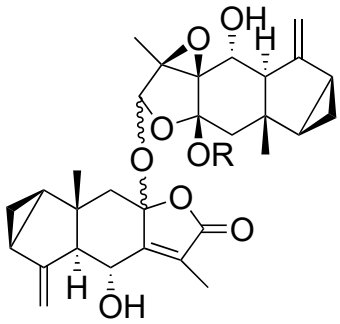
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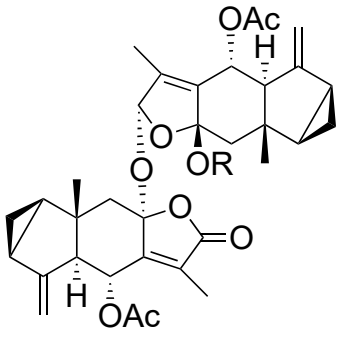
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(182)



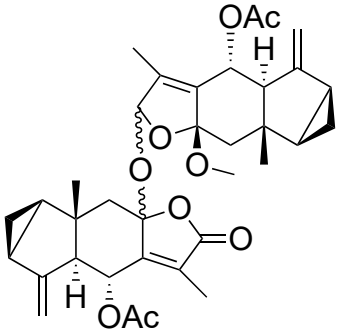
(183) $R_1 = CH_3$, 8*R*, 12′*S*
(184) $R_1 = CH_2CH_3$, 8R, 12′*S*
(185) $R_1 = CH_3$, 8′*S*, 12′*R*



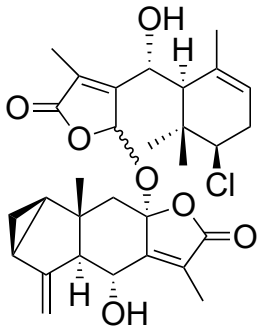
(186) R = CH_3
(187) R = H

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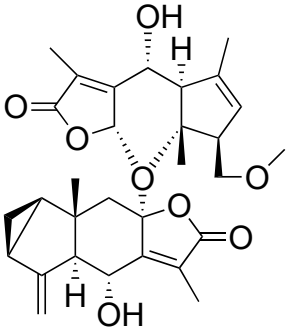
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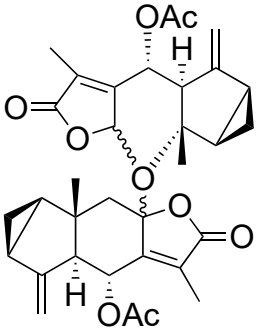
(188) 8*R*, 12′*S*
(189) 8*S*, 12′*R*



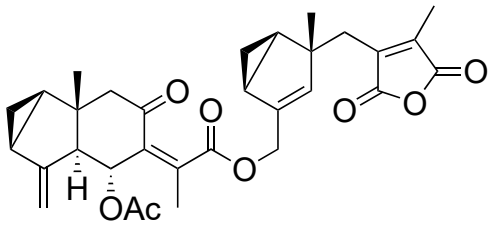
(190) 8′*S*
(191) 8′*R*



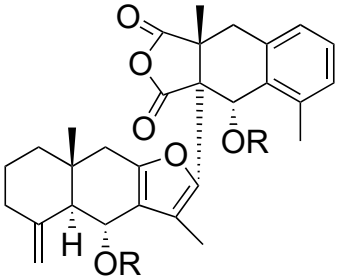
(192)



(193) 8*R*, 8′*R*
(194) 8*R*, 8′*S*
(195) 8*S*, 8′*R*

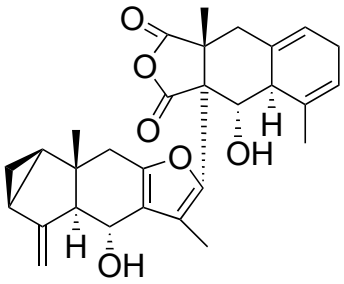


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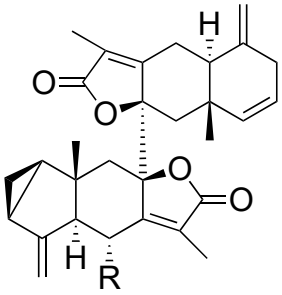


(197) R = OH
(198) R = $COCH_3$

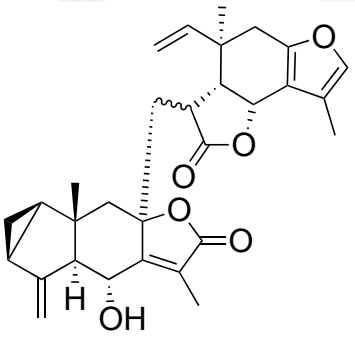
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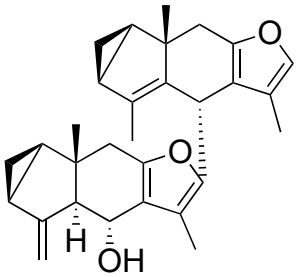
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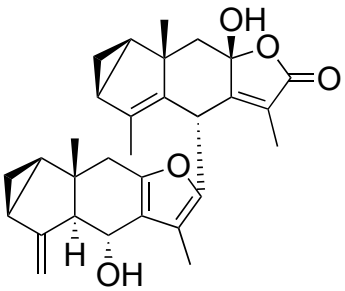
(200) R = H
(201) R = OH



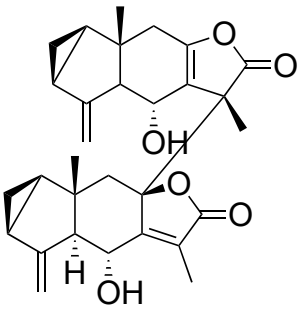
(202) 4′ α-H
(203) 4′ β-H



(204)



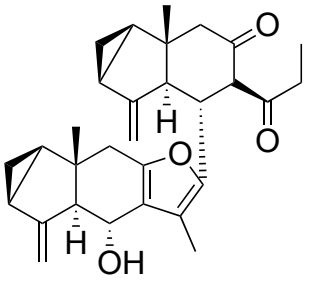
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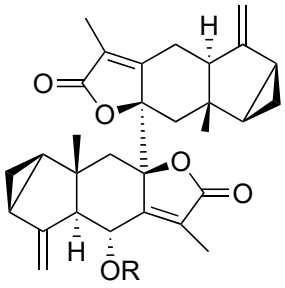
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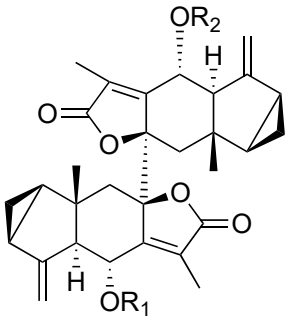
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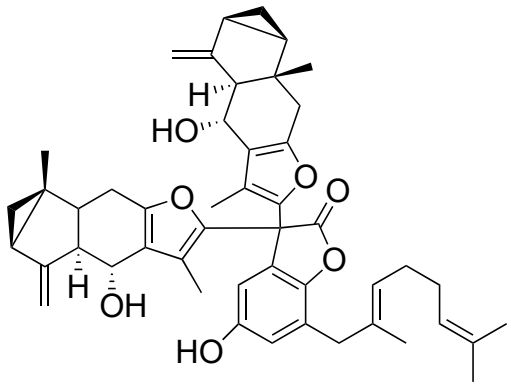
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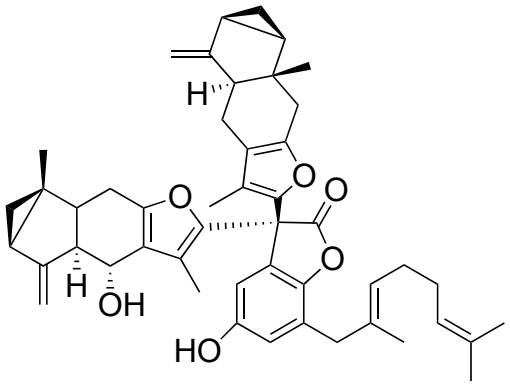
(208) R = H
(209) R = $COCH_3$



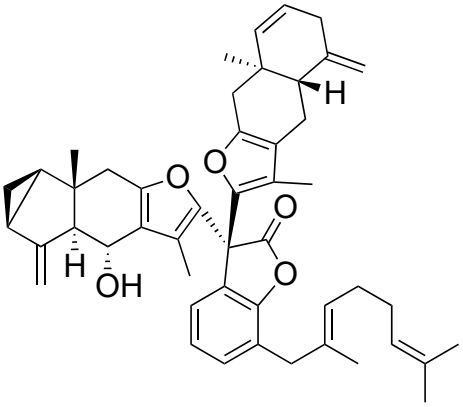
(210) R_1 = $COCH_3$, R_2 = H
(211) R_1 = R_2 = $COCH_3$
(212) R_1 = R_2 = H



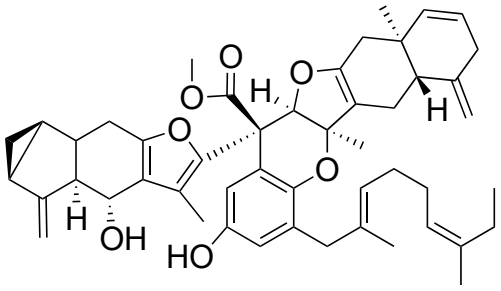
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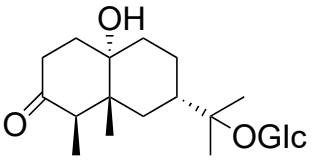
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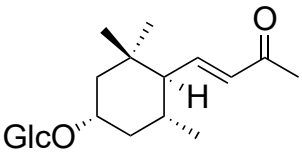
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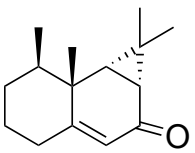
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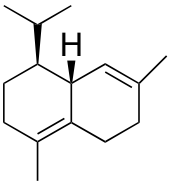
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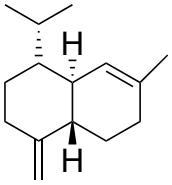
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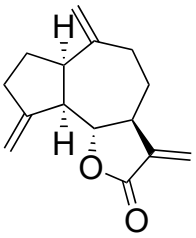
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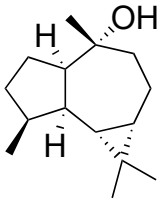
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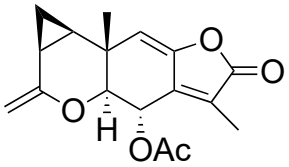
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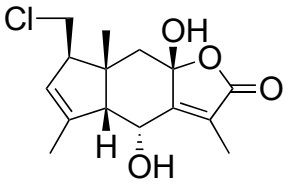
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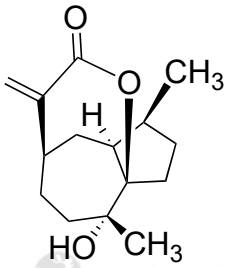
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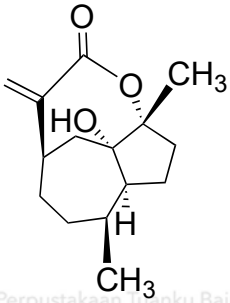
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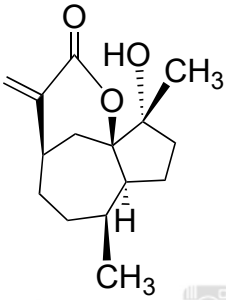
(225)



(226)



(227)



(228)

2.3.2 Alkaloids

Alkaloids are a diverse group of naturally occurring organic compounds predominantly found in plants, characterized by the presence of basic nitrogen atoms. These compounds typically have significant physiological effects on humans and animals, which makes them highly valuable in the field of medicine. Chemically, they often feature nitrogen atoms within heterocyclic rings, contributing to their basic (alkaline) nature. Alkaloids serve various ecological roles, such as defending plants against herbivores and pathogens. In medicine, alkaloids are utilized for their potent pharmacological properties.

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Based on Figure 2.2, alkaloids are divided into several classes based on their chemical structures (Azzeme & Zaman, 2019). Several studies on the alkaloids of *Lindera* species were documented starting from 1994 to 2023, as tabulated in Table 2.5.

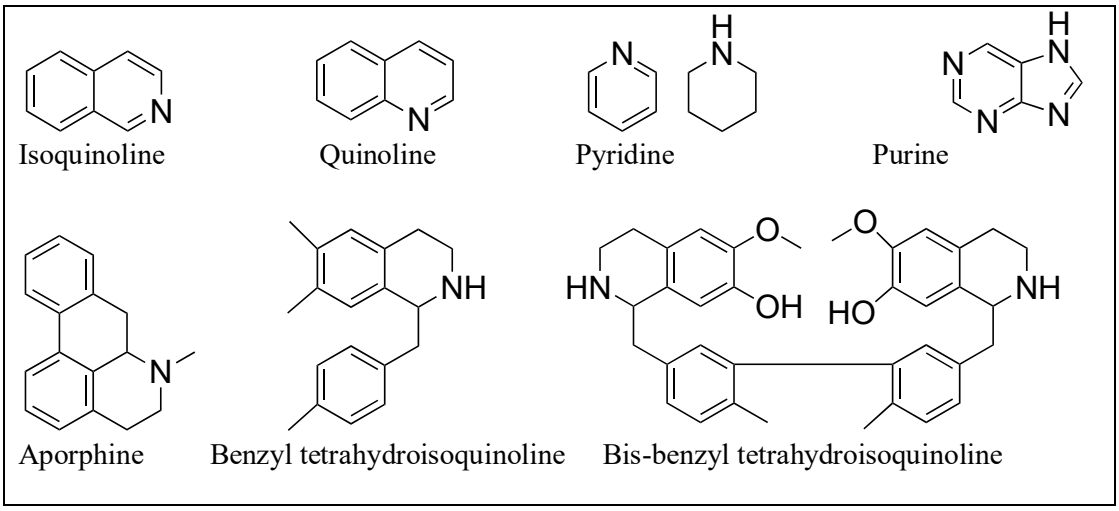


Figure 2.2. Classification of alkaloids

Eight *Lindera* species have been reported on alkaloids which were from *L. aggregata*, *L. glauca*, *L. chunii*, *L. megaphylla*, *L. reflexa*, *L. radix*, *L. myrrha*, and *L. oldhanii* with a total of 65 alkaloids. They were identified as amides (9 compounds), aporphines (33 compounds), benzyl-tetrahydroisoquinolines (7 compounds), bis-benzyltetrahydroisoquinolines (5 compounds), and isoquinolines (5 compounds).

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Table 2.5

Alkaloids isolated from several Lindera species

Compounds	Species	Part	References
AMIDES			
Lindera aggrine B (229)	*L. aggregata*	Roots	Kuo et al., 2020
Dehydrodicentrine (230)	*L. megaphylla*	Flower	Chen et al., 1995
N-*cis*-sinapoyltyramine (231)	*L. glauca*	Aerial	Chang et al., 2001
N-*trans*-sinapoyltyramine (232)	*L. glauca*	Aerial	Chang et al., 2001
N-*cis*-feruloyltyramine (233)	*L. glauca*	Aerial	Chang et al., 2001
N-*trans*-feruloyltyramine (234)	*L. glauca*	Aerial	Chang et al., 2001
Squamolone (235)	*L. glauca*	Aerial	Chang et al., 2001
Northalifoline (236)	*L. aggregata*	Roots	Ma et al., 2015
Thalifoline (237)	*L. aggregata*	Roots	Ma et al., 2015
APORPHINES			
7-Oxohernagine (238)	*L. chunii*	Roots	Zhang et al., 2002
7-Oxohernangerine (239)	*L. chunii*	Roots	Zhang et al., 2002
Hernandonine (240)	*L. chunii*	Roots	Zhang et al., 2002
Lindechunine A (241)	*L. chunii*	Roots	Zhang et al., 2002
Lycicamine (242)	*L. glauca*	Aerial	Chang et al., 2000
Actinodaphnine (243)	*L. aggregata*	Roots	Yang et al., 2020b
Bulbocapnine (244)	*L. aggregata*	Roots	Chen, 2015
Hernangerine (245)	*L. aggregata*	Roots	Zhu et al., 2012
Boldine (246)	*L. aggregata*	Roots	Yang et al., 2020b
D-dicentrine (247)	*L. megaphylla*	Flower	Chen et al., 1995

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Table 2.5 *(continue)*

Compounds	Species	Part	References
Isoboldine (248)	*L. angustifolia*	Roots	Zhao et al., 2005
Laetanine (249)	*L. glauca*	Aerial	Chang et al., 2001
Norboldine (250)	*L. aggregata*	Roots	Gan et al., 2009a
Laurotetanine (251)	*L. aggregata*	Roots	Gan et al., 2009a
N-methyllaurotetanine (252)	*L. aggregata*	Roots	Gan et al., 2009a
Laurolitsin (253)	*L. strychinifolia*	Roots	Cao et al., 2016
Norboldine acetate (254)	*L. aggregata*	Roots	Gan et al., 2009a
N-Nordicentrine (255)	*L. oldhanii*	Leaves	Chen, 1977
Norisoboldine (256)	*L. aggregata*	Roots	Chou et al., 2005
Hernandine (257)	*L. chunii*	Roots	Zhang et al., 2002
Launobine (258)	*L. umbellata*	Stems	Kozuka et al., 1985
Norisocorydine (259)	*L. angustifolia*	Roots	Zhao et al., 2006
N-methylhernangerine (260)	*L. oldhanii*	Leaves	Chen, 1977
Hernavine (261)	*L. myrrha*	Roots	Phan et al., 1994
Hernangerine (262)	*L. aggregata*	Roots	Zhu et al., 2012
Linderaline (263)	*L. aggregata*	Roots	Chou et al., 2005
Lindcarpine (264)	*L. pipericarpa*	Roots	Kiang & Sim, 1967
N-Methylovigerine (265)	*L. oldhanii*	Leaves	Chen, 1977
O-Methylbulbocapnine (266)	*L. megaphylla*	Flower	Chen et al., 1995
N-Methylhernovine (267)	*L. megaphylla*	Flower	Chou et al., 1994
Secoboldine (268)	*L. aggregata*	Roots	Yang et al., 2020b
Secolaurolitsine (269)	*L. aggregata*	Roots	Yang et al., 2020b

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Table 2.5 *(continue)*

Compounds	Species	Part	References
Linderine A (270)	*L. aggregata*	Roots	Duan et al., 2021
BENZYL TETRAHYDROISOQUINOLINE			
(1*S*)-5′-O-p-Hydroxy benzoyl norreticuline (271)	*L. aggregata*	Roots	Yang et al., 2020b
Norjuziphine (272)	*L. aggregata*	Roots	Yang et al., 2020b
Reticuline (273)	*L. aggregata*	Roots	Gan et al., 2009a
Protosinomenine (274)	*L. aggregata*	Roots	Chou et al., 2005
Laudanosoline 3′,4′-dimethyl ether (275)	*L. aggregata*	Roots	Chou et al., 2005
Argemexirine (276)	*L. aggregata*	Roots	Gan et al., 2008
Magnocurarine (277)	*L. angustifolia*	Roots	Zhou et al., 2005
BIS-BENZYL TETRAHYDROISOQUINOLINE			
(1′*S*)-12′-Hydroxyl-linderegatine (278)	*L. aggregata*	Roots	Yang et al., 2020b
(1*R*, 1′*R*)-11,11′-Biscoclaurine (279)	*L. aggregata*	Roots	Yang et al., 2020b
Costaricine (280)	*L. aggregata*	Roots	Yang et al., 2020b
Linderegatine (281)	*L. aggregata*	Roots	Gan et al., 2008
Lindoldhamine (282)	*L. oldhanii*	Leaves	Lu & Chen, 1977
ISOQUINOLINE			
Demethylcoclaurine-7-O-glucoside (283)	*L. aggregata*	Roots	Peng et al., 2020

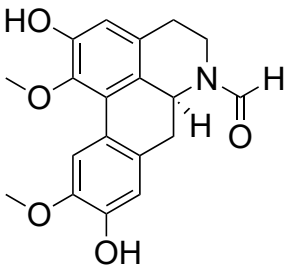
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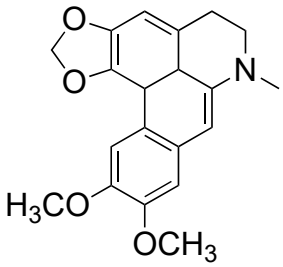
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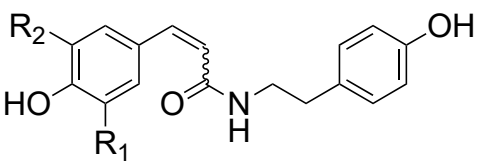
Compounds	Species	Part	References
Karakoramine (284)	*L. aggregata*	Roots	Peng et al., 2020
Pallidine (285)	*L. aggregata*	Roots	Gan et al., 2009a
Salutaridine (286)	*L. aggregata*	Roots	Yang et al., 2020b
N-Methylflavinantine (287)	*L. glauca*	Aerial	Chang et al., 2001
OTHERS			
Norcodeine (288)	*L. radix*	Roots	Zou et al., 2021
Tetrahydroberberine (289)	*L. glauca*	Aerial	Chang et al., 2000
Boldine n-oxide (290)	*L. aggregata*	Roots	Yang et al., 2020b
N-methyllaurotetanine n-oxide (291)	*L. aggregata*	Roots	Yang et al., 2020b
Pronuciferine (292)	*L. aggregata*	Roots	Gan et al., 2009a
Reticuline n-oxide (293)	*L. aggregata*	Roots	Yang et al., 2020b



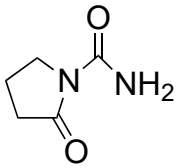
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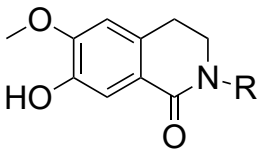
(230)



(231) $R_1 = R_2 = OCH_3$, *E*
(232) $R_1 = R_2 = OCH_3$, *Z*
(233) $R_1 = H$, $R_2 = OCH_3$, *E*
(234) $R_1 = H$, $R_2 = OCH_3$, *Z*



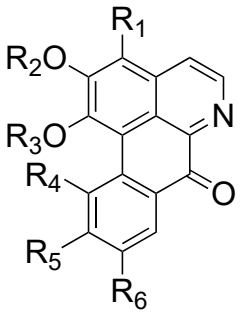
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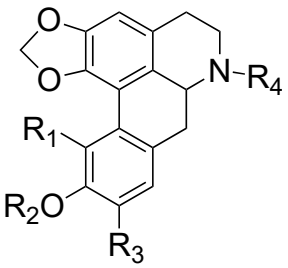
(236) R = H
(237) R = CH_3

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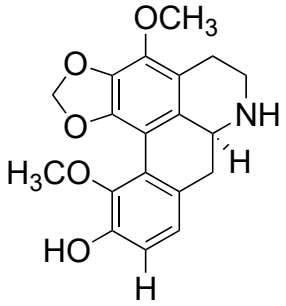
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(239) $R_1 = R_6 = H$, $R_2 = R_3 = -CH_2-$, $R_4 = OCH_3$, $R_5 = OH$
(240) $R_1 = R_6 = H$, $R_2 = R_3 = R_4 = R_5 = -CH_2-$
(241) $R_1 = R_4 = OCH_3$, $R_2 = R_3 = -CH_2-$, $R_5 = OH$, $R_6 = H$
(242) $R_1 = R_4 = R_5 = R_6 = H$, $R_2 = R_3 = CH_3$



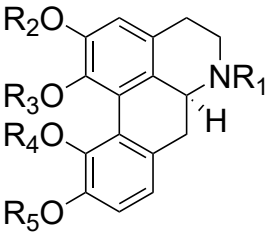
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(244) $R_1 = OH$, $R_2 = R_4 = CH_3$, $R_3 = H$
(245) $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$



(246) $R_1 = R_3 = R_4 = CH_3$, $R_2 = R_5 = H$
(247) $R_1 = R_4 = R_5 = CH_3$, $R_2 = R_3 = -CH_2-$
(248) $R_1 = R_2 = R_4 = CH_3$, $R_3 = R_5 = H$
(249) $R_1 = R_2 = R_4 = H$, $R_3 = R_5 = CH_3$
(250) $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = CH_3$
(251) $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = CH_3$
(252) $R_1 = R_2 = R_3 = R_4 = CH_3$, $R_5 = H$
(253) $R_1 = R_2 = R_5 = Ac$, $R_3 = R_4 = CH_3$
(254) $R_1 = Ac$, $R_2 = R_5 = H$, $R_3 = R_4 = CH_3$
(255) $R_1 = H$, $R_2 = R_3 = -CH_2-$, $R_4 = R_5 = CH_3$
(256) $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = CH_3$



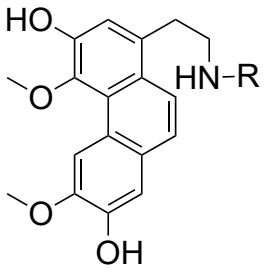
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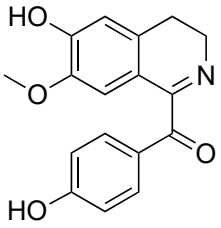
(258) $R_1 = H$, $R_2 = R_3 = R_4 = -CH_2-$, $R_5 = CH_3$
(259) $R_1 = H$, $R_2 = R_3 = R_4 = R_5 = CH_3$
(260) $R_1 = R_4 = CH_3$, $R_2 = R_3 = CH_2$, $R_5 = OH$
(261) $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = CH_3$
(262) $R_1 = R_5 = H$, $R_2 = R_3 = -CH_2-$, $R_4 = CH_3$
(263) $R_1 = R_2 = R_3 = H$, $R_4 = R_5 = CH_3$
(264) $R_1 = R_2 = R_4 = H$, $R_3 = R_5 = CH_3$
(265) $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = -CH_2-$
(266) $R_1 = CH_3$, $R_2 = R_3 = -CH_2-$, $R_4 = H$, $R_5 = CH_3$
(267) $R_1 = R_3 = R_4 = CH_3$, $R_2 = R_5 = H$

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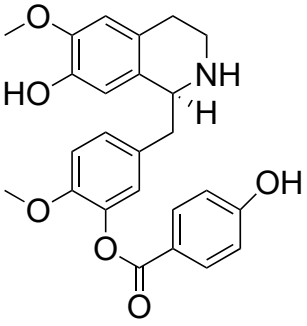
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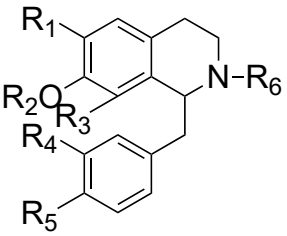
(268) R = CH_3
(269) R = H



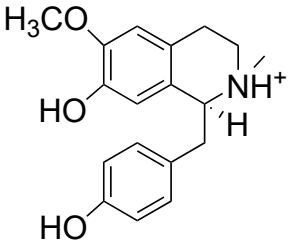
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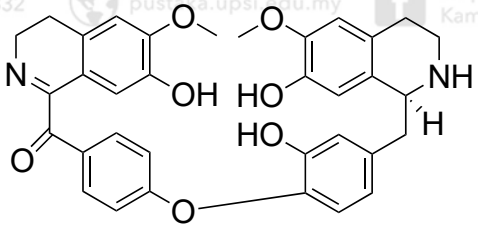
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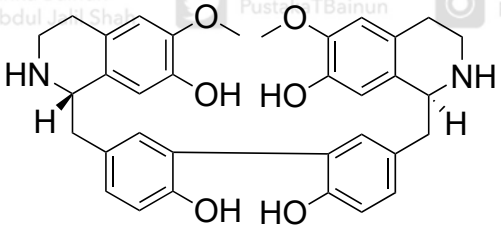
(272) $R_1 = R_4 = R_6 = H$, $R_2 = CH_3$, $R_3 = R_5 = OH$
(273) $R_1 = R_5 = OCH_3$, $R_2 = R_3 = H$, $R_4 = OH$, $R_6 = CH_3$
(274) $R_1 = R_4 = OH$, $R_2 = R_6 = CH_3$, $R_3 = H$, $R_5 = OCH_3$
(275) $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = R_5 = OCH_3$, $R_6 = CH_3$
(276) $R_1 = OH$, $R_2 = R_3 = R_4 = R_6 = H$, $R_5 = OCH_3$



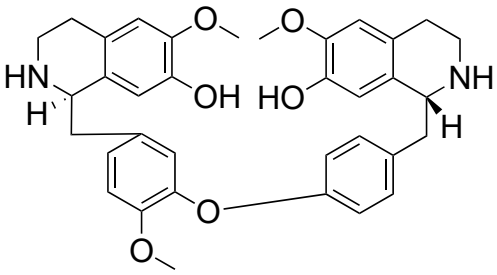
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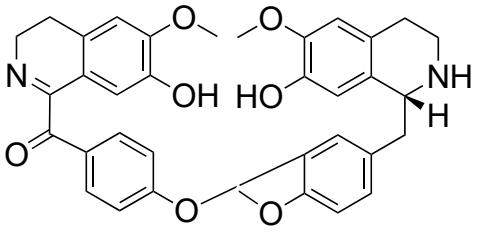
(278)



(279)



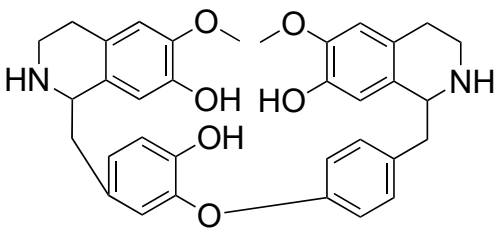
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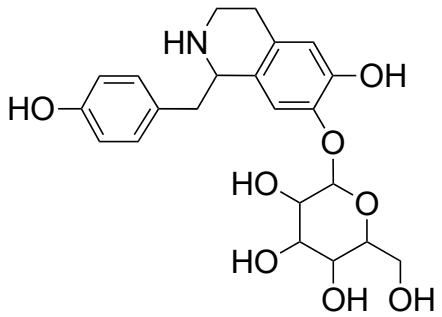
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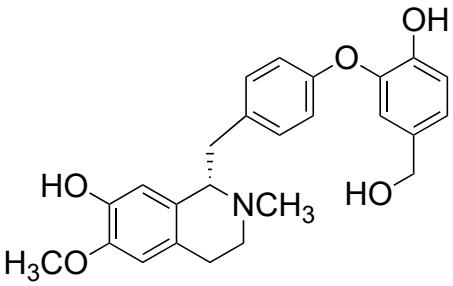
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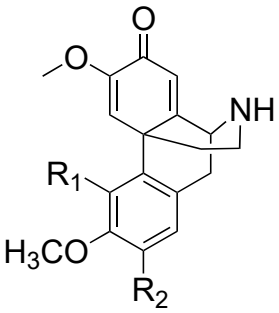
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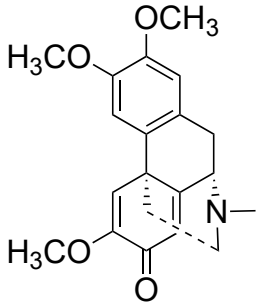
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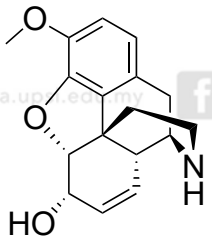
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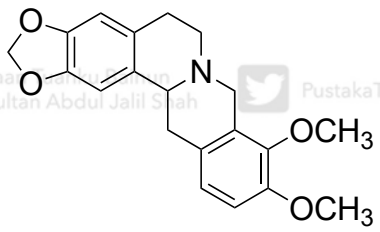
(285) R_1 = H, R_2 = OH
(286) R_1 = OH, R_2 = H



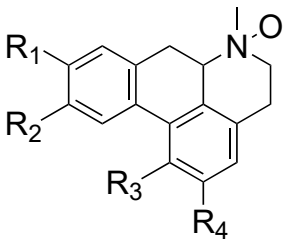
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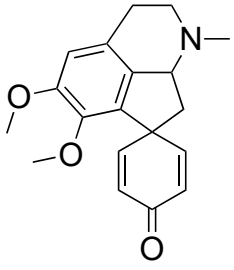
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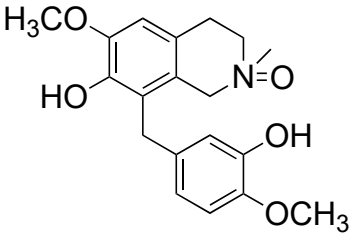
(289)



(290) R_1 = R_4 = OH, R_2 = R_3 = OCH_3
(291) R_1 = OH, R_2 = R_3 = R_4 = OCH_3



(292)



(293)

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2.3.3 Flavonoids

Flavonoids are natural compounds with various phenolic structures found in fruits, vegetables, grains, bark, roots, stems, and flowers. Various subspecies and geographic distributions include various types of flavonoids. These natural products are widely known for therapeutic benefits and today considered a vital component in a number of nutraceutical, pharmacological, medical, and cosmetic applications (Panche et al., 2016).

Based on Figure 2.3, flavonoids can be divided into several classes based on their sources and chemical structures such as anthocyanins, chalcones, flavones, flavonols, flavanols and flavanones (Panche et al., 2016). The various classes of flavonoids differ in oxidation level and substitution pattern of the C ring, while the individual compounds within a class differ in the pattern of substitution of A and B rings (Kumar & Pandey, 2013).

Several studies on the flavonoids of *Lindera* species were documented starting from 1985 to 2022. Seven *Lindera* species have been reported with flavonoids which were from *L. aggregata*, *L. erythcarpa*, *L. umbellata*, *L. lucida*, *L. oxyphlla*, *L. glauca*, and *L. obtusiloba.* There were 42 compounds that was classified to flavonoids isolated from *Lindera* species. They were known as chalcones (5 compounds), dihydrochalcones (10 compounds), flavanones (10 compounds), flavonols (16 compound), and flavone (1 compounds). These isolated compounds were tabulated in Table 2.6.

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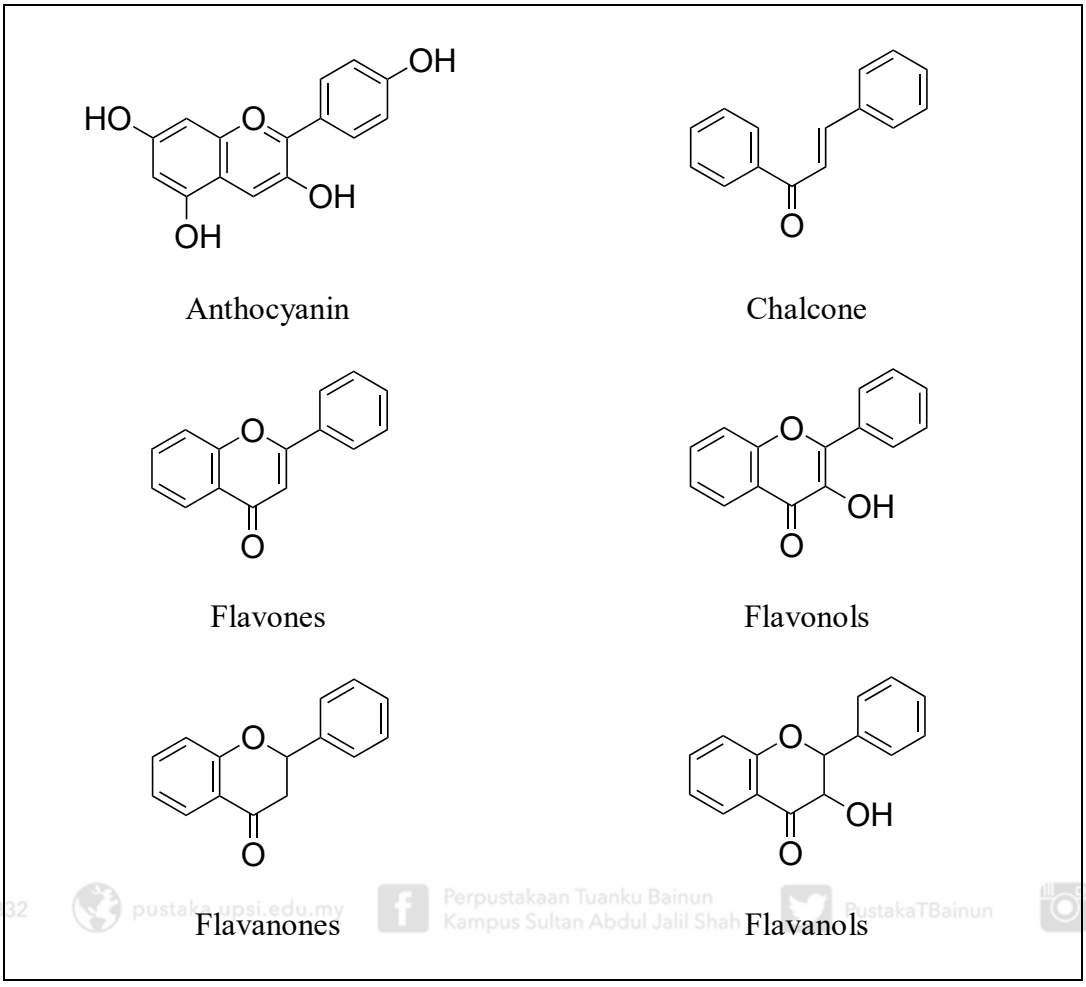


Figure 2.3. Classification of flavonoids

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Table 2.6

Flavonoids isolated from several Lindera species

Compounds	Species	Part	References
CHALCONE			
Flavokawain B (294)	*L. oxyphlla*	Bark	Hosseinzadeh et al., 2013
Kanakugiol (295)	*L. erythrocarpa*	Aerial	Kim et al., 2011
Pedicellin (296)	*L. lucida*	Twigs	Leong et al., 1998
Linderachalcone (297)	*L. umbellata*	Leaves	Ichino et al., 1989b
Neolinderatin (298)	*L. umbellata*	Leaves	Ichino et al., 1989c
DIHYDROCHALCONE			
3′,5′-Dihydroxy-2′,4′,6′-trimethoxydihydrochalcone (299)	*L. lucida*	Twigs	Leong et al., 1998
Dihydrokanakugiol (300)	*L. umbellata*	Leaves	Ichino et al., 1988
Dihydropashanone (301)	*L. umbellata*	Leaves	Ichino et al., 1988
Linderatin (302)	*L. umbellata*	Leaves	Tanaka et al., 1984
Methyllinderatin (303)	*L. umbellata*	Leaves	Ichino et al., 1989c
Kanakugin (304)	*L. erythrocarpa*	Leaves	Kim et al., 2011
Nubigenol (305)	*L. aggregata*	Leaves	Zhang et al., 2003b
Onysilin (306)	*L. oxyphylla*	Bark	Hosseinzadeh et al., 2013
Pinostrobin (307)	*L. umbellata*	Leaves	Ichino et al., 1988
Pinocembrin (308)	*L. umbellata*	Leaves	Ichino et al., 1988
3′-O-methyl-(–)-epicatechin (309)	*L. umbellata*	Twigs	Morimoto et al., 1985

(continue)

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Table 2.6 *(continue)*

Compounds	Species	Part	References
FLAVANONES			
3′,4′ -Di-O-methyl-(–)-epicatechin (310)	*L. umbellata*	Twigs	Morimoto et al., 1985
5,3′-Di-O-methyl-(–)-epicatechin (311)	*L. umbellata*	Twigs	Morimoto et al., 1985
5,7,3′-Tri-O-methyl-(–)-epicatechin (312)	*L. umbellata*	Twigs	Morimoto et al., 1985
Catechin (313)	*L. umbellata*	Stems	Ezaki et al., 1985
	L. aggregata	Stems	Zhang et al., 2003d
Epicatechin (314)	*L. umbellata*	Stems	Ezaki et al., 1985
	L. erythrocarpa	Aerial	Kim et al., 2011
Epigallocatechin (315)	*L. aggregata*	Leaves	Zhang et al., 2003d
Isolinderatone (316)	*L. umbellata*	Leaves	Ichino et al., 1989b
Linderatone (317)	*L. umbellata*	Leaves	Ichino et al., 1989a
Hesperidin (318)	*L. aggregata*	Leaves	Chou et al., 1999
FLAVONE			
5-Hydroxy-6,7,8-trimethoxyflavone (319)	*L. lucida*	Twigs	Leong et al., 1998
Astragaline (320)	*L. aggregata*	Leaves	Luo et al., 2009
Kaempferol (321)	*L. aggregata*	Leaves	Luo et al., 2009
Kaempferol-3-O-L-arabinopyranoside (322)	*L. aggregata*	Leaves	Zhang et al., 2001

(continue)

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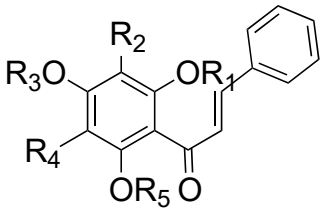
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Table 2.6 *(continue)*

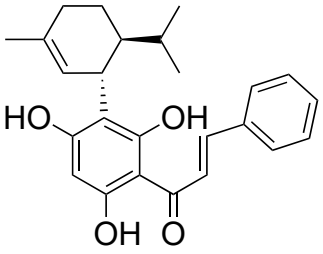
Compounds	Species	Part	References
FLAVONOLS			
Kaempferol-3-O-β-D-galactoside (323)	*L. aggregata*	Leaves	Zhao et al., 2012
Kaempferol-3-O-β-D-galactopyranoside (324)	*L. aggregata*	Leaves	Zhao et al., 2012
Afzelin (325)	*L. obtusiloba*	Stems	Lee et al., 2011
Avicularin (326)	*L. obtusiloba*	Stems	Lee et al., 2011
Kaempferol-3-O-(2″-O-β-D-glucopyranosyl)-α-L-rhamnopyranoside (327)	*L. aggregata*	Leaves	Luo et al., 2009
Isoquercitrin (328)	*L. umbellata*	Branches	Takizawa, 1984
Hyperin (329)	*L. obtusiloba*	Stems	Lee et al., 2011
Rutin (330)	*L. umbellata*	Branches	Takizawa, 1984
Quercetin (331)	*L. aggregata*	Leaves	Zhang et al., 2001
Quercetin-3-O-rhamnoside (332)	*L. aggregata*	Leaves	Zhang et al., 2001
Quercetin-3-O-β-D-galacto-pyranoside (333)	*L. aggregata*	Leaves	Zhang et al., 2001
Quercetin-3-O-β-D-glucoside (334)	*L. aggregata*	Leaves	Liu et al., 2007
Quercetin-3-O-β-D-arabinofuranoside (335)	*L. aggregata*	Leaves	Liu et al., 2007

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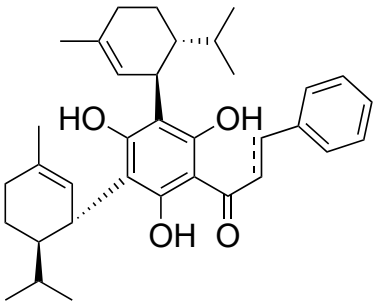
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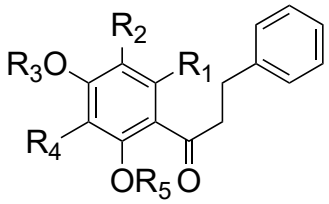
(294) $R_1 = R_3 = CH_3$, $R_2 = R_4 = R_5 = H$
(295) $R_1 = H$, $R_2 = R_4 = OCH_3$, $R_3 = R_5 = CH_3$
(296) $R_1 = R_3 = R_5 = CH_3$, $R_2 = R_4 = OCH_3$



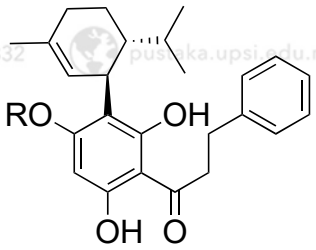
(297)



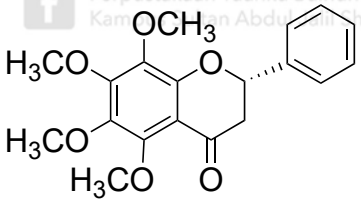
(298)



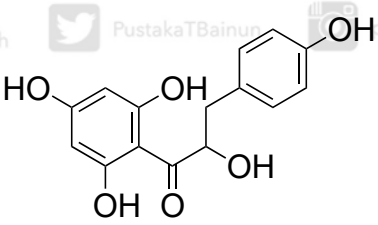
(**299)** $R_1 = OCH_3$, $R_2 = R_4 = OH$, $R_3 = R_5 = CH_3$
(300) $R_1 = R_4 = R_5 = H$, $R_2 = OCH_3$, $R_3 = CH_3$
(301) $R_1 = R_4 = R_5 = H$, $R_2 = OCH_3$, $R_3 = CH_3$



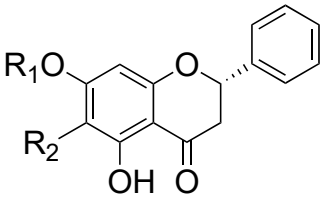
(302) R = H
(303) R = CH_3



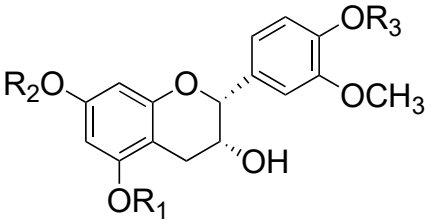
(304)



(305)



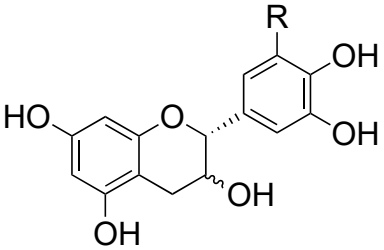
(306) $R_1 = CH_3$, $R_2 = OCH_3$
(307) $R_1 = CH_3$, $R_2 = H$
(308) $R_1 = R_2 = H$



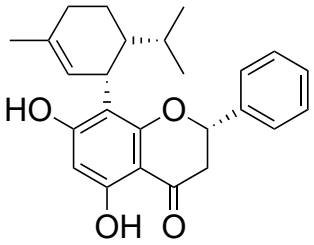
(309) $R_1 = R_2 = R_3 = H$
(310) $R_1 = R_2 = H$, $R_3 = CH_3$
(311) $R_1 = CH_3$, $R_2 = R_3 = H$
(312) $R_1 = R_2 = CH_3$, $R_3 = H$

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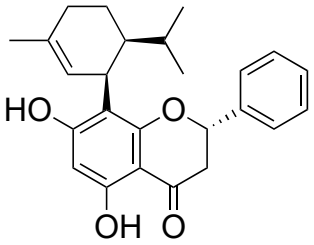
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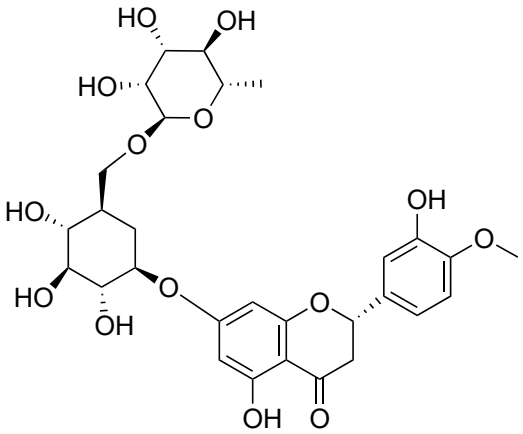
(313) R = H, β-OH
(314) R = H, *α*-OH
(315) R = OH, *α*-OH



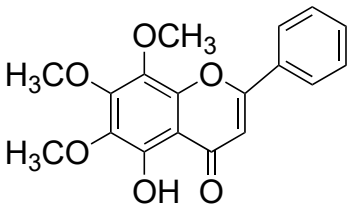
(316)



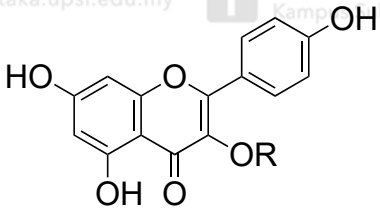
(317)



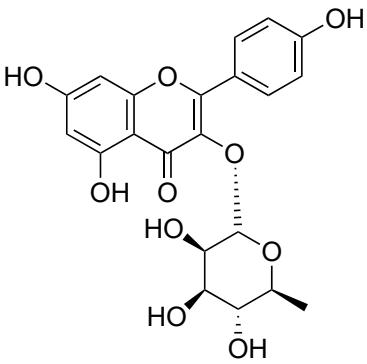
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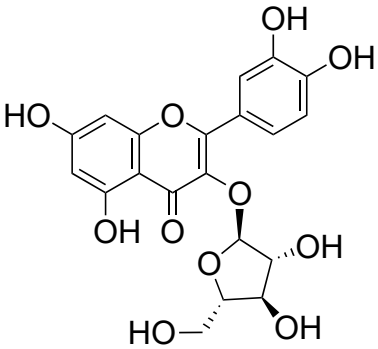
(319)



(320) R = Glucopyranosyl
(321) R = H
(322) R = Arabinfuranosyl
(323) R = Galactosyl
(324) R = Galactopyranosyl



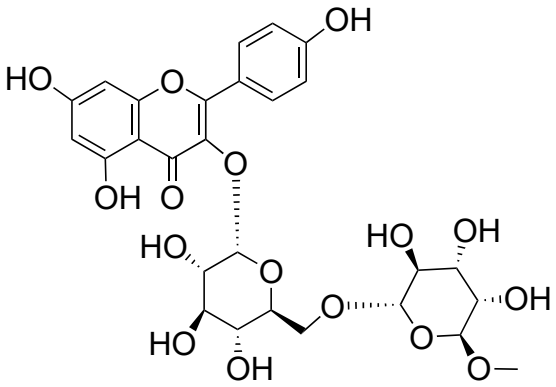
(325)



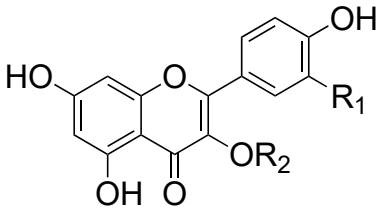
(326)

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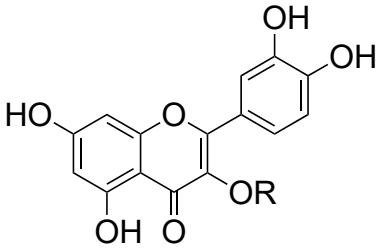
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(327)



(328) R_1 = OH, R_2 = Glc
(329) R_1 = OH, R_2 = Gal
(330) R_1 = OH, R_2 = Glc (6-1) rha



(331) R = H
(332) R = Rhamnosyl
(333) R = Galactopyranosyl
(334) R = Glucosyl
(345) R = Arabinfuranosyl

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2.3.4 Phenolics

Phenolic contain benzene rings with one or more hydroxyl substituents and range from simple phenolic molecules to highly polymerized compounds (Lin et al., 2016). Several studies on the phenolics of *Lindera* species were documented starting from 2006 to 2021. There were 37 compounds classified to phenolics isolated from *Lindera* species. Overall, four *Lindera* species have been reported with phenolics which were from *L. fruticose*, *L. aggregata*, *L. nacusua*, and *L. obtusiloba.* The most reported phenolic compounds are from *L. aggregata* and *L. obtusiloba*, each with eight reports. Besides, *L. fruticosa* and *L. radix* each with seven reports. The root part is the most common part that contains abundant of phenolic compounds. These isolated compounds as tabulated in Table 2.7.

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Table 2.7

Phenolics isolated from several Lindera species

Compounds	Species	Part	References
β-D-(3,4-Disinapoyl) fructofuranosyl-α-D-(6-sinapoyl) glucopyranoside (336)	*L. fruticosa*	Roots	Song et al., 2008
β-D-(3-Sinapoyl) fructofuranosyl-α-D-(6-sinapoyl) glucopyranoside (337)	*L. fruticosa*	Roots	Song et al., 2008
p-Hydroxybenzoic acid (338)	*L. aggregata*	Roots	Ma et al., 2015
1-O-3-Hydroxyphenyl-4,5-dimethoxy-(6′-O-3″,5″-dimethoxygalloyl)-β-D-glucopyranoside (339)	*L. nacusua*	Bark	Lei et al., 2017
1-O-3-Hydroxyphenyl-4,5-dimethoxy-(6′-O-vanilloyl)-β-D-glucopyranoside (340)	*L. nacusua*	Bark	Lei et al., 2017
1-O-3-Hydroxyphenyl-5-methoxyphenol-(6′-O-vanilloyl)-β-D-glucopyranoside (341)	*L. nacusua*	Bark	Lei et al., 2017
4-Hydroxy-6-methoxyphnol-1-O- β-D-(6′-O-syringoly) glucopyranoside (342)	*L. obtusiloba*	Stems	Choi et al., 2013
6′-O-Vanilloyltachioside (343)	*L. aggregata*	Roots	Ma et al., 2015
6-Hydroxy-4-methoxyphenol 1-O-β-D-(6′-O-syringoyl) glucopyranoside (344)	*L. nacusua*	Bark	Lei et al., 2017

(continue)

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Table 2.7 *(continue)*

Compounds	Species	Part	References
2-Methoxy-3,4- methylenedioxy-benzophenone (345)	*L. fruticosa*	Roots	Song et al., 2006
(*S*)-2-Methoxy-3,4-methylene-dioxybenzhydryl alcohol (346)	*L. fruticosa*	Roots	Song et al., 2006
3-Hydroxy-5-methoxybiphenyl (347)	*L. fruticosa*	Roots	Song et al., 2006
3,5-Dimethoxybiphenyl (348)	*L. fruticosa*	Roots	Song et al., 2006
1-Methoxy-2,5,7-trihydroxyxanthone (349)	*L. fruticosa*	Roots	Song et al., 2006
1,7-Dihydroxyxanthone (350)	*L. fruticosa*	Roots	Song et al., 2006
Benzyl 2-hydroxy-6-methoxybenzoate (351)	*L. fruticosa*	Roots	Song et al., 2006
Tyrosol (352)	*L. aggregata*	Roots	Ma et al., 2015
2-(4-Hydroxy-3-methoxyphenyl)-ethanol (353)	*L. aggregata*	Roots	Ma et al., 2015
2-(4-Hydroxy-3,5-dimethoxyphenol)-ethanol (354)	*L. aggregata*	Roots	Ma et al., 2015
2,6-Dimethoxy-p-benzoquinone (355)	*L. aggregata*	Roots	Ma et al., 2015
2,6-Dimethoxy-4-hydroxyphenyl-1-O-β-D-glucopyranoside (356)	*L. obtusiloba*	Stems	Choi et al., 2013
4,6-Dihydroxy-2-methoxyphenyl-1-O-β-D-glucopyranoside (357)	*L. obtusiloba*	Stems	Choi et al., 2013
Isotachioside (358)	*L. obtusiloba*	Stems	Choi et al., 2013

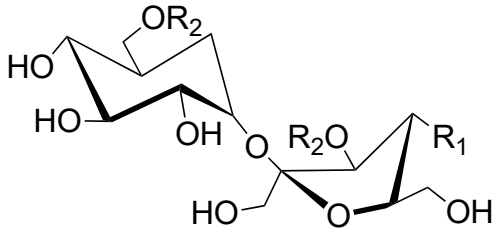
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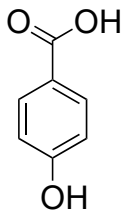
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Table 2.7 *(continue)*

Compounds	Species	Part	References
Koaburaside (359)	*L. obtusiloba*	Stems	Choi et al., 2013
Tachioside (360)	*L. obtusiloba*	Stems	Choi et al., 2013
Cryptochlorogenic acid (361)	*L. radix*	Roots	Zou et al., 2021
3-Hydroxy-1-(4-hydroxyphenyl) propan-1-one (362)	*L. aggregata*	Roots	Ma et al., 2015
4-Hydroxy-3-methoxy acetophenone (363)	*L. aggregata*	Roots	Ma et al., 2015
3-(3,4-Dihydroxyphenyl) propionic acid (364)	*L. glauca*	Aerial	Chang et al., 2000
Ferulic acid (365)	*L. radix*	Roots	Zou et al., 2021
Erigeside C (366)	*L. obtusiloba*	Stems	Choi et al., 2013
Neochlorogenic acid (367)	*L. radix*	Roots	Zou et al., 2021
Protocatechualdehyde (368)	*L. radix*	Roots	Zou et al., 2021
Salidroside (369)	*L. obtusiloba*	Stems	Choi et al., 2013
Syringic acid (370)	*L. glauca*	Aerial	Chang et al., 2000
Vanillic acid (371)	*L. glauca*	Aerial	Chang et al., 2000



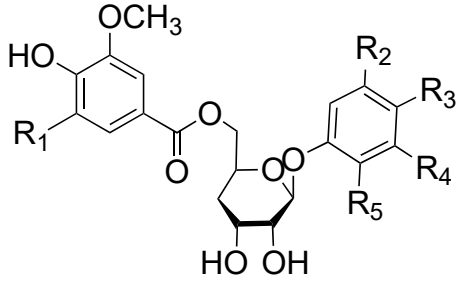
(336) $R_1 = R_2 = CP$ ($X = OCH_3$, $Y = H$)
(337) $R_1 = OH$; $R_2 = CP$ ($X = OCH_3$, $Y = H$)



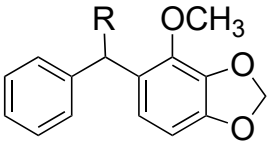
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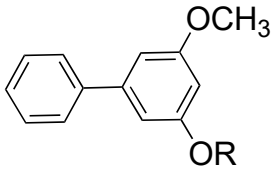
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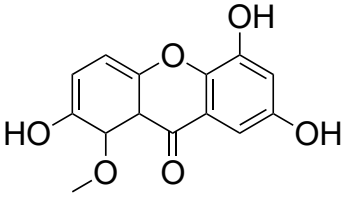
(339) $R_1 = R_3 = R_4 = OCH_3$, $R_2 = OH$, $R_5 = H$
(340) $R_1 = R_5 = H$, $R_2 = OH$, $R_3 = R_4 = OCH_3$
(341) $R_1 = R_3 = R_5 = H$, $R_2 = OH$, $R_4 = OCH_3$
(342) $R_1 = R_5 = OCH_3$, $R_2 = R_4 = H$, $R_3 = OH$
(343) $R_1 = R_2 = R_4 = H$, $R_3 = OH$, $R_5 = OCH_3$
(344) $R_1 = R_3 = OCH_3$, $R_2 = R_4 = H$, $R_5 = OH$



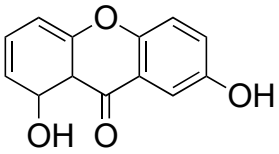
(345) R = C=O
(346) R = α-OH



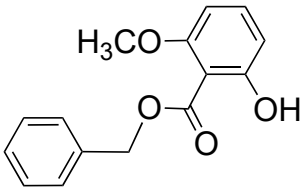
(347) R = H
(348) R = CH_3



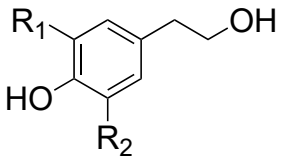
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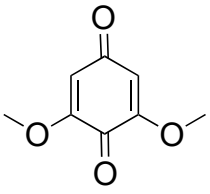
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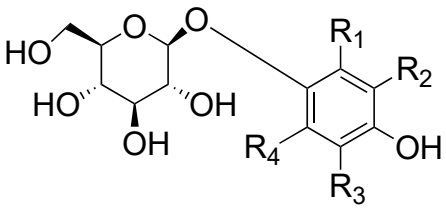
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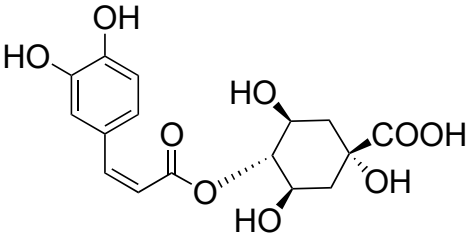
(352) $R_1 = R_2 = H$
(353) $R_1 = OCH_3$, $R_2 = H$
(354) $R_1 = R_2 = OCH_3$



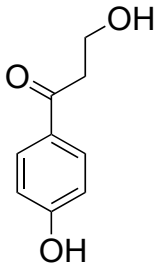
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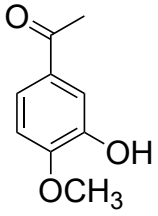
(356) $R_1 = R_4 = OCH_3$, $R_2 = R_3 = H$
(357) $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = OCH_3$
(358) $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$
(359) $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
(360) $R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$



(361)



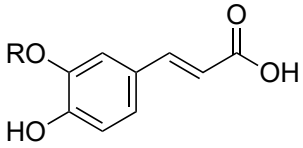
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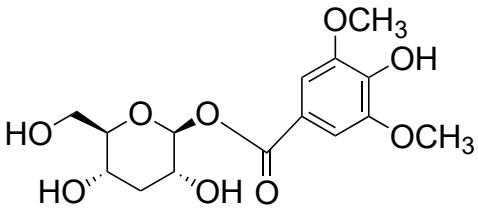
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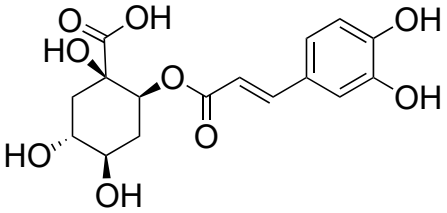
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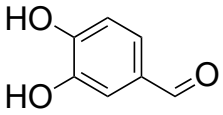
(364) R = H
(365) R = CH_3



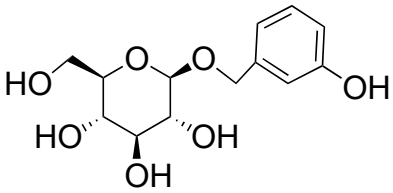
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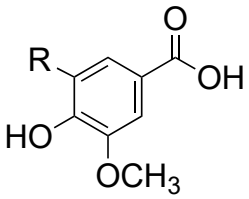
(367)



(368)



(369)



(370) R = H
(371) R = OCH_3

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2.3.5 Miscellaneous Phytochemicals

Another secondary metabolite compounds that have been identified from *Lindera* species are anthraquinones, butanolides, benzoids, benzoids glycosides, lignans, lucidones, steroids, and tannins. These compounds are tabulated in Table 2.8.

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Table 2.8

Miscellaneous phytochemicals isolated from several Lindera species

Compounds	Species	Part	References
ANTHRAQUINONES			
Demethylmacrosporine I (372)	*L. nacusua*	Bark	Wei et al., 2016b
Emodin-6-O-β-D-glucopyranoside (373)	*L. nacusua*	Bark	Wei et al., 2016b
BUTENOLIDES			
(2Z,3S,4S)-2-(11-dodecenylidene)-3-hydroxy-4-methylbutanolide (374)	*L. obtusiloba*	Stems	Kwon et al., 2000
Majorenolide (375)	*L. akoensis*	Roots	Chang et al., 2008
Majorynolide (376)	*L. akoensis*	Roots	Chang et al., 2008
Majoranolide (377)	*L. akoensis*	Roots	Chang et al., 2008
Obtusilactone (378)	*L. akoensis*	Roots	Chang et al., 2008
Isoobtusilactone (379)	*L. akoensis*	Roots	Chang et al., 2008
Obtusilactone A (380)	*L. obtusiloba*	Stems	Kwon et al., 2000
Isoobtusilactone A (381)	*L. obtusiloba*	Stems	Kwon et al., 2000
Secoaggregatalactone A (382)	*L. aggregata*	Roots	Lin et al., 2007
Litsenolide A_2 (383)	*L. akoensis*	Roots	Chang et al., 2008
BENZENOIDS			
Linderagatin A (384)	*L. aggregata*	Roots	Ma et al., 2015
Linderagatin B (385)	*L. aggregata*	Roots	Ma et al., 2015

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Table 2.8 *(continue)*

Compounds	Species	Part	References
BENZENOIDS GLYCOSIDE			
6′-O-vanilloyl-5-hydroxy-2,3-dimethoxyphenol 1-O-β-D-glucopyranoside (386)	*L. aggregata*	Roots	Kuo et al., 2020
LIGNANS			
rel-(2α,3β)-7-O-methylcedrusin (387)	*L. aggregata*	Roots	Ma et al., 2015
Lyoniresinol (388)	*L. aggregata*	Roots	Ma et al., 2015
Evofolin B (389)	*L. aggregata*	Roots	Ma et al., 2015
Reflexanbene A (390)	*L. reflexa*	Leaves	Fu et al., 2022
Reflexanbene C (391)	*L. reflexa*	Leaves	Fu et al., 2022
LUCIDONES			
Linderone A (392)	*L. oxyphylla*	Bark	Hosseinzadeh et al., 2013
Lucidone (393)	*L. erythrocarpa*	Fruits	Oh et al., 2005
Methyllinderone (394)	*L. erythrocarpa*	Fruits	Kim et al., 2011
Methyllucidone (395)	*L. erythrocarpa*	Fruits	Oh et al., 2005
Linderaspirone (396)	*L. aggregata*	Roots	Wang et al., 2010
STEROIDS			
7-Ketositosterol (397)	*L. glauca*	Stem	Huh et al., 2011
7β-Hydroxysitosterol (398)	*L. glauca*	Stem	Huh et al., 2011
β-Sitostenone (399)	*L. glauca*	Aerial	Chang et al., 2000

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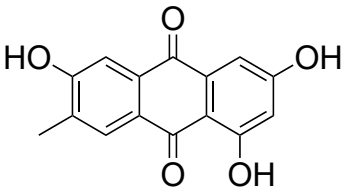
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Table 2.8 *(continue)*

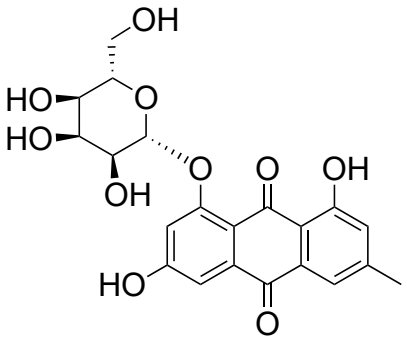
Compounds	Species	Part	References
6β-Hydroxy-β-sitostenone (400)	*L. glauca*	Aerial	Chang et al., 2000
β-Sitosterol (401)	*L. glauca*	Stem	Huh et al., 2011
Stigmasterol (402)	*L. akoensis*	Roots	Chang et al., 2008
Daucosterol (403)	*L. glauca*	Stem	Huh et al., 2011
TANNINS			
Epicatechin-(4β-8,2-O-7)-epicatechin (404)	*L. aggregata*	Stem	Zhang et al., 2003c
Epicatechin-(4β-8,2-O-7)-catechin (405)	*L. aggregata*	Stem	Zhang et al., 2003c
Epicatechin-(4β-8)-catechin (406)	*L. aggregata*	Stem	Zhang et al., 2003c
Procyanidin B_1 (407)	*L. umbellata*	Stem	Ezaki et al., 1985
Procyanidin B_2 (408)	*L. umbellata*	Stem	Ezaki et al., 1985
Procyanidin B_4 (409)	*L. umbellata*	Stem	Ezaki et al., 1985
Trimers A (410)	*L. umbellata*	Stem	Ezaki et al., 1985
Trimers B (411)	*L. umbellata*	Stem	Ezaki et al., 1985
Cinnamtannin B_1 (412)	*L. aggregata*	Stem	Zhang et al., 2003c
Cinnamtannin B_2 (413)	*L. aggregata*	Stem	Zhang et al., 2003c

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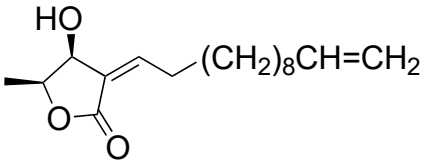
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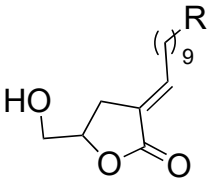
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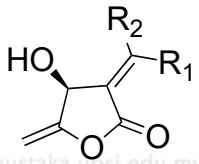
(373)



(374)

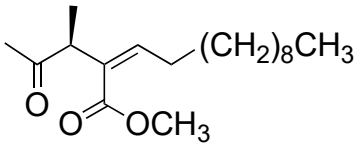


(375) R = H_2C=CH
(376) R = C≡CH
(377) R = CH_2CH_3

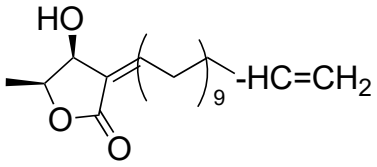


(378) R_1 = -CH_2-$(CH_2)_8$CH=CH_2, R_2 = H
(379) R_1 = H, R_2 = -CH_2-$(CH_2)_8$-CH=CH_2
(380) R_1 = -CH_2-$(CH_2)_{11}CH_3$, R_2 = H
(381) R_1 = H, R_2 = -CH_2-$(CH_2)_{11}CH_3$

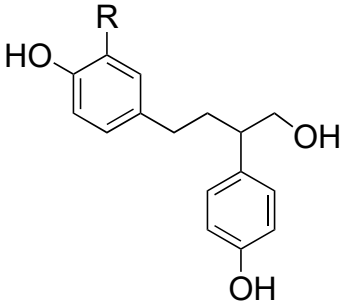
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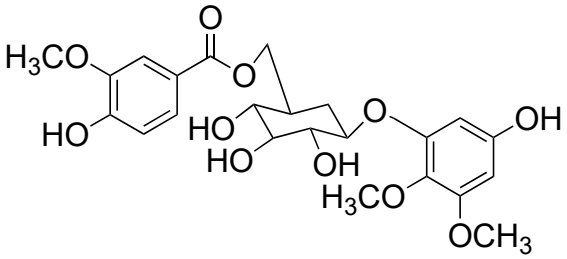
(382)



(383)



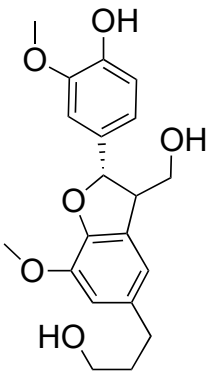
(384) R = H
(385) R = OCH_3



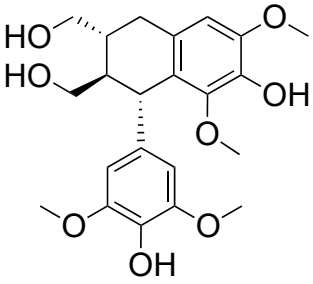
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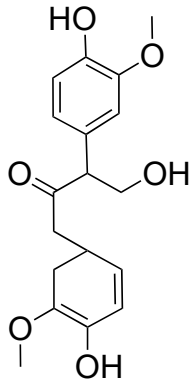
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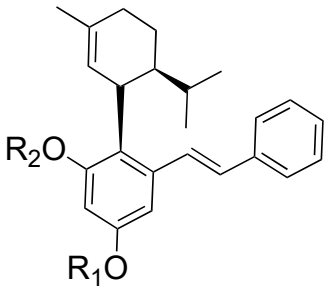
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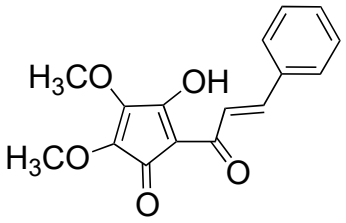
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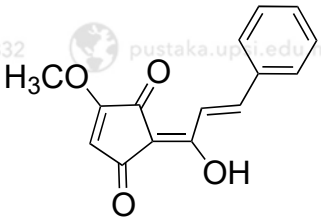
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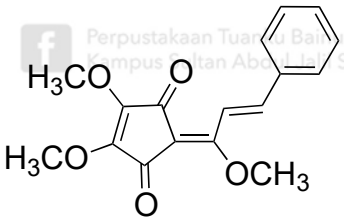
(390) $R_1 = R_2 = H$
(391) $R_1 = R_2 = CH_3$



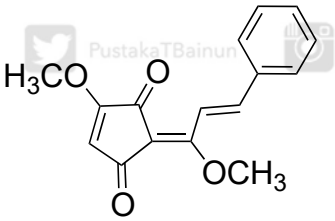
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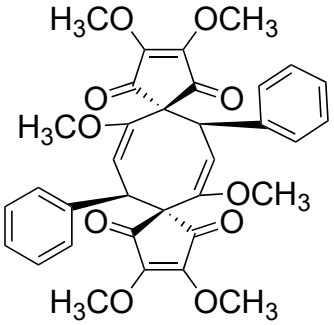
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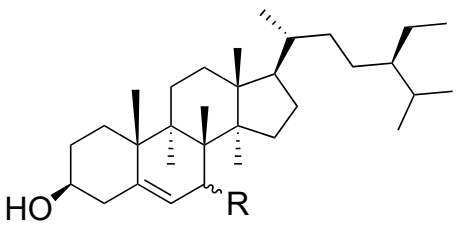
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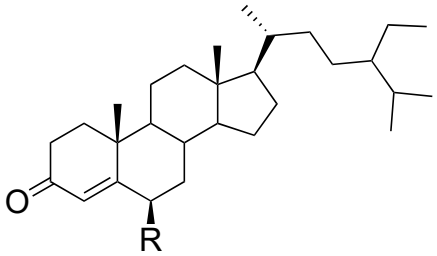
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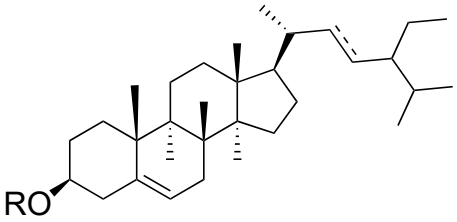
(3976) R = OH
(398) R = 7β-OH

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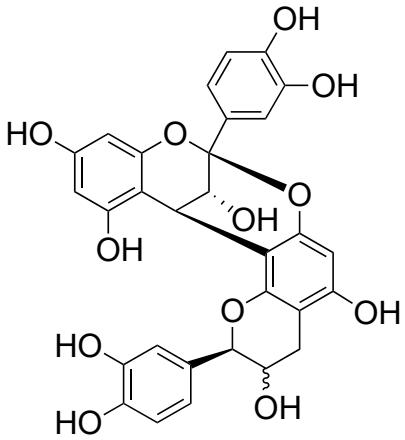
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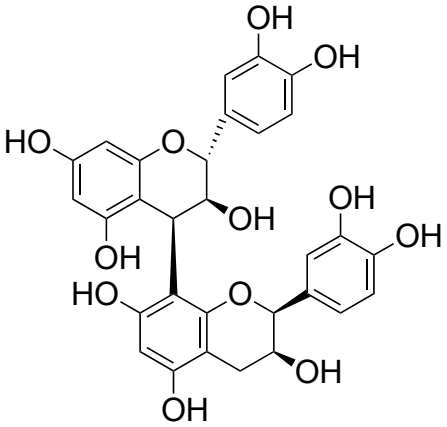
(399) R = H
(400) R = OH



(401) R = H
(402) R = H, □[22]
(403) R = Glc

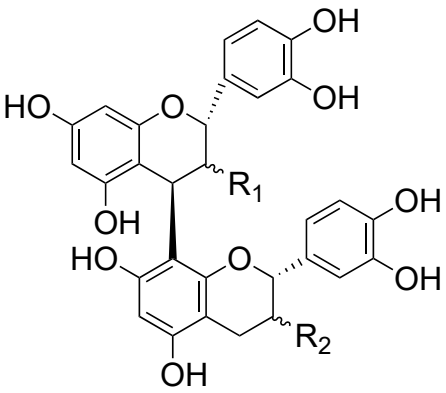


(404) β-OH
(405) α-OH

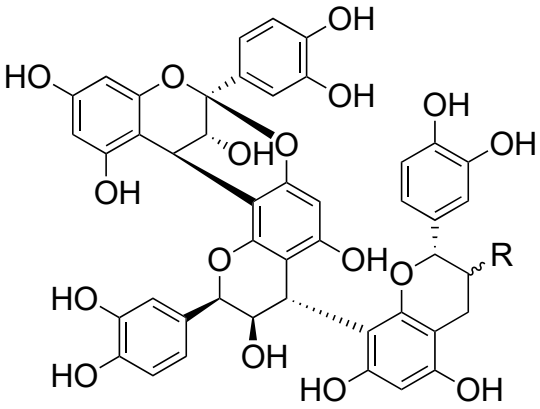


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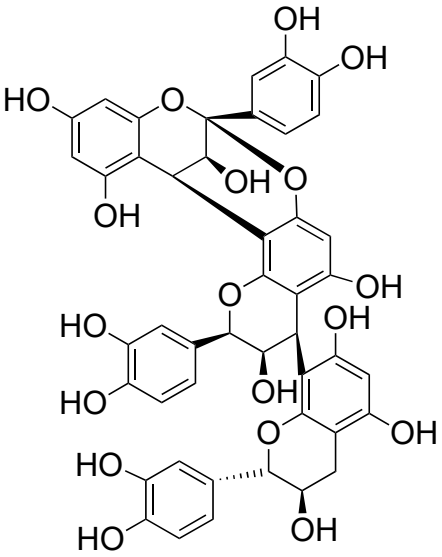
(407) R_1 = α-OH, R_2 = β-OH
(408) R_1 = R_2 = α-OH
(409) R_1 = β-OH, R_2 = α-OH



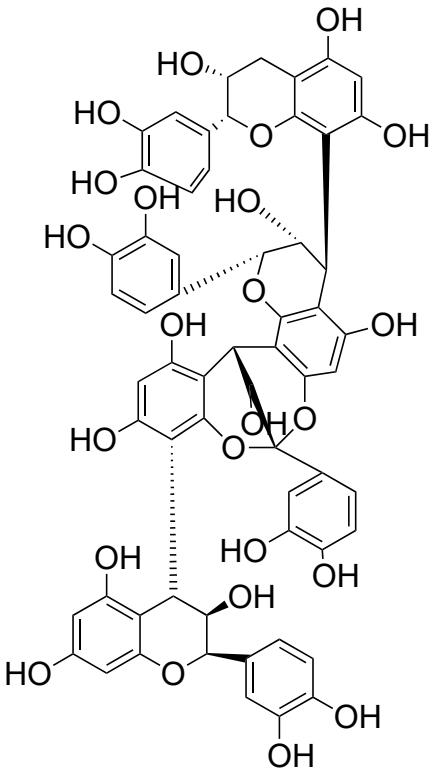
(410) R = α-OH
(411) R = β-OH

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2.4 Biological Activities of *Lindera* Species

Many researchers are attracted to discover more about biological actives as it comprises a vast range of natural products with the potential to be used in medicine, agriculture, and industry. Most of the compound that contains in the plant can be used as an agent in antioxidants, anti-inflammatory, and antibacterial. The literature study reveals that *Lindera* essential oils have been reported to exhibit various biological activities. *L. aggregata* has received the most attention and was widely investigated. Table 2.9 describes the details of the biological activities of several *Lindera* essential oils.

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Eucalyptol and linalool are two examples of major components from *Lindera* essential oils. According to Peana et al. (2002), eucalyptol and linalool have been discovered to have anti-inflammatory properties by lowering the production of inflammatory properties and blocking the activity of enzymes that cause inflammation. Based on Juergens (2014), 1,8-cineole was also described as antibacterial properties against *Staphylococcus aureus* and *Pseudomonas aeruginosa* as it can disrupt the cell membrane of bacteria by inhibiting the growth of bacteria. For antioxidant activity, β-caryophyllene and α-copaene have great effects towards antioxidant properties by lowering and reducing oxidative stress. Besides, these two components can protect the cells from damage due to the free radical oxidation activity (Ferreira et al., 2021)

For anti-inflammatory activity, several different assays were used to determine the properties, such as *in vitro* and animal models (Patil et al., 2019). Haque et al. (2020) used an *in vitro* assay to measure nitric oxide production in the cell, in which the leaf and twig oils of *L. obtusiloba* inhibited strong inhibition with IC_{50} values 0.8 and 8.7 μM, respectively. Besides, *L. aggregata* oil can also have significant inhibition of superoxide anion in human neutrophils, hence it is effective to act as anti-inflammatory agent (Lv et al., 2023). In another study, the leaf oil of *L. myrrha* are shown to have strong antibacterials since it contains α-pinene, β-pinene, and eugenol (Batiha et al., 2023). Duong et al. (2020) stated that the leaf and twig oils of *L. myrrha* showed strong inhibitory effects against *Enterococcus faecium*, *Staphylococcus aureus*, and *Acinetobacter baumannii* with the killing of percentage 85.6%, 86.7%, and 92.1%, respectively. Chen et al. (2021) state that the fruit oil of *L. gluca* also found antibacterial properties against *Shigella flexneri*.

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Table 2.9

Biological activities of several Lindera essential oils

Bioactivities	Essential oils	Description
Anti-allergic	*L. obtusiloba*	The leaf oil has strongly effective in decreasing airway hyper-responsiveness and mucus production in the lung tissue against *Streptococcus pneumoniae* (Lee et al., 2020)
	L. obtusiloba	The root oil inhibited histamine release and proinflammatory cytokine production in mast cells with percentage inhibition 66.9% and 68.1%, respectively (Choi et al., 2013)
	L. obtusiloba	The root oil can suppress the release of histamine from mast cells to prevent itching (Haque et al., 2020)
	L. obtusiloba	The leaf oil significantly inhibited the expression of IL-6 and TNF-α in mast cells to reduce allergic symptoms (Choi et al., 2013)
Anti-arthritic	*L. aggregata*	The leaf oil has shown the development of Treg cells through promoting fatty acid oxidation, thus it can control immune responses including rheumatoid arthritis with EC_{50} value 94% (Zhang et al., 2022)
Antivirus	*L. chunii*	The stem oil inhibited the fusion of HIV-1 infected with IC_{50} values 5.2 – 31.3 μM (Zhang et al., 2003a)

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Table 2.9 *(continue)*

Bioactivities	Essential oils	Description
Antibacterial	*L. myrrha*	The root oil has strong activity against *Enterococcus faecium*, *Staphylococcus aureus*, and *Acinetobacter baumannii* with killing percentage 85.6%, 86.7%, and 92.1%, respectively (Duong et al., 2020)
	L. pulcherrima	The essential oil revealed a strong activity against *Salmonella, Pasturella multocida* and *Escherichia coli* with IC_{50} values 19.0, 18.0, and 10.8 µL respectively. (Joshi & Mathela, 2012)
	L. gluca	The fruit oil has strong activity against *Shigella flexneri* with the inhibition zone diameter 25.4 nm (Chen et al., 2021)
Anticancer	*L. aggregata*	The root oil has exhibited human colorectal cancer cells with IC_{50} value 6.48 µg/mL (Kwak et al., 2022)
	L. aggregata	The root oil exhibited the transforming growth factor (TGF)-β inhibitory activity with IC_{50} value 12.9 µg/mL (Liu et al., 2021a)
	L. aggregata	The root oil showed strongly inhibited against A549 cell line and neuroprotective activity in SH-SY5Y cells (Liu et al., 2021b)

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Table 2.9 *(continue)*

Bioactivities	Essential oils	Description
Anticancer	*L. aggregata*	The root oil showed activity in a human colon cancer cell line with IC_{50} value 9.80 µM (Lv et al., 2023)
Anti-inflammatory	*L. aggregata*	The root oil exhibited human neutrophils with IC_{50} value 7.45 µM (Kuo et al., 2020)
	L. akoensis	The aerial part oil has the ability to decrease the LPS-stimulated production of nitrite in RAW264.7 cells with IC_{50} value 38.3 µM (Kuo et al., 2020)
	L. benzoin	The leaf oil showed strong inhibition in prostaglandin production in an A549 with IC_{50} value 0.82 µM (Ryen et al., 2020)
	L. aggregata	The essential oil displayed the significant inhibition of superoxide anion generation in human neutrophils with IC_{50} values 8.36 µM (Kuo et al., 2020)
	L. obtusiloba	The twig oil inhibited nitric oxide production with IC_{50} values 3.6–26.4 µM (Haque et al., 2020)
Antitumor	*L. gluca*	The essential oil showed weak activity against SMMC-7721 cell line with IC_{50} value 35.2 µM (Liu et al., 2016b)
	L. strychnifolia	The essential oil showed activity against human esophageal cancer Eca-109 cell line with IC_{50} value 24.8 µg/mL (Yan et al., 2014a)

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Table 2.9 *(continue)*

Bioactivities	Essential oils	Description
Cytotoxicity	*L. reflexa*	The root oil showed activity against MGC803 and SMMC-7721 cell lines with IC_{50} values 2.65 and 4.13 μM, respectively (Fu et al., 2019)
	L. strychnifolia	The essential oil has strong activity against liver cancer cell line and breast tumor cell line with IC_{50} values 2.85 and 3.47 μg/mL, respectively (Yan et al., 2014b)
	L. glauca	The twig oil showed strong activity against SK-MEL-2 and HCT-15 cell lines with IC_{50} values ranging from 9.9 to 12.2 μM (Liu et al., 2016b)

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Numerous biologically active compounds have been isolated from *Lindera* species previously by several researchers. Sesquiterpenes, flavonoids, phenolics, and alkaloids are among the compounds which reported mainly on anticancer, antifibrotic, anti-inflammatory, antitumor, antioxidant, anti-arthritic, cytotoxic, anti-allergic, and antihyperlipidemic properties. Isolinderalactone **(77)** has been reported to inhibit antitumor, anticancer, and anti-inflammatory activities. Chuang et al. (2018) discovered that isolinderalactone was able to trigger apoptosis or programmed cell death in a variety of cancer cells, including breast cancer cells and lung cancer cells. Fu et al. (2022) was also found that this compound has a strong inhibitory effect on tumor cell lines MGC803 and SMMC-7721 with IC_{50} values 2.65 and 4.13 μM, respectively. Kwak et al. (2022) managed to discover this compound to exhibit human-resistant colorectal cancer (CRC) cells with IC_{50} value 7.80 μM.

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In alkaloid type, the most reported compound was norisoboldine **(256)**. The compound helps by preventing the release of cytokines that promote inflammation. In addition, it has been demonstrated that norisoboldine prevents the synthesis of prostaglandin E2 (PGE2) and nitric oxide (NO), both are essential for the inflammatory response (Cao et al., 2016). Additionally, Yang et al. (2020b) reported the compound induced production of nitric oxide by lipopolysaccharide in RAW 264.7 cells (IC_{50} value 9.6 μM) as well as vascular endothelial growth factor (VEGF)-induced endothelial cell migration (IC_{50} value 15.1 μM) (Lu et al., 2013).

In flavonoids type, quercetin-3-*O*-rhamnosides **(332)** are the most reported compound that can act as an antioxidant agent. Septembre-Malaterre et al. (2022) was reported, the compound can control the activities of superoxide dismutase (SOD) and glutathione (GSH). In addition, it is also found extremely effective at increasing the body's antioxidant capacity by controlling and regulating glutathione levels (Xu et al., 2019). Koaburaside **(359)** is one of the most reported compounds in phenolic type with mainly for antiallergic effect. It is one of the compounds that significantly used to inhibit the production of histamine (Choi et al., 2013). Histamine is one of the inflammatory molecules that released by the immune system during an allergic reaction, which can result in itching, redness, swelling, and other unpleasant symptoms. Moreover, there were other biological activities of phytochemicals from *Lindera* species that have been reported as described in Table 2.10.

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Table 2.10

Biological activities of several Lindera phytochemicals

Compounds	Species	Biological activities
SESQUITEPENOIDS		
Isolinderalactone (77)	*L. aggregata*	Anticancer: Exhibited human resistant colorectal cancer (CRC) cells with IC_{50} value 7.80 μM (Kwak et al., 2022)
		Antitumor: Exhibited in breast cancer cell lines by lowering the cell proliferation to the concentration of 30-100 μM (Yen et al., 2015)
		Antitumor: Exhibited in human ovarian cancer (OC) cells and inhibit several cancer cell line growth by reducing mitochondrial superoxide and cell proliferation with a dose concentration of 5-50 μM for 24 h (Rajina et al., 2020)
		Anti-inflammatory: Inhibit the invasion and migration of A549 cancer cells by involving the inhibition of MMP-2 and β-catenin protein expression with the range dose concentration 1-10 μM for 24–48 h (Chuang et al., 2018)
	L. reflexa	Anticancer: Strong inhibitory effect on tumor cell lines MGC803 and SMMC-7721 with IC_{50} values 2.65 and 4.13 μM, respectively (Fu et al., 2019)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Isolinderalactone (77)	*L. strychnifolia*	Antitumor: Decreased G2/M phase cell cycle arrest and reactive oxygen species (ROS) generation triggered apoptotic cell death of colorectal cancer (CRC) cells with a dose concentration of 3-9 μM (Kwak et al., 2022)
Linderalactone (108)	*L. aggregate*	Anticancer: Strong inhibition in the proliferation of lung cancer cells A-549 with IC_{50} value 15 μM (Deng et al., 2019)
		Anti-inflammatory: Exhibited liver protection by reducing swelling with EC_{50} value 67.0 μM (Gan et al., 2009b)
Lindenene (149)	*L. communis*	Anticancer: Showed significant activity against H460, ES2 and DU145 cancer cells with IC_{50} values 2.1, 2.8, and 3.0 μg/mL, respectively (Deng et al., 2011)
Lindera aggrenolide H (190)	*L. aggregate*	Anticancer: Exhibit significant transforming growth factor-β inhibitory activity with IC_{50} value 25.9 μM (Liu et al., 2021b)
Linderanoid E (201)	*L. aggregata*	Anticancer: Induced TGF-*β* smad2 phosphorylation at a concentration of 25 μM and have low activity against A549 cells with IC_{50} value 49.9 μM (Liu et al., 2021a)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Linderalide D (216)	*L. aggregata*	Anticancer: Moderate NF-κB inhibitory activity with the inhibitory rate reaching almost 40% at a concentration of 50 μM with IC_{50} value 18.0 (Liu et al., 2019b)
Linderaggrenolide I (191)	*L. aggregata*	Anticancer: Transforming growth factor-β inhibitory activity with IC_{50} value 21.5 μM (Liu et al., 2021b)
Linderolide O (161)	*L. strychinifolia*	Anti-inflammatory: Strongly inhibit lipopolysaccharide-stimulated nitric oxide production in murine RAW 264.7 macrophage cells, with IC_{50} value 6.3 μM (Liu et al., 2016a)
(1*R*,3*S*,4*R*,5*R*,8*S*,10*S*)-4,8-Dihydroxy-1,3-cycloeudesma-7(11)-en-12,8-olide (140)	*L. strychinifolia*	Anti-inflammatory: Strongly inhibit lipopolysaccharide-stimulated nitric oxide production in murine RAW 264.7 macrophage cells, with IC_{50} value 6.3 of 9.6 μM (Liu et al., 2016a)
Linderane (109)	*L. aggregata*	Anti-inflammatory: Showed activity against H2O2-induced oxidative damage on HepG2 cells with EC_{50} value 167.0 (Gan et al., 2009b)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Linderane (109)	*L. aggregata*	Anti-inflammatory: Exhibit liver protection by reducing swelling with EC_{50} value 98.0 μM (Gan et al., 2009b)
Linderagalactone D (100)	*L. aggregata*	Anti-inflammatory: Exhibit H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 67.5 μM (Lv et al., 2023)
Linderolide C (92)	*L. strychinifolia*	Anti-inflammatory: Exhibited LPS-induced RAW264.7 macrophage cells with IC_{50} value 37.8 μM (Sumioka et al., 2011)
Linderagalactone E (101)	*L. aggregata*	Anti-inflammatory: Exhibit H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 42.4 μM (Gan et al., 2009b)
Hydroxylindestenolide (86)	*L. aggregata*	Anti-inflammatory: Exhibit H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 42.4 μM (Lv et al., 2023)
8-Hydroxy-lindestenolide (82)	*L. aggregata*	Anti-inflammatory: Exhibit H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 67.5 μM (Gan et al., 2009b)
Linderolide D (94)	*L. strychinifolia*	Anti-inflammatory: Exhibited LPS-induced RAW264.7 macrophage cells with IC_{50} value 38.7 μM (Sumioka et al., 2011)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Linderolide E (95)	*L. strychinifolia*	Anti-inflammatory: Strong activity towards nitric oxide production in RAW264.7 cells with IC_{50} value 18.3 μM (Sumioka et al., 2011)
Lindera aggredin A (90)	*L. aggregata*	Anti-inflammatory: Exhibited human neutrophils with IC_{50} value 7.45 μM (Kuo et al., 2020)
Linerenone (104)	*L. communis*	Anti-inflammatory: Significant activity against H460, ES2, and DU145 cancer cells with IC_{50} values 2.1, 2.8, and 3.0 μg/mL, respectively (Deng et al., 2011)
Lindera aggredin C (224)	*L. aggregata*	Anti-inflammatory: Inhibit the superoxide anion generation in human neutrophils with IC_{50} value 7.45 μM (Kuo et al., 2020)
Linderolide O (161)	*L. aggregata*	Anti-inflammatory: Reducing redness, swelling, and pain in the body parts with IC_{50} value 6.3 μM (Lv et al., 2023)
Linderolide P (162)	*L. aggregata*	Anti-inflammatory: Reducing redness, swelling, and pain in the body parts with IC_{50} value 9.6 μM (Lv et al., 2023)
Linderagalactone E (101)	*L. aggregata*	Cytotoxicity: Active in HepG2 cells with IC_{50} value 67.5 μM (Gan et al., 2009b)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
3-Oxo-4, 5αH, 8βH-eudesma- 1,7(11)-dien-8, 12-olide (80)	*L. aggregata*	Antitumor: Strong activity against A549 cell line with IC_{50} value 7.2 μM (Ohno et al., 2005)
Eudeglaucone (122)	*L. glauca*	Anti-neuroinflammatory: Inhibited nitric oxide production by lipopolysaccharide with IC_{50} value 15.9 μM (Yu et al., 2016)
ALKALOIDS		
Norisoboldine (256)	*L. aggregata*	Anti-arthritic: Strong agents in the development of Treg cells through promoting fatty acid oxidation with IC_{50} value 10 μM (Wei et al., 2015)
D-dicentrine (247)	*L. megaphylla*	Antitumor: Exhibited hepatoma, melanoma, lung/colon carcinoma, oesophageal lymphoma, and leukaemia cell lines (IC_{50} value 0.41-29.04 μM) (Huang et al., 1998)
Isoboldine (248)	*L. aggregata*	Anti-inflammatory: Reducing the expression of bone matrix-degrading enzymes (IC_{50} value 6.8 μM) (Lv et al., 2023)
Linderaggrine B (229)	*L. aggregata*	Anti-inflammatory: Exhibited superoxide anion generation in human neutrophils with IC_{50} value 9.2 μM (Kuo et al., 2020)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Norboldine (250)	*L. aggregata*	Anticancer: Exhibited BxPC-3 pancreatic cancer cell with IC_{50} value 27.0 μM (Zahari et al., 2014)
		Anti-inflammatory: Inhibited lipopolysaccharide (LPS)-stimulated nitric oxide production in murine RAW 264.7 macrophage cells with IC_{50} value 9.6 μM (Yang et al., 2020b)
N-methyl-laurotetanine (252)	*L. aggregata*	Anti-inflammatory: Inhibit the superoxide anion generation in human neutrophils with IC_{50} value 8.36 μM (Kuo et al., 2020)
Boldine (246)	*L. aggregata*	Anti-inflammatory: Induced production of NO by lipopolysaccharide in RAW 264.7 cells with IC_{50} value 8.7 μM (Yang et al., 2020b)
		Anti-inflammatory: Reducing the expression of bone matrix-degrading enzymes with IC_{50} value 9.5 μM (Lv et al., 2023)
Costaricine (280)	*L. aggregata*	Cytotoxic: Inhibit human colon carcinoma (HCT-116) cell line with IC_{50} value 51.4 μM (Yang et al., 2020b)
Norboldine (250)	*L. aggregata*	Cytotoxic: Inhibit human colon carcinoma (HCT-116) cell line with IC_{50} value 27.1 μM (Yang et al., 2020b)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Boldine (246)	*L. aggregata*	Anti-inflammatory: Induced production of NO by lipopolysaccharide in RAW 264.7 cells with IC_{50} value 8.7 μM (Yang et al., 2020b)
		Anti-inflammatory: Reducing the expression of bone matrix-degrading enzymes with IC_{50} value 9.5 μM (Lv et al., 2023)
Norisoboldine (256)	*L. aggregata*	Anti-inflammatory: Induced production of NO by lipopolysaccharide in RAW 264.7 cells with IC_{50} value 7.8 μM (Yang et al., 2020b)
		Anti-inflammatory: Inhibit vascular endothelial growth factor (VEGF)-induced endothelial cell migration with IC_{50} value 15.1 μM (Lu et al., 2013)
		Anti-inflammatory: Increase the Treg cells in $CD4^+$ T cells and decrease Th17 cells, thus it can help in preventing autoimmune disease with IC_{50} value 18.4 μM (Lv et al., 2015)
FLAVONOIDS		
Avicularin (326)	*L. erythrocarpa*	Anti-inflammatory: Reduced releasing of LDH in H9c2 cells with IC_{50} value 0.7 μM (Kim et al., 2011)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Flavokawain B (294)	*L. oxyphylla*	Anticancer: Strong activity in MCF-7 human breast adenocarcinoma cells with inhibition of 79.7% (Hosseinzadeh et al., 2013)
		Anti-inflammatory: Acts on DPPH radical scavenging activity with IC_{50} value 8.5 µg/mL (Hosseinzadeh et al., 2013)
Quercetin (331)	*L. erythrocarpa*	Anti-inflammatory: Reduced releasing of LDH in H9c2 cells with IC_{50} value 22.3 µM (Kim et al., 2011)
	L. aggregata	Antivirus: Interact and target the S2 domain in SARS-CoV-2 spike proteins with IC_{50} value 93.0 µM (Alavi et al., 2022)
Quercetin-3-O-rhamnoside (332)	*L. aggregata*	Antioxidant: Strong antioxidant capacity and modulation of the Nrf-2 pathway with IC_{50} value 7.5 µM (Haque et al., 2020)
Kaempferol (321)	*L. neesiana*	Antivirus: Act as a 3C protease (3Cpro) inhibitor against enterovirus A71 with IC_{50} value 85.0 µM (Adhikari et al., 2019)
PHENOLICS		
3-Hydroxy-5-methoxybiphenyl (347)	*L. fruticosa*	Antioxidant: Moderate to low-density lipoprotein activity with IC_{50} value 15.5 µM (Song et al., 2006)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
2,6-Dimethoxy-4-hydroxyphenyl-1-O-ß-D-gluco-pyranoside (356)	*L. obtusiloba*	Anti-allergic: Inhibit histamine release and proinflammatory cytokine production in mast cells with inhibition 68.1% (Choi et al., 2013)
		Anti-allergic: Highly suppressed release of histamine from mast cells with IC_{50} value 10.80 µM (Haque et al., 2020)
Koaburaside (359)	*L. obtusiloba*	Anti-allergic: Inhibit histamine release and proinflammatory cytokine production in mast cells with inhibition 66.9% (Choi et al., 2013)
		Anti-allergic: Highly suppressed release of histamine from mast cells with IC_{50} value 9.0 µM (Haque et al., 2020)
1-Methoxy-2,5,7-trihydroxyxanthone (349)	*L. fruticosa*	Antioxidant: Moderate to low-density lipoprotein activity with IC_{50} value 25.5 µM (Song et al., 2006)
3,5-Dimethoxy-biphenyl (348)	*L. fruticosa*	Antioxidant: Moderate to low-density lipoprotein activity with IC_{50} value 48.1 µM (Song et al., 2006)
MISCELLANEOUS		
Epicatechin-(4β-8,2-O-7)-epicatechin (404)	*L. erythrocarpa*	Anti-inflammatory: Reduced releasing of LDH in H9c2 cells with IC_{50} value 0.7 µM (Kim et al., 2011)

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Table 2.10 *(continue)*

Compounds	Species	Biological activities
Cinnamtannin B_1 (412)	*L. glauca*	Antioxidant: Inhibit low-density lipoprotein with IC_{50} value 2.0 mg/mL (Huh et al., 2014)
Cinnamtannin B_2 (413)	*L. glauca*	Antioxidant: inhibit lipid peroxidation and protect against oxidative stress-induced cellular damage (Huh et al., 2014)
Procyanidin B_1 (407)	*L. aggregata*	Antioxidant: Inhibit against HIV-1 integrase with IC_{50} value 25.3 μM (Zhang et al., 2003c)
Procyanidin B_2 (408)	*L. aggregata*	Antioxidant: Inhibit against HIV-1 integrase with IC_{50} value 27.1 μM (Zhang et al., 2003c)
Litsenolide (383)	*L. nacusua*	Antitumor: Inhibit against HL-60 and MCF-3 cell lines with respective IC_{50} values of 20.9 and 17.7 μM (Lei et al., 2017)
Reflexanbene A (390)	*L. reflexa*	Cytotoxic: Moderate against MGC803 and SMMC-7721 cell lines with IC_{50} values 29.6 and 34.3 μM, respectively (Fu et al., 2019)
Reflexanbene C (391)	*L. reflexa*	Cytotoxic: Moderate against MGC803 and SMMC-7721 cell lines with IC_{50} values 47.5 and 54.9 μM, respectively (Fu et al., 2019)

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CHAPTER 3

EXPERIMENTAL

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3.1 Plant Materials

The leaves and roots of *L. subumbelliflora* (SK154/23) and the leaves of *L. caesia* (SA20-07) were collected at Fraser's Hill, Raub, Pahang (3.7119° N, 101.7366° E). All samples were identified by Dr. Shamsul Khamis from Universiti Kebangsaan Malaysia and the voucher specimens were deposited at the Herbarium of UKM.

3.2 Extraction and Analysis of Essential Oils

The fresh samples of the leaf part were cut into small pieces before being placed in a round bottom flask 5 L. After that, distilled water was added up to the point when it completely covers all samples. The mixture was put through a Clevenger apparatus in

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the flask, and the hydrodistillation process lasted for 4 hours. Diethyl ether was used to extract the essential oil and water mixture, followed by drying the mixture over anhydrous $MgSO_4$ and filtering it. The filtrate was evaporated at room temperature to afford the essential oils.

Gas chromatography-flame ionisation detector (GC-FID) and gas chromatography-coupled mass spectrometry (GC-MS) were used to analyse the chemical compositions of the essential oils. The GC-FID analysis was performed on a Shimadzu GC-2010 Plus (Shimadzu) gas chromatograph, fitted with an HP-5 column (25 metres in length, 0.33 micrometres thick, and 0.20 millimetres in diameter). At a flow rate of 1.0 mL/min, helium was used as a carrier gas. The flame ionization detector (FID) temperatures were set at 250°C (injector) and 280°C (detector). The oven's temperature was kept maintained at 50°C for 15 minutes before being gradually raised to 280°C at 5°C/min. The diluted samples (1/100 in diethyl ether, v/v) of 1.0 µL were injected manually (split ratio 10:1) (Salleh et al., 2016).

The Agilent GC-MS 7890A/5975C Series MSD (70 eV direct inlet) were used to record the GC-MS chromatogram with the HP-5MS capillary column (30 m 0.25 mm internal diameter 0.25 µm film thickness). At a flow rate of 1 mL/min, helium was used as the carrier gas. The temperature of the injector was set at 250°C. The oven temperature was programmed from 50°C (5 minutes hold) to 280°C at 10°C/min, and finally held isothermally for 15 minutes. For GC-MS detection, and electron an 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 to 400 amu (Salleh et al., 2016). The chemical components of essential oil have been determined by comparing their

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mass spectra to reference spectra in the library (Wiley) and by comparing their Kovats Indices to data in the literature (Adams, 2001). Without using a correction factor, the quantitative data was derived electronically from the FID area percentage. The equations below have been used to calculate the Kovats Index in relation to a homologous series of *n*-alkanes C_6-C_{30}.

$$KI = 100 \left[\frac{(\log t_{sample}) - (\log t_x)}{(\log t_{x+1}) - (\log t_x)} \right] + 100x$$

t_{sample}	The retention time of the sample component
t_x	The retention time of the saturated hydrocarbons eluted before the sample component
t_{x+1}	The retention time of the saturated hydrocarbon which contains *x*+1 carbon and that just elutes after the sample component
x	Number of carbon atoms in saturated hydrocarbons

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3.3 Multivariate Statistical Analysis of Essential Oils

A statistical technique known as multivariate analysis is utilized to examine complex data sets that encompass multiple variables or factors simultaneously. This method has been extensively used to investigate the interactions among various chemical components due to the intricate and diverse nature of natural products (Shakri et al., 2020). The complexity and diversity of natural products have led to the intensive application of multivariate analysis methods which are hierarchical cluster analysis (HCA) and principal component analysis (PCA).

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Principal component analysis (PCA) is a well-known method and a multivariate exploratory data analysis tool used to determine similarities and differences among samples, and study correlations among variables. PCA is calculated to explore the relationships between samples from various regions and their connection to a specific volatile compound. The GC-MS data was subjected to PCA. The results can be visually inspected through PCA plots to uncover hidden patterns in the dataset. PCA was employed to reveal the interrelationships among the total species of the genus based on the essential oil that shares common constituents with these species (Chun et al., 2011).

Hierarchical Cluster Analysis (HCA) is a statistical analysis method used to identify relationships between variables. It groups variables based on their similarity and then groups those groups together based on their similarity (Zhang et al., 2017). The result of HCA is a dendrogram, which illustrates how the variables are grouped. This is useful for identifying patterns and relationships in large datasets. This method is increasingly accepted as an approach for the quality control of herbal materials.

The chemical components of oils between *L. subumbelliflora* and *L. caesia* were reported using PCA and HCA, which facilitate the clustering of chemical components, identification of variability, and presentation of results in figures (Izenman, 2008). This analysis utilized Pearson correlations with Statistical Software for Excel (XLSTAT) 2022. The correlation matrix is displayed graphically due to the initial PCA. Following this, HCA analysis was conducted to cluster subjects with similar characteristics. XLSTAT was chosen for its simplicity in interpretation and effectiveness in explaining variation in the dataset.

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3.4 Extraction and Analysis of Phytochemicals

In this study, isolation of phytochemicals was conducted on the leaves and roots extracts of *L. subumbelliflora*. The dried samples were extracted using cold extraction technique using *n*-hexane, EtOAc, and MeOH as solvents to obtain the crude extracts. The gravity column chromatography (CC) was performed using Merck SiO_2 (70-230 Mesh), whereas thin layer chromatography (TLC) analysis was achieved with 0.20 mm precoated silica gel aluminium sheets (Merck Kieselgel $60F_{254}$). The preparative thin layer chromatography (PTLC) has been conducted using a 1 mm thin glass plate of Merck SiO_2 $60F_{254}$. In chromatographic technique, the solvent systems *n*-hexane, EtOAc, DCM, $CHCl_3$, Et_2O, and MeOH have been utilized. The spots on the TLC plate were identified by ultraviolet (UV) light at 254 nm and 365 nm, followed by spraying using the vanillin sulphuric acid reagent. The analytical grade of reagents was used in this study.

For structural elucidation, IR, NMR, and MS have been used in this study. The Perkin Elmer Series 1600 spectrophotometer (KBr pellet for solid samples and NaCl discs for liquid sample) and Perkin Elmer Spectrum 100 FT-IR Spectrometer was used to record the IR spectra. The JEOL Spectrometer (JNM-ECX-500) were used to record the 1D and 2D NMR spectra. The chemical shifts were reported in ppm. The residual solvent ($CDCl_3$ and MeOD) was used as an internal standard. Lastly, the Thermo Fisher Scientific's Liquid Chromatography Mass Spectrometry was being used to obtain the mass spectral data.

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3.5 Isolation and Characterization of Phytochemicals from *L. subumbelliflora*

Cold extraction of the dried ground leaves of *L. subumbelliflora* was performed *via* polarity gradient of *n*-hexane (3 days), EtOAc (3 days), and MeOH (3 days). The *n*-hexane extract (LSLH, 3.5 g) was subjected to column chromatography (CC) and eluted with *n*-hexane:DCM (70:30) to give 5,6-dehydrokawain **(414)**. However, purification of EtOAc and MeOH leaves extracts by CC did not afford any pure compound. The purification process of *L. subumbelliflora* leaves extract are summarized in Figure 3.1.

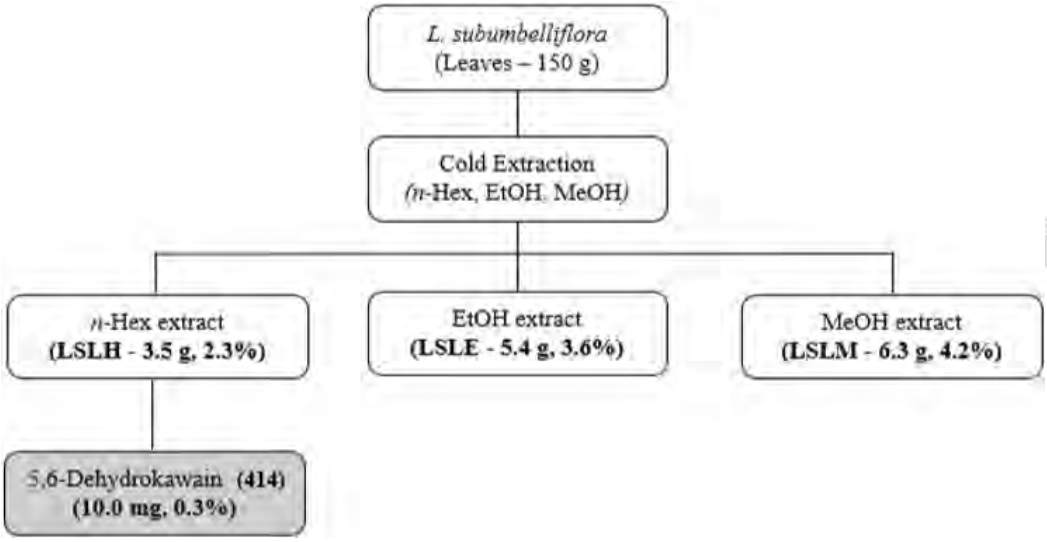


Figure 3.1. Flow chart for the purification process of *L. subumbelliflora* leaves extract

Cold extraction of the dried ground roots of *L. subumbelliflora* was performed *via* a polarity gradient of *n*-hexane (3 days), EtOAc (3 days), and MeOH (3 days). The *n*-hexane leaves extract (LSRH, 8.1 g) was subjected to CC to afford 6 fractions (LSRH A-F). Fraction LSRH A was subjected to CC and eluted with *n*-hexane:DCM (60:40) to give pinostrobin **(307)**. The combined fraction LSRH E with *n*-hexane:DCM (70:30) was purified followed by PTLC to afford β-sitosterol **(401)** and pinocembrin **(308)**.

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Purification of the EtOAc extract (LSRE, 11.3 g) by CC eluted with 3 type of solvent which is *n*hexane, EtOAc and MeOH had afforded 5 fractions (LSRE A-E). Fraction LSRE E were purified using solvent *n*-hex:EtOAc (60:40) to attain 4-hydroxy-3-methoxyacetophenone **(363)** and ferulic acid **(365)**. Meanwhile, purification of the MeOH extract (LSRM, 10.3 g) by CC eluted with 3 type of solvent which is *n*hexane, EtOAc and MeOH was afforded 5 fractions (LSRM A-E). The combined fraction LSRM C and LSRM D was purified by PTLC to afford quercetin **(331)** (EtOAc:MeoH, 80:20) and syringic acid **(370)** (EtOAc:MeoH, 75:25). The purification process of *L. subumbelliflora* roots extract are summarized in Figure 3.2.

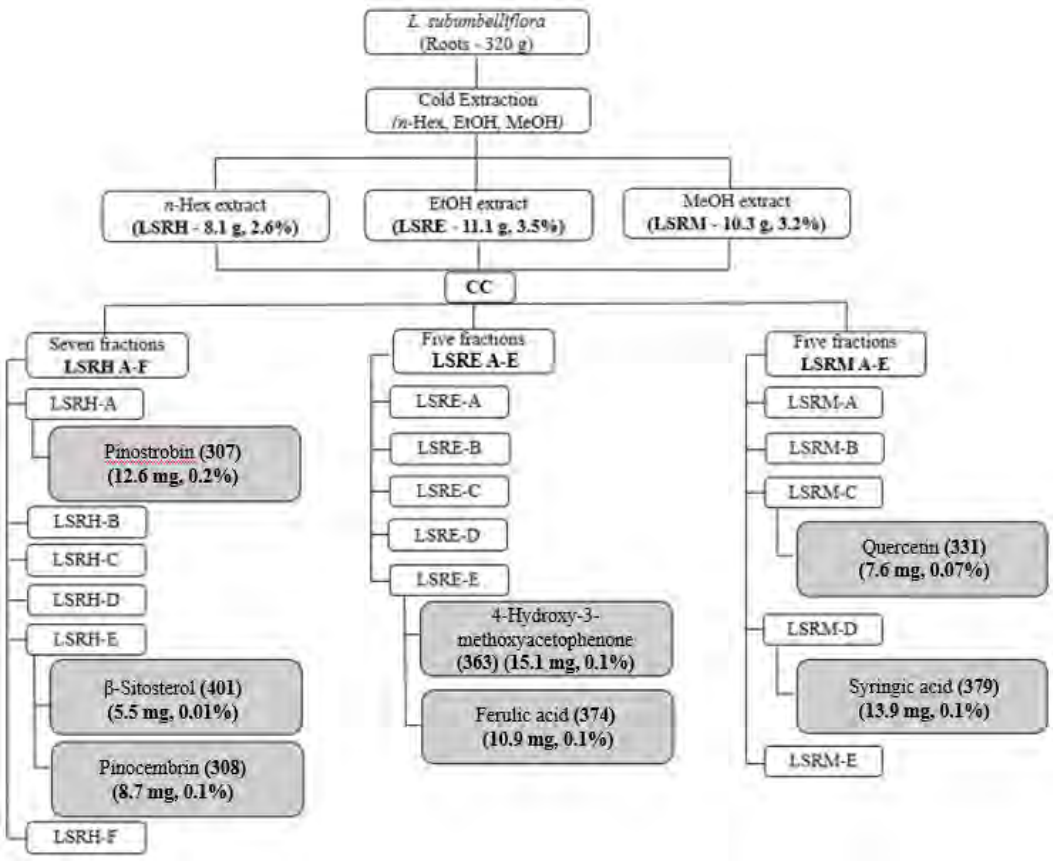


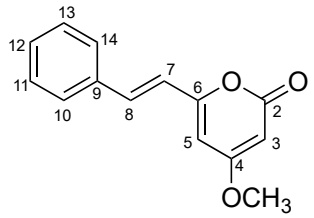
Figure 3.2. Flow chart for the purification process of *L. subumbelliflora* roots extract

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3.6 Spectral Data of Isolated Phytochemicals

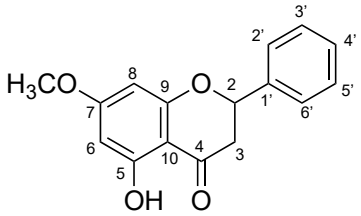
A total of eight compounds were successfully isolated from the leaves and roots part of *L. subumbelliflora*. These compounds were identified by spectroscopy techniques such as IR, NMR (1D and 2D) and MS, as well as comparison with those reported in the literatures.



Name	:	5,6-Dehydrokawain **(414)**
Appearance	:	Pale yellow solid
Weight	:	10.0 mg
IR (KBr) (λ_{max})	:	3077 (sp^2 C-H), 2954 (sp^3 C-H), 1723 (C=O), 1555 and 1447 (C=C aromatic), 1257 (C-O) cm^{-1}
^{1}H NMR	:	δ 3.85 (3H, s, OCH_3), 5.52 (1H, d, *J* = 2.1 Hz, H-3), 5.97 (1H, d, *J* = 2.1 Hz, H-5), 6.59 (1H, d, *J* = 16.0 Hz, H-7), 7.36-7.51 (5H, m, H-10 – H-14), 7.53 (1H, d, *J* = 16.0 Hz, H-8)
^{13}C NMR	:	δ 55.9 (OCH_3), 88.9 (C-3), 101.4 (C-5), 118.7 (C-7), 127.5 (C-10/C-14), 128.9 (C-11/C-13), 129.5 (C-12), 135.2 (C-9), 135.8 (C-8), 158.7 (C-4), 164.1 (C-6), 171.1 (C-2)
MS *m/z*	:	228 $[M]^+$ $C_{14}H_{12}O_3$

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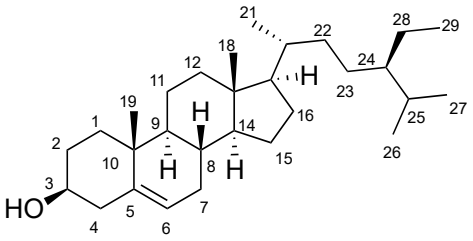
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Name	:	Pinostrobin **(307)**
Appearance	:	Colourless crystalline needles
Weight	:	12.6 mg
IR (KBr) (λ_{max})	:	3445 (OH), 2973 (sp^3 C-H), 1614 (C=O), 1541 (C=C aromatic), 1252 (C-O) cm^{-1}
^{1}H NMR	:	δ 2.84 (1H, dd, *J* = 2.9 and 14.8 Hz, H-3a), 3.10 (1H, dd, *J* = 13.0 and 15.0 Hz, H-3b), 3.84 (3H, s, OCH_3), 5.44 (1H, dd, *J* = 2.9 and 13.0 Hz, H-2), 6.10 (1H, d, *J* = 2.3 Hz, H-6), 6.11 (1H, d, *J* = 2.3 Hz, H-8), 7.42-7.48 (5H, m, H-2′ – H-6′), 12.05 (1H, s, OH)
^{13}C NMR	:	δ 43.4 (C-3a/C-3b), 55.7 (OCH_3), 79.3 (C-2), 94.3 (C-8), 95.2 (C-6), 103.2 (C-10), 126.2 (C-2′/C-6′), 128.9 (C-3′/C-4′/ C-5′), 138.4 (C-1′), 162.8 (C-9), 164.2 (C-5), 168.0 (C-7), 195.8 (C-4)
MS *m/z*	:	270 $[M]^+$ $C_{16}H_{14}O_4$

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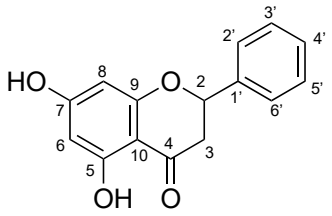
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Name	:	β-Sitosterol **(401)**
Appearance	:	White solid
Weight	:	5.5 mg
IR (KBr) (λ_{max})	:	3435 (OH), 2937 (sp^3 C-H), 1652 (C=C), 1052 (C-O) cm^{-1}
^{1}H NMR	:	δ 0.70 (3H, s, H-18), 0.83 (3H, d, *J* = 6.8 Hz, H-27), 0.85 (3H, d, *J* = 6.8 Hz, H-26), 0.86 (3H, d, *J* = 7.8 Hz, H-29), 0.94 (3H, d, *J* = 6.5 Hz, H-21), 1.02 (3H, s, H-19), 1.20-2.33 (29H, m, overlapping CH and CH_2), 3.55 (1H, m, H-3), 5.37 (1H, d, *J* = 5.2 Hz, H-6)
^{13}C NMR	:	δ 11.8 (C-29), 11.9 (C-18), 18.7 (C-21), 19.0 (C-27), 19.3 (C-19), 19.7 (C-26), 21.0 (C-11), 23.1 (C-28), 24.3 (C-15), 26.1 (C-23), 28.2 (C-16), 29.2 (C-25), 31.6 (C-2), 31.9 (C-8/C-7), 33.9 (C-22), 36.1 (C-20), 36.5 (C-10), 37.5 (C-1), 39.8 (C-12), 42.3 (C-4/C-13), 45.8 (C-24), 50.1 (C-9), 56.0 (C-17), 56.7 (C-14), 71.8 (C-3), 121.7 (C-6), 140.7 (C-5)
MS *m/z*	:	414 $[M]^+$ $C_{29}H_{50}O$

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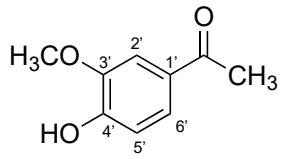
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Name	:	Pinocembrin **(308)**
Appearance	:	White solid
Weight	:	8.7 mg
IR (KBr) (λ_{max})	:	3100 (OH), 1629 (C=O), 1580 and 1486 (C=C aromatic), 1166 (C-O) cm^{-1}
^{1}H NMR	:	δ 2.74 (1H, dd, *J* = 3.0 and 17.2 Hz, H-3a), 3.0 (1H, dd, *J* = 13.0 and 17.2 Hz, H-3b), 5.35 (1H, dd, *J* = 3.0 and 13.0 Hz, H-2), 5.93 (1H, d, *J* = 2.2 Hz, H-6), 5.94 (1H, d, *J* = 2.2 Hz, H-8), 7.36-7.42 (5H, m, H-2′-H-6′), 11.97 (1H, s, 5-OH)
^{13}C NMR	:	δ 43.4 (C-3a/C-3b), 79.3 (C-2), 95.5 (C-8), 96.8 (C-6), 103.3 (C-10), 126.2 (C-2′/C-6′), 128.9 (C-3′/C-4′/C-5′), 138.3 (C-1′), 163.1 (C-9), 164.4 (C-7), 164.5 (5-OH), 195.8 (C-4)
MS *m/z*	:	256 $[M]^{+}$ $C_{15}H_{12}O_4$

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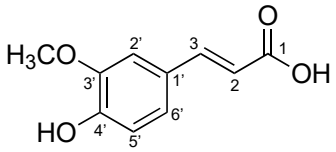
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Name	:	4-Hydroxy-3-methoxyacetophenone **(363)**
Appearance	:	White crystalline solid
Weight	:	15.1 mg
IR (KBr) (λ_{max})	:	3230 (OH), 1696 (C=O), 1519 and 1456 (C=C aromatic), 1102 (C-O) cm^{-1}
^{1}H NMR	:	δ 2.56 (3H, s, CH_3), 3.91 (3H, s, 3′-OCH_3), 6.31 (1H, s, 4′-OH), 6.95 (1H, d, *J* = 8.7 Hz, H′-5), 7.52 (1H, s, H-2′), 7.53 (1H, d, *J* = 8.7 Hz, H-6′)
^{13}C NMR	:	δ 26.2 (CH_3), 56.0 (3′-OCH_3), 110.1 (C-2′), 114.1 (C-5′), 124.2 (C-6′), 129.6 (C-1′), 146.5 (C-3′), 150.8 (4′-OH), 196.9 (C-1)
MS *m/z*	:	166 $[M]^+$ $C_9H_{10}O_3$

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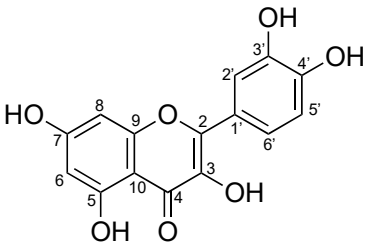
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Name	:	Ferulic acid **(365)**
Appearance	:	Brownish yellow solid
Weight	:	10.9 mg
IR (KBr) (λ_{max})	:	3432 (OH), 1687 (C=O), 1617 (C=C olefinic), 1591 and 1512 (C=C aromatic), 1266 (C-O) cm^{-1}
^{1}H NMR	:	δ 3.97 (3H, s, OCH_3), 6.31 (1H, d, *J* = 15.0 Hz, H-2′), 6.96 (1H, d, *J* = 8.9 Hz, H-5′), 7.08 (1H, d, *J* = 1.9 Hz, H-2′), 7.13 (1H, dd, *J* = 1.9 and 8.2 Hz, H-6′), 7.73 (1H, d, *J* = 15.0 Hz, H-3)
^{13}C NMR	:	δ 56.0 (OCH_3), 109.5 (C-6′), 114.2 (C-3′), 114.8 (C-2), 123.7 (C-2′), 126.6 (C-1′), 146.8 (C-3), 147.3 (C-5′), 148.5 (C-4′), 171.3 (C-1)
MS *m/z*	:	194 $[M]^+$ $C_{10}H_{10}O_4$

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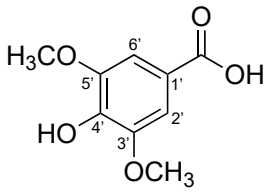
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Name	:	Quercetin **(331)**
Appearance	:	Yellow solid
Weight	:	7.6 mg
IR (KBr) (λ_{max})	:	3270 (OH), 1663 (C=O), 1606 and 1448 (C=C aromatic), 1259 (C-O) cm^{-1}
^{1}H NMR	:	δ 6.26 (1H, d, *J* = 2.0 Hz, H-6), 6.51 (1H, d, *J* = 2.0 Hz, H-8), 6.98 (1H, d, *J* = 8.5 Hz, H-5′), 7.68 (1H, dd, *J* = 2.1 and 8.5 Hz, H-6′), 7.82 (1H, d, *J* = 2.1 Hz, H-2′), 12.16 (1H, s, 5-OH)
^{13}C NMR	:	δ 93.6 (C-8), 98.3 (C-6), 103.2 (C-10), 114.9 (C-5′), 115.3 (C-2′), 120.6 (C-6′), 122.9 (C-1′), 135.9 (C-3), 145.0 (C-3′), 146.1 (C-2), 147.5 (C-4′), 156.9 (C-9), 161.4 (C-5), 164.2 (C-7), 175.7 (C-4)
MS *m/z*	:	302 $[M]^{+}$ $C_{15}H_{10}O_7$

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Name	:	Syringic acid (**370)**
Appearance	:	White crystalline solid
Weight	:	13.9 mg
IR (KBr) (λ_{max})	:	3230 (OH), 2942 (sp^3 C-H), 1695 (C=O), 1615 and 1519 (C=C aromatic) cm^{-1}
^{1}H NMR	:	δ 3.95 (6H, s, 3′/5′-OCH_3), 5.97 (1H, s, 4′-OH), 7.38 (2H, s, H-2′/H-6′)
^{13}C NMR	:	δ 56.5 (3′/5′-OCH_3), 107.3 (C-2′/C-6′), 120.0 (C-1′), 140.0 (4′-OH), 146.7 (C-3′/C-5′), 170.7 (C-1)
MS *m/z*	:	198 $[M]^+$ $C_9H_{10}O_5$

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3.7 Biological Activities

3.7.1 Antioxidant Activity

The DPPH free radical scavenging assay of the crude extracts and isolated phytochemicals has been investigated as designated by Salleh et al. (2016) with slight modifications. The DPPH solution was freshly prepared in MeOH. The sample in MeOH (170 µL) with concentrations 20-100 µg/mL was obtained by two-fold dilution and mixed with the DPPH solution (30 µL). The mixture has been allowed to stand for 30 min at room temperature in the dark and then the absorbance will be recorded at 517 nm. The percentage inhibition of DPPH (%) was calculated using the following formula: $I\% = [A_{blank} – A_{sample} / A_{blank}] \times 100$. The IC_{50} value was defined as the amount of antioxidant necessary to decrease the initial DPPH concentration by 50%, was calculated from the results. Ascorbic acid and butylated hydroxytoluene were used as a standard and diluted to the same concentration as samples. All tests were carried out in triplicate.

3.7.2 Antibiofilm Activity

The antibiofilm activity of the essential oils, crude extracts, and isolated phytochemicals was investigated using a semiquantitative static biofilm assay (Mokhtar et al. 2021). Standardized cultures of *Candida albicans* and *Streptococcus mutans* (OD_{620nm}) were used in the biofilm procedure, with concentrations of 500 µg/mL for the sample and 3×10^4 cells/mL for the microbes. Negative controls contained only inoculated broth,

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while positive controls contained 0.12% chlorhexidine. The suspensions were mixed thoroughly using a vortex mixer for 30 seconds and pipetted into each well of a sterile 96-well plate which was then incubated for 72 h at 37°C aerobically, and the medium was replenished aseptically every 24 h. The experiment was performed in three biological replicates and three technical replicates to ensure reproducibility.

After incubation, the crystal violet (CV) assay was performed according to previous protocol to quantify the biofilm biomass (Arzmi et al., 2016). Initially, the wells containing biofilms were washed twice with sterile PBS to remove the non-adherent cells. Later, the biofilms in the wells were fixed by adding 200 µL of MeOH and incubating for 15 min at 25°C. The supernatant was discarded, and the plate was air-dried for 45 min. Then, 200 µL of 0.1% (w/v) CV solution was added to each well and incubated for 20 min at 25°C. The plate was washed gently twice using sterile distilled water to remove the unbound stain. Subsequently, the biofilms were detained with 200 µL of 33% (v/v) acetic acid for 5 minutes at room temperature. Finally, 100 µL of the acetic acid solution was transferred to a new sterile 96-well plate, and the absorbance was measured at the optical density (OD) 620 nm wavelength (OD_{620nm}) using a microtiter plate reader (Tecan NanoQuant Infinite M200, CA). Each assay was performed three times and mean absorbance values were used to measure the inhibition of biofilm formation as follows:

$$\frac{\text{Mean } OD_{620nm} \text{ of positive control} - \text{Mean } OD_{620nm} \text{ of experimental}}{\text{Mean } OD_{620nm} \text{ of positive control}} \times 100$$

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CHAPTER 4

RESULTS AND DISCUSSION

4.1 Extraction of Essential Oils

In this study, two *Lindera* species known as *L. subumbelliflora* and *L. caesia* were studied for their essential oil compositions. Table 4.1 summarizes the fresh weight, percentage, yield, and appearance of the essential oils.

Table 4.1

The details of Lindera essential oils

Species	Part	Weight (g)	Yield (%)	Appearance
L. subumbelliflora	Leaf	300	0.20	Pale yellow
L. caesia	Leaf	200	0.15	Pale yellow

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4.2 Analysis of Essential Oils

4.2.1 Chemical Composition of *L. subumbelliflora* Essential Oil

The GC-FID and GC-MS analysis (Figure 4.1) of the leaf oil of *L. subumbelliflora* led to the identification of 28 components, representing 99.6% of the total oil. The chemical components identified are listed in Table 4.2. Analysis of the chemical components successfully identified the *L. subumbelliflora* leaf oil consisting of several groups of components with sesquiterpene hydrocarbons (58.5%) as the major group components, followed by oxygenated hydrocarbon (31.9%). The major components were characterized by β-eudesmol **(45)** (14.6%), *cis*-α-bergamotene **(415)** (11.0%), α-copaene **(20)** (8.5%), dodecen-1-ol **(417)** (8.5%), (*E*)-nerolidol **(13)** (8.3%), rosifoliol **(416)** (6.8%), and δ-cadinene **(9)** (6.2%).

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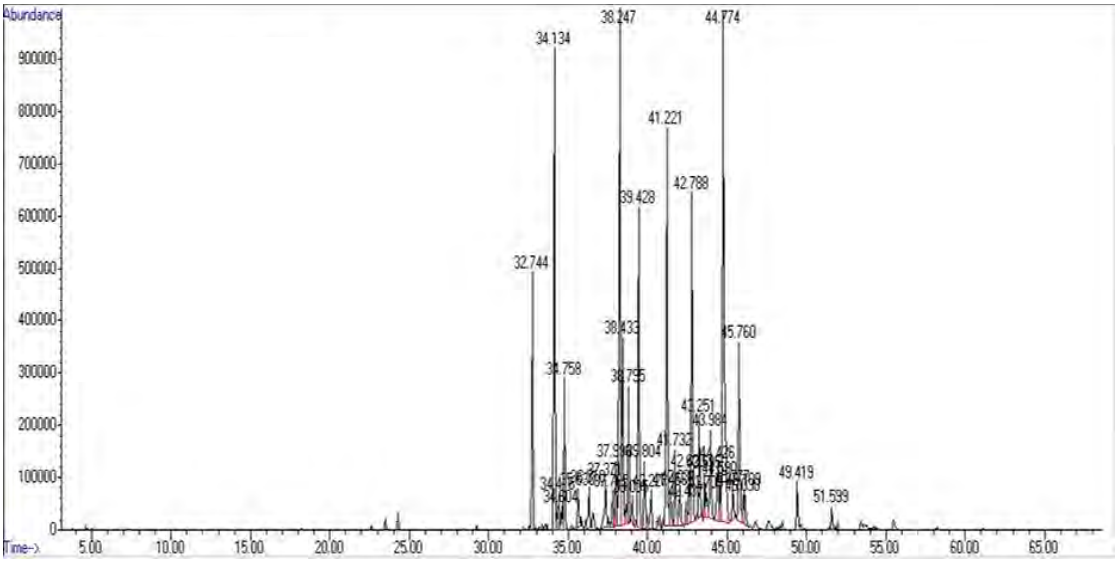


Figure 4.1. Chromatogram of *L. subumbelliflora* essential oil

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Table 4.2

Chemical components identified from L. subumbelliflora essential oil

No	Components	KI[a]	KI[b]	Percentage (%)
1	α-Copaene (20)	1375	1374	8.5
2	Dodecanal (418)	1408	1408	0.6
3	*cis*-α-Bergamotene (415)	1412	1411	11.0
4	β-Caryophyllene (12)	1415	1417	2.7
5	α-Humulene (14)	1452	1452	1.0
6	Dodecen-1-*ol* (417)	1470	1469	8.5
7	β-Selinene (38)	1490	1489	0.8
8	δ-Selinene (419)	1492	1492	1.1
9	γ-Amorphene (420)	1495	1495	0.5
10	Viridiflorene (1)	1496	1496	1.1
11	α-Muurolene (421)	1502	1500	4.9
12	(*E*,*E*)-α-Farnesene (422)	1505	1505	2.3
13	(*Z*)-α-Bisabolene (423)	1508	1506	1.1
14	γ-Cadinene (33)	1510	1513	2.3
15	δ-Cadinene (9)	1520	1522	6.2
16	*cis*-Cadina-1,4-diene (424)	1535	1533	1.7
17	Selina-3,7(11)-diene (425)	1542	1545	4.2
18	(*E*)-Nerolidol (13)	1560	1561	8.3
19	Caryophyllenyl alcohol (426)	1570	1570	0.8
20	Cubeban-11-ol (427)	1595	1595	0.5
21	Guaiol (428)	1599	1600	1.1

(continue)

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Table 4.2 *(continue)*

No	Components	KI[a]	KI[b]	Percentage (%)
22	Rosifoliol (416)	1602	1602	6.8
23	γ-Eudesmol (429)	1632	1630	4.2
24	α-Muurolol (430)	1642	1640	0.9
25	t-Muurolol (431)	1645	1644	1.8
26	β-Eudesmol (45)	1648	1649	14.6
27	Bulnesol (432)	1670	1670	0.6
28	α-Bisabolol (433)	1685	1685	1.4
Group components				
	Sesquiterpene hydrocarbons			58.5
	Oxygenated sesquiterpenes			31.9
	Others			9.2
Total identified (%)				99.6

KI[a] – Kovats index experimental; KI[b] – Kovats index from literature (Adams, 2001)

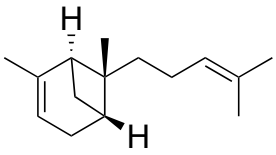
The sesquiterpene hydrocarbons are mainly composed of *cis*-α-bergamotene **(415)** (11.0%), α-copaene **(1)** (8.5%) and δ-cadinene **(9)** (6.2%). As a comparison with previous studies, similar trends are observed in various species. For instance, α-copaene **(1)** was found as major component in several *Lindera* species such as *L. glauca* (China: fruit oil, 13.1%) (Sun et al., 2023), *L. obtusiloba* (Korea: leaf oil 31.4%) (Chung & Moon, 2011), and *L. pipericarpa* (Malaysia: leaf oil 31.4%) (Ali & Jantan, 1993). Besides, δ-cadinene **(9)** has also been reported lavishly in *L. obtusiloba* (Korea: fruit oil, 13.8%) (Yang et al., 2022), *L. chunii* (Korea: stem oil 6.5%) (Liu et al., 2013), and *L. glauca* (China: fruit oil 6.2%).

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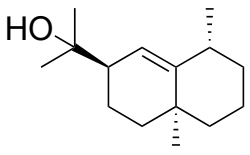
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The *L. subumbelliflora* leaf oil also revealed the presence of oxygenated sesquiterpenes, accounting for 11 components (31.9%). A notable compound in this category is β-eudesmol **(45)** (14.6%), which was also reported previously from *L. obtusiloba* (Korea: leaf oil 10.0%) (Yang et al., 2022) and *L. pulcherrima* (India: leaf oil 4.1%) (Joshi et al., 2010). Meanwhile, the existence of (*E*)-nerolidol **(13)** as the major component in sesquiterpene hydrocarbon was also found in *L. erythrocarpa* (Korea: leaf oil 26.9 %) (Kim et al., 2009), *L. obtusiloba* (Korea: leaf oil 6.8 %) (Chung and Moon 2011), and *L. pipericarpa* (Malaysia: leaf oil 6.1 %) (Ali and Jantan 1993).

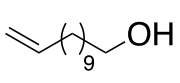
β-Eudesmol is one of the most studied and major bioactive sesquiterpenes, mainly extracted from *Atractylodes lancea* rhizomes. It has potential antitumor and antiangiogenic activities and is an inhibitor of tumour growth by inhibiting angiogenesis by suppressing CREB activation of the growth factor signalling pathway. It also stimulates neurite outgrowth in rat pheochromocytoma cells with activation of mitogen-activated protein kinases. It may be a promising lead compound for enhancing neural function, and it may help to explain the underlying mechanisms of neural differentiation (Acharya et al., 2021).



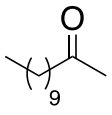
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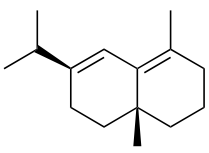
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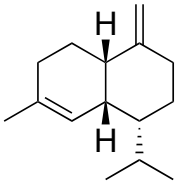
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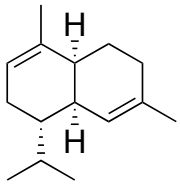
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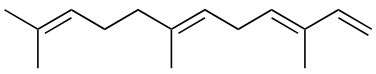
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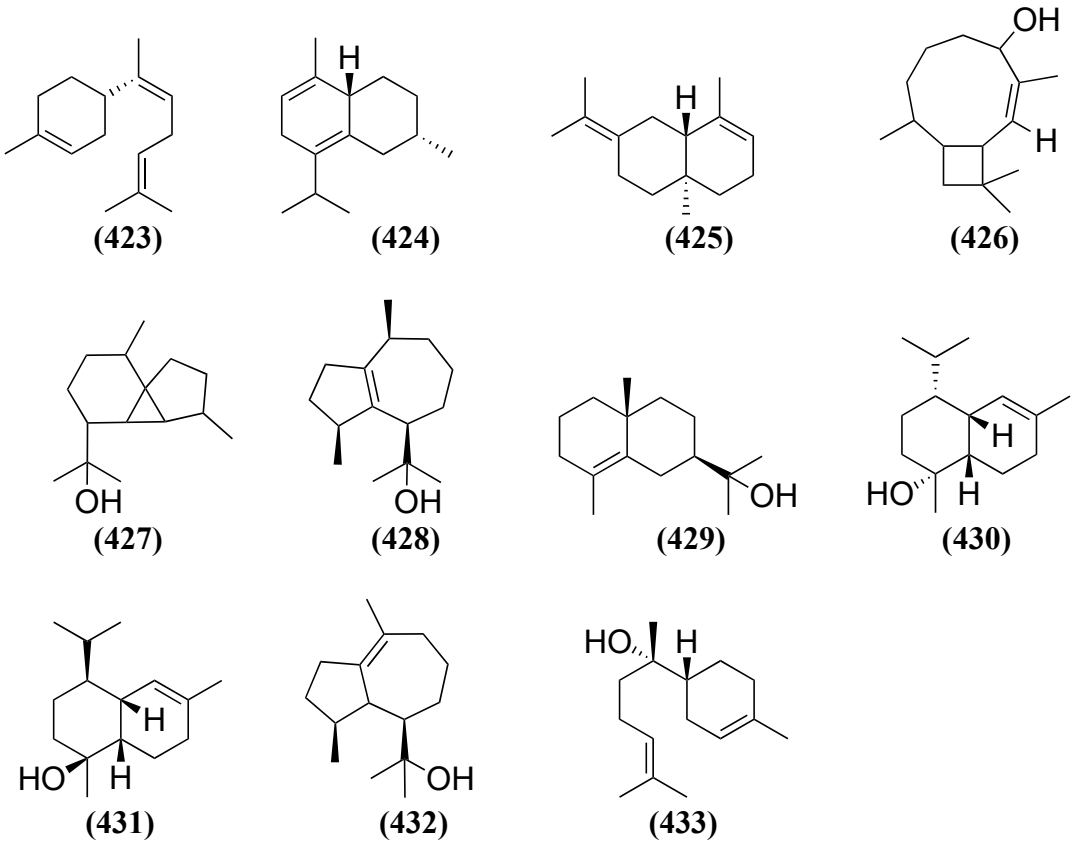
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(423) **(424)** **(425)** **(426)**

(427) **(428)** **(429)** **(430)**

(431) **(432)** **(433)**

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4.2.2 Chemical Composition of *L. caesia* Essential Oil

The GC-FID and GC-MS analysis (Figure 4.2) of *L. caesia* leaf oil led to the identification of 39 components, representing 96.7% of the total oil. The chemical components identified are listed in Table 4.3. The chemical composition of *L. caesia* leaf oil also reveals a diverse range of components, prominently featuring oxygenated monoterpenes and sesquiterpenes. Oxygenated monoterpenes represent a significant portion of the oils, constituting 39.8% of the total 17 components, while oxygenated sesquiterpenes comprise 35.9% of the oils with a total of 6 components.

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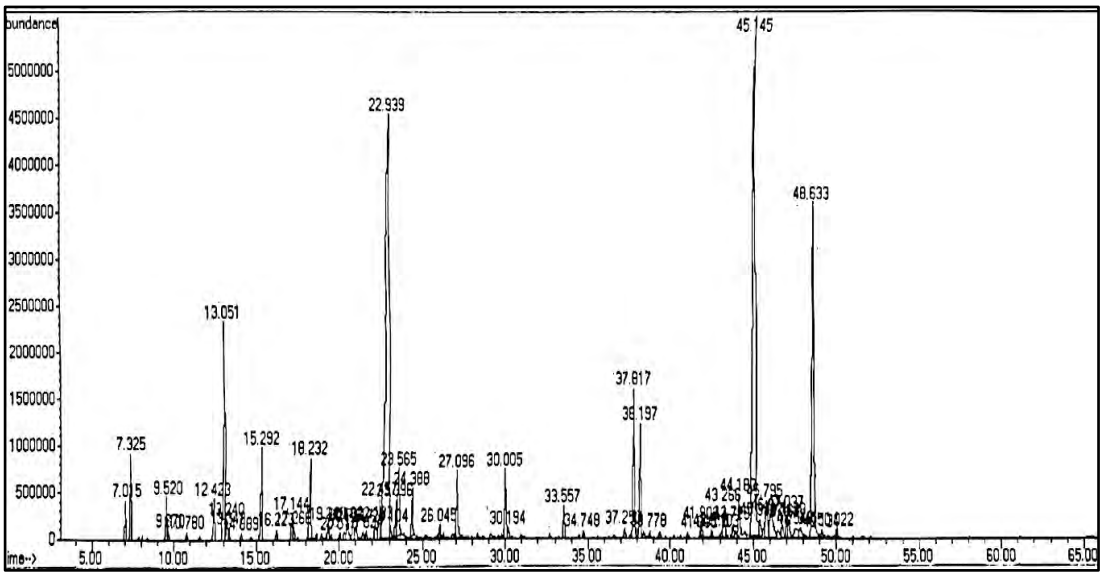


Figure 4.2. Chromatogram of *L. caesia* essential oil

Oxygenated monoterpenes are led by terpinen-4-ol **(434)** (26.3%), emphasizing its abundance in comparison to other components. The other major components included *neo*-intermedeol (23.2%) **(435)**, eudesma-4,11-dien-3-one (10.4%) **(436)**, and o-cymene (5.3%) **(437)**. Nevertheless, terpinen-4-ol **(434)** in *L. caesia* leaf oil represent the first chemical component reported for this genus. Likewise, it has been identified as the major component in other species of Lauraceae family such as *Cinnamomum illicioides* (bark oil, 10.4%) (Giang et al. 2006), *C. glanduliferum* (bark oil, 7.57%) (Taha et al. 2017), *C. longepaniculatum* (leaf oil, 8.63%) (Huang et al. 2022), *Neolitsea variabillima* (leaf oil, 9.3%) (Su et al. 2013), and *Licaria rigida* (bark oil, 10.7%) (da Silva et al. 2016). Analysis also found that the identification of monoterpene hydrocarbons (12.7%), mainly composed of o-cymene **(437)** (10.4%). Besides, sesquiterpene hydrocarbons (8.3%) were contributed with the presence of β-elemene **(74)** (2.3%), β-caryophyllene **(12)** (0.2%), β-selinene **(38)** (3.3%), (*E*,*E*)-α-farnesene **(422)** (0.2%), and α-selinene **(438)** (2.3%).

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Table 4.3

Chemical components identified from L. caesia essential oil

No	Components	KI[a]	KI[b]	Percentage (%)
1	α-Thujene (49)	925	924	0.6
2	α-Pinene (16)	930	932	1.3
3	Sabinene (35)	970	969	0.9
4	β-Pinene (439)	974	974	0.2
5	β-Myrcene (58)	985	988	0.2
6	α-Phellandren-8-ol (440)	1000	1002	0.6
7	α-Terpinene (441)	1015	1014	0.9
8	*p*-Cymen-8-ol (442)	1020	1020	0.8
9	o-Cymene (437)	1022	1022	5.3
10	Limonene (44)	1025	1024	0.5
11	1,8-Cineole (70)	1028	1026	0.3
12	γ-Terpinene (443)	1052	1054	1.8
13	α-Terpinolene (444)	1085	1086	0.6
14	*p*-Cymene (445)	1086	1089	0.4
15	Linalool (61)	1095	1095	1.8
16	*trans*-Pinocarveol (446)	1135	1135	0.3
17	Camphor (447)	1140	1141	0.6
18	Pinocarvone (448)	1162	1160	0.2
19	Borneol (449)	1165	1165	0.6
20	*p*-Mentha-1,5-dien-8-ol (450)	1165	1166	1.4
21	*cis*-Linalool oxide (451)	1172	1173	0.2

(continue)

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Table 4.3 *(continue)*

No	Components	KI[a]	KI[b]	Percentage (%)
22	Terpinen-4-ol (434)	1175	1174	26.3
23	α-Terpineol (452)	1185	1186	1.7
24	Verbenone (453)	1205	1204	0.8
25	*trans*-Carveol (454)	1015	1215	0.7
26	Cuminaldehyde (455)	1236	1238	0.3
27	Geraniol (456)	1250	1249	1.7
28	*p*-Thymol (457)	1285	1289	1.5
29	β-Elemene (74)	1290	1289	2.3
30	β-Caryophyllene (12)	1415	1417	0.2
31	β-Selinene (38)	1488	1489	3.3
32	α-Selinene (438)	1496	1498	2.3
33	(*E*,*E*)-α-Farnesene (422)	1505	1505	0.2
34	Longipinocarveol (458)	1565	1567	0.3
35	Spathulenol (10)	1577	1577	0.1
36	Caryophyllene oxide (459)	1582	1582	0.3
37	Isoaromadendrene epoxide (460)	1638	1639	1.6
38	*neo*-Intermedeol (435)	1658	1658	23.2
39	Eudesma-4,11-dien-3-one (436)	1685	1687	10.4
Group components				
	Monoterpene hydrocarbons			12.7
	Oxygenated monoterpenes			39.8
	Sesquiterpene hydrocarbons			8.3

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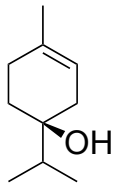
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Table 4.3 *(continue)*

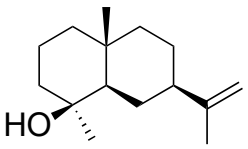
No	Components	KI[a]	KI[b]	Percentage (%)
	Oxygenated sesquiterpenes			35.9
Total identified (%)				99.6

KI[a] – Kovats index experimental; KI[b] – Kovats index from literature (Adams, 2001)

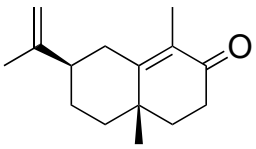
Terpinen-4-ol **(434)**, a naturally occurring monoterpene, is the main bioactive component of tea tree oil, while and its availability in other aromatic plants such as oranges, origanum, and black pepper are well established. Importantly, terpinen-4-ol **(434)** exhibits significant antimicrobial effects on viruses, bacteria, and fungi, as well as anti-arthritic, anti-tumorous, anti-cancerous, as well as antidiabetic natural products (Deen et al., 2023). This variation in chemical composition among *Lindera* species due to developmental stages, environmental conditions, growth phases, and genetic mutations. These factors have a significant impact on the plant's biosynthetic pathways, leading to variations in the relative proportions of unique compounds (Lichman, 2021)



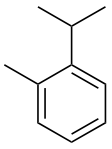
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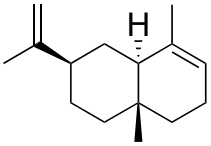
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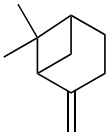
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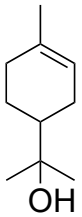
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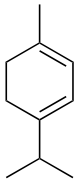
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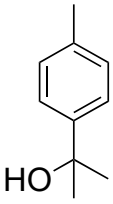
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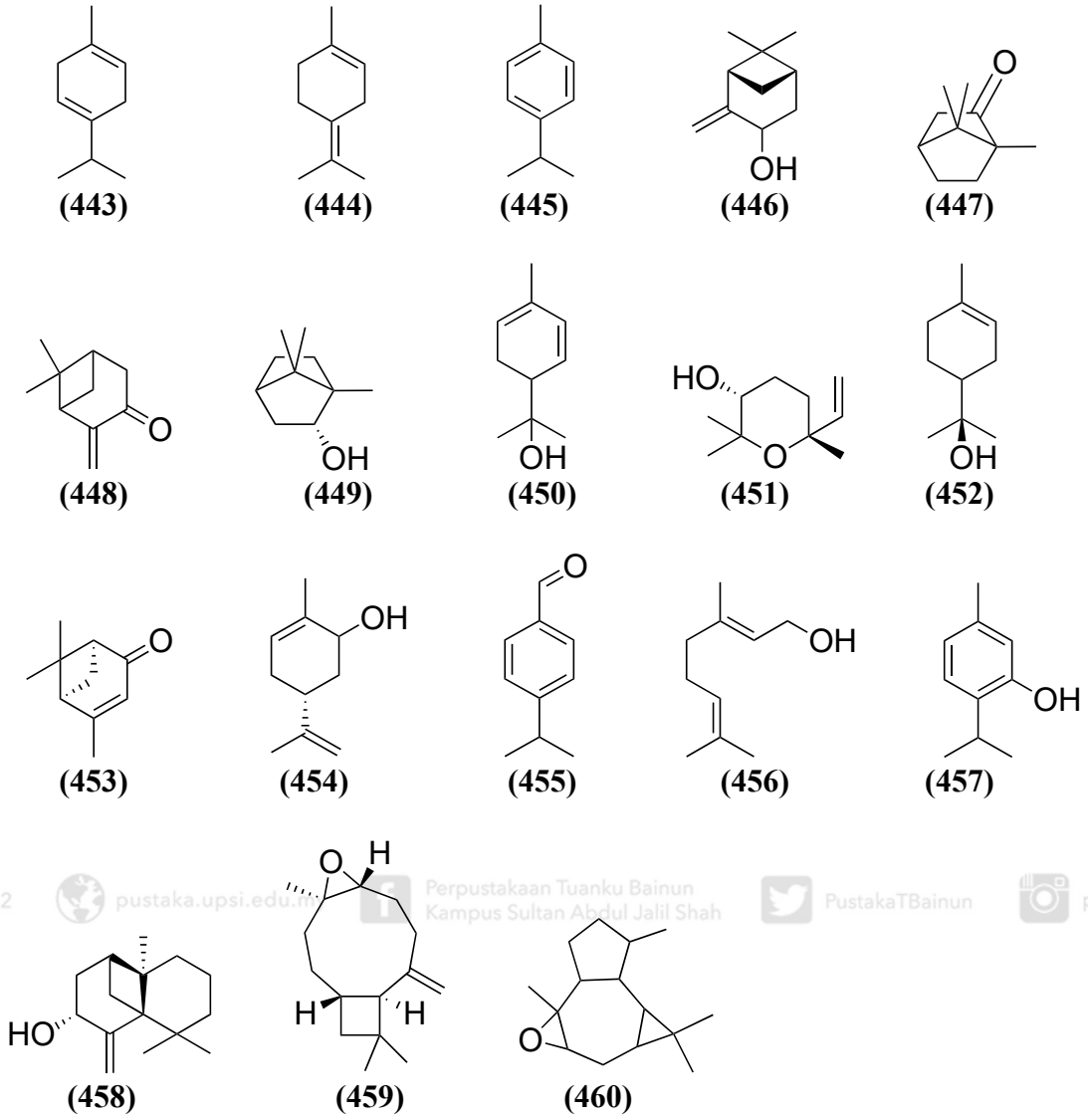
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4.3 Multivariate Statistical Analysis of Essential Oils

Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) have been used for the calculations to point out some considerations regarding their similarities between each of the *Lindera* species. PCA is focused on reducing the dimensionality of the data, whereas HCA is focused on clustering the taxonomic relationship of data points. By using PCA and HCA, it offers valuable insights into the

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multivariate analysis of essential oils between two species and reveal distinct patterns and groupings within the essential oil components.

The biplot (A) illustrates of PCA results, displaying the distribution of essential oil components across two principal components: F1 and F2. F1 explains 93.89% of the variance, while F2 accounts for 6.21%, together capturing the total variance in the dataset. Three distinct clusters (Cluster I, Cluster II, and Cluster III) have been identified, based on their similarities and differences between the *Lindera* species as shown in Figure 4.3.

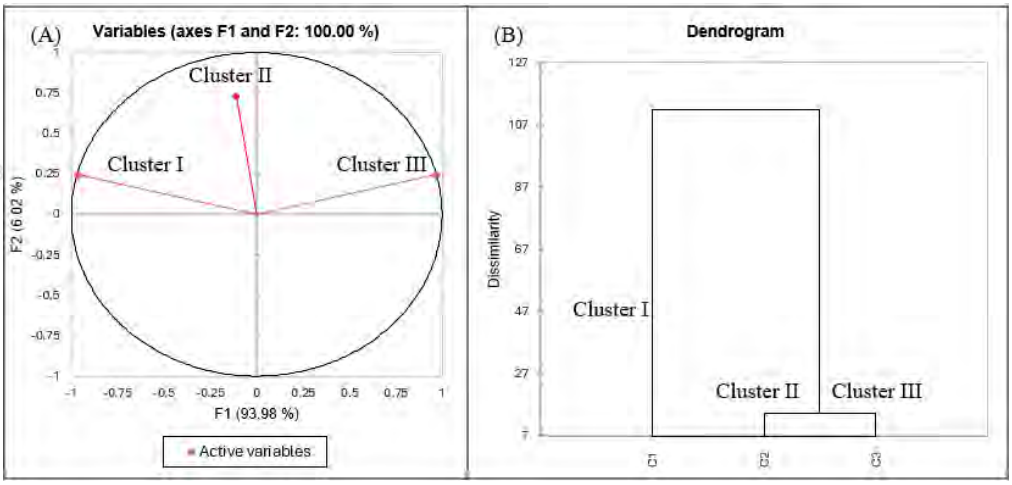


Figure 4.3. PCA (**A**) and HCA (**B**) analysis of *Lindera* essential oils

Cluster I, represented by *L. subumbelliflora* positioned in the lower left quadrant, contains components with negative scores on both F1 and F2, suggesting these components are less prevalent or have lower concentrations in the species. The particular components that being analyzed in this cluster I are α-copaene, dodecanal, *cis*-α-bergamotene, β-caryophyllene, α-humulene, dodecen-1-*ol*, β-selinene, δ-selinene, γ-amorphene, viridiflorene, α-muurolene, (*E*,*E*)-α-farnesene, (*Z*)-α-bisabolene, γ-

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cadinene, δ-cadinene, *cis*-cadina-1,4-diene, selina-3,7(11)-diene, (*E*)-nerolidol, caryophyllenyl alcohol, cubeban-11-ol, guaiol, rosifoliol, γ-eudesmol, α-muurolol, t-muurolol, β-eudesmol, bulnesol and α-bisabolol that ranging from 0.5 - 14.6%. Cluster II, located in the upper right quadrant, shows positive scores on both F1 and F2, indicating the components within this cluster have similarities. The similarities component that from these two species *Lindera* are (*E*,*E*)-α-farnesene, β-caryophyllene and β-selinene.

Cluster III, represented by *L. caesia* found in the lower right quadrant, includes components with a positive score on F1 and a negative score on F2, representing a unique set of components positively related to F1 but negatively related to F2. The components that being analyzed in this cluster III are α-thujene, α-pinene, sabinene, β-pinene, β-myrcene, α- phellandren-8-ol, α-terpinene, p-cymen-8-ol, o-cymene, limonene, 1,8-cineole, γ-terpinene, α-terpinolene, p-cymene, linalool, trans-pinocarveol, camphor, pinocarvone, borneol, p-mentha-1,5-dien-8-ol, cis-linalool oxide, terpinen-4-ol, α-terpineol, verbenone, trans-carveol, cuminaldehyde, geraniol, p-thymol, β-elemene, β-caryophyllene, β-selinene, α-selinene, (E,E)-α-farnesene, longipinocarveol, spathulenol, caryophyllene oxide, isoaromadendrene epoxide, neo-intermedeol and eudesma-4,11-dien-3-one that ranging from 0.1 - 26.3%.

Figure 4.3 shows dendrogram (B), representing HCA, shows the dissimilarities between the identified clusters. The vertical axis denotes dissimilarity, with higher values indicating greater differences between clusters. Cluster I, being distinct, might represent a unique set of predominant essential oil compositions in *L. subumbelliflora*

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species. In cluster II they are more closely related, indicating their essential oils compositions are similar in Cluster I and Cluster III.

The results from the multivariate analysis have several practical applications. For instance, in the fields of pharmacology and aromatherapy, identifying the specific components that differentiate the essential oils can lead to the development of targeted treatments or products (Buriani et al., 2020). In addition, by characterizing the chemical profiles of plants, researchers can develop standards to ensure consistency and quality in products derived from these plants (Gad et al., 2022). This analysis also contributes to the standardization and quality control of essential oil products in the market.

Overall, the combination of the biplot and the dendrogram provides a comprehensive view of the essential oil composition differences between the two species. The PCA identifies distinct groupings of components, while HCA further elucidates the relationships and dissimilarities among these groupings, offering essential insights into the chemical composition and potential functional properties of the essential oils from the two species. These results may be correlated with other factors involving genetic determination and environmental factors that can influence their chemical composition.

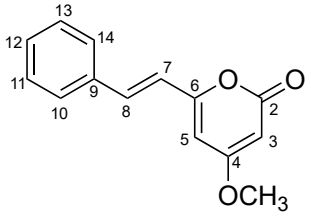
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4.4 Isolation of Phytochemical from *L. subumbelliflora*

A total of eight compounds were successfully isolated from *L. subumbelliflora* species. A chalcone; 5,6-dehydrokawain **(414)** was isolated from the leaves extract, while seven compounds were isolated from the roots extract comprising of dihydrochalcones; pinostrobin **(307)**, pinocembrin **(308)**; steroid; β-sitosterol **(401)**, phenolics; 4-hydroxy-3-methoxy acetophenone **(363)**, ferulic acid **(365)**, syringic acid **(370)**, and flavonol; quercetin **(331)**. These compounds were isolated and purified using various chromatographic techniques, followed by identification by modern spectroscopic techniques and comparison with those reported in the literatures.

4.4.1 5,6-Dehydrokawain (414)



(414)

Isolation of the *n*-hexane extract gave the major compound **(414)** as a pale yellow solid (10.0 mg, 0.3%). The IR spectrum (Figure 4.4A) revealed the existence of sp^2 C-H stretching at 3077 cm^{-1}, sp^3 C-H at 2954 cm^{-1}, carbonyl group at 1723 cm^{-1}, C=C aromatic at 1555 and 1447 $^{-1}$, and C-O stretching 1257 cm^{-1}. The ^{1}H NMR spectrum (Figure 4.4B) revealed the presence of a methoxy group at 4-OCH_3 were observed at δ 3.85. Two doublets observed at δ 6.59 (J = 16.0 Hz) and 7.53 (J = 16.0 Hz) were

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assigned to olefinic protons H-7 and H-8, respectively. The large coupling constant, J = 16.0 Hz suggested that these protons were in a *trans* orientation. Another two sets of doublets appeared at δ 5.52 and 5.97 (J = 2.1 Hz) were attributed to olefinic protons H-3 and H-5, of pyran-2-one respectively. The aromatic protons (H-10 to H-14) were observed as multiplet signals at δ 7.36-7.51. The COSY spectrum (Figure 4.4C) supported the correlations between the two olefinic protons. Proton H-7 (δ 6.59) was correlated with proton H-8 (δ 7.53), while proton H-3 (δ 5.52) was correlated with proton H-5 (δ 5.97). The assignments of the protons and carbons correlations are summarized in Table 4.4.

The ^{13}C NMR (Figure 4.4D) and DEPT spectra (Figure 4.4E) revealed the presence of fourteen carbons; one methoxy carbon at δ 55.9 (4-OCH_3), nine methine carbons at δ 88.9 (C-3), 101.4 (C-5), 118.7 (C-7), 127.5 (C-10/C-14), 128.9 (C-11/C-13), 129.5 (C-12), and 135.8 (C-8), three quaternary carbons at δ 135.2 (C-9), 164.1 (C-6), and 158.7 (C-4), and a carbonyl carbon at δ 171.1 (C-2). The MS spectrum (Figure 4.11F) gave a molecular ion peak at *m/z* 228, corresponding to a molecular formula $C_{14}H_{12}O_3$. The HMQC spectrum (Figure 4.4G) showed the methoxy carbon at δ 55.9 were directly attached to the protons at δ 3.85 (4-OCH_3). Besides, four methine carbons, H-8 (δ 7.53), H-7 (δ 6.59), H-5 (δ 5.97) and H-3 (δ 5.52) were confirmed directly attached to carbon C-8 (δ 135.8), C-7 (δ 118.7), C-5 (δ 101.4), and C-3 (δ 88.9), respectively. Meanwhile, the HMBC correlation (Figure 4.4H) showed the correlation between H-5 (δ 5.97) with C-3 (δ 88.9), C-7 (δ 118.7), C-2 (δ 171.1), and C-4 (δ 158.7). Besides, it also showed the correlation between H-7 (δ 6.59) with C-5 (δ 101.4), C-9 (δ 135.2) and, C-4 (δ 158.7) and H-3 (δ 5.97) with C-5 (δ 101.4) and C-2 (δ 171.1).

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Table 4.4

*NMR data of 5,6-dehydrokawain **(414)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz) (414)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
2	-	171.1	-	171.1
3	5.52 (1H, d, 2.1)	88.9	5.51 (1H, d, *J* = 2.0)	88.9
4	-	158.7	-	158.7
5	5.97 (1H, d, 2.1)	101.4	5.96 (1H, d, *J* = 2.0)	101.3
6	-	164.1	-	164.0
7	6.59 (1H, d, 16.0)	118.7	6.60 (1H, d, *J* = 16.0)	118.6
8	7.53 (1H, d, 16.0)	135.8	7.52 (1H, d, *J* = 16.0)	135.8
9	-	135.2	-	135.2
10	7.36 – 7.51 (5H, m)	127.5	7.31 – 7.54 (5H, m)	127.4
11	7.36 – 7.51 (5H, m)	128.9	7.31 – 7.54 (5H, m)	128.9
12	7.36 – 7.51 (5H, m)	129.5	7.31 – 7.54 (5H, m)	129.4
13	7.36 – 7.51 (5H, m)	128.9	7.31 – 7.54 (5H, m)	128.9
14	7.36 – 7.51 (5H, m)	127.5	7.31 – 7.54 (5H, m)	127.4
4-OCH_3	3.85 (3H, s)	55.9	3.84 (3H, s)	55.9

[a]Data from literature (Sirat & Jani, 2013)

Therefore, based on the comparison of spectral data, compound (**414**) was identified as 5,6-dehydrokawain, which was previously isolated from the leaves of *L. umbellata* (Kusumoto et al., 2022; Sirat & Jani, 2013).

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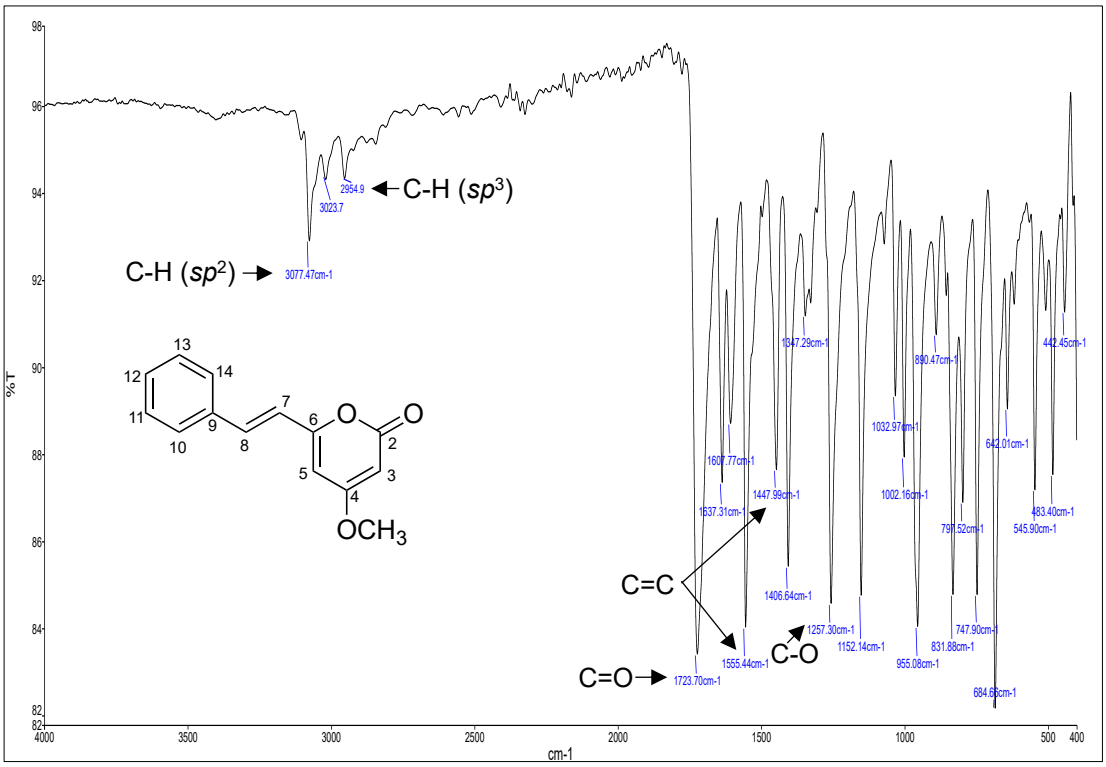


Figure 4.4A. IR spectrum of 5,6-dehydrokawain **(414)**

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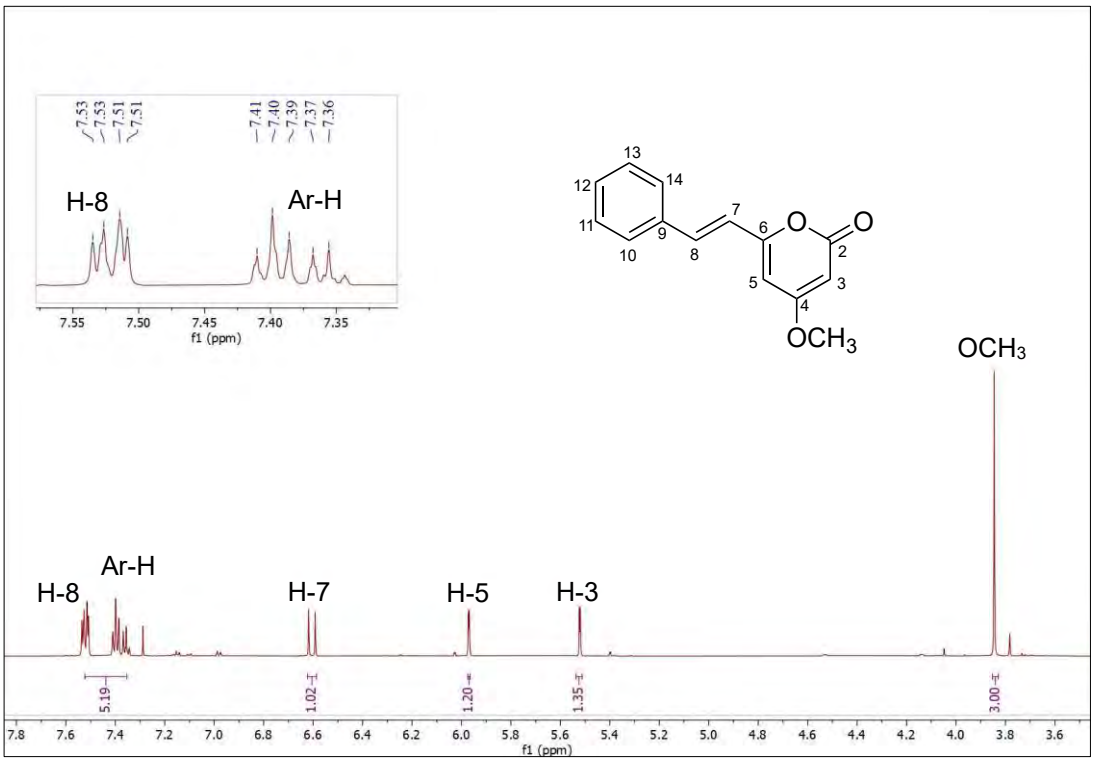


Figure 4.4B. ^{1}H NMR spectrum of 5,6-dehydrokawain **(414)**

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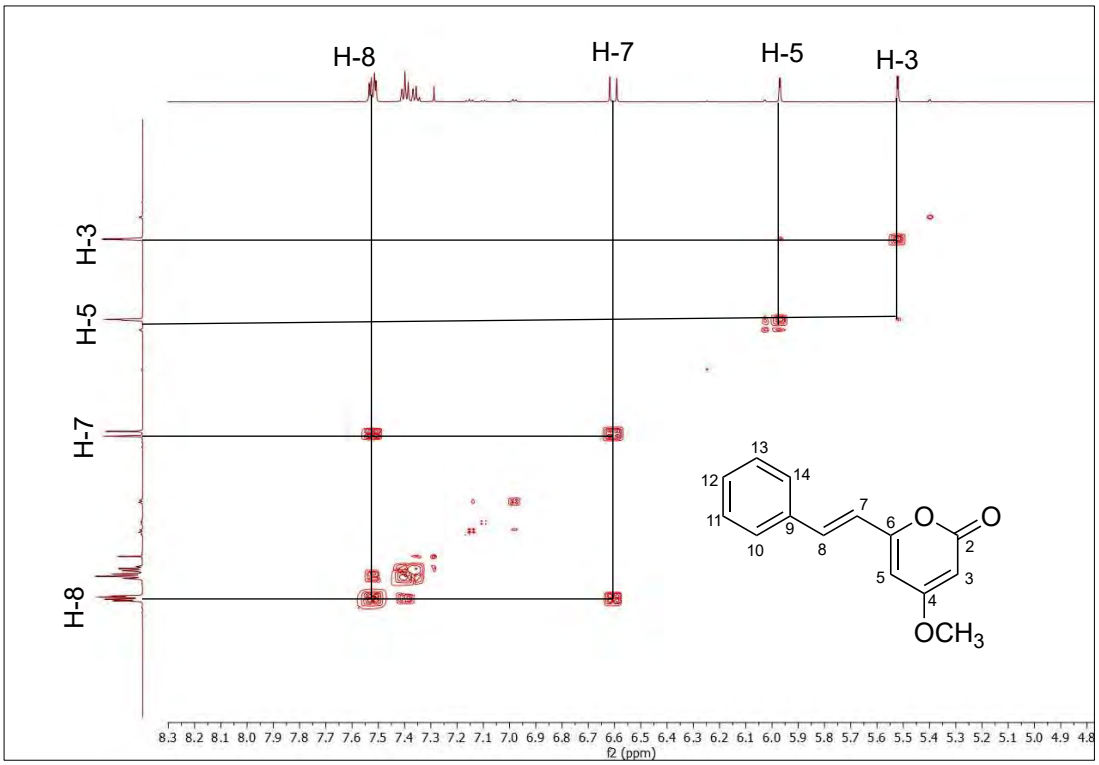


Figure 4.4C. COSY spectrum of 5,6-dehydrokawain **(414)**

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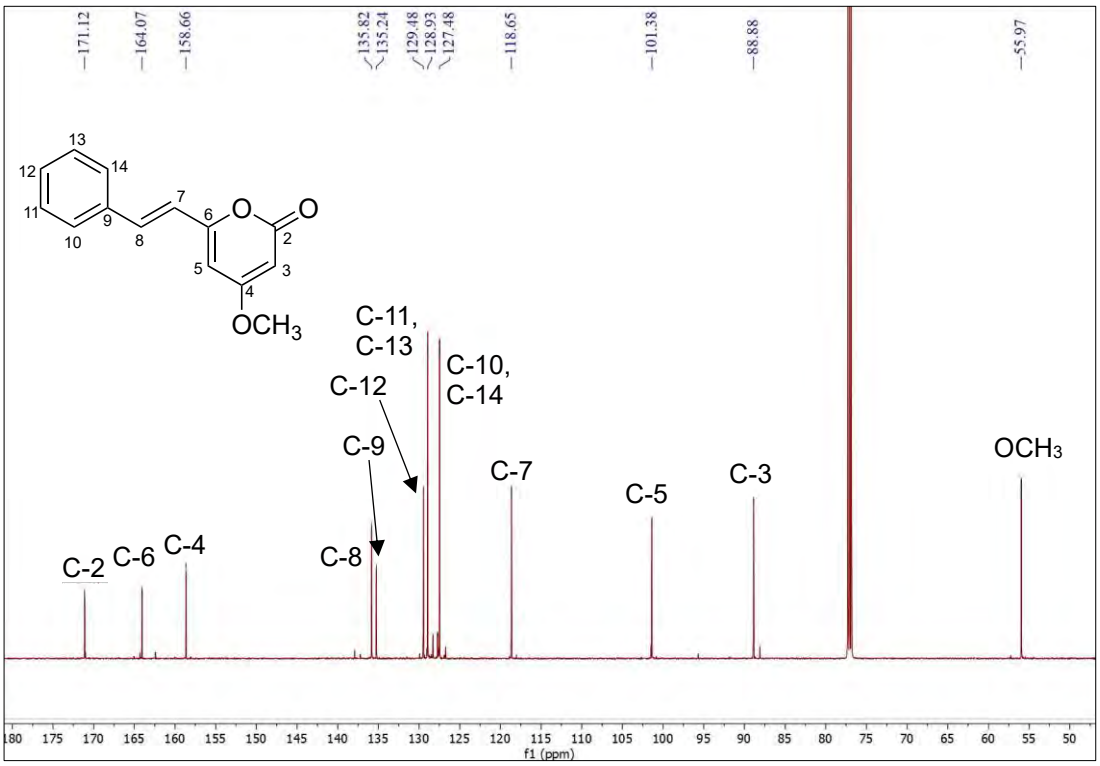


Figure 4.4D. ^{13}C NMR spectrum of 5,6-dehydrokawain **(414)**

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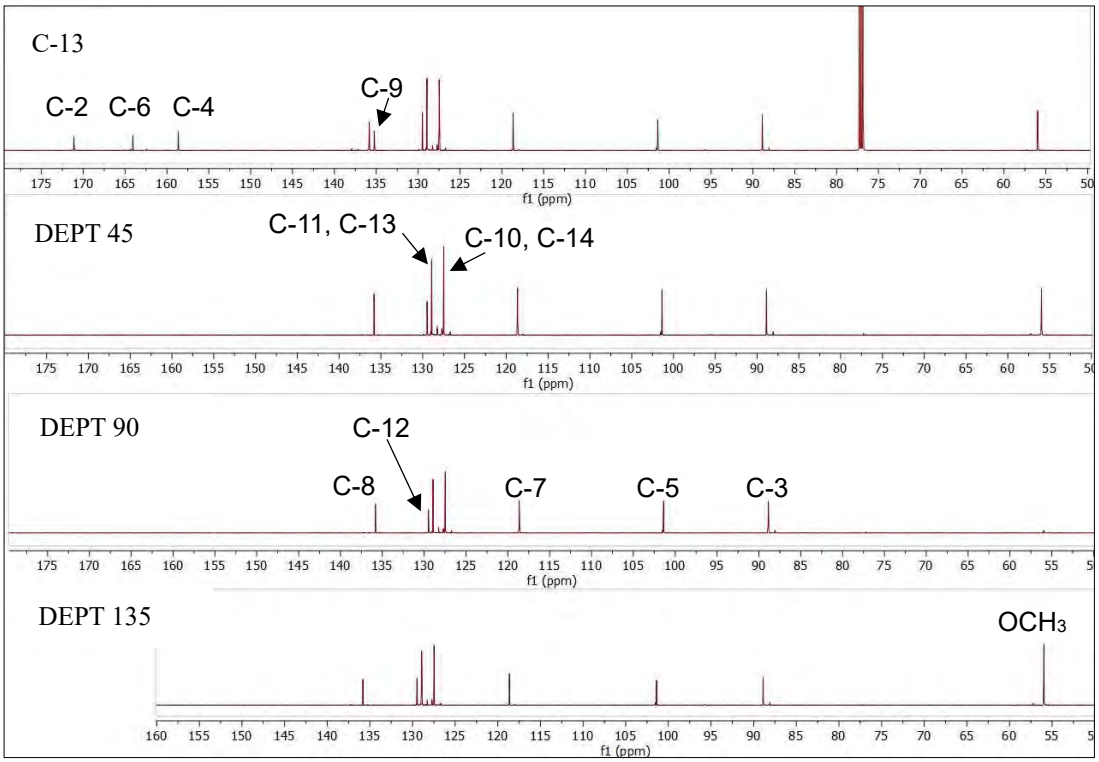


Figure 4.4E. DEPT spectra of 5,6-dehydrokawain **(414)**

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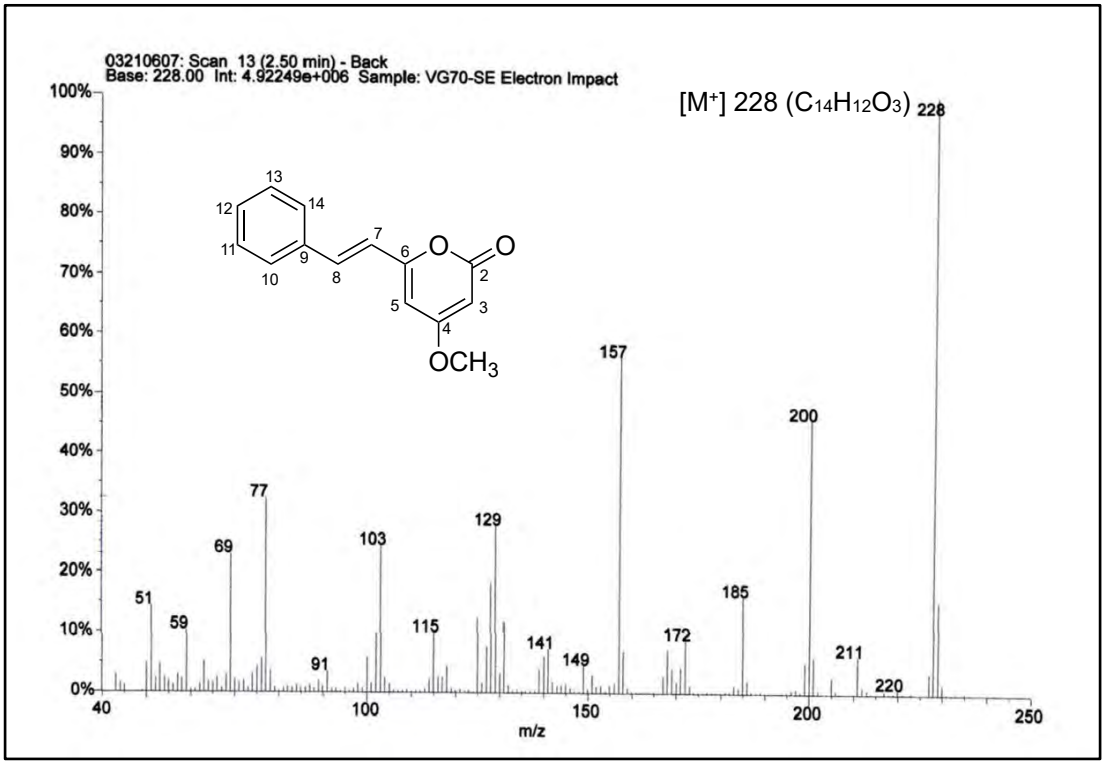


Figure 4.4F. MS spectrum of 5,6-dehydrokawain **(414)**

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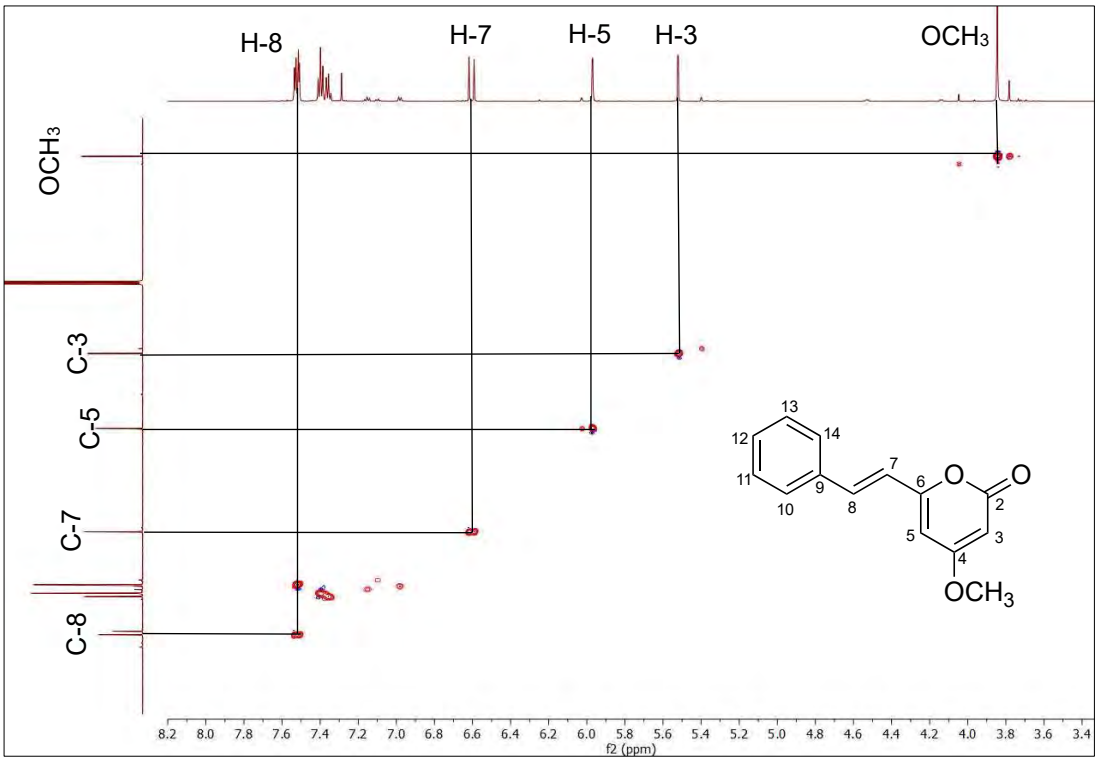


Figure 4.4G. HMQC spectrum of 5,6-dehydrokawain **(414)**

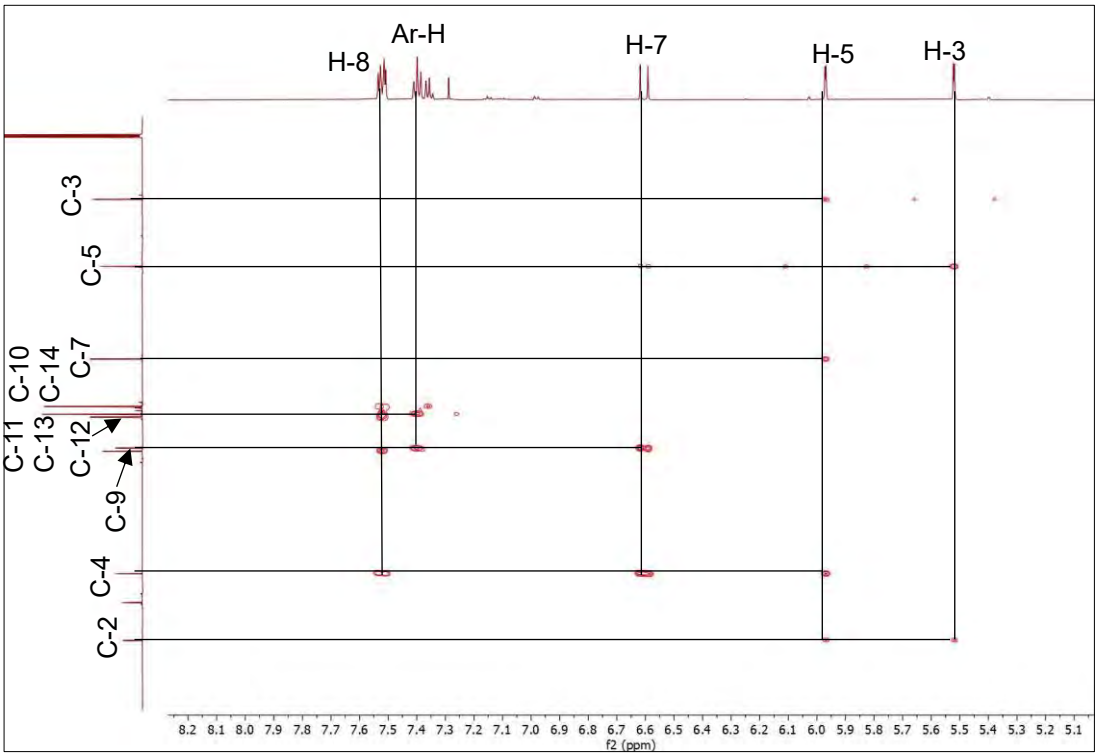
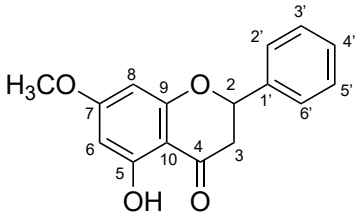


Figure 4.4H. HMBC spectrum of 5,6-dehydrokawain **(414)**

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4.4.2 Pinostrobin (307)



(307)

Isolation of the *n*-hexane roots extract by CC afforded compound **(307)** (12.6 mg, 0.2%) as colourless crystalline needles. The IR spectrum (Figure 4.5A) displayed an absorption band at 3445 cm^{-1} corresponding to chelating O-H stretching, whereas sp^3 C-H at 2973 cm^{-1} and carbonyl group was observed at 1614 cm^{-1}. The C=C aromatic stretching appeared at 1514 cm^{-1}, while C-O stretching was observed at 1252 cm^{-1}.

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The ^{1}H NMR spectrum (Figure 4.5B) supported the presence of hydroxyl group which was represented by a singlet signal at δ 12.05. The downfield absorption caused by the chelation effect of intermolecular hydrogen bonding that decreases the electron density around the proton and thus moves the proton absorption to a lower field. Another singlet peak was observed at δ 3.84, assigned to a methoxy group (7-OCH_3). The *meta*-coupled signals appeared at δ 6.10 and 6.11 (J = 2.3 Hz), which were attributed to aromatic protons H-6 and H-8, respectively. In addition, three set doublet of doublet signal, each integrated for one proton were observed at δ 2.84 (J = 2.9 Hz and 14.8 Hz), 3.10 (J = 13.0 Hz and 15.0 Hz) and 5.44 (J = 2.9 Hz and 13.0 Hz,) were assigned for H-3a, H-3b and H-2, respectively. In addition, a multiplet signal resonated at δ 7.42-7.48 integrating for five protons of aromatic protons, H-2′ – H-6′ of ring B. Besides,

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based on chemical shift pattern comparison of H-2, H-3a and H-3b, the configuration at H-3 was deduced as R configuration (Yang et al., 2022b).

The COSY spectrum (Figure 4.5C) showed correlation between H-2 (δ 5.44) with H-3a (δ 2.84) and H-3b (δ 3.10), as well as between H-6 (δ 6.10) with H-8 (δ 6.11). The ^{13}C NMR (Figure 4.5D) and DEPT spectra (Figure 4.5E) indicated the presence of sixteen carbons including one methyl, one methylene, one carbonyl carbon, eight methine and five quaternary carbon atoms. The carbon signal of methoxy group (7-OCH_3) was clearly assigned at δ 55.7, while the carbonyl carbon (C-4) was also observed at δ 195.8. The single signal position of methylene carbon (C-3a/C-3b) was observed at δ 43.4. Eight methine carbons were detected at δ 79.3 (C-2), 94.3 (C-8), 95.2 (C-6), 126.2 (C-2′, C-6′) and 128.9 (C-3′, C-4′, C-5′) as well as five quaternary carbons at δ 103.2 (C-10), 138.4 (C-1′), 162.8 (C-9), 164.2 (C-5) and 168.0 (C-7). The ^{1}H NMR and ^{13}C NMR data as tabulated in Table 4.5.

The ^{13}C NMR data were supported by the MS spectrum (Figure 4.5F), which gave a molecular ion peak *m/z* 270 consistent with a molecular formula $C_{16}H_{14}O_4$. In the HMQC spectrum (Figure 4.5G), the aromatic protons at δ 7.42-7.48 (H-2′ – H-6′) were found directly attached to carbons resonated at δ 126.2 (C-2′, C-6′) and 128.9 (C-3′, C-4′, C-5′). Two aromatic protons of the ring A (H-8 and H-6) were found correlated with carbons at δ 94.3 (C-8) and 95.2 (C-6). The methine proton, H-2 (δ 5.44) was confirmed attached to carbon at δ 79.3 (C-2). Meanwhile, two unequivalent methylene protons, H-3 (δ 2.84 and 3.10) showed a cross peak with C-3a/C-3b (δ 43.4).

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Table 4.5

*NMR data of pinostrobin **(307)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz) (307)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
2	5.44 (1H, dd, 2.9, 13.0)	79.3	5.40 (1H, dd, 2.8, 12.8)	79.0
3a	2.84 (1H, dd, 2.9, 14.8)	43.4	2.80 (1H, dd, 2.8, 14.9)	44.1
3b	3.10 (1H, dd, 13.0, 15.0)	43.4	3.06 (1H, dd, 12.8, 15.1)	-
4	-	195.8	-	195.7
5	-	164.2	-	162.7
6	6.10 (1H, d, 2.3)	95.2	6.05 (1H, d, 2.7)	95.0
7	-	168.0	-	167.8
8	6.11 (1H, d, 2.3)	94.3	6.05 (1H, d, 2.7)	94.1
9	-	162.8	-	164.0
10	-	103.2	-	103.0
1′	-	138.4	-	138.3
2′	7.42 – 7.48 (5H, m)	126.2	7.41 – 7.47 (5H, m)	126.0
3′	7.42 – 7.48 (5H, m)	128.9	7.41 – 7.47 (5H, m)	128.8
4′	7.42 – 7.48 (5H, m)	128.9	7.41 – 7.47 (5H, m)	126.0
5′	7.42 – 7.48 (5H, m)	128.9	7.41 – 7.47 (5H, m)	126.0
6′	7.42 – 7.48 (5H, m)	126.2	7.41 – 7.47 (5H, m)	126.0
7-OCH_3	3.84 (3H, s)	55.7	3.80 (3H, s)	55.6
5-OH	12.05 (1H, s)	164.2	12.00 (1H, s)	162.7

[a]Data from literature (Nyokat et al., 2017)

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The HMBC spectrum (Figure 4.5H) exhibited a long-range correlation of hydroxyl proton at δ 12.05 and carbon C-10 (δ 103.2), C-6 (δ 95.2) and C-7 (δ 168.0). The signal proton of H-6 (δ 6.10) was found correlated with C-10 (δ 103.2), C-5 (δ 164.2) and C-7 (δ 168.0), while proton of H-8 (δ 6.11) correlated with C-6 (δ 95.2), C-7 (δ 168.0), C-5 (δ 164.2), and C-10 (δ 103.2). The methine proton of H-2 (δ 5.44) was correlated to C-1′ (δ 138.4), C-2′ and C-6′ (δ 126.2). The signal at δ 3.10 (H-3b) was also correlated to C-2 (δ 79.3), C-4 (δ 195.8), and C-1′ (δ 138.4), while for H-3a (δ 2.84) correlated with C-4 (δ 195.8) and C-10 (δ 103.2).

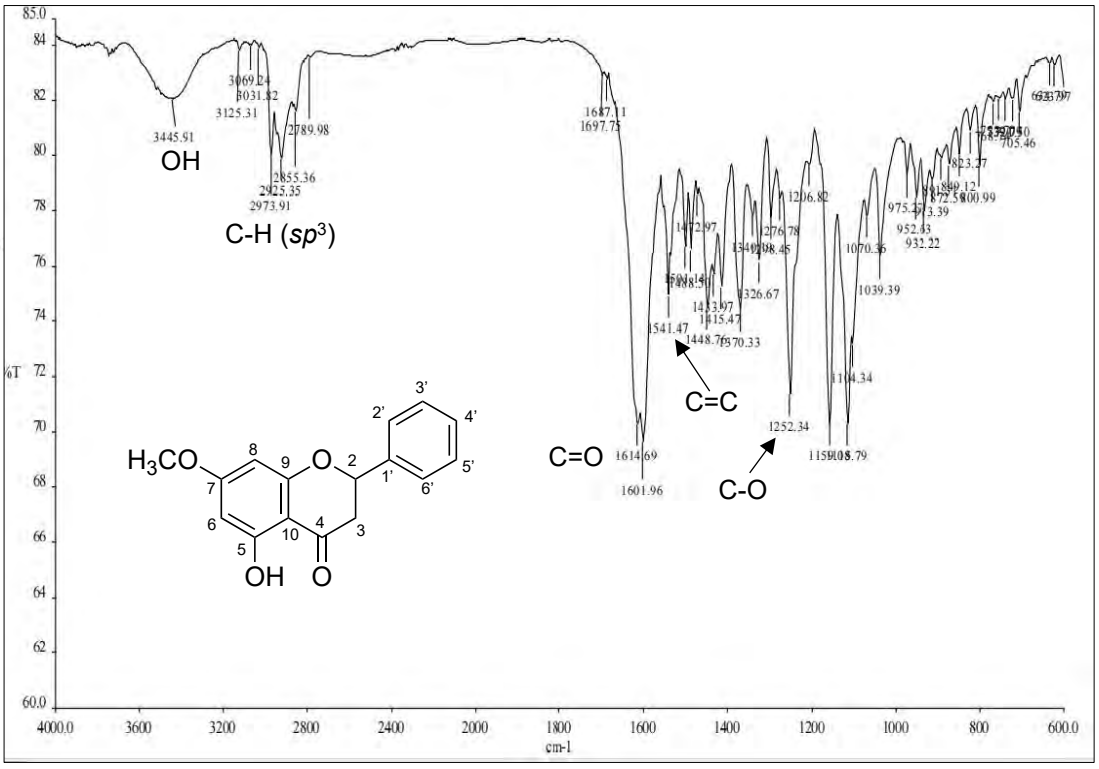


Figure 4.5A. IR spectrum of pinostrobin **(307)**

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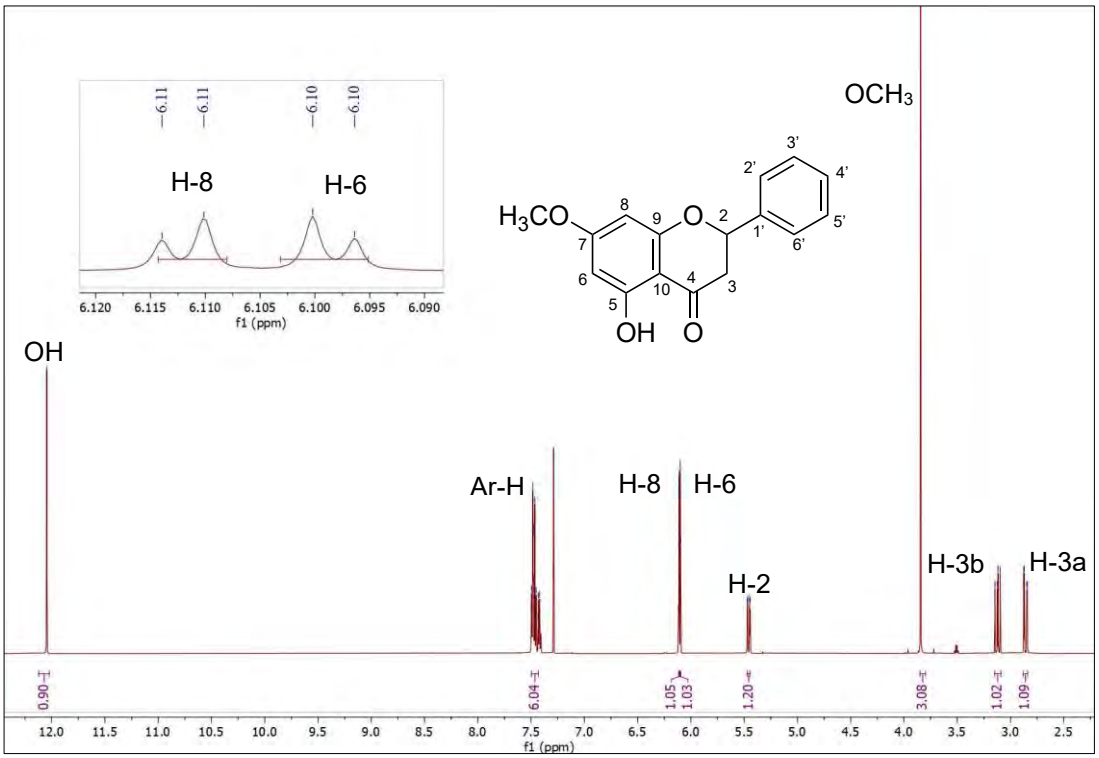


Figure 4.5B. ^{1}H NMR spectrum of pinostrobin **(307)**

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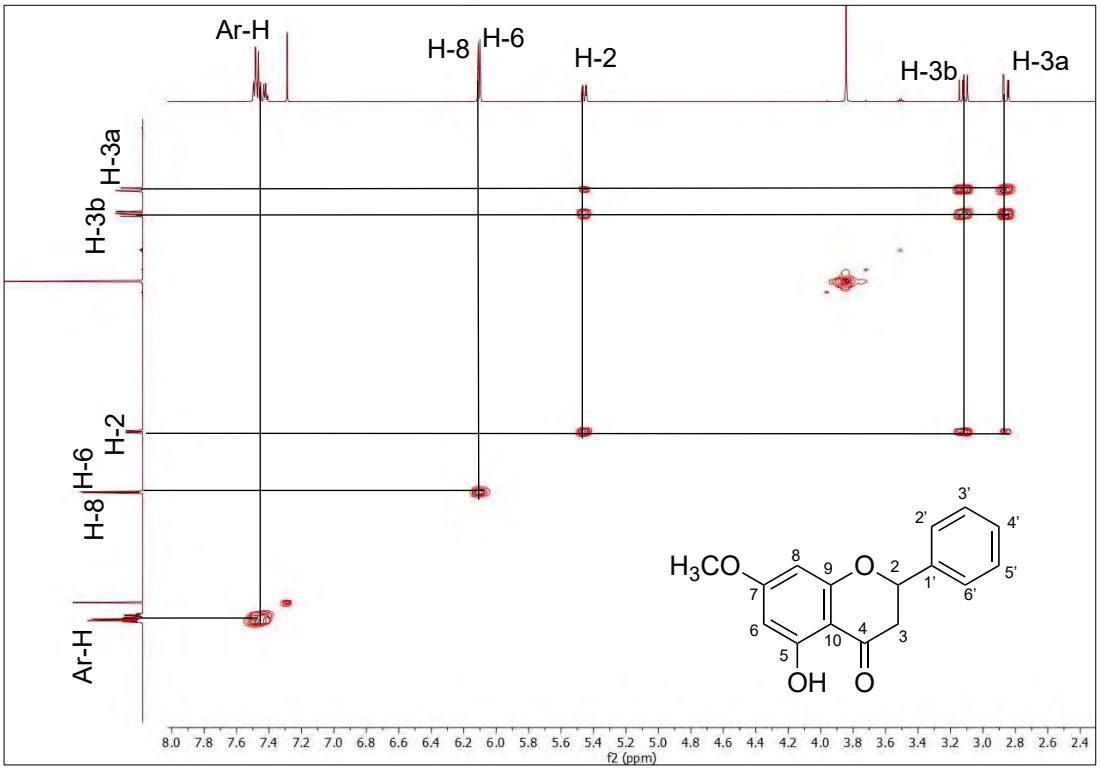


Figure 4.5C. COSY spectrum of pinostrobin **(307)**

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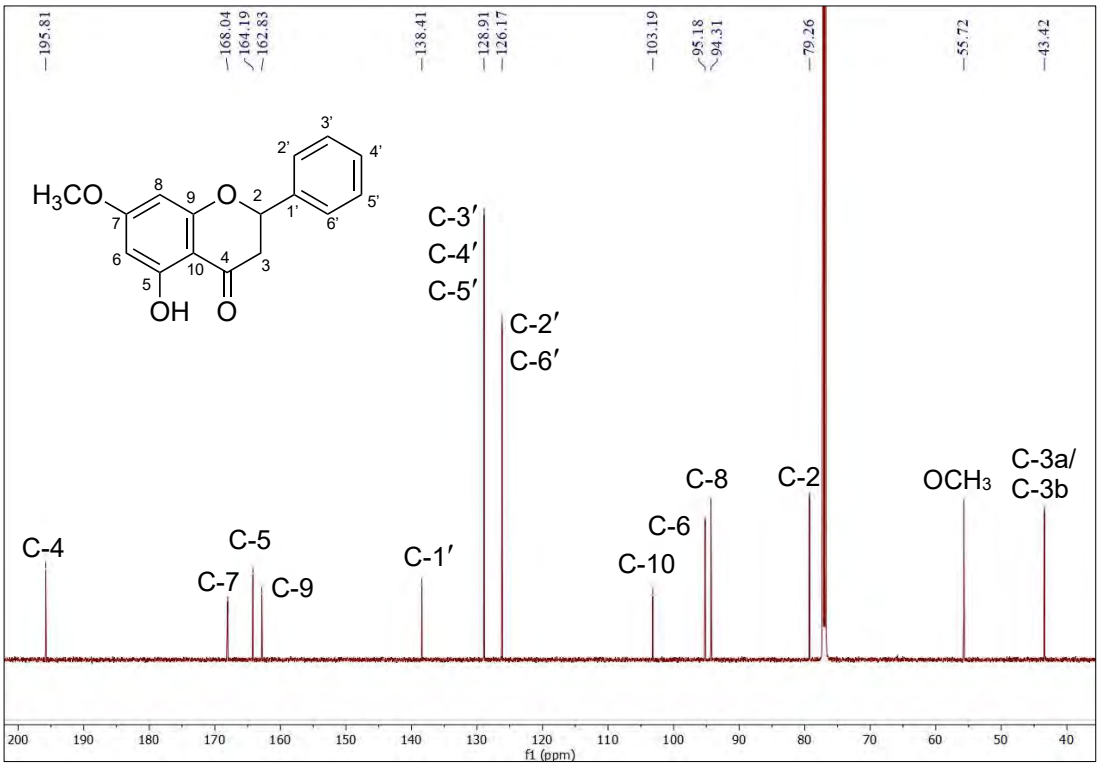


Figure 4.5D. ^{13}C NMR spectrum of pinostrobin **(307)**

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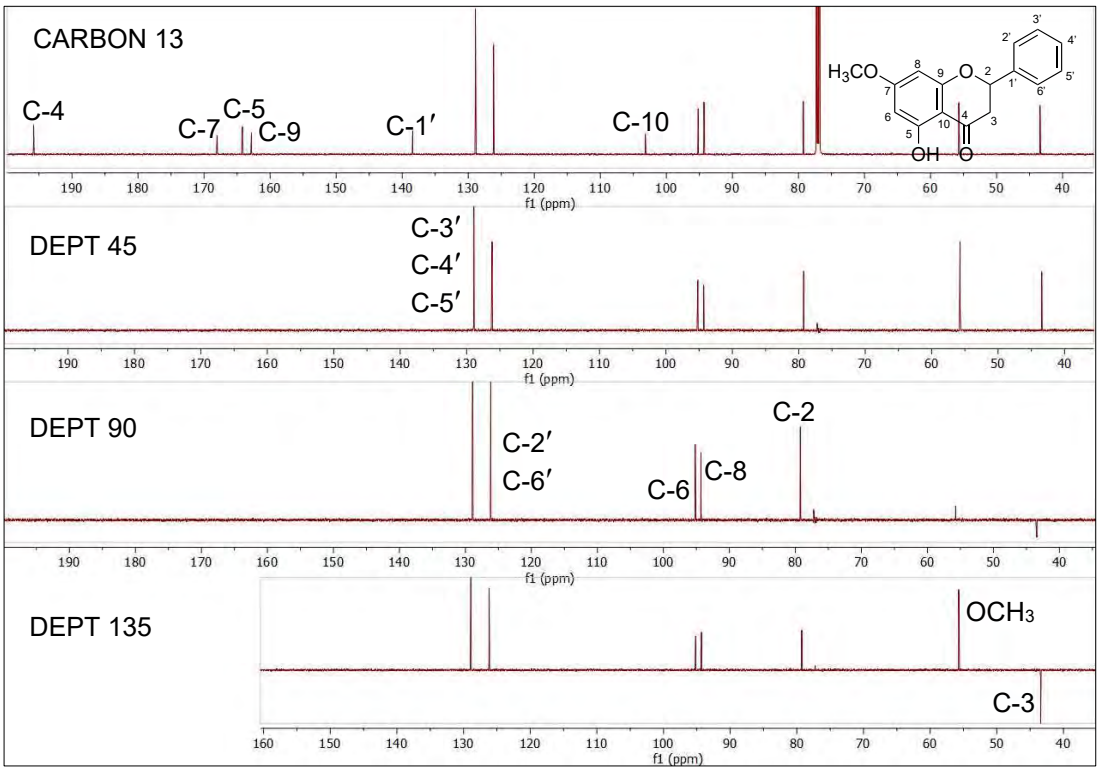


Figure 4.5E. DEPT spectra of pinostrobin **(307)**

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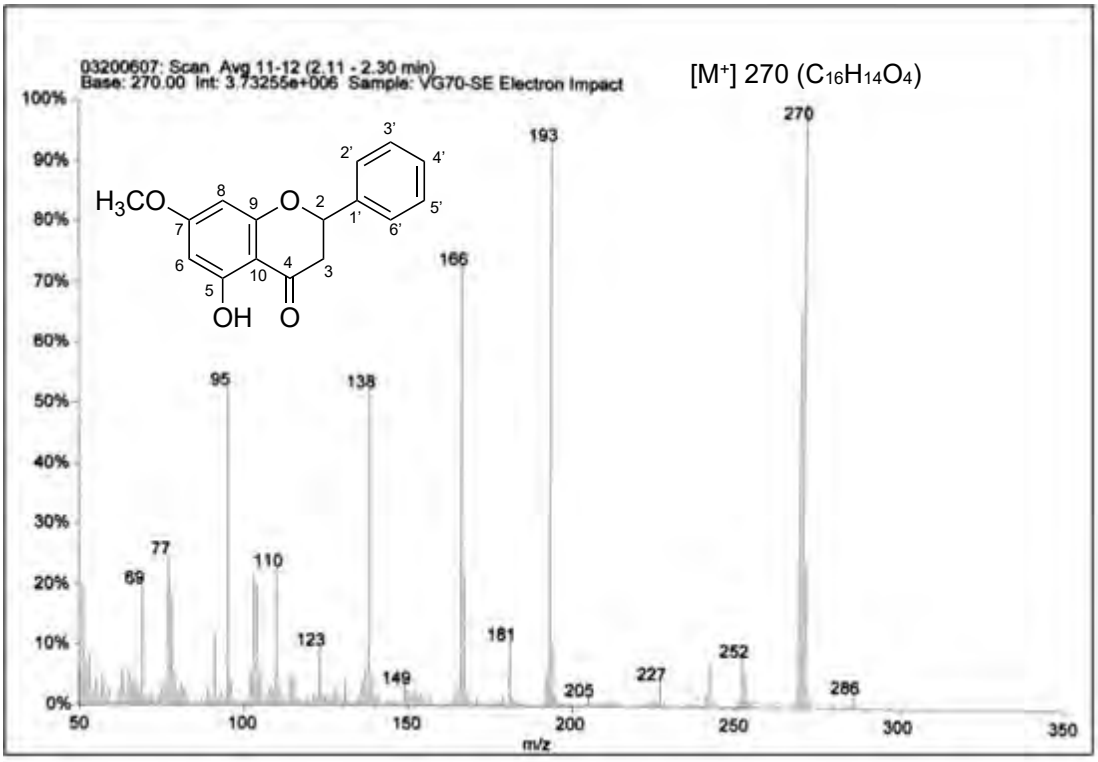


Figure 4.5F. MS spectrum of pinostrobin **(307)**

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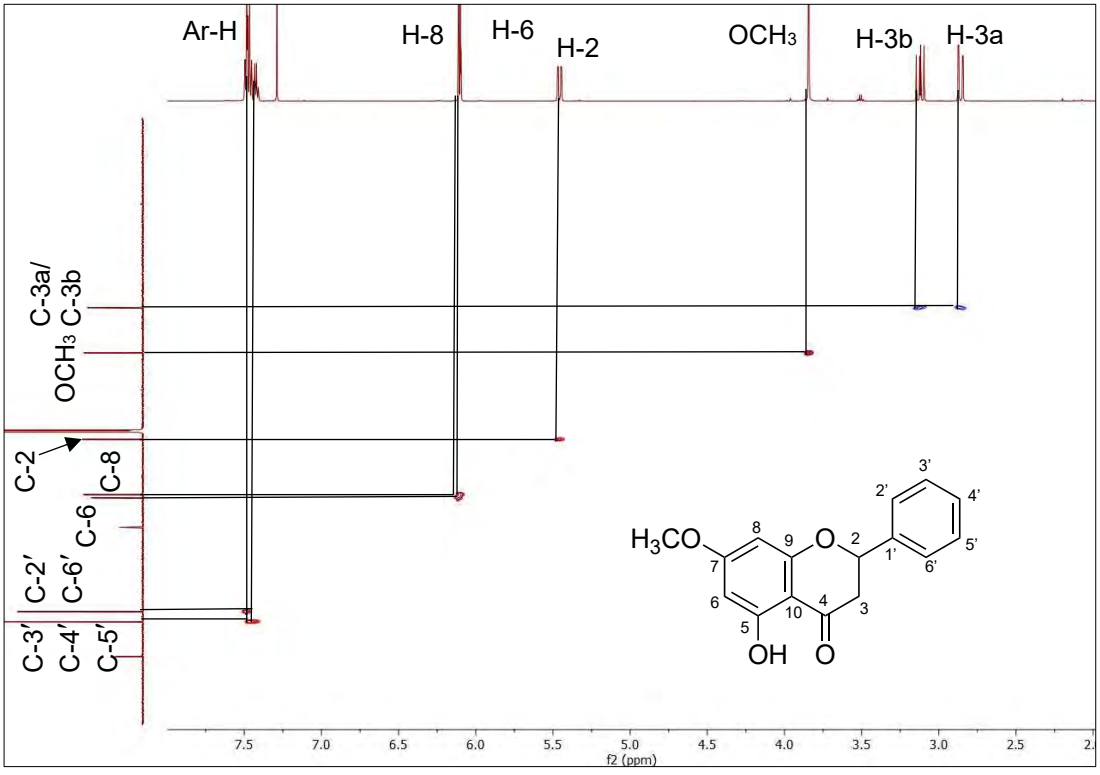


Figure 4.5G. HMQC spectrum of pinostrobin **(307)**

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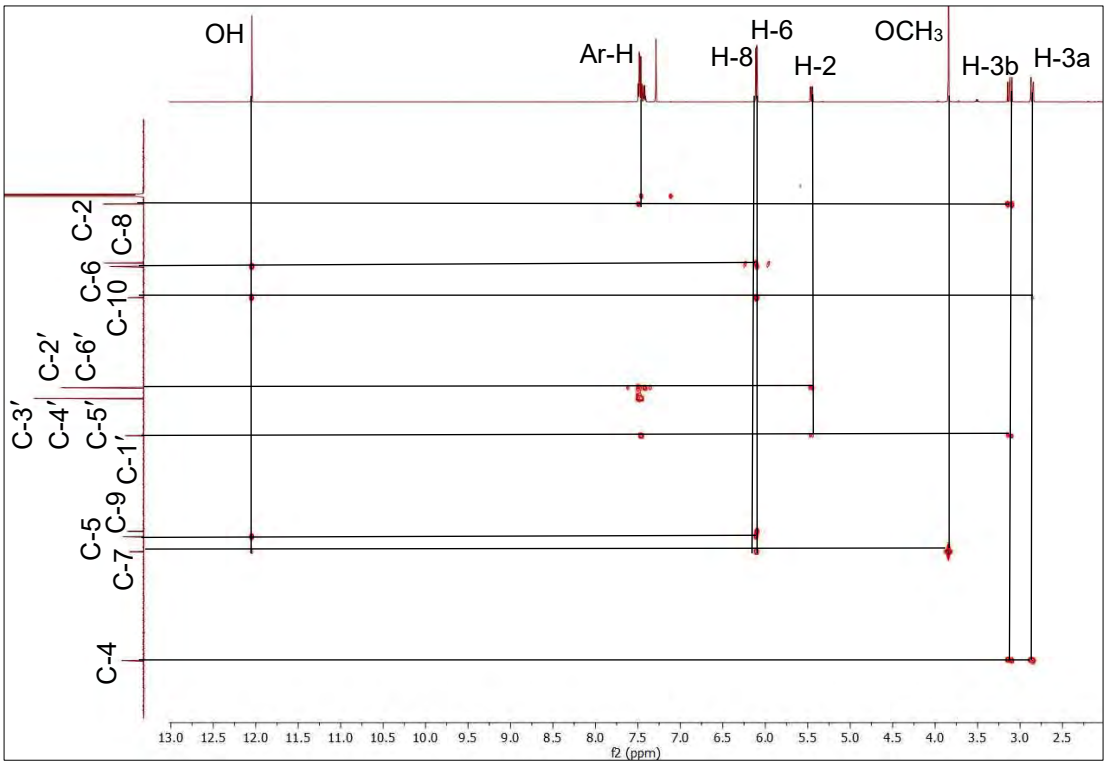
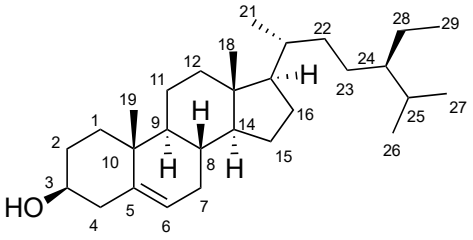


Figure 4.5H. HMBC spectrum of pinostrobin **(307)**

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Compound **(307)** was identified as 5-hydroxy-7-methoxyflavanone or also known as pinostrobin, based on the comparison of its physical properties and spectral data. It has been previously reported from *L. umbellata* (Kusumoto et al., 2022), *L. reflexae radix* (Wang et al., 2016b) and *L. aggregata* (Hai et al., 2016).

4.4.3 β-Sitosterol (401)



(401)

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Isolation of the fraction LSRH E using CC followed by washing with cold *n*-hexane was successfully yielded compound **(401)** as a white solid. The IR spectrum (Figure 4.6A) displayed the presence of OH stretching at 3435 cm^{-1}, sp^3 C-H stretching at 2937 cm^{-1}, C=C stretching at 1652 cm^{-1}, and C-O stretching at 1052 cm^{-1}.

The ^{1}H NMR spectrum (Figure 4.6B) displayed two singlet signals at δ 0.70 and 1.02, which correspond to the methyl groups of H-18 and H-19, respectively. Four doublets resonated at δ 0.83, 0.85, 0.94, and 0.86 were attributed to four methyl groups of H-27, H-26, H-21, and H-29, respectively. Another doublet signal resonated at δ 5.37 (J = 5.2 Hz) and were attributed to H-6. The signal of H-3 was resonated as a multiplet at δ 3.55.

The presence of 29 carbon atoms was confirmed by its ^{13}C NMR (Figure 4.6C) and DEPT spectra (Figure 4.6D). It comprises of six methyl, eleven methylene, nine methines, and three quaternary carbons. Additionally, the MS spectrum (Figure 4.6E) exhibited a molecular ion peak at *m/z* 414, corresponding to the molecular formula $C_{29}H_{50}O$. The parameters for ^{1}H and ^{13}C NMR data as presented in Table 4.6.

Based on the basis of the studied spectral data and a literature comparison, compound **(401)** was identified as (3β)-stigmast-5-en-3-ol or commonly known as β-sitosterol. Previously, it has been isolated from the roots of *L. aggregata* (Hai et al., 2016), stem wood of *L. glauca* (Huh et al., 2011), and the roots of *L. akoensis* (Chang et al., 2008).

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Table 4.6

*NMR data of β-sitosterol **(401)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 600 MHz) (401)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 600 MHz)[a]	δ_C (ppm)
1	**	37.5	**	37.5
2	**	31.6	**	31.9
3	3.55 (1H, m)	71.8	3.51 (1H, m)	72.0
4	**	42.3	**	42.5
5	-	140.7	-	140.9
6	5.37 (1H, d, 5.2)	121.7	5.34 (1H, d, 5.2)	121.9
7	**	31.9	**	32.1
8	**	31.9	**	32.1
9	**	50.1	**	50.3
10	-	36.5	-	36.7
11	**	21.0	**	21.3
12	**	39.8	**	39.9
13	-	42.3	-	42.6
14	**	56.7	**	56.9
15	**	24.3	**	24.3
16	**	28.2	**	28.5
17	**	56.0	**	56.3
18	0.70 (3H, s)	11.9	0.67 (3H, s)	12.2
19	1.02 (3H, s)	19.3	1.00 (3H, s)	20.1

(continue)

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Table 4.6 *(continue)*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 600 MHz) (401)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 600 MHz)[a]	δ_C (ppm)
20	**	36.1	**	36.5
21	0.94 (3H, d, 6.5)	18.7	0.92 (3H, d, 6.0)	18.5
22	**	33.9	**	33.8
23	**	26.1	**	26.3
24	**	45.8	**	45.5
25	**	29.2	**	29.4
26	0.85 (3H, d, 6.8)	19.7	0.83 (3H, d, 7.2)	19.6
27	0.83 (3H, d, 6.8)	19.0	0.79 (3H, d, 7.2)	19.0
28	**	23.1	**	23.3
29	0.86 (3H, d, 7.8)	11.8	0.85 (3H, d, 8.0)	12.0

[a]Data from literature (Du et al., 2001)
**1.20-2.33 (29H, m, overlap CH and CH_2)

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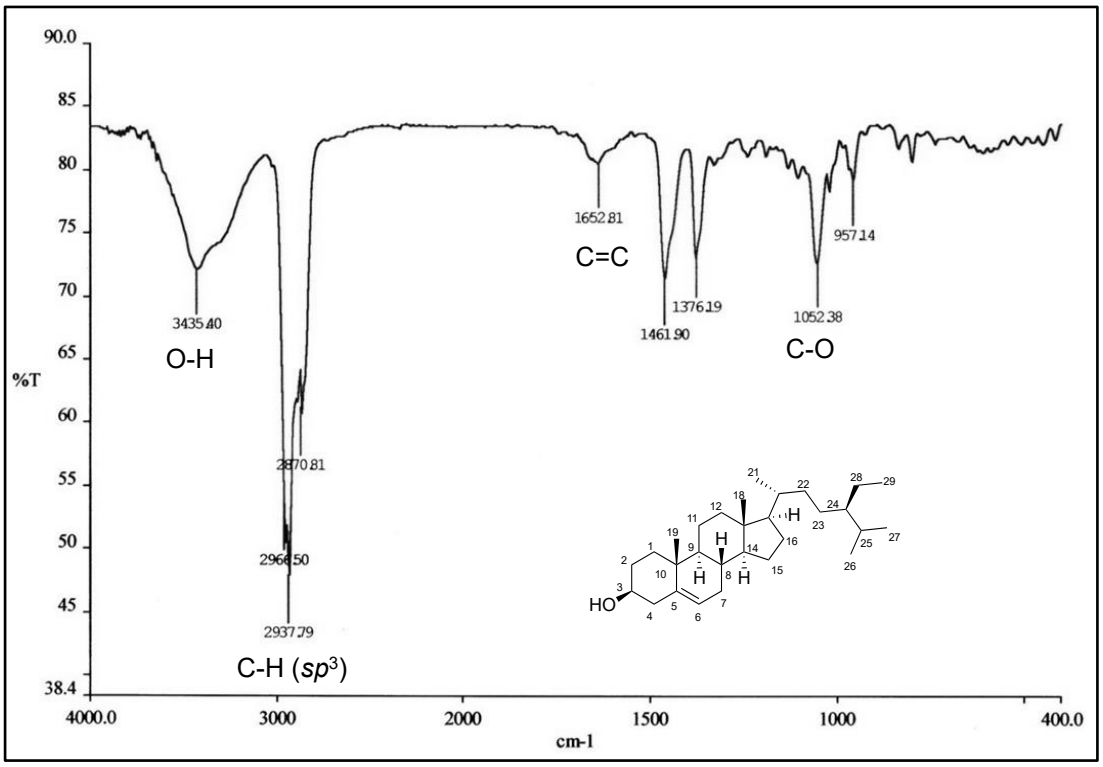


Figure 4.6A. IR spectrum of β-sitosterol **(401)**

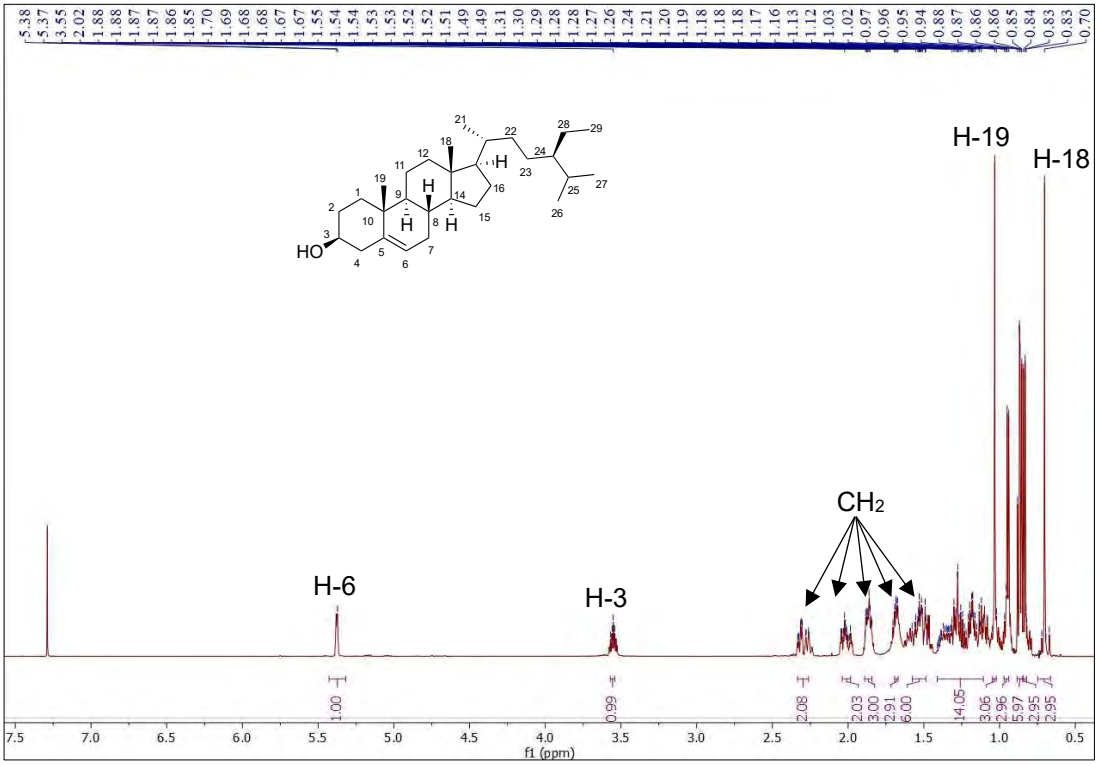


Figure 4.6B. ^{1}H NMR spectrum of β-sitosterol **(401)**

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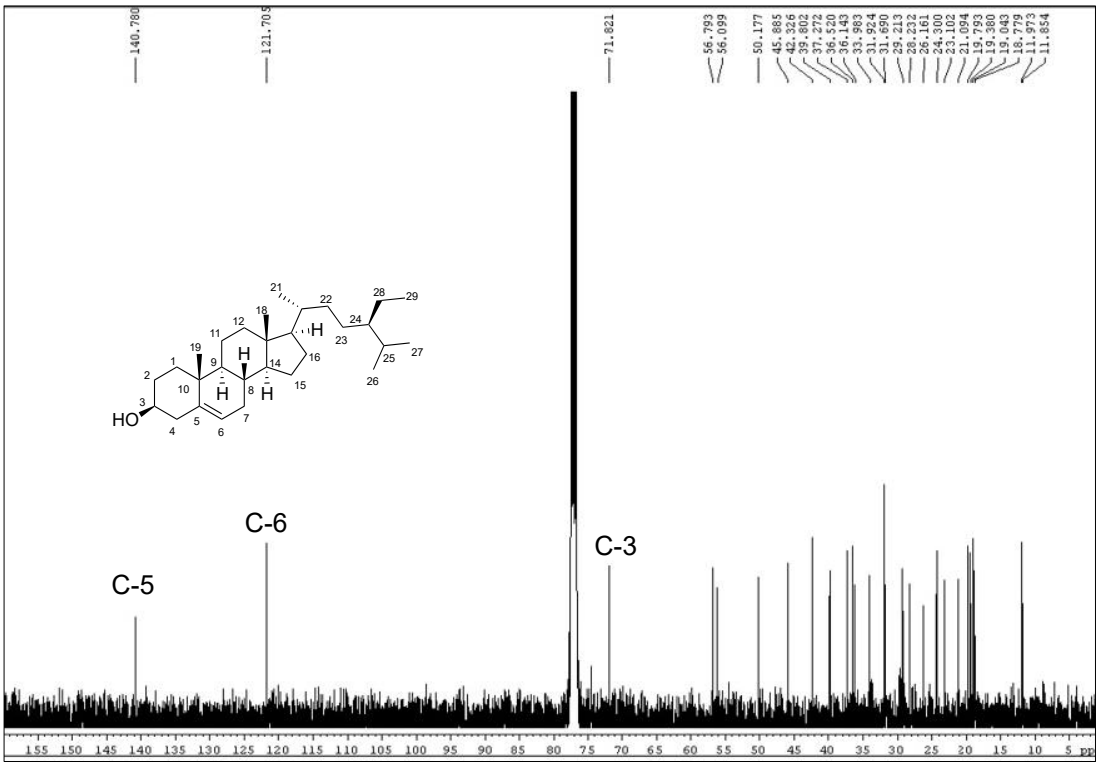


Figure 4.6C. ^{13}C NMR spectrum of β-sitosterol **(401)**

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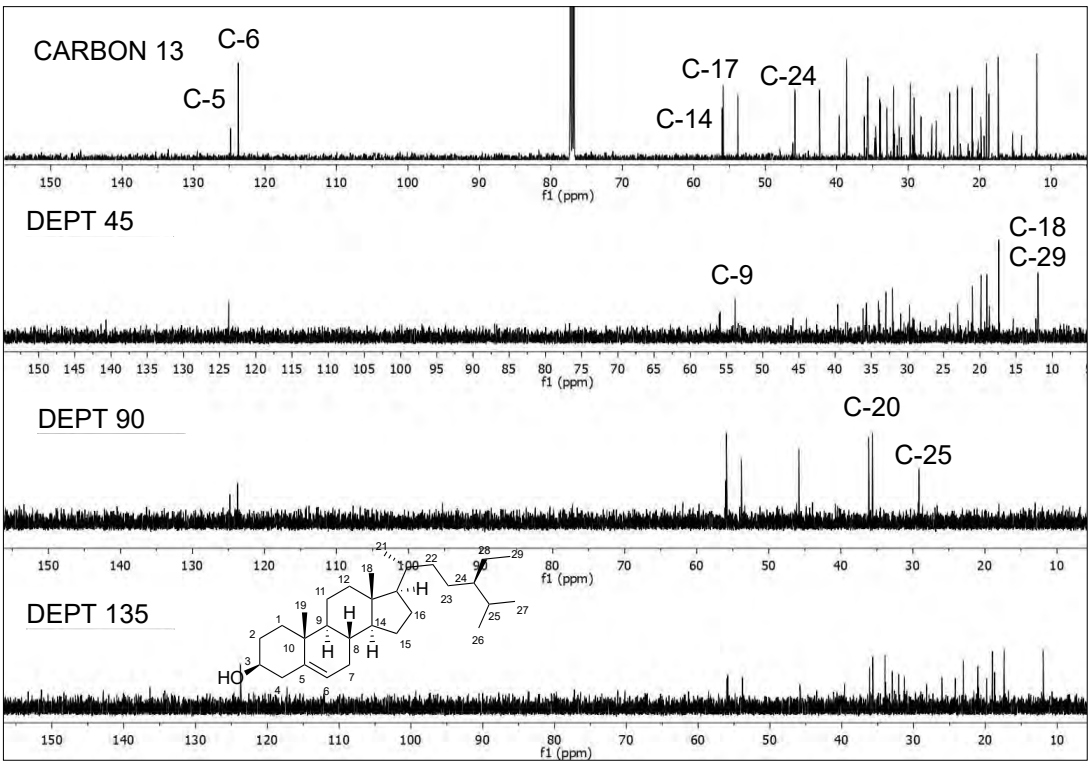


Figure 4.6D. DEPT spectra of β-sitosterol **(401)**

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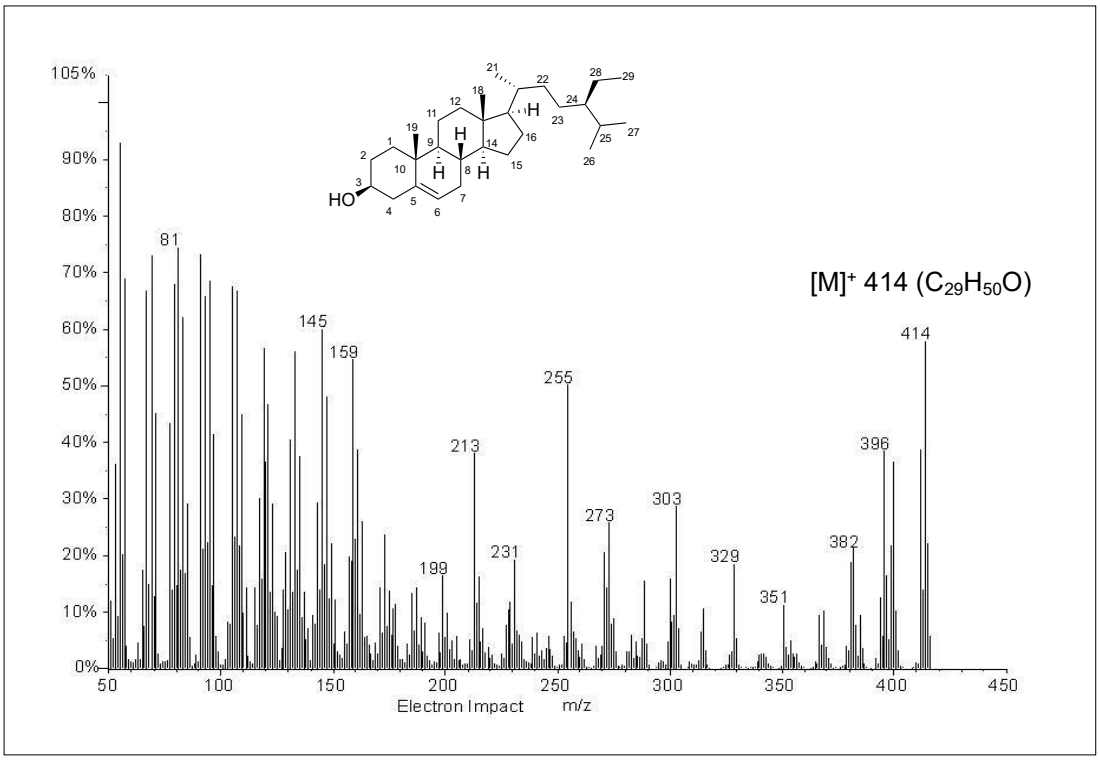
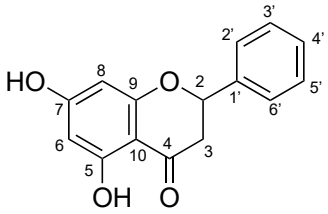


Figure 4.6E. MS spectrum of β-sitosterol **(401)**

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4.3.4 Pinocembrin (308)



(308)

Isolation of the EtOAc root extract by CC afforded compound **(308)** (8.7 mg, 0.1%) as a white solid. The IR spectrum (Figure 4.7A) showed the absorption band of hydroxyl group at 3100 cm^{-1}, conjugated carbonyl at 1629 cm^{-1}, benzene ring functionalities at 1580 cm^{-1} and 1486 cm^{-1}, while for C-O it is stretching at 1166 cm^{-1}.

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The ^{1}H NMR spectrum (Figure 4.7B) of compound **(308)** was almost identical to compound **(307)** (Figure 4.5B). The similarities of those spectra were observed, as the presence of *meta*-coupled signals, the multiplet peak for aromatic protons, and the singlet peak at the downfield region (5-OH). The only difference between both spectra was the absence of a methoxy signal at C-7 with additional proton OH in the ^{1}H NMR spectrum of compound **(308)**. Besides, based on chemical shift pattern comparison of H-2, H-3a and H-3b, the stereochemistry at H-3 was deduced as R configuration (Yang et al., 2022). In addition, the COSY spectrum (Figure 4.7C) showed correlation between H-2 (δ 5.35) with H-3a (δ 2.74), H-3b (δ 3.00).

Analysis of the ^{13}C NMR (Figure 4.7D) and DEPT spectra (Figure 4.7E) exhibited the presence of fifteen carbons, embracing of one methylene carbon at δ 43.4 (C-3), eight methine carbons at δ 79.3 (C-2), 95.5 (C-8), 96.8 (C-6), 126.2 (C-2′/C-6′), and 128.9 (C-3′/C-4′/C-5′), five quaternary carbons at δ 103.3 (C-10), 138.3 (C-1′), 163.1 (C-9), 164.5 (C-5), and 164.4 (C-7), and a carbonyl carbon at downfield region, δ 195.8 (C-4). The ^{13}C NMR data was further supported by the MS spectrum (Figure 4.7F) which gave a molecular ion peak at *m/z* 256 consistent with a molecular formula $C_{15}H_{12}O_4$. The complete ^{1}H NMR and ^{13}C NMR data as tabulated in Table 4.7. In the HMQC spectrum (Figure 4.7G), the aromatic protons at δ 7.36-7.42 (H-2′-H-6′) were found directly attached to carbons resonated at δ 126.2 (C-2′, C-6′) and 128.9 (C-3′, C-4′, C-′5). Two aromatic protons of the ring A which were *meta*-coupled (H-6 and H-8) were correlated with carbons at δ 96.8 (C-6) and 95.5 (C-8). Two methine protons, H-2 (δ 5.35) and H-6 (δ 5.93) were confirmed attached to carbon at δ 79.3 (C-2) and δ 96.8 (C-6), respectively. In addition, the two unequivalent methylene protons δ 2.74 (H-3a) and 3.00 (H-3b) showed a cross peak with a carbon at δ 43.4 (C-3a/C-3b).

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Table 4.7

*NMR data of pinocembrin **(308)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz) (308)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
2	5.35 (1H, dd, 3.0, 13.0)	79.3	5.33 (1H, dd, 3.5, 12.9)	80.4
3a	2.74 (1H, dd, 3.0, 17.2)	43.4	2.83 (1H, dd, 3.5, 17.0)	44.1
3b	3.00 (1H, dd, 13.0, 17.2)	43.4	3.10 (1H, dd, 12.9, 17.4)	44.1
4	-	195.8	-	197.3
6	5.93 (1H, d, 2.2)	96.8	5.87 (1H, d, 1.9)	96.2
7	-	164.4	-	164.6
8	5.94 (1H, d, 2.2)	95.5	5.87 (1H, d, 1.9)	97.2
9	-	163.1	-	164.6
10	-	103.3	-	103.3
1′	-	138.3	-	140.3
2′	7.36 – 7.42 (5H, m)	126.2	7.34 – 7.45 (5H, m)	127.3
3′	7.42 – 7.48 (5H, m)	128.9	7.34 – 7.45 (5H, m)	129.6
4′	7.42 – 7.48 (5H, m)	128.9	7.34 – 7.45 (5H, m)	129.7
5′	7.42 – 7.48 (5H, m)	128.9	7.34 – 7.45 (5H, m)	129.6
6′	7.42 – 7.48 (5H, m)	126.2	7.34 – 7.45 (5H, m)	127.3
5-OH	11.97 (1H, s)	164.4	12.00 (1H, s)	165.4

[a]Data from literature (Nyokat et al., 2017)

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The HMBC spectrum (Figure 4.7H) exhibited a long-range correlation of hydroxyl proton at δ 11.97 with carbon C-7 (δ 164.4), C-10 (δ 103.3), and C-6 (δ 96.8). The signal at δ 5.94 (H-8) correlated with C-7 (δ 164.4), C-9 (δ 163.1), C-6 (δ 96.8) and C-10 (δ 103.3). The methine proton of H-6 (δ 5.93) was found correlated with C-5 (δ 164.5), C-7 (δ 164.4), C-10 (δ 103.3), and C-8 (δ 95.5).

Based on the comparison of spectral data and physical properties, the structure of compound **(308)** was identified as 5,7-dihydroxyflavanone or known as pinocembrin. This compound was reported previously from the roots of *L. reflexa* (Wang et al., 2016) and *L. aggregata* (Hai et al., 2016).

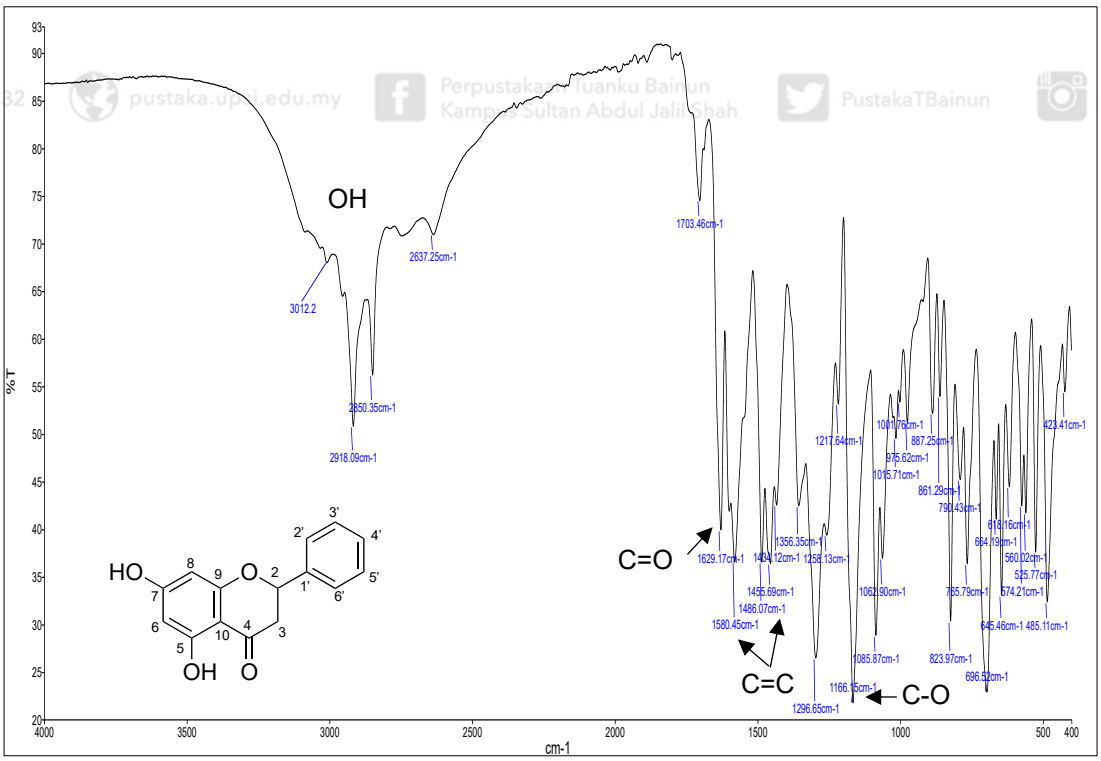


Figure 4.7A. IR spectrum of pinocembrin **(308)**

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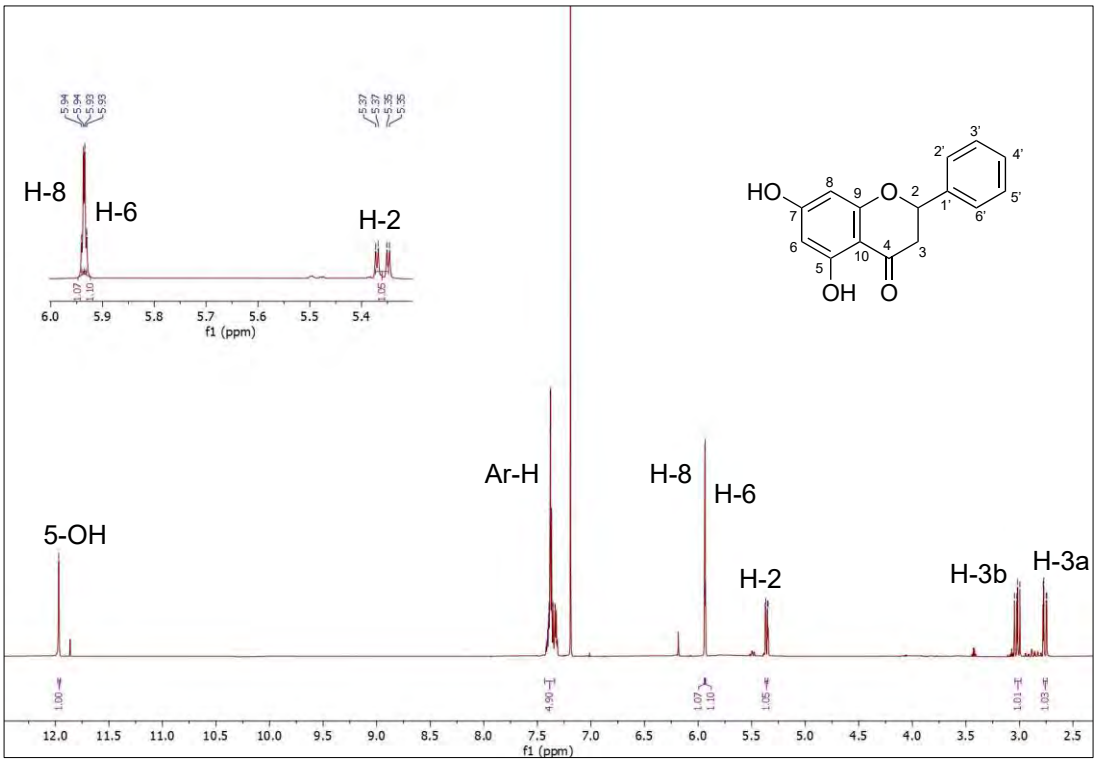


Figure 4.7B. ^{1}H NMR spectrum of pinocembrin **(308)**

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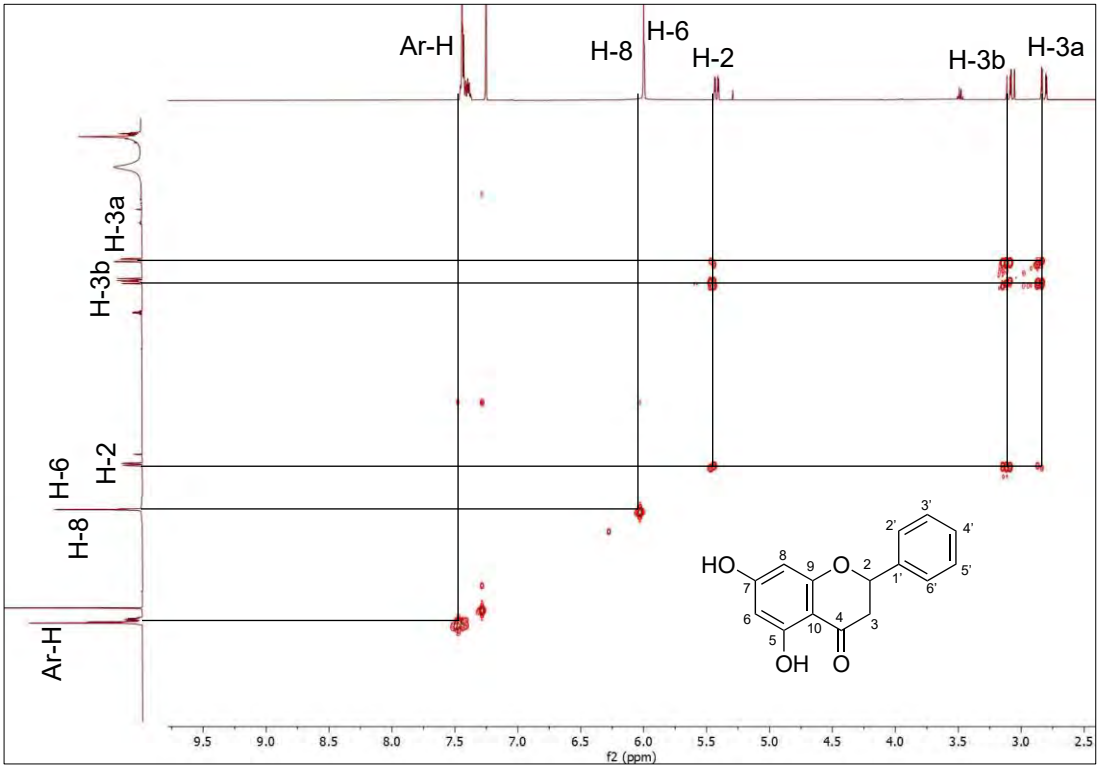


Figure 4.7C. COSY spectrum of pinocembrin **(308)**

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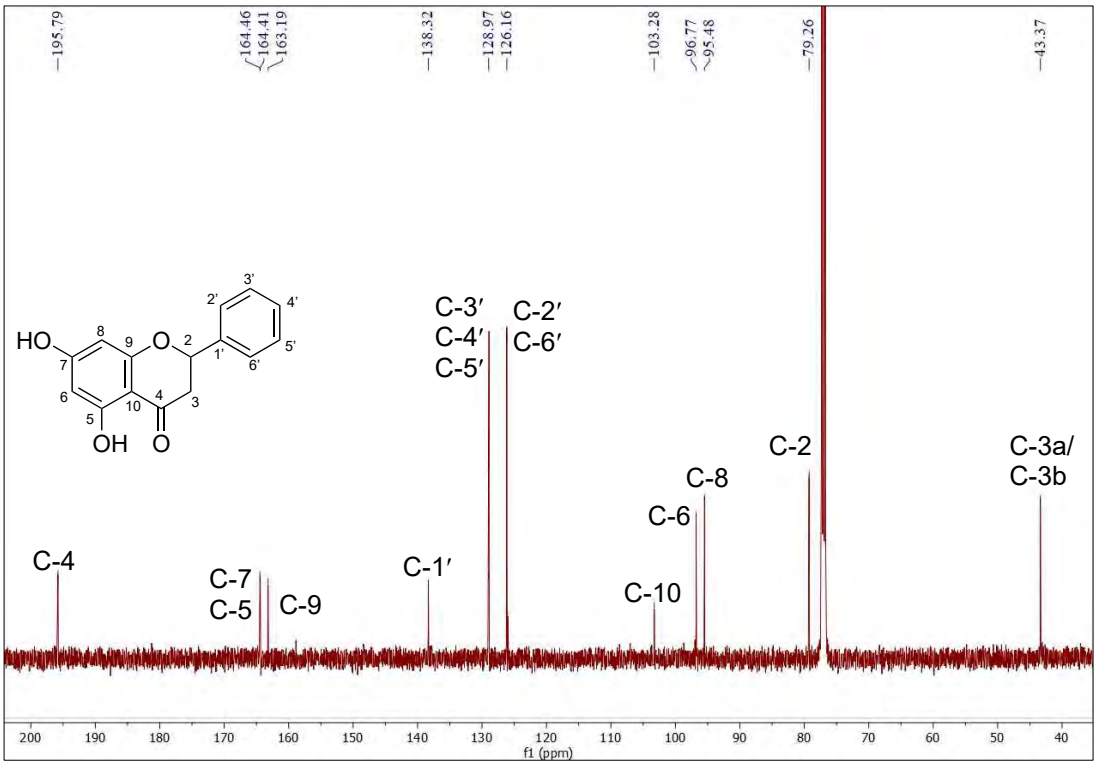


Figure 4.7D. ^{13}C NMR spectrum of pinocembrin **(308)**

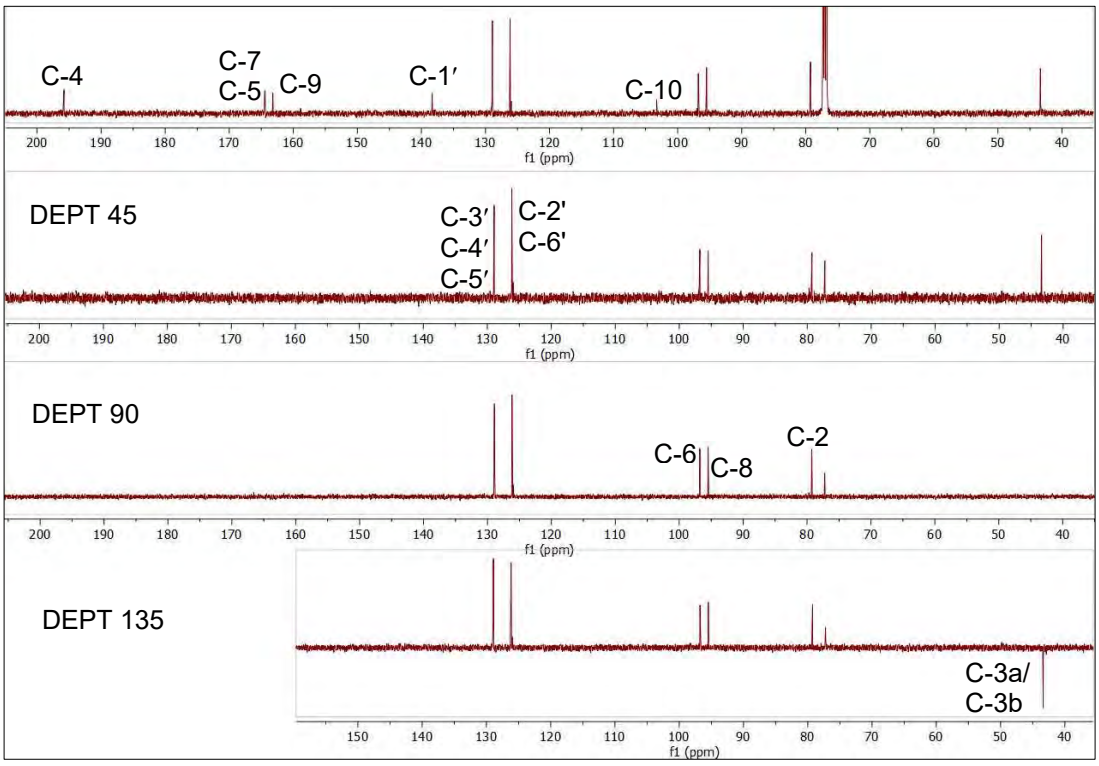


Figure 4.7E. DEPT spectra of pinocembrin **(308)**

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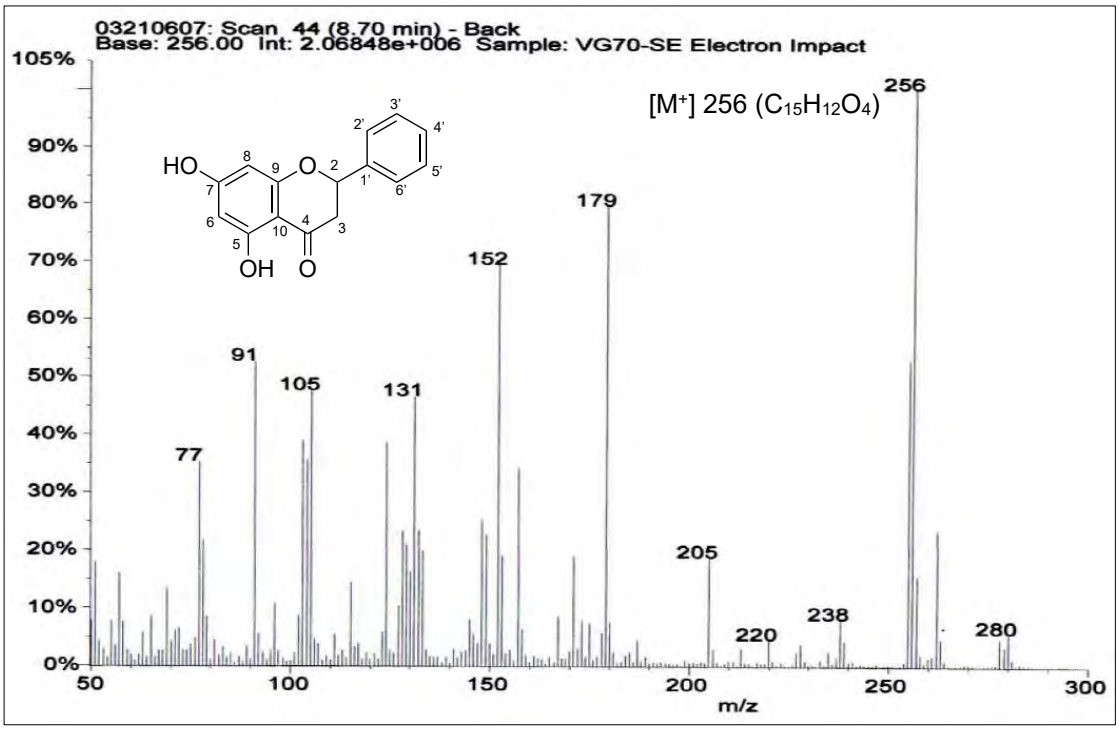


Figure 4.7F. MS spectrum of pinocembrin **(308)**

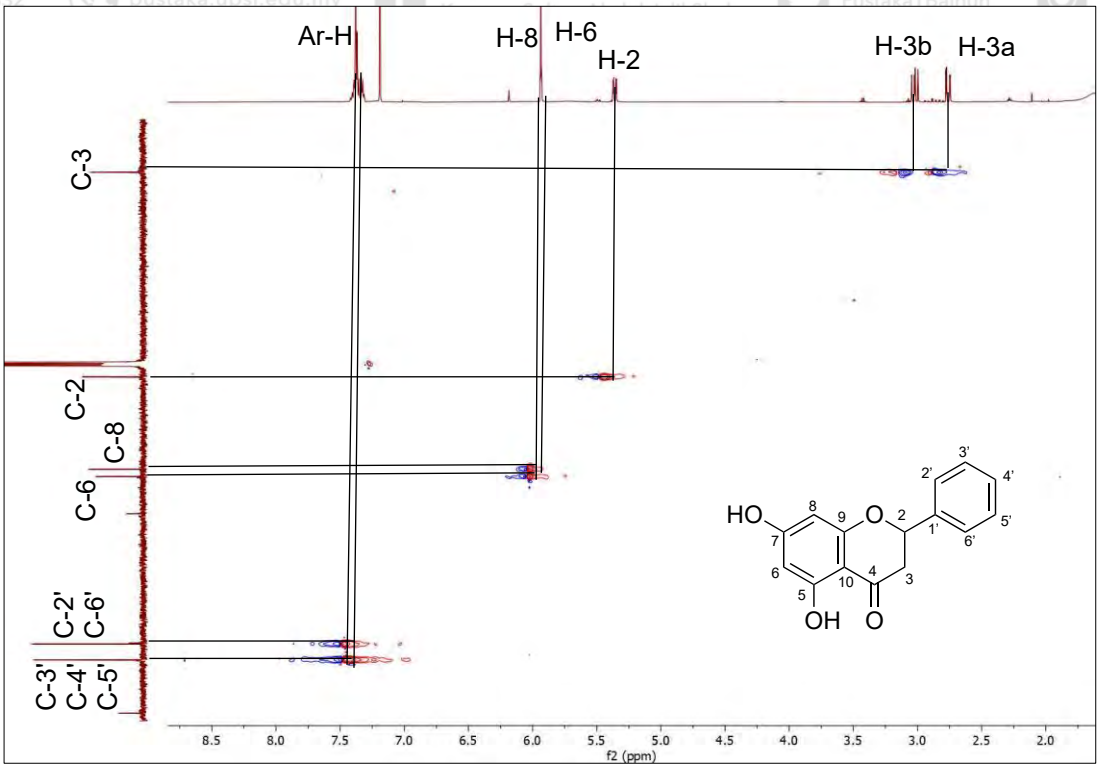


Figure 4.7G. HMQC spectrum of pinocembrin **(308)**

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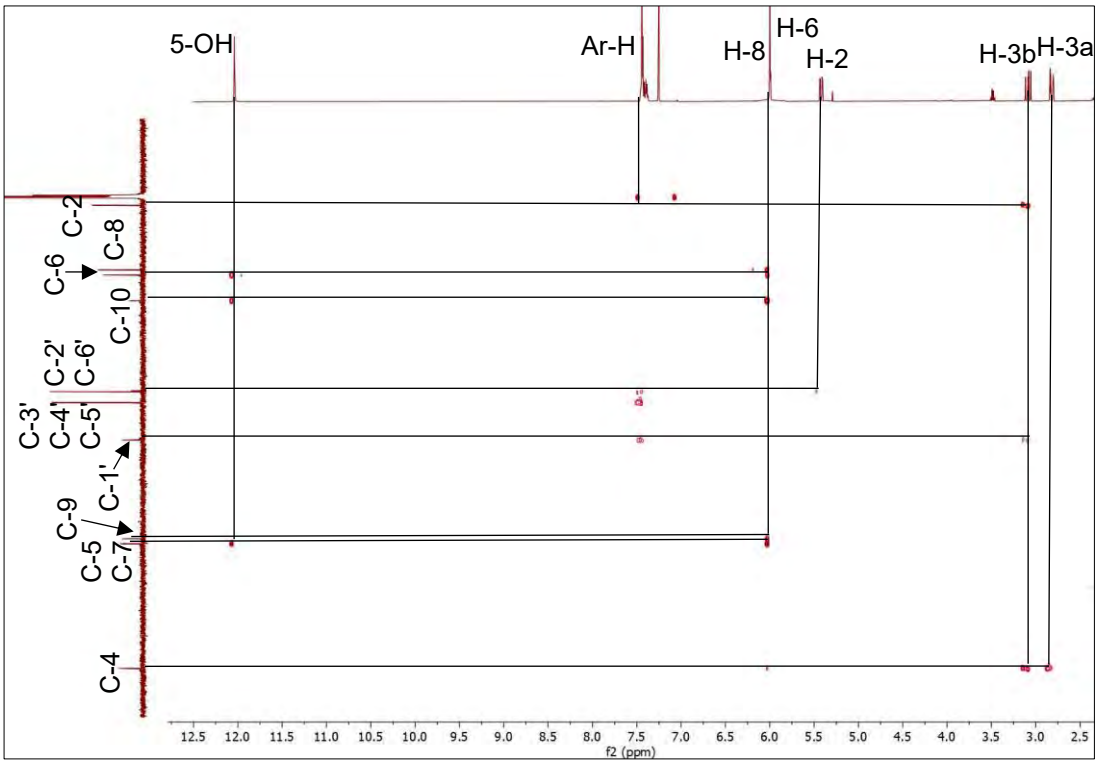
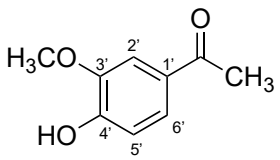


Figure 4.7H. HMBC spectrum of pinocembrin **(308)**

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4.4.5 4-Hydroxy-3-methoxyacetophenone (363)



(363)

Isolation of the EtOAc root extract by CC was afforded the compound **(363)** as a white crystalline solid (15.1 mg, 0.1%). The IR spectrum (Figure 4.8A) displayed a broad absorption band at 3230 cm^{-1} corresponding to O-H group, whereas the absorption band at 1696 cm^{-1} corresponds to carbonyl group. The C=C aromatic stretching appeared at 1519 and 1456 cm^{-1}, while C-O stretching was observed at 1102 cm^{-1}.

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The ^{1}H NMR spectrum (Figure 4.8B) supported the presence of methoxy groups at 3.91, which attached to 3′-OCH_3. The *ortho*-coupled appeared as doublet signals at δ 7.53 and δ 6.95 with (J = 8.7 Hz) were attributed to protons H-6′ and H-5′, respectively. Besides, three singlet signal was observed at δ 6.31, 2.56, and 7.52 were complemented to hydroxyl, methyl groups, and H-2′, respectively.

The ^{13}C NMR spectra (Figure 4.8C) indicated the presence of nine carbons including one carbonyl, one methoxy, one methyl, three methine, and three quaternary carbon atoms. The carbonyl, methoxy, and methyl signals were observed at δ 196.9 (C-1), 56.0 (3′-OCH_3), and 26.2 (CH_3), respectively. Besides, three signals for methine carbons were observed at δ 110.1 (C-2′), 114.2 (C-5′), and 124.2 (C-6′) as well as three quaternary carbons at δ 129.6 (C-1′) 146.5 (C-3′) and 150.8 (4′-OH). The ^{13}C NMR data was further supported by the MS spectrum (Figure 4.8D), which gave a molecular ion peak at *m/z* 166 consistent with a molecular formula $C_9H_{10}O_3$. The complete ^{1}H NMR and ^{13}C NMR data as tabulated in Table 4.8.

The COSY spectrum (Figure 4.8E) showed the connectivity between aromatic protons H-2′ (δ 7.52), H-6′ (δ 7.53), and H-5′ (δ 6.95). In the HMQC spectrum (Figure 4.8F), the signals at δ 7.52 (H-2′) and δ 7.53 (H-6′) were found directly attached to carbons resonating at δ 110.1 (C-2′) and 124.2 (C-6′). Besides, the methoxy proton (δ 3.91) and methyl proton (δ 2.56) were confirmed directly connected to its carbon at δ 56.0 and δ 26.2 accordingly. The HMBC spectrum (Figure 4.8G) exhibited a correspondence correlation of proton H-5′ (δ 6.95) with C-1 (δ 196.9), C-1′ (δ 129.6), C-2′ (δ 110.1), C-3′ (δ 146.5), and 4′-OH (δ 150.8). Besides, there were also significant complement of protons H-2′ (δ 7.52) and H-6′ (δ 7.53) on C-7′ (δ 196.9), C-1′ (δ 129.6),

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C-3′ (δ 146.5), and C-4′ (δ 150.8). In addition, for proton CH_3 it showed the interconnection with C-1 (δ 196.9), C-1′ (δ 129.6), C-6′ (δ 124.2) and C-2′ (δ 110.1).

Table 4.8

*NMR data of 4-hydroxy-3-methoxyacetophenone **(363)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz) (363)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
1′	-	129.6	-	130.1
2′	7.52 (1H, s)	110.1	7.54 (1H, s)	109.7
3′	-	146.5	-	146.6
5′	6.95 (1H, d, 8.7)	114.1	6.96 (1H, d, 8.0)	113.8
6′	7.53 (1H, d, 8.7)	124.2	7.55 (1H, d, 8.0)	124.0
CH_3	2.56 (3H, s)	26.2	2.57 (3H, s)	26.2
3′-OCH_3	3.91 (3H, s)	55.9	3.95 (3H, s)	56.0
4′-OH	6.31 (1H, s)	150.8	6.31 (1H, s)	150.4
C=O	-	196.9	-	196.9

[a]Data from literature (Singathi et al., 2022)

Based on the comparison of its physical properties and spectral data, compound **(372)** was concluded as 4-hydroxy-3-methoxyacetophenone or commonly known as apocynin. It has been isolated previously from the roots of *L. aggregata* (Ma et al., 2015; Singathi et al., 2022).

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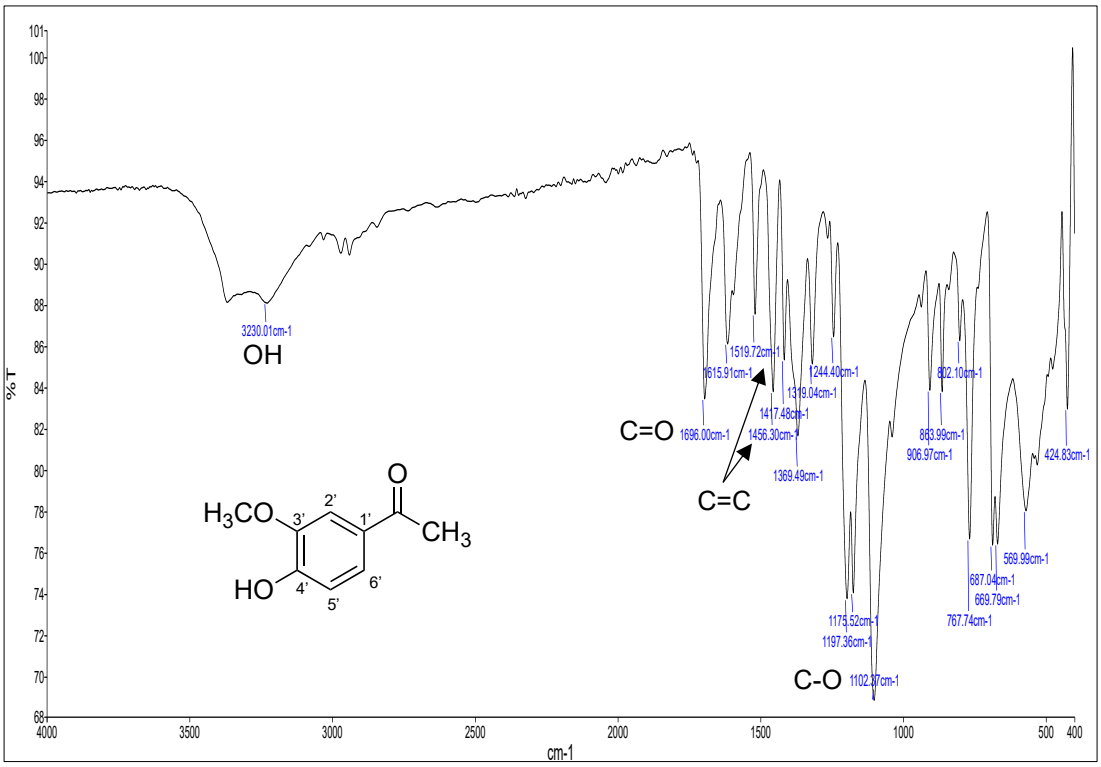


Figure 4.8A. IR spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

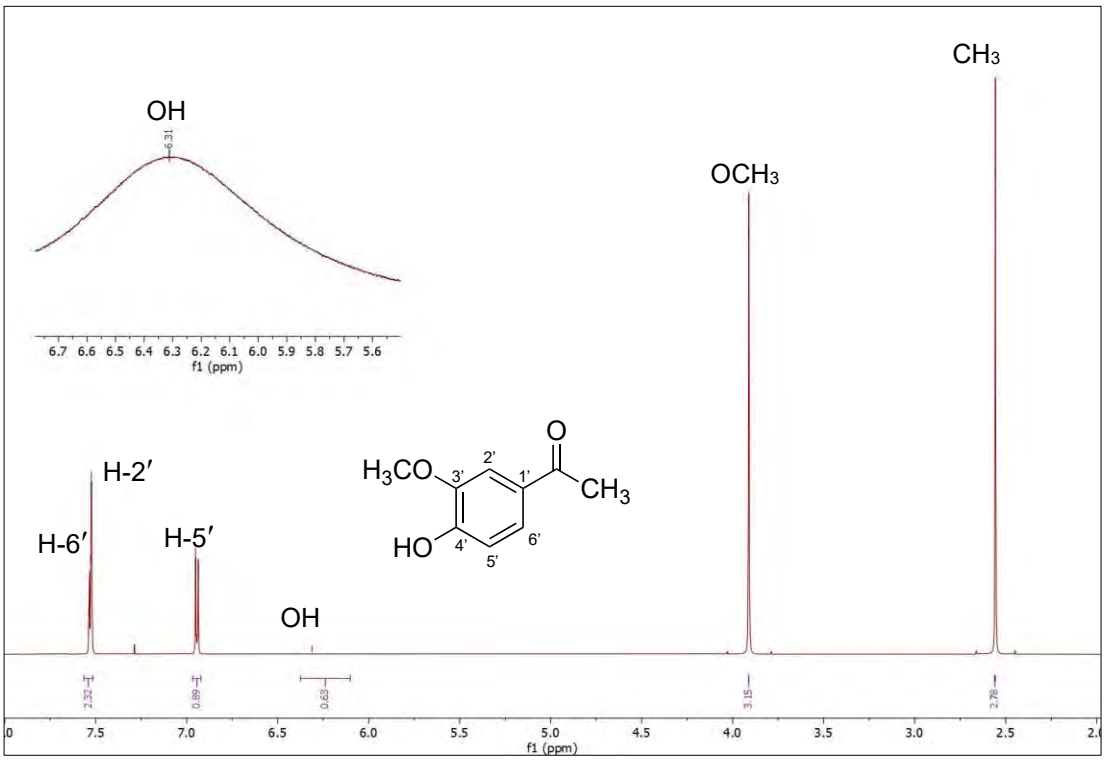


Figure 4.8B. ^{1}H NMR spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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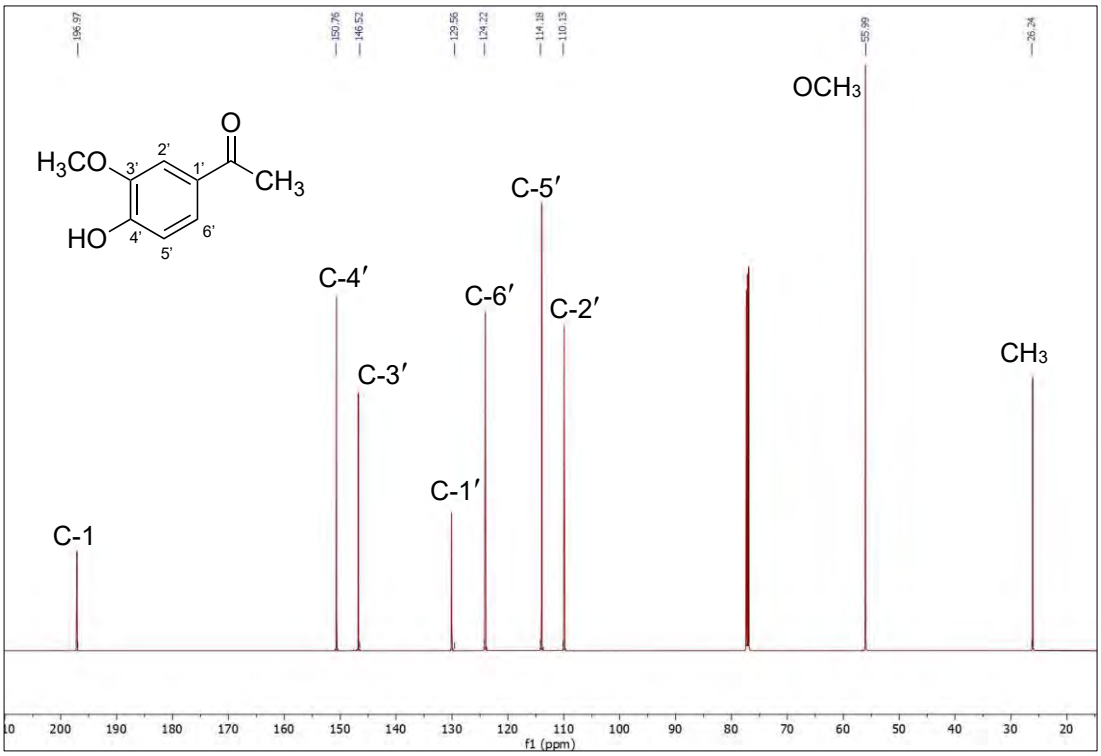


Figure 4.8C. ^{13}C NMR spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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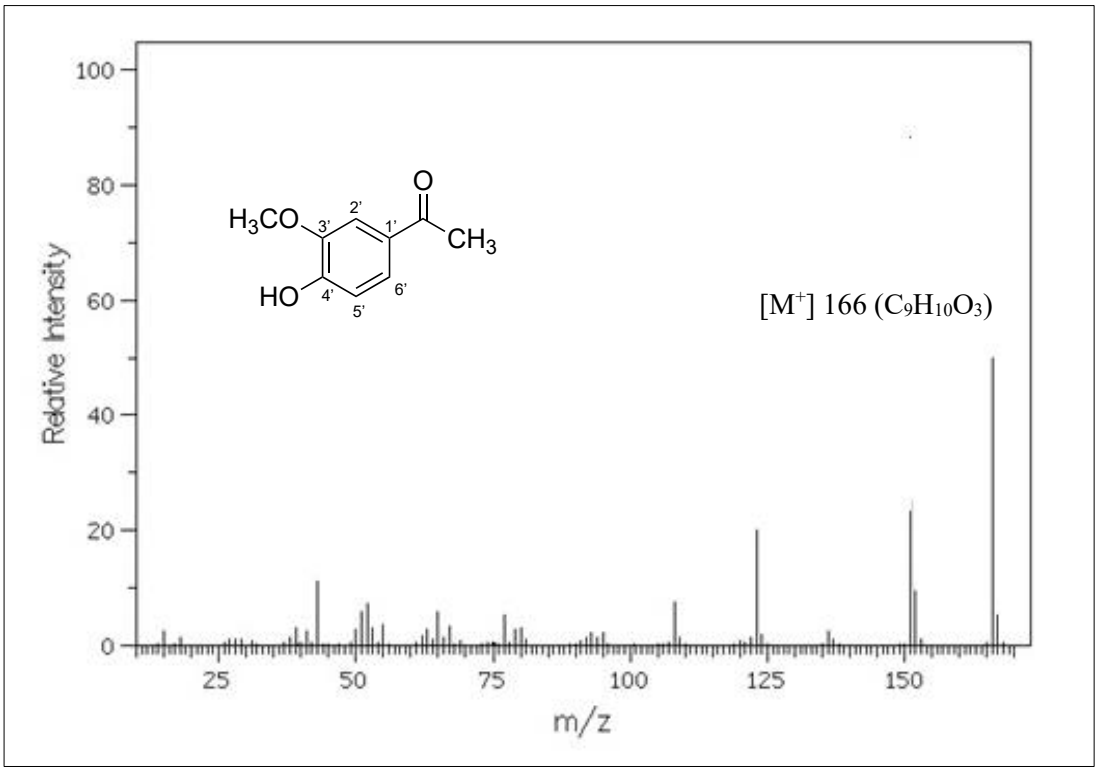


Figure 4.8D. MS spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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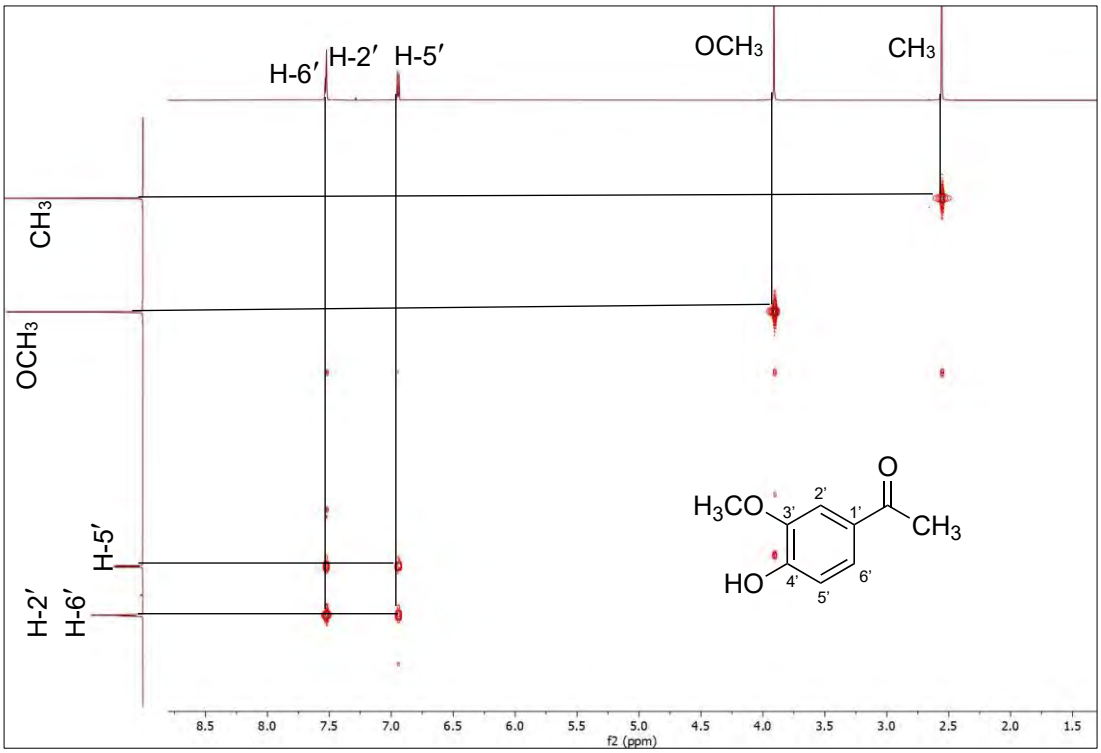


Figure 4.8E. COSY spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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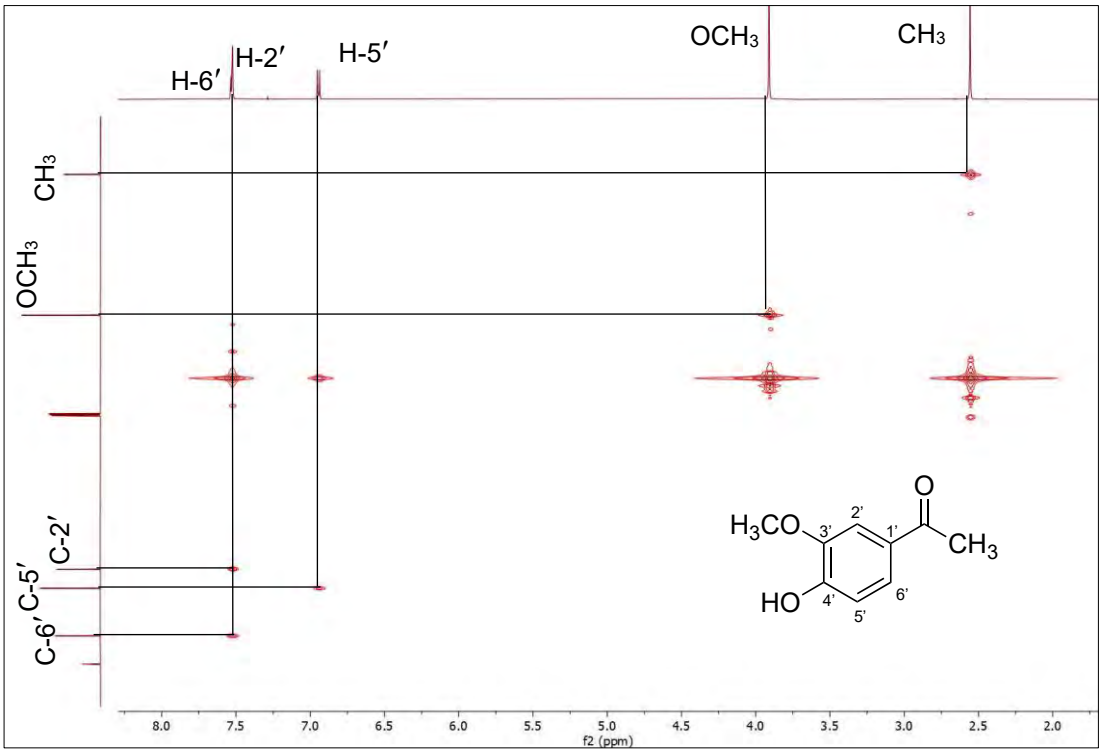


Figure 4.8F. HMQC spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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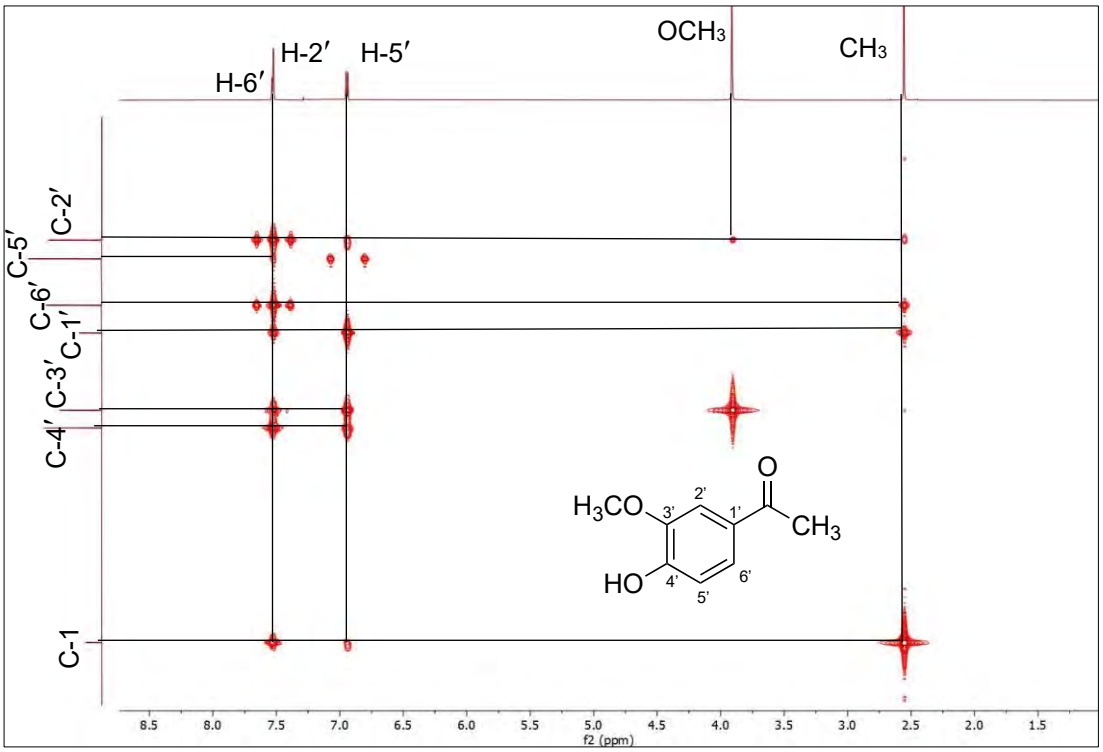
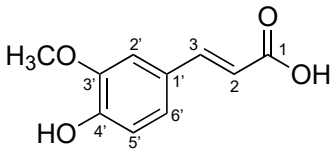


Figure 4.8G. HMBC spectrum of 4-hydroxy-3-methoxyacetophenone **(363)**

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4.4.6 Ferulic Acid (365)



(365)

Isolation of the EtOAc root extract by CC afforded compound **(365)** (10.9 mg, 0.1%) as a brownish yellow solid. The IR spectrum (Figure 4.9A) showed a broad absorption band at 3432 cm^{-1} corresponding to OH group. Meanwhile, a band at 1687 cm^{-1} was established for the carbonyl group, while stretching 1617 cm^{-1} corresponds to alkenes

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(olefins). Furthermore, the absorption band at 1591 and 1512 cm^{-1} was assigned to C=C aromatic, whereas the band at 1266 cm^{-1} was assigned to C-O.

The ^{1}H NMR spectrum (Figure 4.9B) displayed a singlet signal δ 3.97 corresponding to a methoxy group. Signals for aromatic protons were observed as doublet at δ 6.96 (J = 8.9 Hz, H-5′) and 7.08 (J = 1.9 Hz, H-2′) as well as doublet of doublet signal at δ 7.13 (J = 1.9 and 8.2 Hz, H-6′). The COSY spectrum (Figure 4.9G) supported the correlations between these protons. Another doublet signal was observed at δ 7.73 and 6.31 corresponding to the olefinic protons H-3 and H-2, respectively. The *trans*-position of these protons was confirmed by the coupling constant of 15.0 Hz.

The ^{13}C NMR (Figure 4.9C) and DEPT spectra (Figure 4.9D) showed the presence of 10 signals, comprising of 6 aromatic carbon and 4 aliphatic chain. The aromatic signals were revealed at δ 109.5 (C-6′), 114.2 (C-3′), 123.7 (C-2′), 126.6 (C-1′), 147.3 (C-5′), and 148.5 (C-4′). In addition, the aliphatic chain was observed at δ 56.0 (3′-OCH_3), 114.8 (C-2), 146.8 (C-3), and 171.1 (C-1). The ^{13}C NMR data was further supported by the MS spectrum (Figure 4.9H), which gave a molecular ion peak at *m/z* 194 consistent with a molecular formula $C_{10}H_{10}O_4$.

In the HMQC spectrum (Figure 4.9E), three methine protons, H-2′ (δ 7.08), H-6′ (δ 7.13), and H-3′ (δ 7.73) were found directly attached to C-2′ (δ 123.7), C-6′ (δ 109.5) and C-3 (δ 146.8) respectively. In the HMBC spectrum (Figure 4.9F), the signals of methine proton at δ 7.73 (H-3) were correlated with C-6′ (δ 109.5), C-2′ (δ 123.7), C-2 (δ 114.8) and C-1 (δ 171.3) while the signal at δ 6.31 (H-2) was correlated to carbons C-3 (δ 146.8) and C-1 (δ 171.3). Besides, the signal resonated at δ 7.13 (H-6′)

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correlated with C-2′ (δ 123.7) and C-5′ (δ 147.3), while the signal at δ 7.08 (H-2′) correlated with C-6′ (δ 109.5) and C-5′ (δ 147.3). The complete assignments of the protons and carbons are summarized in Table 4.9.

Table 4.9

*NMR data of ferulic acid **(365)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz) (365)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
1	-	171.3	-	171.4
2	6.31 (1H, d, 15.0)	114.8	6.34 (1H, d, 15.0)	114.8
3	7.73 (1H, d, 15.0)	146.8	7.75 (1H, d, 15.0)	146.8
1′	-	126.6	-	126.6
2′	7.08 (1H, d, 1.9)	123.7	7.09 (1H, d, 2.0)	123.8
3′	-	114.2	-	114.4
4′	-	148.5	-	148.4
5′	6.96 (1H, d, 8.9)	147.3	6.97 (1H, d, 9.0)	147.1
6′	7.13 (1H, dd, 1.9, 8.2)	109.5	7.14 (1H, dd, 2.0, 8.0)	109.5
3′-OCH_3	3.97 (3H, s)	56.0	3.98 (3H, s)	56.0

[a]Data from literature (Sajjadi et al., 2012)

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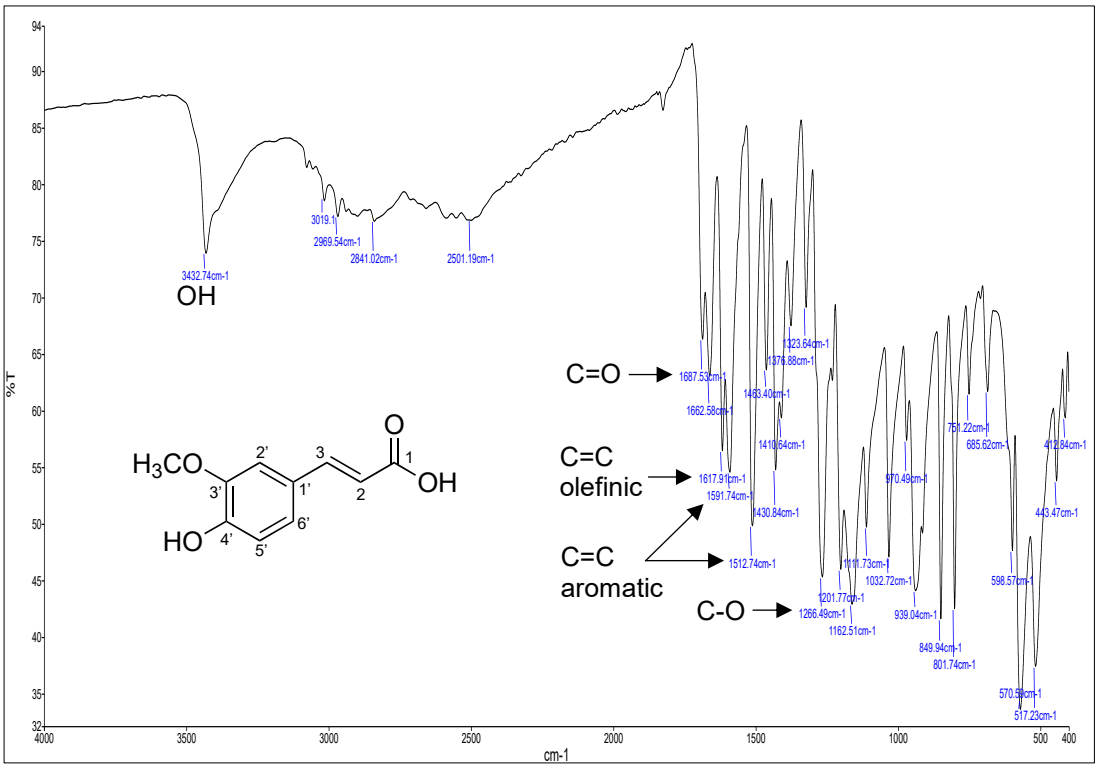


Figure 4.9A. IR spectrum of ferulic acid **(365)**

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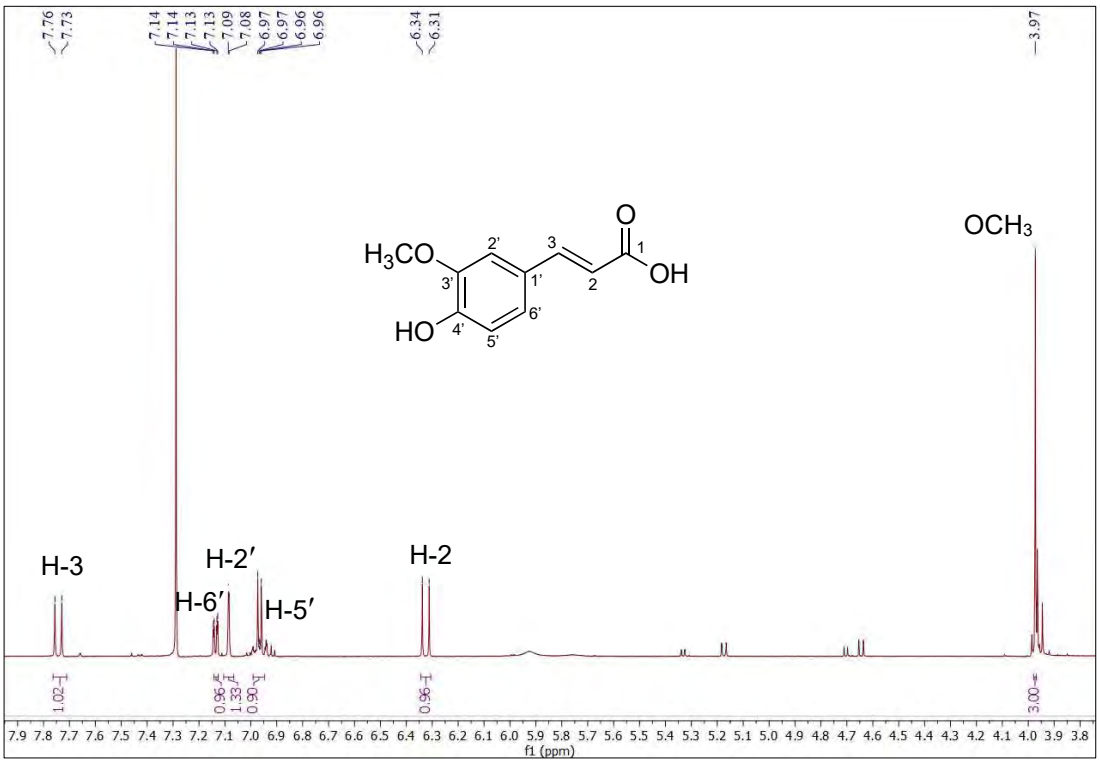


Figure 4.9B. ^{1}H NMR spectrum of ferulic acid **(365)**

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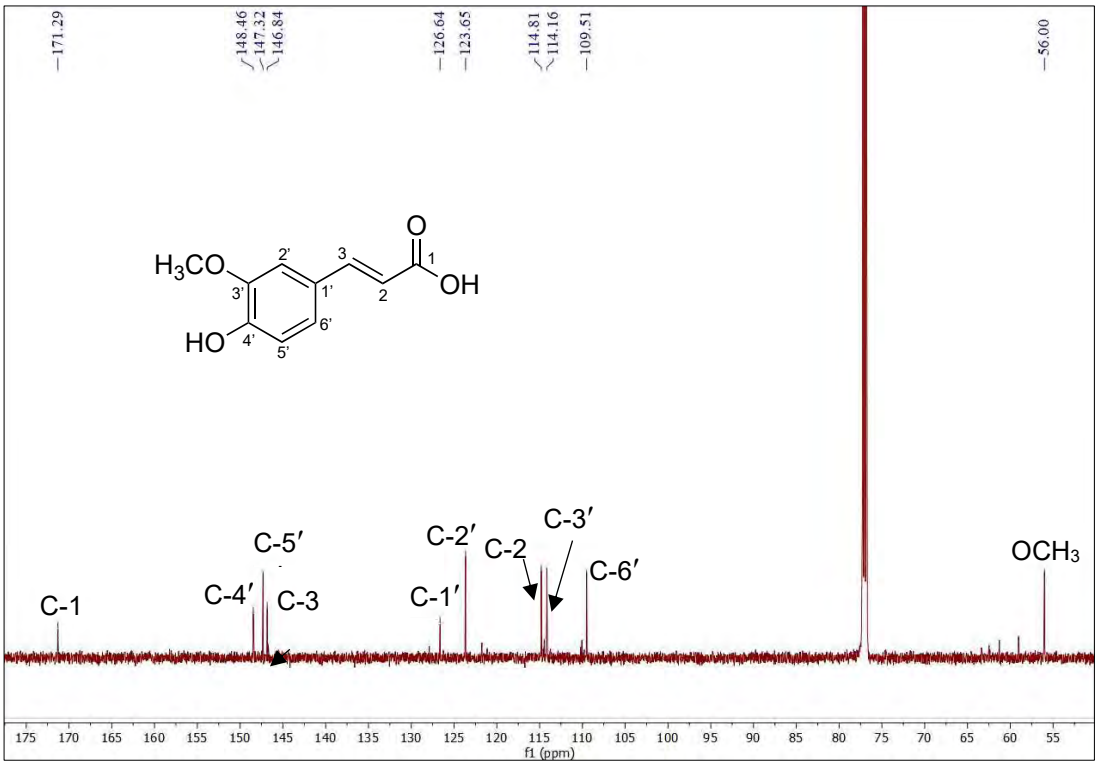


Figure 4.9C. ^{13}C NMR spectrum of ferulic acid **(365)**

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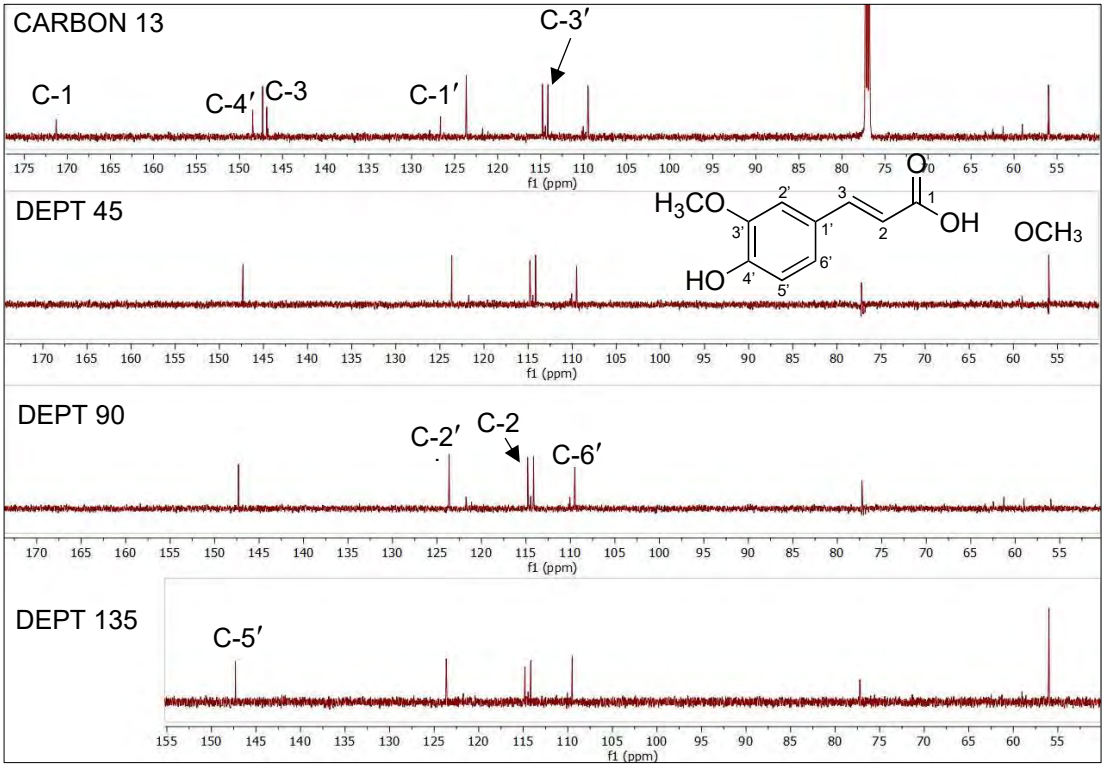


Figure 4.9D. DEPT spectra of ferulic acid **(365)**

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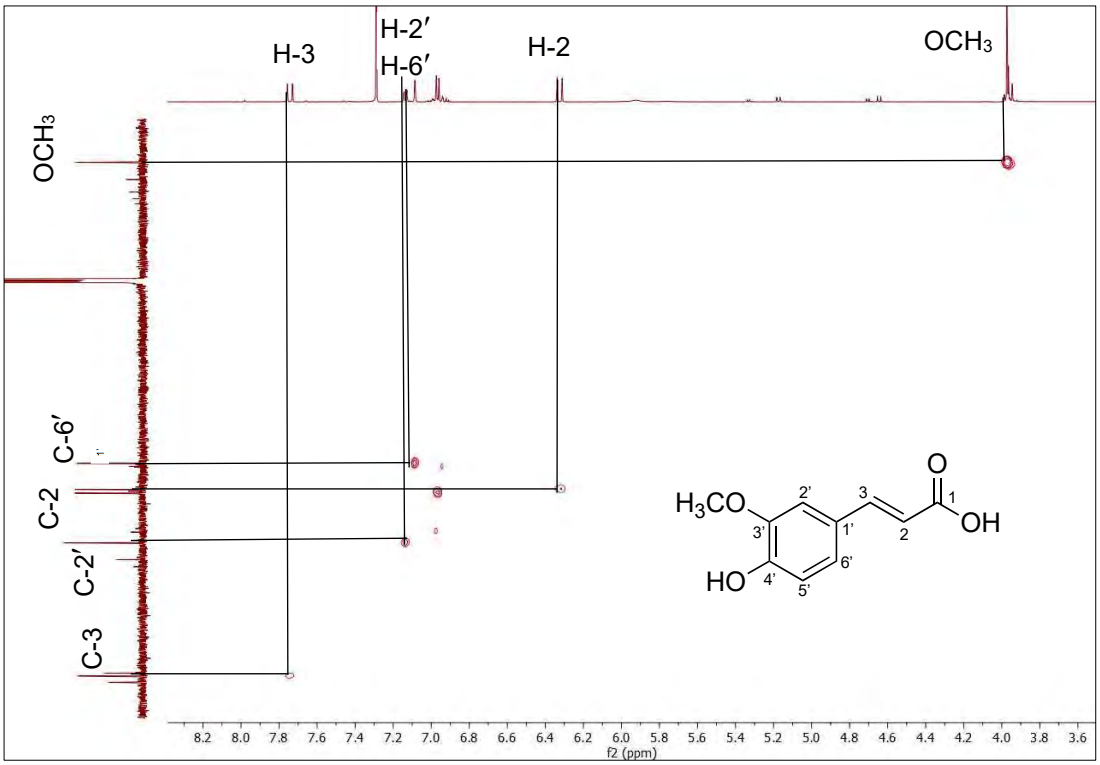


Figure 4.9E. HMQC spectrum of ferulic acid **(365)**

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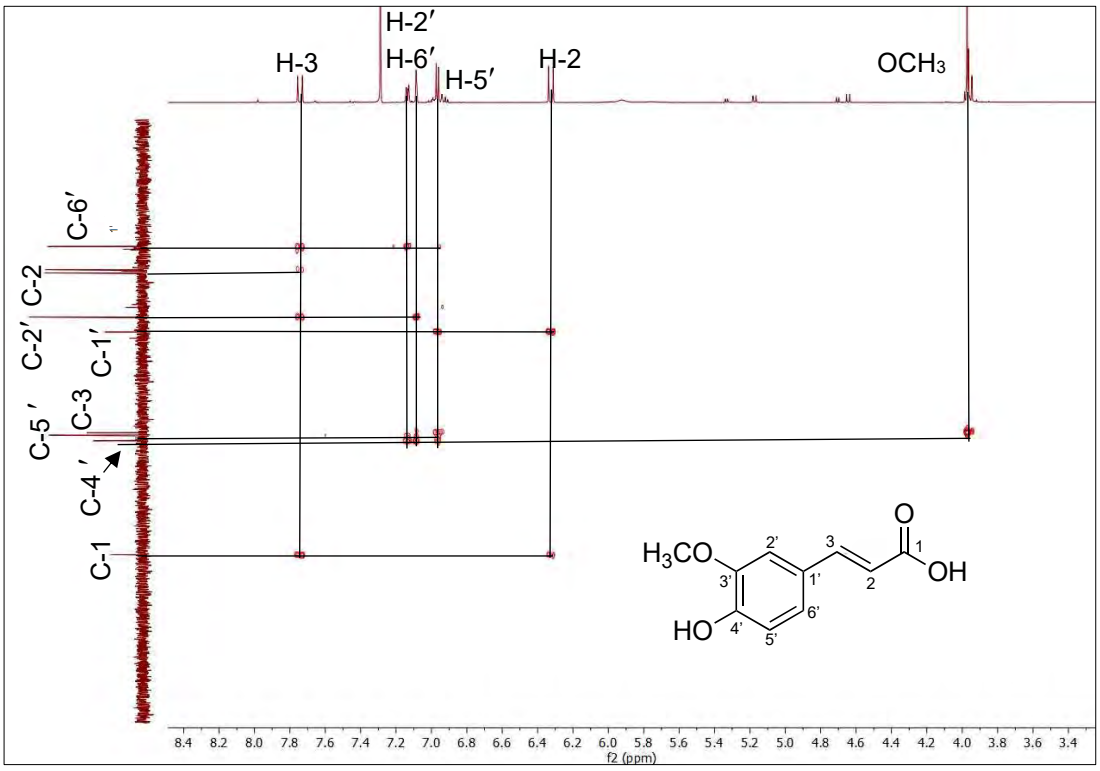


Figure 4.9F. HMBC spectrum of ferulic acid **(365)**

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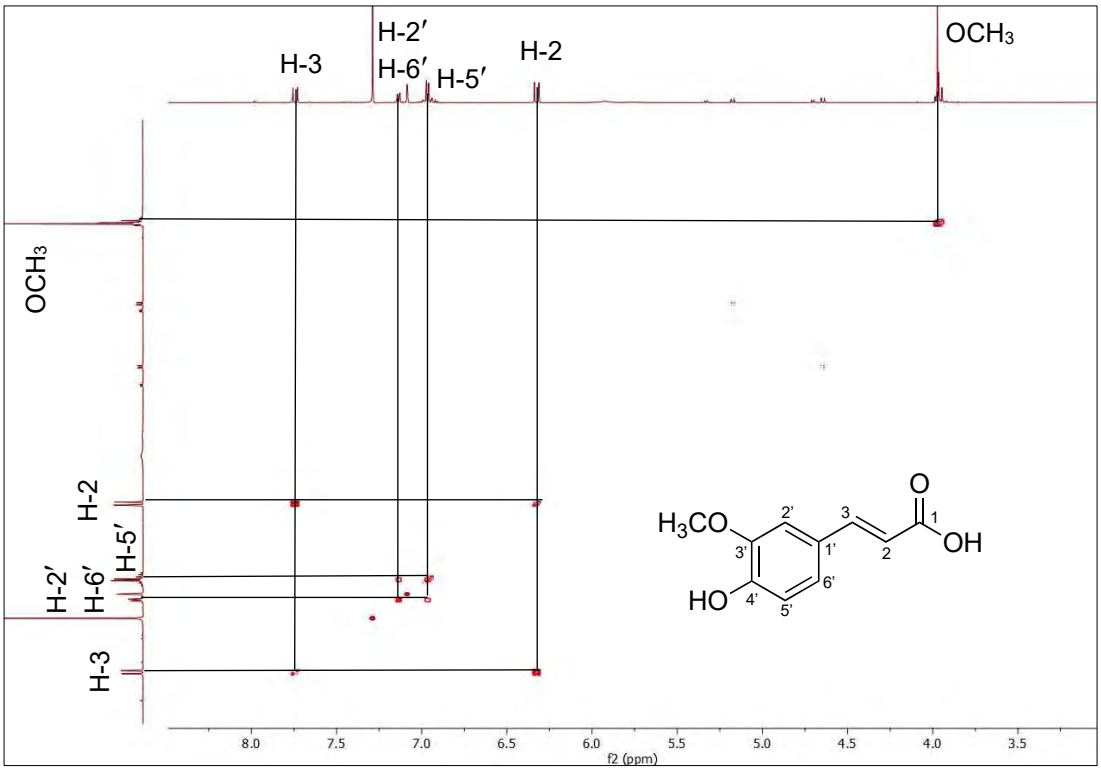


Figure 4.9G. COSY spectrum of ferulic acid **(365)**

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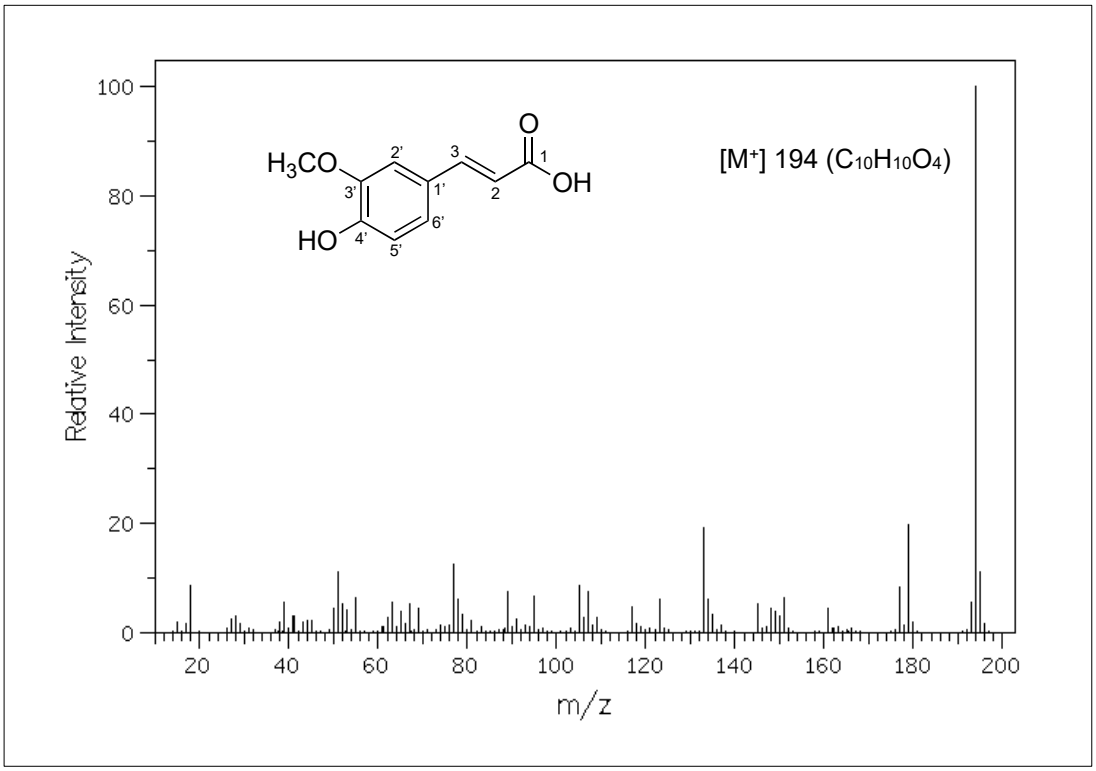


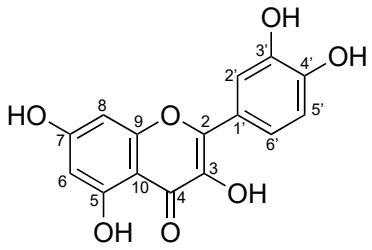
Figure 4.9H. MS spectrum of ferulic acid **(365)**

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From the spectral analysis and compared with a previous report (Sajjadi et al., 2012), compound (**365**) was identified as (*E*)-3-(4-hydroxy-3-methoxyphnyl)prop-2-enoic acid or also known as ferulic acid. It has been reported previously from the leaves of *L. benzoin* (Ingersoll et al., 2010) and the roots of *L. reflexae radix* (Zou et al., 2021).

4.4.7 Quercetin (331)



(331)

Isolation of the MeOH root extract by CC afforded the compound **(331)** (7.6 mg, 0.1%) as a yellow solid. The IR spectrum (Figure 4.10A) displayed a broad absorption band at 3270 cm^{-1} corresponding to chelating O-H. The carbonyl of aryl ketonic stretching appeared at 1663 cm^{-1}, while C-O of aryl ether stretching was observed at 1259 cm^{-1}. The vibration frequency in the region of 1606 and 1448 cm^{-1} was assigned to C=C aromatic ring.

The ^{1}H NMR spectrum (Figure 4.10B) showed a doublet signal at δ 6.26 and δ 6.51 corresponding to H-6 and H-8, respectively. The other three aromatic signals at δ 7.82 (d, J = 2.1 Hz), δ 7.68 (dd, J = 8.5 and 2.1 Hz), and 6.98 (d, J = 8.5 Hz) were

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assigned to protons H-2', H-6' and H-5', respectively. The COSY spectrum (Figure 4.10C) showed correlation between H-6 (δ 6.26) with H-8 (δ 6.51).

The ^{13}C NMR spectrum (Figure 4.10D) indicated the presence of fifteen carbons. Ten quaternary carbons were observed at δ 103.2 (C-10), 122.9 (C-1'), 135.9 (C-3), 145.0 (C-3′), 146.1 (C-2), 147.5 (C-4'), 156.9 (C-9), 161.4 (C-5), 164.2 (C-7), and 175.7 (C-4). Besides, five methine carbons were observed at δ 93.6 (C-8), 98.3 (C-6), 114.9 (C-5'), 115.3 (C-2'), and 120.6 (C-6'). The ^{13}C NMR data was further supported by the MS spectrum (Figure 4.10E), which gave a molecular ion peak at *m/z* 302 consistent with a molecular formula $C_{15}H_{10}O_7$. The NMR details as tabulated in Table 4.10.

In the HMQC spectrum (Figure 4.10F), three aromatic protons of ring B at δ 6.98 (H-5'), 7.68 (H-6') and 7.82 (H-2') were found directly attached to carbons resonated at δ 114.9 (C-5′), 120.6 (C-6′), and 115.3 (C-2′), respectively. Two methine protons of ring A, H-6 (δ 6.26) and H-8 (δ 6.51), which were *meta*-coupled correlated with carbons at δ 98.3 (C-6) and 93.6 (C-8). The HMBC spectrum (Figure 4.10G) exhibited a long-range correlation of H-6 (δ 6.26) and C-8 (δ 93.6), C-10 (δ 103.2), C-5 (δ 161.4), and C-7 (δ 164.2). Besides, proton of H-8 (δ 6.51) was correlated with C-6 (δ 98.3), C-10 (δ 103.2), C-9 (δ 156.9) and C-7 (δ 164.2). In addition, the quaternary carbon of C-4' (δ 147.5) was correlated with proton at δ 6.98 (H-5'), δ 7.68 (H-6') and δ 7.82 (H-2'), while the methine carbon of C-3' (δ 144.9) were directly attached to proton δ 6.98 (H-5') and δ 7.82 (H-2').

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Table 4.10

*NMR data of quercetin (**331**) and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($(CD_3)_2CO$, 600 MHz) (331)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($(CD_3)_2CO$, 600 MHz)[a]	δ_C (ppm)
2		146.1		146.1
3		135.9		135.9
4		175.7		175.7
5	12.16 (1H, s)	161.4	12.48 (1H, s)	161.4
6	6.26 (1H, d, 2.0)	98.3	6.26 (1H, d, 1.9)	98.3
7	-	164.2	-	164.1
8	6.51 (1H, d, 2.0)	93.6	6.52 (1H, d, 1.9)	93.6
9	-	156.9	-	156.9
10	-	103.2	-	103.3
1′		122.9		122.9
2′	7.82 (1H, d, 2.1)	115.3	7.82 (1H, d, 2.0)	115.4
3′		145.0		145.0
4′		147.5		147.5
5′	6.98 (1H, d, 8.5)	114.9	6.99 (1H, d, 8.6)	114.9
6′	7.68 (1H, dd, 2.1, 8.5)	120.6	7.69 (1H, dd, 2.0, 8.6)	121.5

[a]Data from literature (Mennai et al., 2020)

Compound **(331)** identified as quercetin or 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one based on the comparison on literature review which was previously isolated from leaves of *L. aggragata* (Zhang et al., 2001) *L. erythrocarpa* (Kim et al., 2011), and roots of *L. myrrha* (Nguyen et al., 2021).

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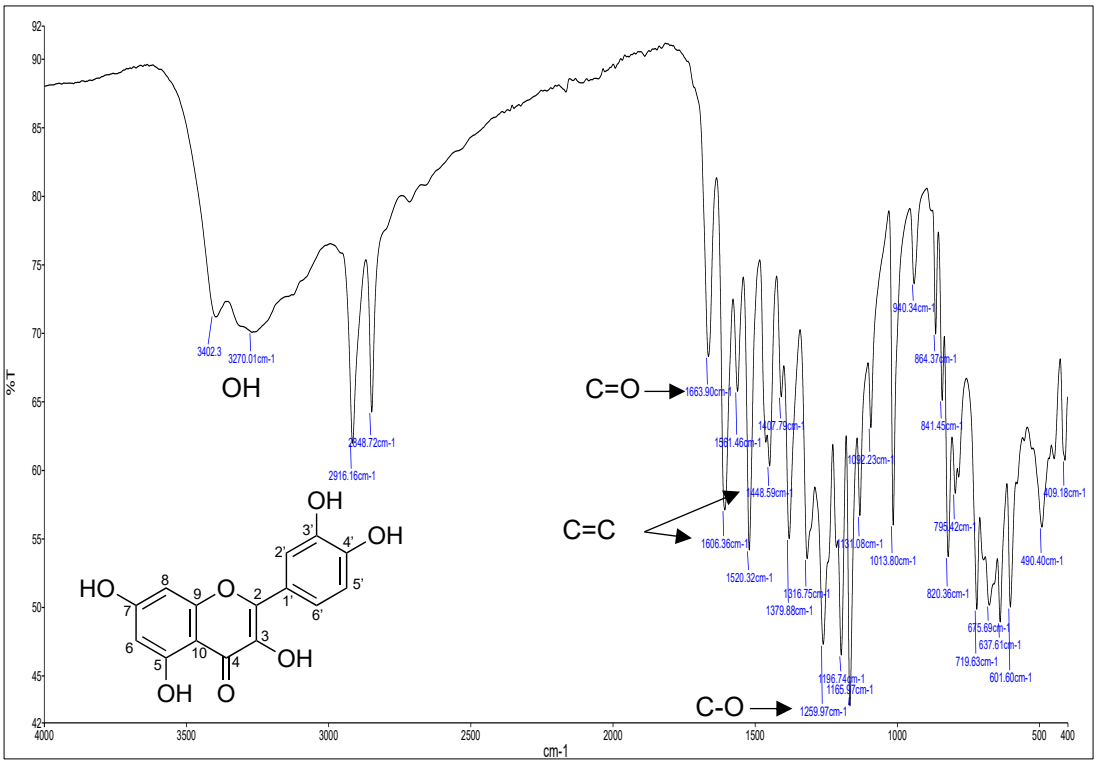


Figure 4.10A. IR spectrum of quercetin **(331)**

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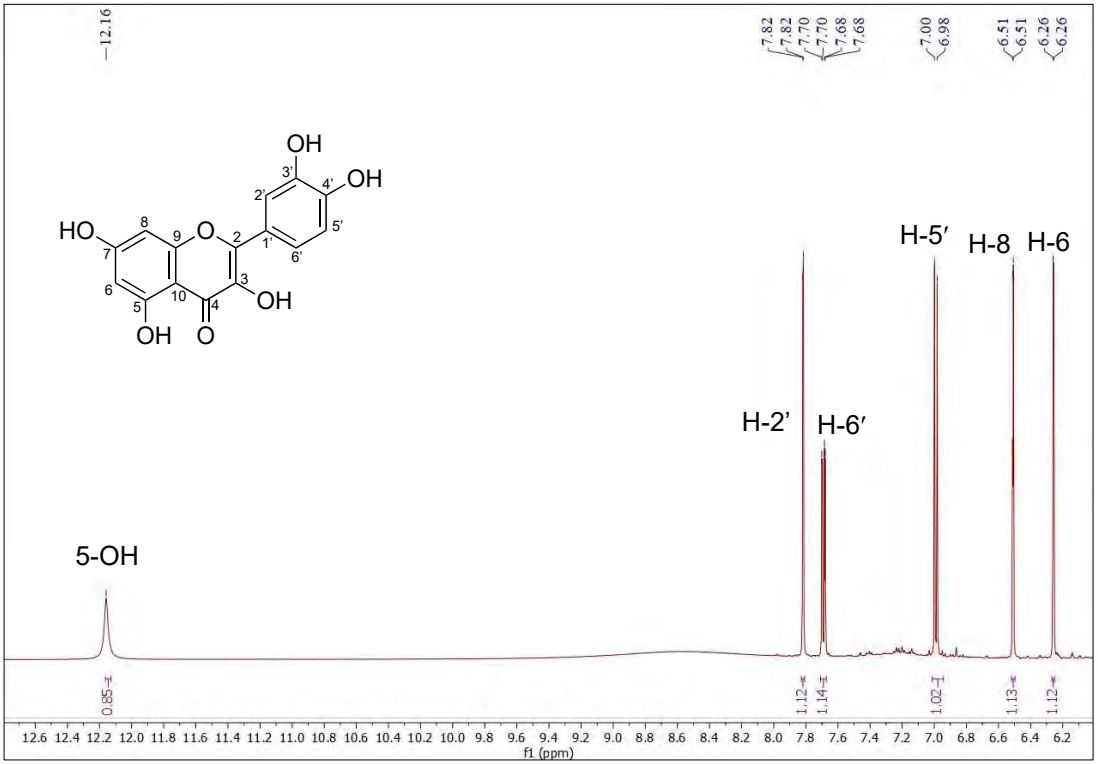


Figure 4.10B. ^{1}H NMR spectrum of quercetin **(331)**

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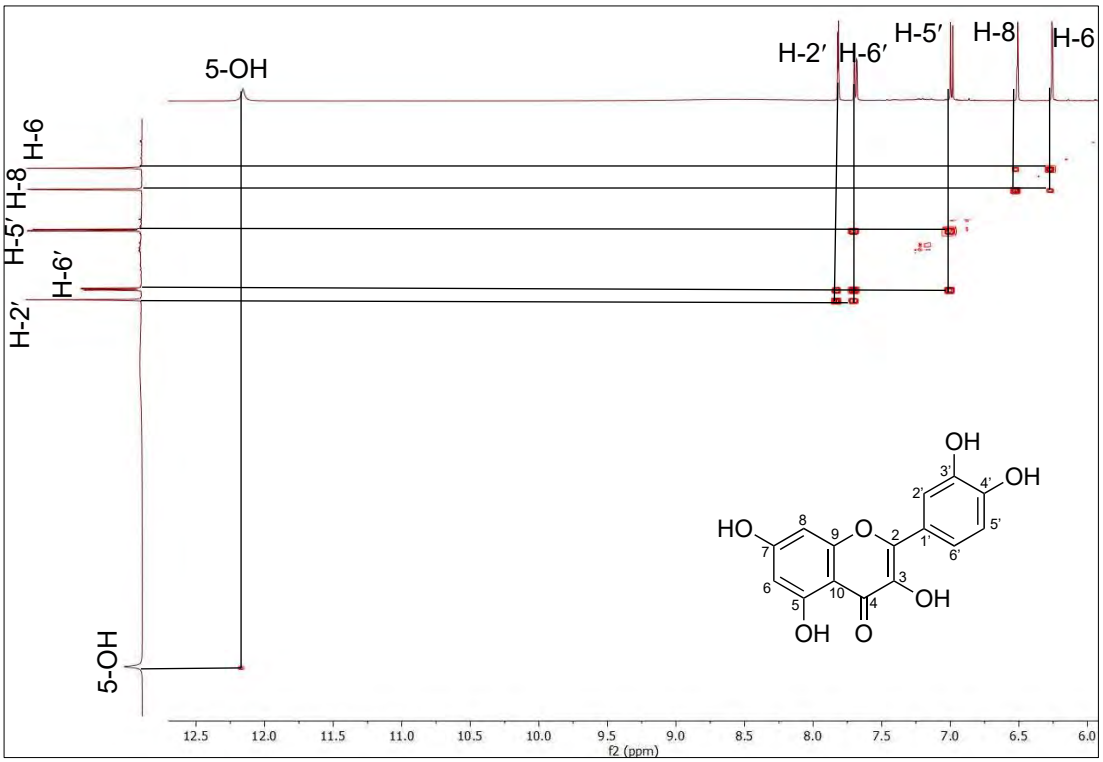


Figure 4.10C. COSY spectrum of quercetin **(331)**

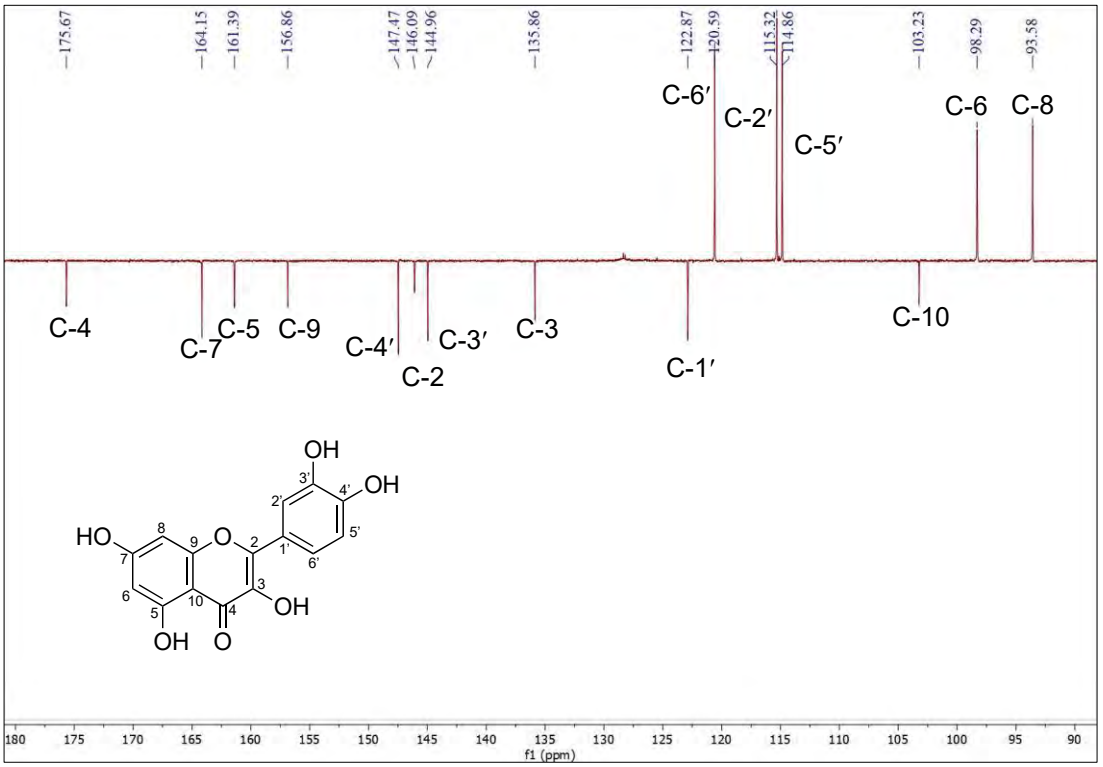


Figure 4.10D. ^{13}C NMR spectrum of quercetin **(331)**

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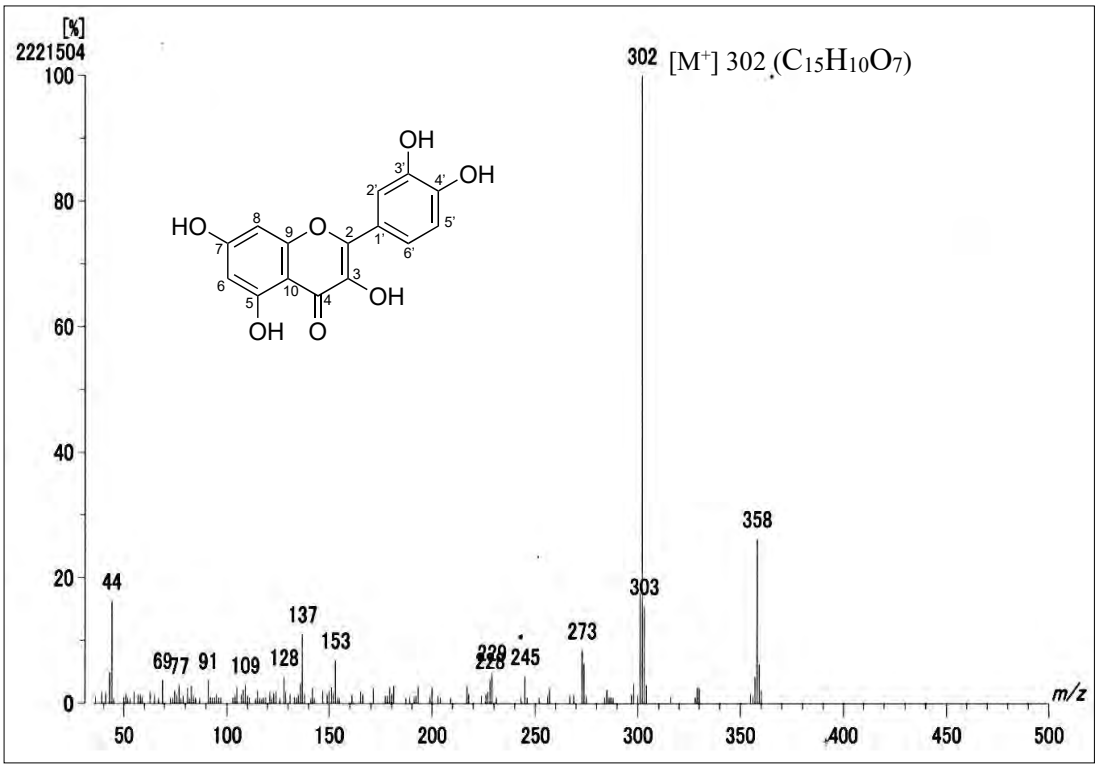


Figure 4.10E. MS spectrum of quercetin **(331)**

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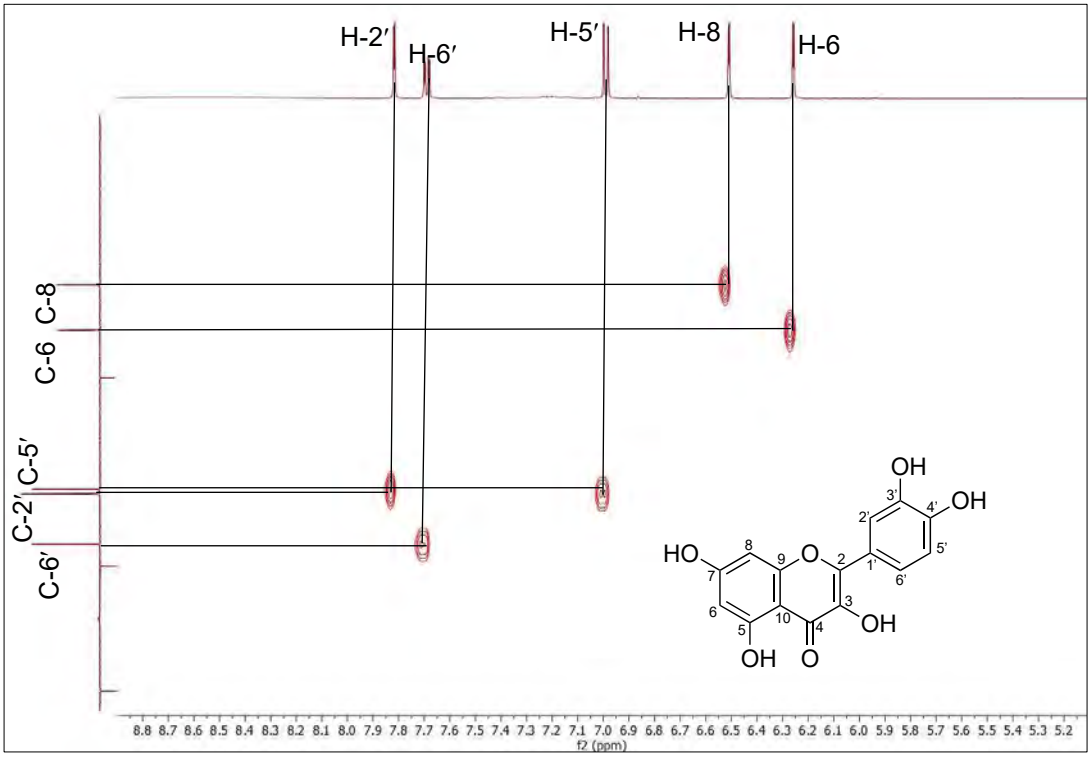


Figure 4.10F. HMQC spectrum of quercetin **(331)**

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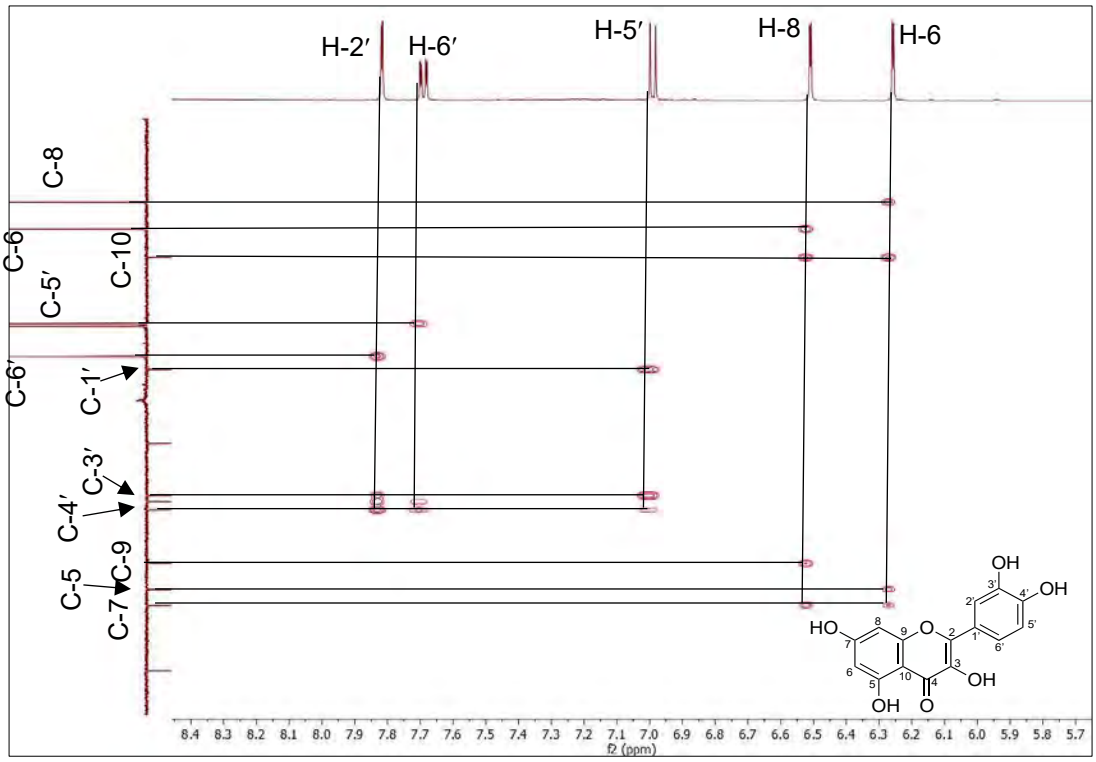
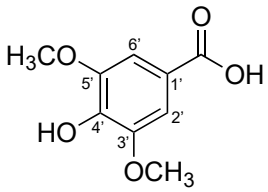


Figure 4.10G. HMBC spectra of quercetin **(331)**

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4.4.8 Syringic Acid (370)



(370)

Isolation of the MeOH root extract by CC afforded the compound **(370)** (13.9 mg, 0.1%) as a white crystalline solid. The IR spectrum (Figure 4.11A) displayed a broad absorption band at 3230 cm^{-1} (hydroxyl), 2942 (sp^3 C-H), 1695 cm^{-1} (carbonyl), 1615 and 1519 cm^{-1} (C=C aromatic).

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The ^{1}H NMR spectrum (Figure 4.11B) supported the presence of three singlet signals that appeared at δ 7.38 (H-2′ and H-6′) and δ 3.95 correspond to methoxy group of 3′-OCH_3 and 5′-OCH_3. Another singlet peak at δ 5.97 was assigned to a hydroxyl group. The ^{13}C NMR spectra (Figure 4.11C) indicated the presence of nine carbons. The carbon signal of methoxy group was clearly assigned at δ 56.5, while carbonyl carbon was observed at δ 170.7. Signal positions of methine, carbon C-2′ and C-6′ were observed at δ 107.3, whereas four quaternary carbons were observed at δ 120.0 (C-1′), 140.0 (C-4′), and 146.7 (C-3′, C-5′). The ^{13}C NMR data was supported by the MS spectrum (Figure 4.11D), which gave a molecular ion peak at *m/z* 198 consistent with a molecular formula $C_9H_{10}O_5$. The ^{1}H NMR and ^{13}C NMR data as tabulated in Table 4.11

Besides, the COSY spectrum (Figure 4.11E) showed a correlation between meta-proton of H-2′ and H-6′ at δ 7.38. In the HMQC spectrum (Figure 4.11F), the signals at δ 7.38 (H-2′/H-6′) were found directly attached to carbons resonated at δ 107.3 (C-2′/C-6′), while the methyl proton for 3′/5′-OCH_3 (δ 3.95) was confirmed attached to carbon at δ 146.7 (C-3′/C-5′). The HMBC spectrum (Figure 4.11G) exhibited a long-range correlation of H-2′/H-6′ (δ 7.38 with carbon C-1′ (δ 120.0), C-4′ (δ 140.0), C-1 (δ 170.7) and C-3′/C-5′ (δ 146.7).

Compound (**370**) was identified as syringic acid (4-Hydroxy-3,5-dimethoxybenzoic acid) based on the comparison of its physical properties and spectral data which was previously isolated from aerial parts of *L. glauca* (Chang et al., 2000) and the roots of *L. radix* (Zou et al., 2021).

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Table 4.11

*NMR data of syringic acid **(370)** and literature*

C	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500MHz) (379)	δ_C (ppm)	δ_H (ppm) (Int. mult. *J* in Hz) ($CDCl_3$, 500 MHz)[a]	δ_C (ppm)
1′	-	120.0	-	120.1
2′	7.38 (2H, s)	107.3	7.36 (2H, s)	107.5
3′	-	146.7	-	146.9
5′	-	146.7	-	146.9
6′	7.38 (2H, s)	107.3	7.36 (2H, s)	107.5
4′-OH	5.97 (1H, s)	140.0	6.03 (1H, s)	140.2
3′-OCH_3	3.95 (6H, s)	56.5	3.96 (6H, s)	56.6
5′-OCH_3	3.95 (6H, s)	56.5	3.96 (6H, s)	56.6
C=O	-	170.7	-	170.9

[a]Data from literature (Wisetsai et al., 2019)

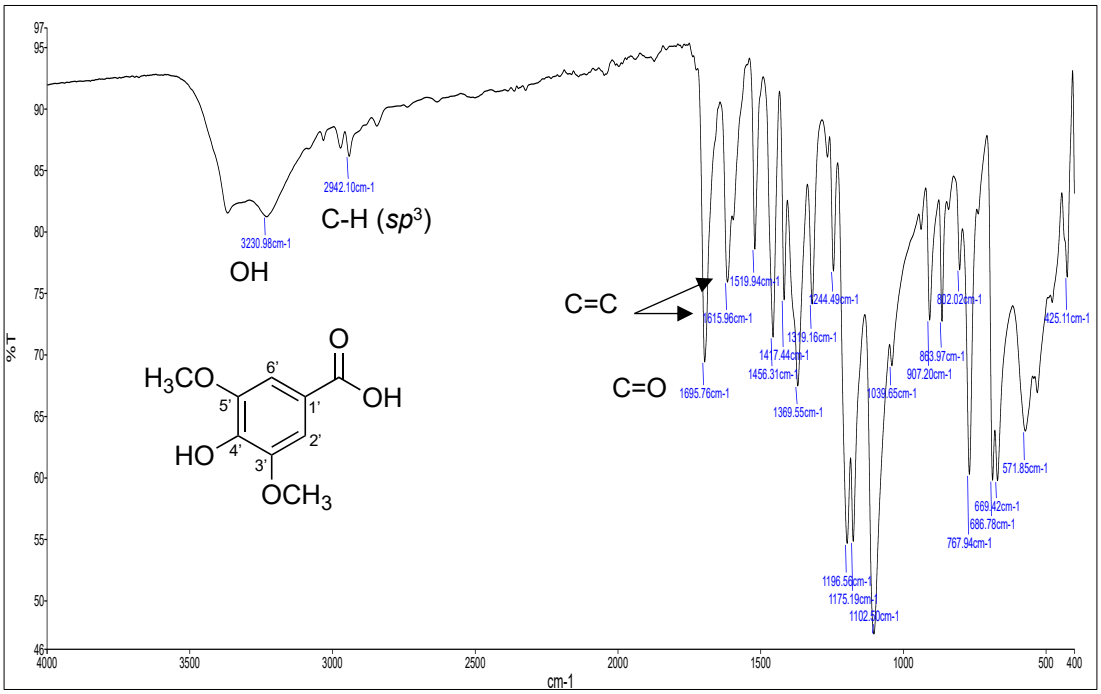


Figure 4.11A. IR spectrum of syringic acid **(370)**

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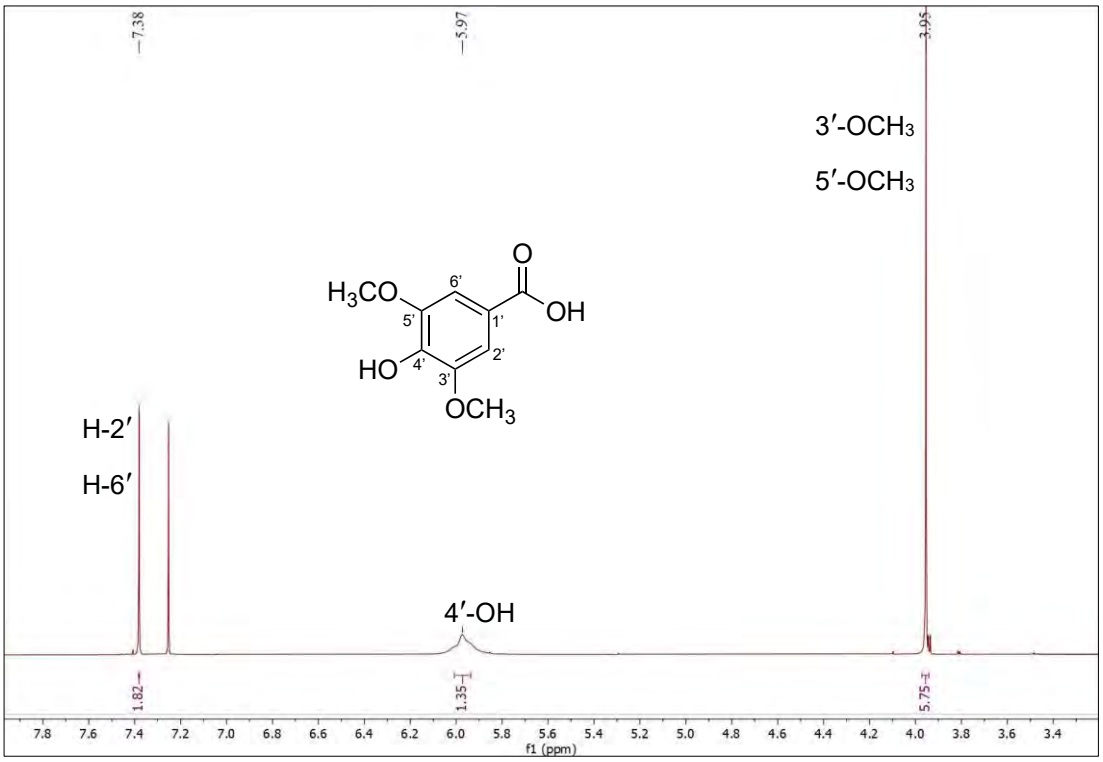


Figure 4.11B. ^{1}H NMR spectrum of syringic acid **(370)**

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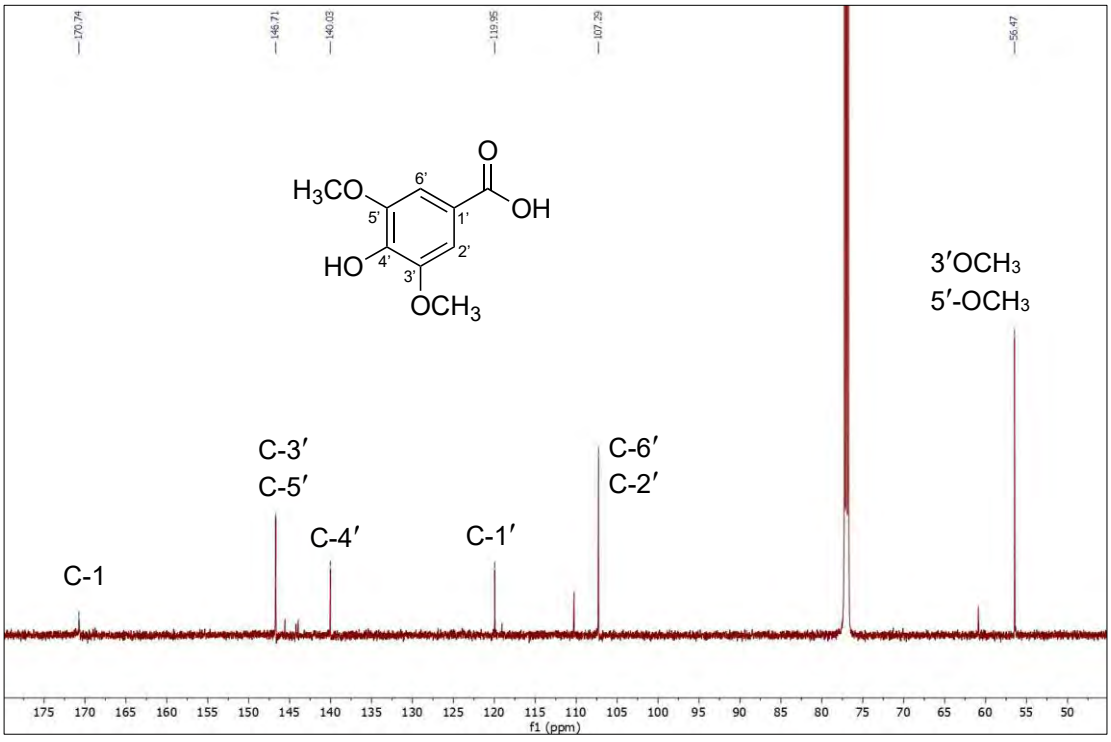


Figure 4.11C. ^{13}C NMR spectrum of syringic acid **(370)**

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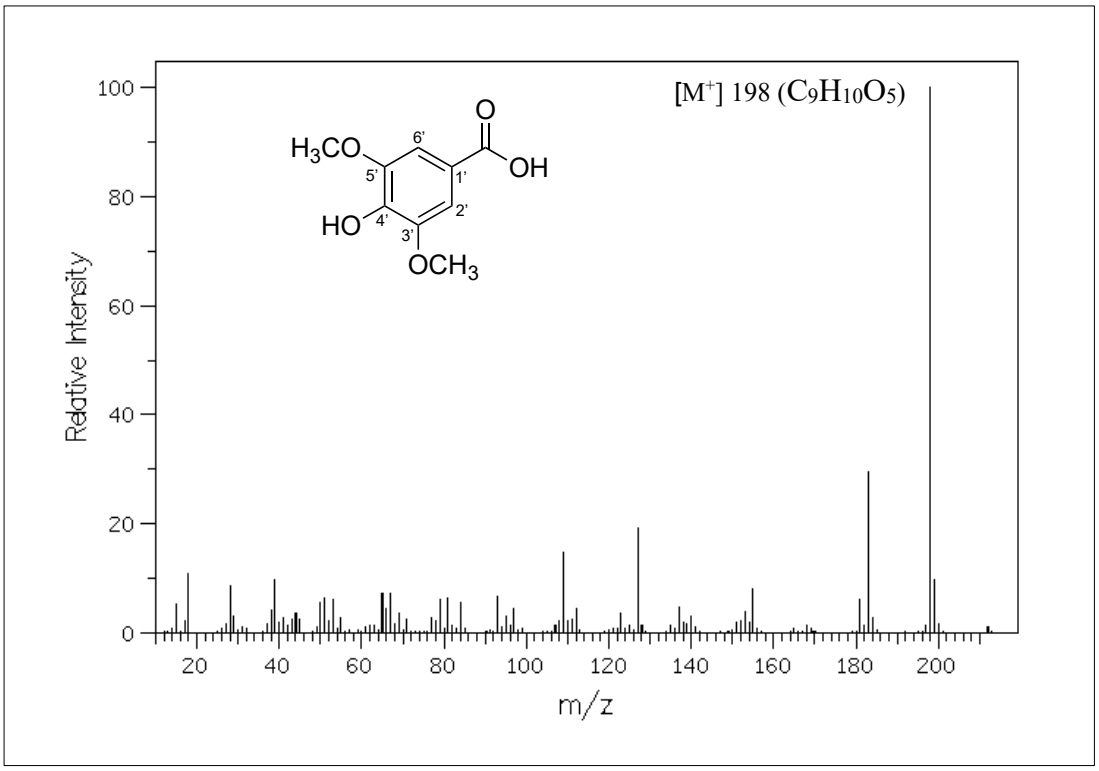


Figure 4.11D. MS spectrum of syringic acid **(370)**

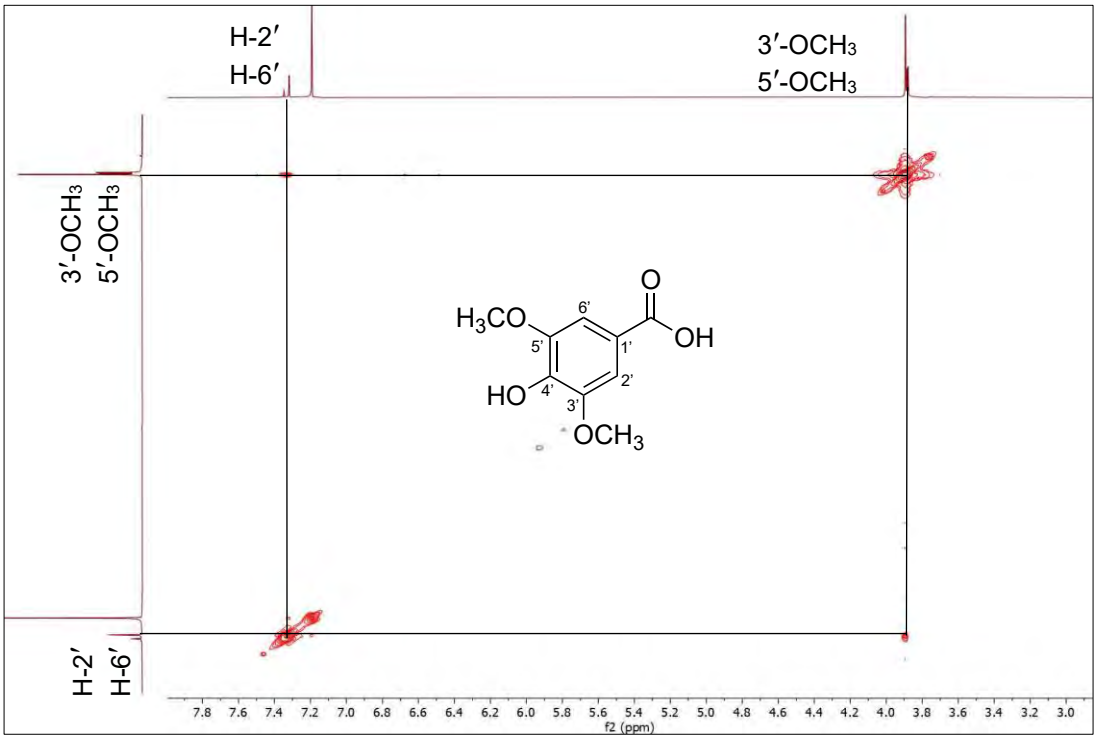


Figure 4.11E. COSY spectrum of syringic acid **(370)**

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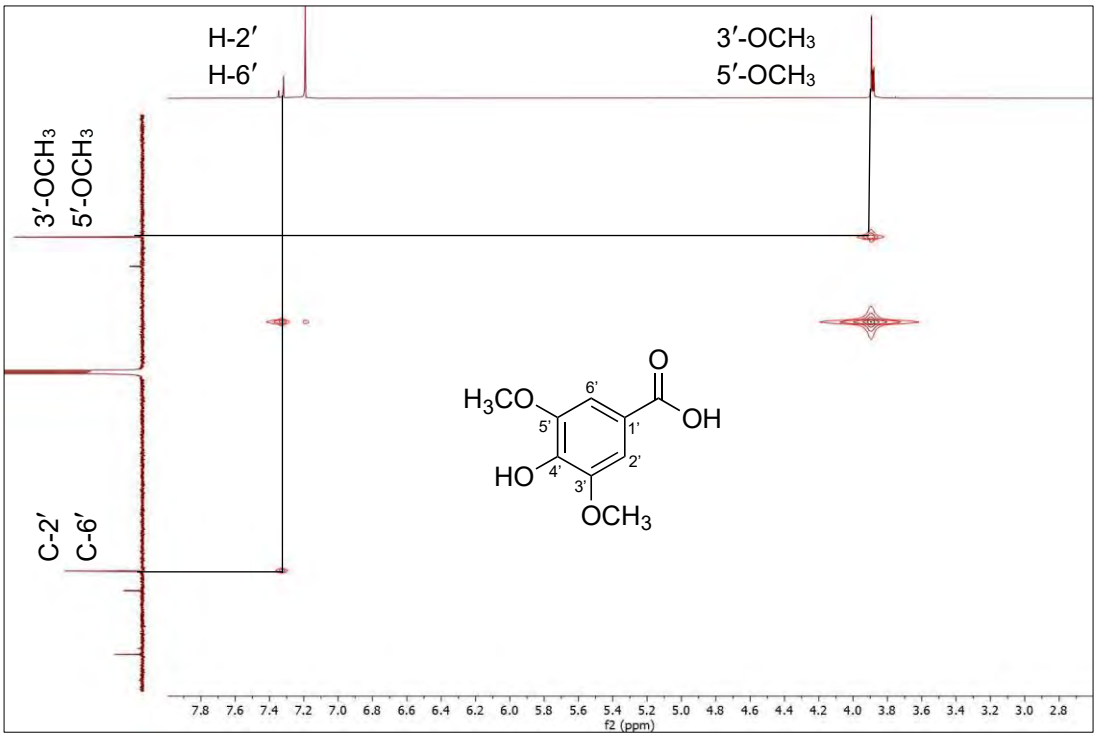


Figure 4.11F. HMQC spectrum of syringic acid **(370)**

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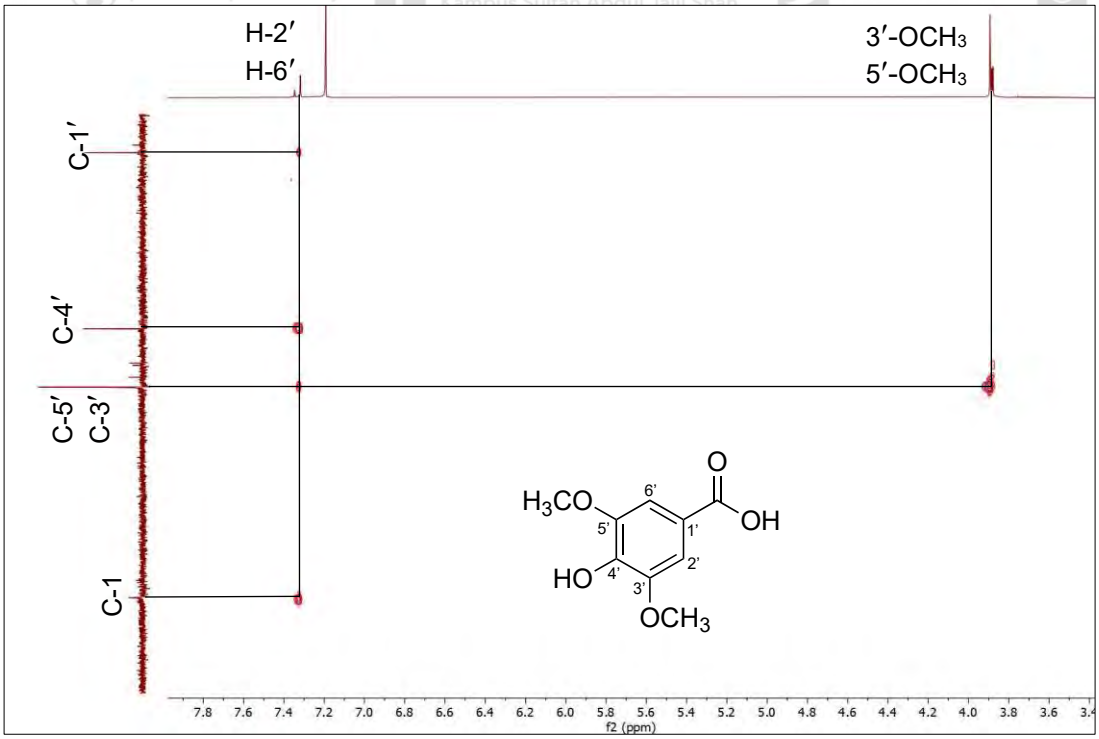


Figure 4.11G. HMBC spectrum of syringic acid **(370)**

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4.5 Biological Activities

4.5.1 Antioxidant Activity

Antioxidant is a substance that can prevent or slow down oxidative damage to cells and molecules caused by free radicals. Free radicals are highly reactive molecules with unpaired electrons that can damage DNA, proteins, and other cellular components. Oxidative damage is associated with various health problems such as aging, cancer, and cardiovascular diseases (Pham-Huy et al., 2008). The assessment of antioxidant activity can be categorized into two main mechanisms: hydrogen atom transfer-based assays, including the oxygen radical absorption capacity test, the hydroxyl radical antioxidant capacity test, the total peroxyl radical trapping antioxidant parameter test, the total oxyradical scavenging capacity test and electron transfer-based assays, which encompass the cupric reducing antioxidant power test, the ferric reducing antioxidant power test, and Folin-Ciocalteu test (Siddeeg et al., 2021)

Chemical constituents from the groups of phenolics (flavonoids, tocopherols, and phenolic acids), nitrogen compounds (amines, alkaloids, chlorophyll derivatives, and amino acids) and carotenoids are examples of natural antioxidants. On the other hand, synthetic antioxidants that have phenolic structures with varying levels of alkyl substitution such as butylated hydroxytoluene and butylated hydroxyanisole. However, synthetic antioxidants have potential in carcinogenicity. Hence, the development of alternative antioxidants of natural origin has attracted considerable attention and is generally thought to be a desirable development (Wu et al., 2009)

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In the context of this study, the evaluation of the antioxidant potential of crude extracts and phytochemicals was using DPPH free radical scavenging assay. The DPPH method serves as a primary screening tool for the discovery of novel antioxidant compounds in organic extracts sourced from natural materials like herbs, spices, fruits, and vegetables (Shahidi & Zhong, 2015). This method employs the stable free radical known as 2,2-diphenyl-1-picrylhydrazyl (DPPH) to assess the free radical scavenging capacity. As hydrogen atoms or electrons are transferred to the unpaired electron in DPPH, the absorbance at 515 nm decreases proportionally, indicating the reduction of DPPH to its non-radical form. A high free radical scavenging ability is traditionally associated with strong antioxidant properties.

The percentage inhibitions at different concentrations of crude extracts are further summarized in Figure 4.12, providing a comprehensive overview of its antioxidant activities. All extracts showed significant differences compared to the positive control, ascorbic acid (AA) and butylated hydroxytoluene (BHT). Notably, both methanolic extracts, LSRM and LSLM displayed the strongest activity with IC_{50} values of 77.4 and 80.8 µg/mL, respectively, indicating its notably DPPH radical scavenging capability. This potency is attributed to its richness in antioxidants, such as polyphenols, flavonoids, and phenolic compounds, known for their ability to neutralize free radicals. Meanwhile, the LSRH and LSRE extracts also demonstrated effective DPPH scavenging with IC_{50} values of 89.8 and 90.9 µg/mL, respectively. However, the weak activity of other extracts, possibly due to the presence of non-polar compounds that have limited ability to act as free radical scavengers. Table 4.12 summarized the activity of the crude extracts with their IC_{50} values

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Table 4.12

DPPH radical scavenging of the crude extracts

Extracts	Inhibition at 200 µg/mL (%)	IC_{50} (µg/mL)
LSLH	84.8 ± 0.02	106.7
LSLE	86.7 ± 0.01	96.7
LSLM	83.0 ± 0.01	80.8
LSRH	90.3 ± 0.01	89.8
LSRE	79.2 ± 0.01	90.9
LSRM	86.9 ± 0.01	77.4
AA	84.9 ± 0.54	44.5
BHT	83.7 ± 0.03	95.8

Data represent mean ±SD of three independent experiments; AA – Ascorbic acid; BHT - butylated hydroxytoluene; LSLH: *L. subumbelliflora* leaf hexane; LSLE: *L. subumbelliflora* leaf ethyl acetate; LSLM: *L. subumbelliflora* leaf methanol; LSRH: *L. subumbelliflora* root hexane; LSRE: *L. subumbelliflora* root ethyl acetate; LSRM: *L. subumbelliflora* root methanol; Data obtained was expressed as means ±SD and compares using a student's t-test. The statistical analyses employed one-way ANOVA ($p<0.05$). A statistical package (SPSS version 11.0) was used for the data analysis.

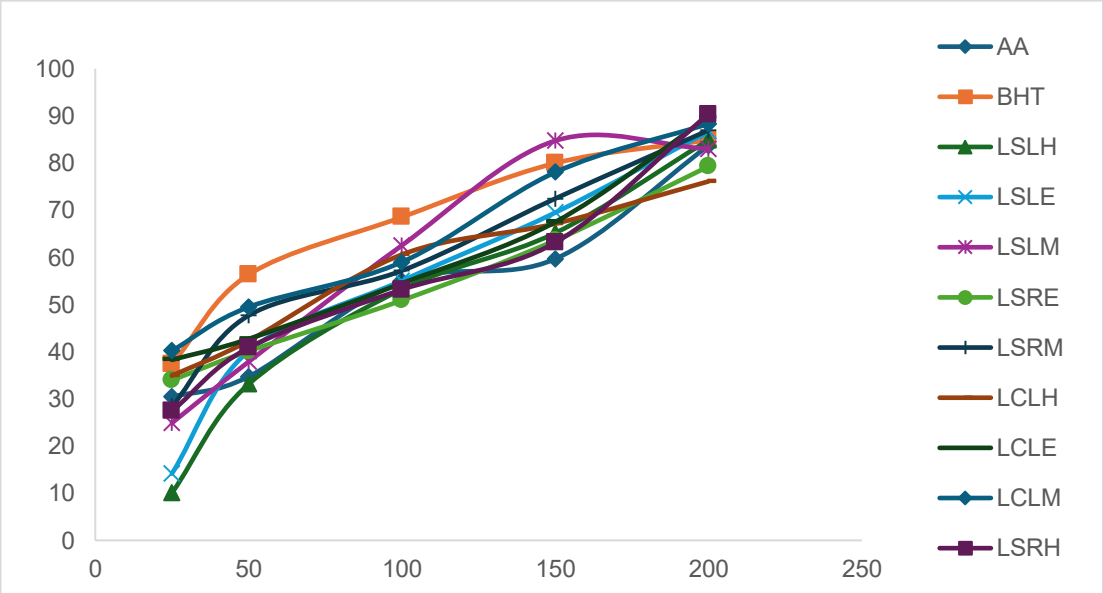


Figure 4.12. Percentage inhibition of DPPH radical scavenging of *Lindera* extracts at different concentrations

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Besides, eight compounds were selected for DPPH radical scavenging activity and the results are tabulated in Table 4.13, whereas the percentage inhibition are shown in Figure 4.13.

Table 4.13

DPPH radical scavenging activity of the isolated phytochemicals

Compounds	Inhibition at 200 µg/mL (%)	IC_{50} (µg/mL)
5,6-Dehydrokawain (414)	88.5 ± 0.03	78.5
Pinostrobin (307)	84.7 ± 0.03	96.7
β-Sitosterol (401)	88.9 ± 0.02	77.5
Pinocembrin (308)	79.3 ± 0.01	90.9
4-Hydroxy-3-methoxy-acetophenone (363)	86.1 ± 0.02	85.0
Ferulic acid (365)	88.7 ± 0.03	67.5
Quercetin (331)	89.0 ± 0.01	55.2
Syringic acid (370)	91.0 ± 0.02	75.8
Ascorbic acid	84.9 ± 0.54	44.5
Butylated hydroxytoluene	83.7 ± 0.03	95.8

Data represent mean ±SD of three independent experiments; Data obtained was expressed as means ±SD and compares using a student's t-test. The statistical analyses employed one-way ANOVA ($p<0.05$). A statistical package (SPSS version 11.0) was used for the data analysis.

Among the isolated compounds, quercetin **(331)**, ferulic acid **(365)**, and syringic acid **(370)** displayed the highest antioxidant activity with IC_{50} values 55.2, 67.5, and 75.8 µM respectively. These phenolic compounds can act as an antioxidant by neutralizing free radicals through electron or hydrogen atom donation in the presence of hydroxyl groups. Free radicals are highly reactive molecules with unpaired electrons,

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which makes them unstable and prone to cause damage to cells, proteins, and DNA. The phenolic hydroxyl groups in these compounds can donate electrons or hydrogen atoms to the free radicals, thus effectively stabilizing them (Kostić et al., 2023).

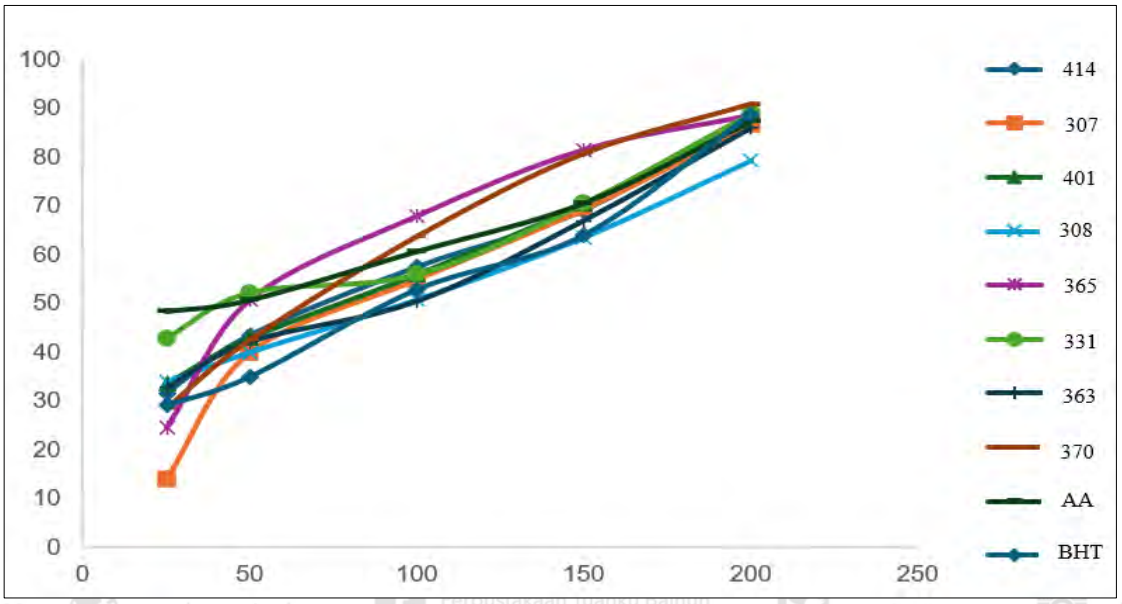


Figure 4.13. Percentage inhibition of DPPH radical scavenging of isolated phytochemicals at different concentrations

In addition, 5,6-dehydrokawain **(414)** also exhibits strong activity with IC_{50} values 78.5 µM. This compound contains conjugated double bonds leading to the presence of unpaired electrons. These unpaired electrons are efficient at donating electrons to stabilize free radicals, and it can interrupt radical chain reactions by reacting with it and neutralizing free radicals such as DPPH radicals (Nimse & Pal, 2015). Besides, for 4-hydroxy-3-methoxy-acetophenone **(363)** and pinostrobin **(307)** showed low antioxidant activity as it might be associated with methoxyl group in their structures to interact effectively with free radicals (Platzer et al., 2022).

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4.5.2 Antibiofilm Activity

Biofilms are complex communities of microorganisms that adhere to surfaces and encased in a self-produced extracellular matrix. Antibiofilm refers to substances or treatments that are specifically designed to prevent the formation of biofilms or to disrupt existing biofilms. Antibiofilm agents work by targeting various stages of biofilm formation and maintenance. They may inhibit the initial attachment of bacteria to surfaces, interfere with the formation of the extracellular matrix that holds the biofilm together, disrupt communication between bacteria (quorum sensing), or directly kill bacteria within the biofilm (Mishra et al., 2020).

In the context of dentistry, *Candida albicans* and *Streptococcus mutans* can form biofilms on various surfaces within the oral cavity, including teeth, dental implants, and mucosal surfaces. In the case of *Streptococcus mutans*, biofilms contribute significantly to the formation of dental plaque, which is a precursor to tooth decay and gum disease. *Candida albicans* can also form biofilms on oral mucosal surfaces, leading to conditions such as oral candidiasis. To highlight the importance of developing an effective antibiofilm, now researchers are actively exploring antibiofilm strategies to prevent and combat oral infections and maintain oral health (Falsetta et al., 2014). The ability to inhibit biofilm formation was evaluated using essential oils, crude extracts, and isolated phytochemicals from *L. subumbelliflora* against *Streptococcus mutans* and *Candida albicans*. In this study, the quantification of biofilm formation has been conducted with 0.12% chlorhexidine as the positive control. The effect of essential oils, crude extracts, and isolated phytochemicals on the percentage of inhibition of biofilm formation is given in Table 4.14.

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Table 4.14

Antibiofilm activity of the essential oils, crude extracts, and isolated phytochemicals

Samples/microbes	Inhibition rate (%) at 500 µg/mL	
	Streptococcus mutans	*Candida albicans*
LSEO	47.9 ± 0.07	38.3 ± 0.26
LCEO	51.4 ± 0.12	31.3 ± 0.15
LSLH	85.7 ± 0.21	32.1 ± 0.24
LSLE	96.6 ± 0.02	47.3 ± 0.02
LSLM	87.3 ± 0.17	45.4 ± 0.01
LSRH	79.5 ± 0.24	35.7 ± 0.08
LSRE	97.6 ± 0.02	48.1 ± 0.01
LSRM	99.2 ± 0.01	49.2 ± 0.02
5,6-Dehydrokawain (414)	73.9 ± 0.28	35.1 ± 0.02
Pinostrobin (307)	89.3 ± 0.04	39.1 ± 0.02
β-Sitosterol (401)	91.3 ± 0.04	35.2 ± 0.03
Pinocembrin (308)	98.0 ± 0.01	43.7 ± 0.02
4-Hydroxy-3-methoxy-acetophenone (363)	92.7 ± 0.01	40.8 ± 0.03
Ferulic acid (364)	93.0 ± 0.06	41.8 ± 0.02
Quercetin (331)	98.4 ± 0.04	45.7 ± 0.07
Syringic acid (370)	98.2 ± 0.01	40.1 ± 0.05
Clorohexidine 0.12 %	99.5 ± 0.01	51.9 ± 0.01

Data represent mean ±SD of three independent experiments; Data obtained was expressed as means ±SD and compares using a student's t-test. The statistical analyses employed one-way ANOVA ($p<0.05$). A statistical package (SPSS version 11.0) was used for the data analysis.

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The essential oil of *L. subumbelliflora* (LSEO) increased the biofilm of *Candida albicans* by 38.3%, however, decreased the biofilm of *Streptococcus mutans* by 47.9% when treated with 500 µg/mL. Besides, for the essential oil of *L. caesia* (LCEO), it increased the biofilm of *Candida albicans* by 31.3%, and it decreased the biofilm of *Streptococcus mutans* by 51.4% when treated with the same concentration. This finding suggested a higher concentration than 500 µg/mL, the essential oil may have the potential to inhibit the biofilm of *Candida albicans*. The effectiveness of essential oils against these pathogens can be attributed to their chemical composition, which often includes compounds like terpenes, phenols, and aldehydes. These components possess antimicrobial properties that can disrupt the biofilm formation of bacteria and fungi. The interaction between essential oils and microbial biofilms involves mechanisms such as membrane disruption, interference with cell signalling, and inhibition of enzyme activity. This dual action against these pathogens highlights the potential of essential oils as natural alternatives in combating oral biofilm-related infections (Arzmi et al., 2016).

All extracts showed significant differences compared to positive and negative controls. The most effective sample against *Streptococcus mutans* and *Candida albicans* was LSRM, with an inhibition rate of 99.2% and 49.2%, comparable to the positive control of 0.12% chlorhexidine at 99.5% and 51.9%, respectively. Plant extracts that contain a plethora of secondary metabolites such as polyphenols, alkaloids, flavonoids, and terpenoids, can exhibit various biological activities including antibiofilm properties (Dubale et al., 2023). These compounds interfere with biofilm formation by disrupting microbial adhesion to surfaces, inhibiting the production of extracellular polymeric substances, and impairing quorum sensing mechanisms

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essential for biofilm maturation. For instance, polyphenolic compounds such as flavonoids can chelate metal ions by destabilizing biofilm matrix formation (Makarewicz et al., 2021), while terpenoids may disrupt microbial cell membranes, leading to biofilm disintegration (Mahizan et al., 2019).

In addition, this also may be due to the synergistic interactions between different bioactive compounds within plant extracts that can contribute to their enhanced antibiofilm activity compared to individual components. Synergistic combinations penetrate the matrix of the biofilm and cause the death of cells. The complex mixture of phytochemicals present in the extracts may target multiple pathways involved in biofilm formation and maintenance, resulting in a broader spectrum of antimicrobial action and reduced likelihood of microbial resistance development (Khameneh et al., 2021).

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Among the tested compounds, quercetin **(331)** and pinocembrin **(308)** showed highly effective efficacy against *Streptococcus mutans* with inhibition rates of 98.4% and 98.0%, respectively. Both compounds contain phenolic structures for forming hydrogen bonds with enzyme active sites, bacterial cell walls, and fungal cell membranes. This interaction can disrupt their integrity and function, inhibiting biofilm formation and microbial growth (Makarewicz et al., 2021). Flavonoids also exhibit antioxidant properties, which could further enhance their antibiofilm efficacy by mitigating oxidative stress-induced damage to microbial components like DNA, proteins, and lipids (Al-Khayri et al., 2022).

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It is also noteworthy that the efficacy inhibition against *Streptococcus mutans* does not have the same level against *Candida albicans*. For example, syringic acid **(370)** exhibits a high inhibition rate against *Streptococcus mutans* (98.2%) but a comparatively lower rate against *Candida albicans* (40.1%). Ferulic acid **(365)** and 4-hydroxy-3-methoxy-acetophenone **(363)** also exhibited a high inhibition rate against *Streptococcus mutans* compared to *Candida albicans*. These compounds contain methoxy groups, which can influence their lipophilicity. Compounds with higher lipophilicity tend to interact more readily with lipid-based structures, especially in bacterial cell membranes than fungus cell membranes (Echeverría et al., 2017).

Overall, it clearly shows that these *Lindera* extracts and isolated compounds are more substantial against *Streptococcus mutans* than those of *Candida albicans*. This may be due to the specificity of the active compounds. The bioactive compounds in *Lindera* extract may be more specifically toxic to the cellular or biofilm structures of *Streptococcus mutans* than those of *Candida albicans*. Different microorganisms have unique cell wall compositions and metabolic pathways, which can influence the susceptibility to certain compounds. For example, bacterial cells, like those of *Streptococcus mutans*, have different protective mechanisms and biofilm formation pathways compared to the eukaryotic cells of fungi like *Candida albicans*. Besides, the biofilm matrix of *Streptococcus mutans* might be less dense or have a composition that allows the extract to penetrate more effectively compared to the biofilm matrix of *Candida albicans*, which can be more robust or have a different three-dimensional structure that impedes penetration (Li et al., 2023).

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CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

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5.1 Conclusions

Hydrodistillation of the fresh leaves of *L. subumbelliflora* and *L. caesia* gave a yield of 0.20% and 0.15% of the respective oils. The results revealed that the studied essential oils are predominantly made up of β-eudesmol (14.6%), *cis*-α-bergamotene (11.0%), α-copaene (8.5%), dodecen-1-ol (8.5%), and (*E*)-nerolidol (8.3%), for *L. subumbelliflora* leaves oil, whereas terpinen-4-ol (26.3%), *neo*-intermedeol (23.2%), and eudesma-4,11-dien-3-one (10.4%) for *L. caesia* leaves oil. To the best of our knowledge, this is the first report on the chemical compositions of the essential oils from *L. subumbelliflora* and *L. caesia*.

Phytochemical studies of *L. subumbelliflora* leaves have been successfully afforded 5,6-dehydrokawain, meanwhile the root part had yielded seven compounds

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which comprised of two flavannones (pinostrobin and pinocembrin), a sterol (β-sitosterol), phenolics (4-hydroxy-3-methoxy acetophenone, ferulic acid, and syringic acid), and a flavonol (quercetin).

The essential oils, crude extracts, and isolated phytochemicals were evaluated for their antioxidant and antibiofilm activity. The methanolic roots and leaves extract of *L. subumbelliflora* displayed the strongest activity among the tested extracts with IC_{50} values of 77.4 and 80.8 µg/mL, respectively. Among the isolated phytochemicals, quercetin, ferulic acid, and syringic acid displayed the highest antioxidant activity with IC_{50} values 55.2, 67.5, and 75.8 µM, respectively. For antibiofilm activity, the leaves and roots of ethyl acetate and methanolic extracts showed the highest inhibition against *Streptococcus mutans* with the value ranging from 96.6 - 99.2%. Among the isolated phytochemicals, quercetin and pinocembrin show highly effective against *Streptococcus mutans* (98.4%) and *Candida albicans* (45.7%). Based on these data, it clearly shows that *Lindera* extract and isolated phytochemicals is showed potential activity against *Streptococcus mutans* than that of *Candida albicans*.

5.2 Recommendations

Numerous recommendations and suggestions are proposed for upcoming research such as the phytochemical analysis by using modern isolation methods such as molecular distillation, supercritical fluid chromatography, molecularly imprinted technology, and simulated moving bed chromatography. It is recommended to use modern and current isolation and separation techniques for instance recycling preparative HPLC and

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centrifugal partition chromatography for isolation of polar extracts in addition to the minor compounds. In addition, bioassay-guided isolation and qualitative structure-activity relationship (QSAR) are also suggested for the phytochemistry and biological activity studies for other species. Further investigation and exploration is necessary to clarify the underlying mechanisms of these naturally occurring bioactive compounds.

Furthermore, the selection of other *Lindera* species might be of interest. The essential oil and phytochemicals isolated from the genus *Lindera* may bear the potential for drug development due to its high concentration of phenolics. In addition, multivariate data analysis may be used as quality control tools for the identification and characterization of essential oils and other phytochemicals from different species that are to be utilized as raw materials in traditional herbal products. However, numerous investigations should be carried out on their mode of action and their probable toxicological effects, as well as preclinical trials in order to optimize their potential uses for therapeutic applications.

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PUBLICATIONS

1. **Zaini, N.N.M.**, Salleh, W.M.N.H.W.*, Salihu, A.S. & Shaharudin, S.M. (**2024**). Assessment of variability of essential oil components in the genus *Lindera* (Lauraceae) by multivariate analysis. *Malaysian Journal of Chemistry (Scopus)*, 26(1), 271-280.

2. **Zaini, N.N.M.**, Salleh, W.M.N.H.W.*, Arzmi, M.H., Salihu, A.S. & Ghani, N.A. (**2023**). Chemical composition of essential oil from *Lindera caesia* Reinw. ex Fern.-Vill. and its antifungal, antibiofilm, and molecular docking studies. *Natural Product Research (Q3)*. doi: 10.1080/14786419.2023.2298720 (in press)

3. **Zaini, N.N.M.**, Salleh, W.M.N.H.W.*, Arzmi, M.H., Salihu, A.S. & Ghani, N.A. (**2023**). Chemical composition of essential oil from *Lindera subumbelliflora* Kosterm and its effect on the susceptibility and biofilm activities of *Candida albicans* and *Streptococcus mutans. Natural Product Research (Q3)*. doi: 10.1080/14786419.2023.2278164 (in press)

4. **Zaini, N.N.M.**, Salleh, W.M.N.H.W.*, Salihu, A.S., & Abed, S.A. (**2024**). A review on chemical constituents and pharmacological action of the genus Lindera. *Journal of Science and Mathematics Letters, 12*(2), 50-73.

5. **Zaini, N.N.M.** & Salleh, W.M.N.H.W.*. (**2023**). A systematic review of the essential oils and biological activities of the genus *Lindera* (Lauraceae). *La Rivista Italiana delle Sostanze Grasse (Q4)*. Accepted

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7. **Zaini, N.N.M.**, Salleh, W.M.N.H.W.*, Ghani, N.A., Rasol, N.E., Arzmi, M.H., Salihu, A.S., Khamis, S. & Mahsop, H.S.M. (**2023**). Chemical constituents from *Lindera subumbelliflora. Chemistry of Natural Compounds (Q4).* Accepted

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CONFERENCES

1. 38th International Conference on Natural Products (ICNP)
   Aloft, Kuala Lumpur, 11-13th September 2023.
   Title: Chemical composition of essential oil from *Lindera subumbelliflera* Kosterm and its effect on the susceptibility and biofilm activities of *Candida albicans* and *Streptococcus mutans* (Poster Presenter – Best Poster)

2. 39th International Conference on Natural Products (ICNP)
   Aloft, Kuala Lumpur, 9-11th September 2024.
   Title: Chemical Constituents Of *Lindera Subumbelliflora* Kosterm And Its Effect On The Antioxidant And Antibiofilm Activities (Oral Presenter)

3. International Postgraduate Colloquium (IPAC)
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   Title: Investigation of Antioxidant and Antibiofilm Properties of *Lindera subumbelliflora* Kosterm

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Assessment of Variability of Essential Oil Components in the Genus *Lindera* (Lauraceae) by Multivariate Analysis

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Essential oils hold tremendous medicinal attributes and are greatly exploited industrially worldwide. *Lindera* is an important genus of the Lauraceae family of plants which are known for their medicinal values. In the present study, eleven studies reported on *Lindera* essential oils were selected and reviewed. Then the variability of essential oil components in the genus *Lindera* were assessed by multivariate analysis. The chemical analysis enabled the identification of qualitative and quantitative differences among the essential oils. The essential oils were characterized by high proportions of germacrene B, spathulenol, nerolidol, β-caryophyllene, dihydromyrcene, furanosesquiterpenoid, sesquithuriferol, and linalool. Then, the differences in the chemical profiles of the essential oil were confirmed by the multivariate statistical analysis, which was determined *via* principal component analysis (PCA) and hierarchical clustering analysis (HCA). The analysis classified the *Lindera* species into four different clusters. Group A of cluster analysis (*L. obtusiloba*) was highly correlated with α-copaene and β-eudesmol and group B of cluster analysis (*L. strychnifolia, L. umbellata* and *L. pulcherrima*) were highly correlated with linalool and 1,8-cineole. Moreover, group C of cluster analysis (*L. erythrocarpa, L. pipericarpa, L. nacusua* and *L. glauca*) were highly correlated with spathulenol, α-humulene and β-phellandrene, whereas for group D (*L. chunii, L. communis* and *L. fragrans*) were highly correlated with β-farnesene and β-caryophyllene. This data analysis may be used for the identification and characterization of essential oils from different *Lindera* species that are to be used as raw materials of traditional herbal products. However, there is much variation in the essential oil compositions of *Lindera* essential oils, both within subspecies and between geographical locations; much additional investigation is necessary to more fully characterize the volatile phytochemistry of this plant.

Keywords: Lauraceae; *Lindera*; essential oil; multivariate; PCA; HCA

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Lauraceae, one of the most primitive families of plants, belongs to the Magnoliidae subclass, is a family of pantropical plants that includes trees and shrubs. It is composed of approximately 55 subgenera totalling over 3,000 species. The family is highly diversified in South-east Asia, Madagascar, Northern South America, and the east coast of Brazil [1]. The genus *Cinnamomum*, *Litsea*, *Lindera*, *Neolindera*, and *Parabenzoin* are the example of well-known subgenera in Lauraceae family [2].

Lindera is a genus of about 100 species of flowering plants. It can be found all over the world in tropical, subtropical climates, and temperate zones of Asia and Midwestern America [3]. Generally, the leaves are plain, stipule-free, opposite, spiral, whorled, and alternate. The flowers are differently accrescent and are bisexual, actinomorphic, tiny, regular, greenish-white, or yellow in colour, aromatic, and trimerous. Most of the flowers have six sepals that are arranged in two cycles. The fruits, which are baccate or drupaceous and frequently seated or surrounded by a persistent and cup-shaped corolla, have taxonomic significance [4]. Table 1 shows the medicinal uses of several *Lindera* species [4-18].

Essential oils as secondary metabolites involve complex mixtures of natural compounds with versatile organic structures, metabolites such as terpenes, phenols, and ketones represented with useful medicinal properties [19]. Essential oils have been utilised for thousands of years for their therapeutic and medicinal effects. In addition, essential oils are important natural sources and are used as raw materials for the production of fragrance compounds in cosmetics, as flavouring additives for food and beverages, as scenting agents in a variety of household products, and as intermediates

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in the synthesis of other perfume chemicals [20]. Meanwhile, essential oils from aromatic and medicinal plants have been known since antiquity to possess biological activities, most notably antibacterial, anti-inflammatory, antifungal, and antioxidant properties [21-23].

Some of the common medicinal uses of essential oils include in relieving pain in inflammation, boosting mood, fighting infections and boosting the immune system and promoting relaxation [24]. For example, the extracted eucalyptus oil from leaves was used to treat respiratory issues like cough and colds as this essential oil are rich in eucalyptol, 1,8-cineole, limonene, citronellal, and citral [25]. Besides, garlic essential oil contains a variety of organosulfur compounds, such as the most representative diallyl disulfides and diallyl trisulfides, which have attracted great interest in medicine, food, and agriculture [26]. Lavender essential oil has a sweet floral aroma and contains a high percentage of esters, mostly linalyl acetate. The oil is often used for its anti-inflammatory, calming, headache, relieving, sedative, and skin healing properties [27]. Peppermint essential oils are commonly used as a fragrance in soaps, cosmetics, and as spices since it possesses a fresh, minty and cooling effect due to menthol. Other chemical compounds are 1,8-cineole, methyl acetate, methofuran, isomenthone, limonene, β-pinene, α-pinene, germacrene, *trans*-sabinene hydrate and pulegone [28]. For medical use, peppermint oil can be taken orally as a dietary supplement for gastrointestinal complications [29]. Due to their numerous possible uses and advantages, *Lindera* essential oils are widely accessible in commerce and have gained popularity recently. This has shown that further investigation of this species is required in order to discover more about the information that affect the chemical components and composition of each species.

Table 1. Traditional uses of several *Lindera* species.

Species	Traditional uses
L. aggregata	Remedy for rheumatic, cardiac, and renal illnesses [4]
	Treat conditions affecting the digestive system, metabolism, inflammation, and urinary system [5]
L. akoensis	Used to treat stomach pain, fever, respiratory infections, headaches, migraines, and reducing inflammation or swelling [6]
L. angustifolia	Relieve the swelling caused by contusions, rheumatic pain, and stomachaches [7]
	Used to treat carminative diuretics and pain relievers especially in nervous headache and migraine [8]
L. erythrocarpa	Used to treat multiple cardioprotective and cancerous disorders [9]
	Treating digestive disorders, thirst, pain, and neuralgia [10]
	Used to treat diabetic properties and breast cancer [4]
L. fragrans	Acts as an effective barrier that prohibits mosquitoes, rheumatic numbness, and low back pain [11]
	Remedy for bad breath [12]
	Treat depressive-like behaviours that prolonged mild stress caused [13]
L. pulcherrima	Used as spice for the remedy of cold, fever, and cough [14]
L. radix	Used in pelvic inflammatory disease [15]
L. glauca	Treat several kinds of stomach and heart discomfort problems, rheumatoid arthritis, extravasation, and contusion [16]
L. neesiana	To treat indigestion, gastric disorders, constipation, and intestinal issues [17]
L. obtusiloba	Treatment for type II diabetes by lowering blood glucose levels as well as improved blood circulation, inflammation, fever, and abdominal pain [4]
L. umbellata	To treat neuralgia, stiff neck, and back pain [18]

A statistical method named multivariate analysis is used to analyze complex data sets that contain several variables or factors at once. Multivariate analysis has been widely employed in this sector to study the interactions between various chemical components because of the complexity and diversity of natural products [30]. Even though classical statistical analyses of massive amounts of heterogeneous data can yield valuable insights for the study of any particular variable, neither they nor the ability to group samples with uniform properties allow for a comprehensive understanding of the relationships between various variables. Multivariate statistical methods, such as hierarchical cluster analysis (HCA) and principal component analysis (PCA), which allow for the clustering of objects, identification of variability, and presentation of results in figures [31].

Principle component analyses (PCA) is well-known method where the multivariate exploratory data analyses tool that is used to determine the similarities and differences among samples, identify groups of

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samples and study correlations among the variables [32]. Besides, PCA are calculated to explore the relationship between the samples from various regions and their relation to a specific volatile compound, the GC-MS data was subjected to PCA. The PCAs can be plotted by visual inspection of the data to point out the hidden pattern in the dataset. PCA was used to reveal the interrelationships among the total species of the genus based on the essential oil that have common constituents of these species [33].

Hierarchical Cluster Analysis (HCA) is a method of statistical analysis used to identify relationships between variables. It involves grouping variables together based on their similarity, and then grouping those groups together based on their similarity [34]. The output of HCA is a dendrogram, which shows how the variables are grouped together. This can be useful in identifying patterns and relationships in large datasets. This method is now gaining acceptance as one of the approaches for quality control of herbal materials [35].

By doing a cluster analysis, it was possible to determine the variation of chemical components in each *Lindera* essential oil. It is an effective way to provide some evidence showing the relationship between the species in various regions and their chemical composition. The relationship between *Lindera* species and the chemical components of those oils were reported in this study by using PCA and HCA. Besides, the revealed patterns and interpretative schemes aid researchers in developing ideas about the possible activities of the phytocomplex's cluster of chemicals, as PCA and HCA are recognized as tools for quality control of herbal medicines [36].

EXPERIMENTAL

The selection of the article was conducted through searches using Scopus, PubMed, Scielo, Science-Direct, and Google Scholar. The keywords used were '*Lindera'* and 'essential oil'. Articles covering the period from the beginning of the database until June 2023 were all viewed. The protocol for performing the current study was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [37]. First, duplicate articles were excluded, titles and abstracts were then read, and the inclusion and exclusion criteria were applied. In this study, *Lindera* species reporting on the essential oils composition from the leaf part were selected. Lastly, all articles resulting from the previous stages were fully read, and the inclusion and exclusion criteria were applied again. At the end of the final step, the articles that fulfilled all criteria were selected for this study. Additionally, a manual search of the reference lists of the included studies were conducted. The inclusion criteria for the current study were original research articles in English. The exclusion criteria were articles without search terms in their title and abstract, review articles, articles without its full-text available, articles with- out one of the keywords, and articles without the composition of the essential oils. Overall, eleven *Lindera* species reporting on the essential oils composition from the leaf part were selected for multivariate statistical analysis. The details are presented in Table 2.

Statistical Software for Excel (XLSTAT) 2022's Pearson correlations were used for the analysis. The correlation matrix are shown graphically as a result of the PCA, which was completed first. Then, the process continued with HCA analysis, which aims to cluster the subjects with comparable characteristics. In this study, agglomerative hierarchical clusters (HCA) with unweight and pair-group average methods were used to do cluster analysis on *Lindera* species. As a result, *Lindera* species with comparable chemical components were clustered together into a cluster, which produced valuable indications for the prediction of chemical and bioactivity equivalent to the species [47].

Table 2. Previous studies on *Lindera* essential oils.

No.	Species [Lable]	Locality	Year	Components (No. %)	Yield (%)	References
1.	*L. chunii* [L. Chu]	China	2013	34 (96.2)	0.5	[38]
2.	*L. communis* [L. Com]	China	1999	23 (NM)	NM	[39]
3.	*L. erythrocarpa* [L. Ery]	Korea	2017	15 (63.7)	0.2	[10]
4.	*L. fragrans* [L. Fra]	China	2021	62 (76.4)	0.9	[11]
5.	*L. glauca* [L. Gla]	Vietnam	2022	34 (90.0)	0.2	[40]
6.	*L. nacusua* [L. Nac]	China	2016	22 (64.4)	0.1	[41]
7.	*L. obtusiloba* [L. Obt]	Korea	2011	27 (67.8)	4.3	[42]
8.	*L. pulcherrima* [L. Pul]	India	2009	35 (97.5)	1.2	[43]
9.	*L. pipericarpa* [L. Pip]	Malaysia	1993	22 (98.3)	1.0	[44]
10.	*L. strychnifolia* [L. Str]	China	2009	51 (94.5)	0.4	[45]
11.	*L. umbellata* [L. Umb]	Japan	2020	58 (91.4)	NM	[46]

NM: not mentioned

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Table 3. Major components identified in *Lindera* essential oils.

No	Components	Percentage (%)										
		L. Chu	***L. Com***	***L. Ery***	***L. Fra***	***L. Gla***	***L. Nac***	***L. Obt***	***L. Pip***	***L. Pul***	***L. Str***	***L. Umb***
	Monoterpene Hydrocarbons											
1	α-Pinene	-	-	4.5	-	-	-	-	-	-	-	-
2	β-Phellandrene	-	-	-	-	19.0	-	-	-	-	-	-
3	Myrcene	-	-	-	-	17.9	-	-	-	-	-	-
4	(*E*)-β-ocimene	-	-	-	-	9.1	-	-	-	-	-	-
5	Limonene	-	-	-	-	-	-	-	5.5	-	-	-
6	Dihydromyrcene	-	-	-	-	-	-	-	11.1	-	-	-
7	β-Myrcene	-	-	-	-	-	-	-	-	-	-	7.6
	Oxygenated Monoterpenes											
8	Methyl cinnamate	-	-	8.5	-	-	-	-	-	-	-	-
9	1,8-Cineole	-	-	-	-	-	-	-	-	-	5.3	13.7
10	Linalool	-	-	-	-	-	-	-	-	-	-	42.8
	Sesquiterpenes Hydrocarbons											
11	Germacrene B	6.2	-	-	-	-	-	7.5	-	-	-	-
12	γ-Muurolene	4.4	-	-	-	-	-	-	-	-	-	-
13	β-Caryophyllene	-	6.7	14.4	4.0	29.2	8.7	32.1	32.1	5.4	-	-
14	α-Humulene	-	-	8.4	-	18.0	-	-	-	-	-	-
15	Germacrene D	-	-	4.8	-	-	-	-	-	26.0	-	-
16	Aromadendrene	-	-	-	-	17.1	-	-	-	-	-	-
17	γ-Cadinene	-	-	-	-	10.1	-	-	-	-	-	-
18	(*E*)-β-caryophyllene	-	-	-	-	14.6	-	-	-	-	-	-
19	β-Selinene	-	-	-	-	-	5.0	-	-	-	4.6	-
20	δ-Cadinene	-	-	-	-	-	-	-	-	-	-	-
21	α-Copaene	-	-	-	-	-	-	31.4	31.4	-	-	-
	Oxygenated Sesquiterpenes											
22	Globulol	11.6	-	-	-	-	-	-	-	-	-	-
23	Ledol	10.2	-	-	6.8	-	-	-	-	-	-	-
24	Spathulenol	-	22.5	-	27.6	4.6	-	-	-	-	-	-
25	Nerolidol	-	-	26.9	-	-	-	6.8	6.1	-	-	-
26	Humulene epoxide II	-	-	-	-	5.3	-	-	-	-	-	-
27	β-Eudesmol	-	-	-	-	-	-	-	-	5.0	-	7.6
28	Hedycaryol	-	-	-	-	-	-	-	-	-	-	-
29	α-Eudesmol	-	-	-	-	-	-	-	4.3	-	-	-
30	Furanodienone	-	-	-	-	-	-	-	-	49.1	-	-
31	Curzerenone	-	-	-	-	-	-	-	-	17.6	-	-
32	Furanosesquiterpenoid	-	-	-	-	-	-	-	-	79.3	-	-
33	Sesquithuriferol	-	-	-	-	-	-	-	-	-	35.9	-
34	14-oxy-α-Muurolene	-	-	-	-	-	-	-	-	-	16.5	-
	Others											
35	Neophytadiene	-	-	-	-	-	4.5	-	-	-	-	-
36	*endo*-1,3,3-Trimethyl-2-norbornanol	-	10.0	-	-	-	-	-	-	-	-	-
37	Geranyl acetate	-	-	7.8	-	-	-	-	-	-	-	-
38	Hexahydrofarnesyl acetone	-	-	-	-	-	6.8	-	-	-	-	-
39	Palmitic acid	-	-	-	-	-	4.4	-	-	-	-	-
40	Bornyl acetate	-	-	-	-	-	-	-	-	-	-	-
	Percentage	**32.4**	**39.2**	**75.3**	**38.4**	**144.9**	**29.4**	**77.8**	**90.5**	**182.4**	**62.3**	**71.7**

L. Chu – L. chunii, L. Com – L. communis, L. Ery – L. erythrocarpa, L. Fra – L. fragrans, L. Gla – L. glauca, L. Nac – L. nacusua, L. Obt – L. obtusiloba, L. Pip – L. pipericarpa, L. Pul – L. pulcherrima, L. Str – L. strychnifolia, L. Umb – L. umbellata

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RESULTS AND DISCUSSION

In this study, eleven *Lindera* species from earlier research was analysed. The findings showed that most of *Lindera* species were reported mainly from China (5 studies), followed by Korea (2 studies), whereas Vietnam, Japan, India, and Malaysia each were reported in one study. The percentage yields of the essential oils ranged from 0.1 to 4.3%. The essential oil of *L. glauca* gave β-caryophyllene (29.25), α-humulene (18.0%), and aromadendrene (17.1%) as the major components [40]. In addition, *L. pipericarpa* and *L. pulcherrima* showed the highest percentage with 98.3% and 97.5%, respectively [43]. The major components identified in the essential oils are listed in Table 3. The essential oil of *L. pipericarpa* constituted about 60% of sesquiterpene hydrocarbons and identified dominantly with β-caryophyllene (32.1%) and α-copaene (31.4%) [44]. Besides, the essential oil of *L. pulcherrima* were made up predominantly of oxygenated sesquiterpenes, constituted of furanosesquiterpenoid and furanodienone with 79.3% and 49.1% of the total oil, respectively. Meanwhile, sesquithuriferol (35.9%) and 14-oxy-α-muurolene (16.5%) are shown as high concentration in *L. strychnifolia* essential oil [45]. Furthermore, other components which are *endo*-1,3,3-trimethyl-2-norbornanol and geranyl acetate, are also present as major components in *L. communis* and *L. erythrocarpa* oils, respectively [48]. Generally, the chemical variations discovered between the *Lindera* species might have possibly relied on the environment in which the plant existed and was collected in addition to seasonal variations at the time. These factors influence the plant's biosynthetic pathways and consequently, the relative proportion of the main characteristic components [49].

To evaluate whether the identified essential oils components could be useful in reflecting the taxonomic relationship among the different species and the components of all essential oil, PCA and HCA were used [50]. These statistical analyses have been used for the calculations to point out some considerations regarding their similarities between each of the *Lindera* species. Figure 1 shows the HCA analyses were separated into 4 clusters; Clusters I, II, III, and IV. In Cluster I there is only *L. obtusiloba* that include, while the results of PCA biplot analysis revealed that Cluster I could be distinguished by the presence of seven components, which are bornyl acetate, β-eudesmol, α-eudesmol, α-copaene, dihydromyrcene, hedycaryol and 2,2-bis(prop-2-enoxy-methyl)-butan-1-ol. Besides, *L. strychnifolia*, *L. umbellata*, and *L. pulcherrima* were in Cluster II that were characterised by the occurrence of eighteen components, which are germacrene B, globulol, γ-muurolene, hexahydro-farnesyl acetone, β-selinene, neophytadiene, palmitic acid, δ-cadinene, limonene, furanodienone, curzerenone, furanosesquiterpenoid, furanodiene, sesquithuriferol, 14-oxy-α-muurolene, 1,8-cineole, linalool and β-myrcene. Meanwhile, Clusters III have shown the highest number of *Lindera* species which are *L. erythrocarpa, L. pipericarpa, L. nacusua*, and *L. glauca*. The results of PCA biplot analysis revealed that Cluster III could be distinguished by the presence of seven components, which are germacrene D, α-humulene, (*E*)-β-ocimene, (*E*)-β-caryophyllene, humulene epoxide II, β-phellandrene, aromadendrene, γ-cadinene, myrcene, ledol, geranyl acetate and methyl cinnamate. In Cluster IV, it consists of *L. chunii*, *L. communis*, and *L. fragrans*. Based on PCA analyses results, the occurrence components were β-caryophyllene, *endo*-1,3,3-trimethyl-2-norbornanol, nerolidol, α-pinene, β-farnesene, and spathulenol.

The PCA results are shown in Figure 2. Five factors of accumulated variation (23.36-75.59%) of the data have been generated with a corresponding eigenvalue and percentage of variance (Table 3). The five principle components were considered to have the most important as it represents 23.36 of the accumulated variation with an eigenvalue of 10.05. Eigenvalue number was used to choose the number of principal components needed to be retained [51]. The components that contribute significantly to factor 1 are hedycaryol, bornyl acetate, α-copaene, β-farnesene, dihydromyrcene, α-eudesmol, and 2,2-bis(prop-2-enoxy-methyl)butan-1-ol with a eigenvalue and significance level of 10.05% and 23.36% respectively. β-phellandrene, myrcene, aromadendrene, γ-cadinene, (*E*)-β-ocimene, (*E*)-β-caryophyllene and humulene epoxide II were contributed to the factor 2, which explained 18.43% of the variance with an eigenvalue of 7.93. The third and fifth principal components explained 13.99% and 9.48% of the variance, respectively, while for the fourth principal component there were no related components significantly.

To evaluate the accuracy of this classification, the cluster obtained was further confirmed by PCA (Figure 2). Similarly, the species of *Lindera* were divided into 4 defined groups: Group I consisted of *L. obtusiloba* (L. Obt). Group II consisted of *L. strychnifolia* (L. Str), *L. umbellata* (L. Umb), and *L. pulcherrima* (L. Pul). Group III consisted of *L. erythrocarpa* (L. Ery), *L. pipericarpa* (L. Pip), *L. nacusua* (L. Nac) and *L. glauca* (L. Gla). Group IV consisted of *L. chunii* (L. Chu), *L. communis* (L. Com), and *L. fragrans* (L. Fra).

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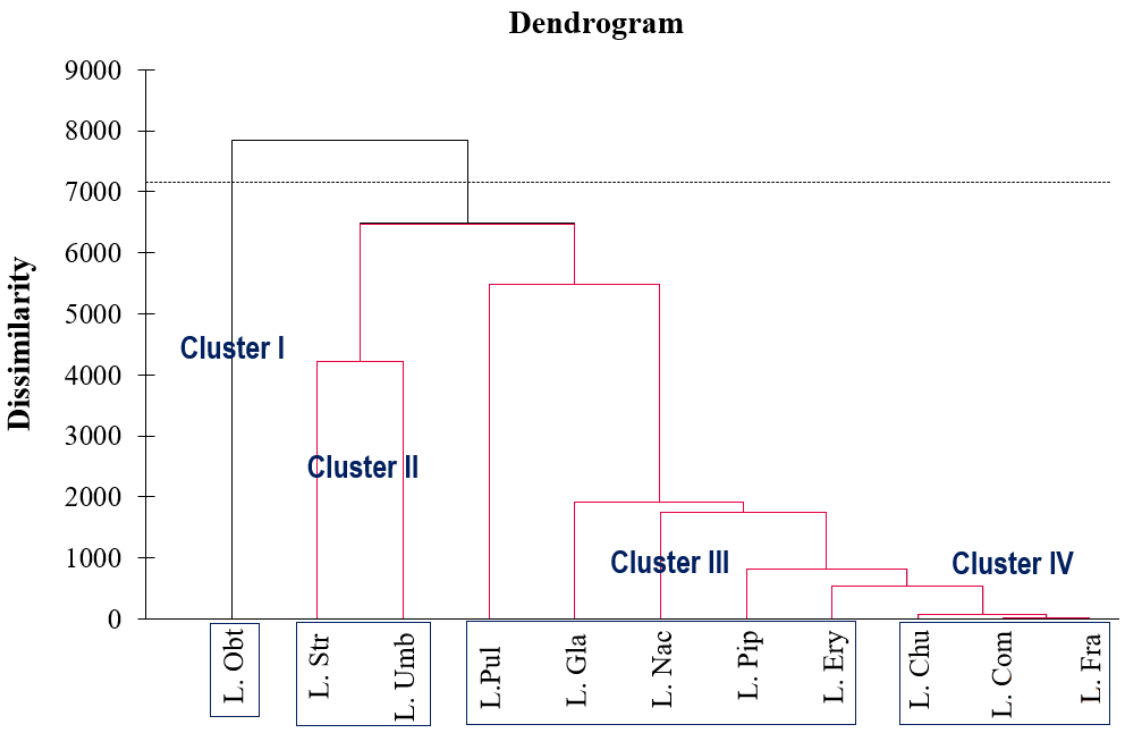


Figure 1. HCA analyses of *Lindera* essential oils.

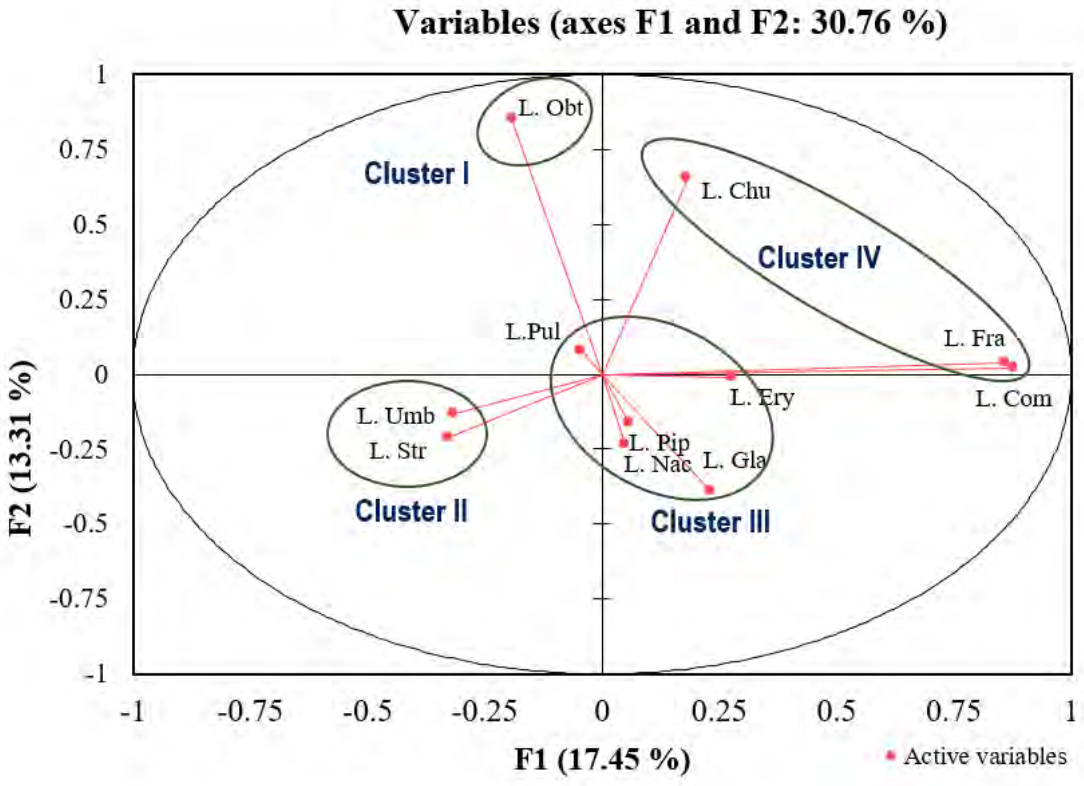


Figure 2. PCA analyses of *Lindera* essential oils.

Table 4. Eigenvalues and cumulative variance of factors obtained from principal component analysis (PCA) based on the chemical composition of essential oils of *Lindera* species.

Composition	Factors				
	1	2	3	4	5
Germacrene B	0.64	0.19	-0.16	-0.18	0.56
Globulol	-0.02	-0.17	-0.11	-0.33	0.71**
Ledol	-0.09	-0.17	-0.07	-0.38	0.70**
γ-Muurolene	-0.02	-0.17	-0.11	-0.33	0.71**
Spathulenol	-0.48	0.44	-0.07	-0.09	0.21
endo-1,3,3-Trimethyl-2-norbornanol	-0.10	-0.05	0.03	-0.15	0.09
β-Caryophyllene	0.05	0.49	0.57	-0.25	-0.26
Nerolidol	0.60	0.29	0.16	-0.33	-0.39
α-Humulene	-0.40	0.63	0.13	-0.17	-0.43
Germacrene D	-0.01	-0.08	0.83**	0.09	-0.35
α-Pinene	0.66	0.35	0.16	-0.26	-0.43
Methyl cinnamate	0.01	0.05	0.32	-0.43	-0.60
Geranyl acetate	0.01	0.05	0.32	-0.43	-0.60
β-Phellandrene	-0.54	0.79**	-0.14	0.20	0.02
Myrcene	-0.54	0.79**	-0.14	0.20	0.02
Aromadendrene	-0.54	0.79**	-0.14	0.20	0.02
γ-Cadinene	-0.54	0.79**	-0.14	0.20	0.02
(*E*)-β-ocimene	-0.54	0.79**	-0.14	0.20	0.02
(*E*)-β-Caryophyllene	-0.54	0.79**	-0.14	0.20	0.02
Humulene epoxide II	-0.54	0.79**	-0.14	0.20	0.02
Hexahydrofarnesyl acetone	-0.10	-0.22	-0.05	-0.30	-0.26
β-Selinene	-0.10	-0.42	-0.41	0.14	-0.41
Neophytadiene	-0.10	-0.22	-0.05	-0.30	-0.26
Palmitic acid	-0.10	-0.22	-0.05	-0.3	-0.27
δ-Cadinene	0.63	0.05	-0.45	0.41	-0.19
Limonene	0.645	0.14	-0.30	0.24	0.02
β-Eudesmol	0.65	0.2	0.51	0.47	0.13
Hedycaryol	0.88**	0.42	-0.12	0.08	0.03
Bornyl acetate	0.88**	0.42	-0.12	0.08	0.03
α-Copaene	0.69**	0.30	-0.05	-0.06	-0.03
β-Farnesene	0.88**	0.42	-0.12	0.08	0.03
Dihydromyrcene	0.88**	0.42	-0.12	0.08	0.03
α-Eudesmol	0.88**	0.42	-0.12	0.08	0.03
2,2-Bis(prop-2-enoxy-methyl)butan-1-ol	0.88**	0.42	-0.12	0.08	0.03
Furanodienone	-0.01	-0.16	0.79**	0.55	0.14
Curzerenone	-0.01	-0.16	0.79**	0.55	0.14
Furanosesquiterpenoid	-0.01	-0.16	0.79**	0.55	0.14
Furanodiene	-0.01	-0.16	0.79**	0.55	0.14
Sesquithuriferol	-0.03	-0.34	-0.49	0.48	-0.29
14-oxy-α-Muurolene	-0.03	-0.34	-0.49	0.48	-0.29
1,8-Cineole	-0.04	-0.44	-0.58	0.54	-0.23
Linalool	-0.02	-0.24	-0.29	0.24	-0.01
β-Myrcene	-0.04	-0.44	-0.58	0.54	-0.23
Eigenvalue	**10.05**	**7.93**	**6.02**	**4.44**	**4.08**
% of variance	**23.36**	**18.43**	**13.99**	**10.31**	**9.48**
Cumulative (%)	**23.36**	**41.80**	**55.80**	**66.10**	**75.59**

Note: **significant ≥70

The scatter plot showed the phytochemical distance among the samples in the plot that reflects their relationships. These strict correlations were also evidenced in biplots, where these species resulted very closed or overlapped, especially for *L. communis* (L. Com), *L. fragrans* (L. Fra) and *L. erythrocarpa* (L. Ery) because of the positive loadings in Group IV and the smallest negative value in group III, that due to the highest content of spathulenol (27.6-22.5%). Besides, the PCA revealed a weaker interrelationship in the composition of essential oils in Groups I and III. This might be a result of the high production in *L. obtusiloba* (L. Obt) which is α-copaene (31.4%) and dihydromyrcene (11.1%) while, in *L. glauca* (L. Gla)

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is β-phellandrene and aromadendrene with the percentage 19.0% and 17.1% respectively. These findings might be related to other elements that influence the genetic composition and places of origin of *Lindera* plants, which range from subtropical climates to temperate zones [16]. As a result, the pattern of variation in essential oil content may be a reflection of pressure in different ecological and geographic contexts (ecotypes). Although there is a notable variation in oil composition that needs to be minimized with further genetic research, the significant correlation between the multivariate analysis and essential oil constituents allows the identification of chemical similarities among *Lindera* species to evaluate their potential use as industrial products.

CONCLUSION

In conclusion, the data of this study indicates that there were significant differences in the chemical components of *Lindera* essential oils, which were collected from different regions. Besides, multivariate statistical analyses seem to be very useful to investigate and establish the natural correlation within complex taxonomic groups. The most useful technique seems to be is HCA and PCA because of its graphical presentation that permits a much more clear indication of the proximity between the different species. The PCA and HCA results analyses revealed that the selected oils were classified into four different clusters based on their similarities. However, additional research may be needed to identify the factors including genetics, environment, development stages, and biotic interactions that affect the production of secondary metabolites in plants. These data may be useful information when choosing species with economic potential for the pharmaceutical industry.

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Chemical composition of essential oil from *Lindera subumbelliflora* Kosterm and its effect on the susceptibility and biofilm activities of *Candida albicans* and *Streptococcus mutans*

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Chemical composition of essential oil from *Lindera subumbelliflora* Kosterm and its effect on the susceptibility and biofilm activities of *Candida albicans* and *Streptococcus mutans*

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ABSTRACT

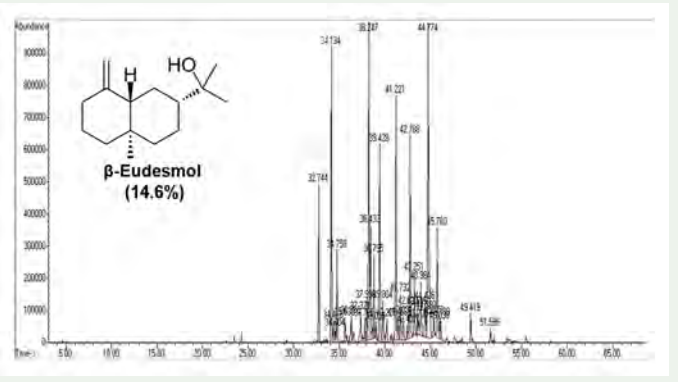
The chemical composition of the essential oil of *Lindera subumbelliflora* (Lauraceae) was investigated for the first time. The essential oil was obtained by hydrodistillation and fully characterised by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). The antifungal activity of *L. subumbelliflora* essential oil was tested against *Candida albicans* and *Streptococcus mutans* using the broth microdilution assay, whereas the microbial biofilms were determined using a semi-quantitative static biofilm. A total of 28 components (99.6%) were successfully identified, which were characterised by β-eudesmol (14.6%), *cis*-α-bergamotene (11.0%), α-copaene (8.5%), dodecen-1-ol (8.5%), and (*E*)-nerolidol (8.3%). The essential oil exhibited activity against *Candida albicans* and *Streptococcus mutans* with MIC values of 250 and 500 µg/mL, respectively. The essential oil increased the biofilm of *Candida albicans* by 38.25%, however, decreased the biofilm of *Streptococcus mutans* by 47.89% when treated with 500 µg/mL. Thus, the essential oil has a promising application in dentistry *via* inhibition of the growth of *Candida albicans* and *Streptococcus mutans*. However, the antibiofilm activity of the essential oil is only applicable for cariogenic *Streptococcus mutans*.

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1. Introduction

The genus *Lindera* is a member of the Lauraceae family, which consists of approximately 100 species that are widely distributed in tropical and subtropical areas throughout the world. *Lindera* are evergreen or deciduous trees or shrubs (Cao et al. 2016). Most *Lindera* plants, particularly *L. aggregata,* are a well-known traditional Chinese medicine that has important medicinal value and health benefits. The roots, stems, and leaves of *L. aggregata* are included in 'Chinese Pharmacopoeia'. Besides, *L. aggregata* extract is usually indicated for treating urinary system diseases such as enuresis and urinary stones and has pronounced effects on chronic gastritis and rheumatoid arthritis (Zhang and Wang 2000; Xing et al. 2017). Meanwhile, *L. communis* and *L. glauca* are rich sources of fatty acids. *Lindera* plants are also suitable for manufacturing soaps and lubricants and are used for extracting lauric acid. In addition, several *Lindera* plants are rich in essential oils and are used for producing spices, fragrances, and building timber (Flora of China Editorial Committee 2010; Sakurai et al. 2021).

A review of the literature showed that several species of the genus *Lindera* have been investigated for their chemical compounds and biological activities. Previous phytochemical investigations on *Lindera* species led to the isolation of sesquiterpenoids (dimeric and trimeric), alkaloids, flavonoids, butanolides, lucidones, and phenylpropanoids (Cao et al. 2016). Despite the fact that *Lindera* plants have a wide range of pharmacological and biological qualities, numerous research have focussed on its analgesic, anti-inflammatory, anticancer, and antihypertensive effects. Meanwhile, butanolides and lucidones have shown great potential in developing anticancer agents, while aporphine alkaloids have shown great potential in developing antiarthritic and antinociceptive agents (Lv et al. 2022). *Lindera subumbelliflora* Kosterm (syn. *Litsea subumbelliflora* (Blume) Ng) is a shrub or small tree up to 5 m high. It is distributed in hill forests up to 900 m asl and found mainly in Malaysia (Burkill 1966).

Essential oils are a class of natural products with pharmacological properties, which include antimicrobial, antiseptic, anti-inflammatory, and antioxidant activities. These products are described as a mixture of volatile constituents produced as secondary metabolites by aromatic plants (Salleh et al. 2022, 2021a, 2021b, Anuar et al. 2021).

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Previously, the essential oils of *Allium tubeorosum*, *Cinnamomum cassia*, *Cinnamomum zeylanicum*, and *Coriandrum sativum* are potentially effective to treat oral candidiasis. Oral candidiasis is an opportunistic infection that affects the oral cavity and could worsen the severity of an underlying disease. A literature survey revealed that no report on the essential oil of this species towards oral pathogens *Candida albicans* and *Streptococcus mutans* was involved in oral candidiasis and dental caries, respectively (Arzmi et al. 2016). Therefore, this study reports the essential oil composition and its effect on the susceptibility and biofilm activities of *Candida albicans* and *Streptococcus mutans* from the leaf oil of *L. subumbelliflora*.

2. Results and discussion

The list of chemical components identified in the essential oil is shown in Table S1. The GC-FID and GC-MS analysis of the essential oil revealed the presence of twenty-eight components with the constitution of 99.6%. Sesquiterpene hydrocarbons were the most dominant components in the essential oil, which accounted for 58.5%, followed by oxygenated sesquiterpenes indicating 31.9%. The most abundant components of the essential oil were β-eudesmol (14.6%), *cis*-α-bergamotene (11.0%), α-copaene (8.5%), dodecen-1-ol (8.5%), (*E*)-nerolidol (8.3%), rosifoliol (6.8%), and δ-cadinene (6.2%). The other minor components detected in the essential oil in more than 2% were (*E*,*E*)-α-farnesene (2.3%), γ-cadinene (2.3%), α-humulene (2.7%), selina-3,7(11)-diene (4.2%), γ-eudesmol (4.2%), and α-muurolene (4.9%). Similar to our results, β-eudesmol, α-copaene, (*E*)-nerolidol, and δ-cadinene (6.2%) have been reported lavishly in other *Lindera* species. β-Eudesmol has been reported from *L. obtusiloba* (leaf oil, 10.0%; root oil, 4.0%) (Hwang et al. 2013; Yang et al. 2022) and *L. pulcherrima* (leaf oil, 4.1%) (Joshi et al. 2010). Besides, α-copaene from *L. glauca* (fruit oil, 13.1%) (Sun et al. 2023), *L. obtusiloba* (leaf oil, 31.4%) (Chung and Moon 2011), and *L. pipericarpa* (leaf oil, 31.4%) (Ali and Jantan 1993). (*E*)-Nerolidol from *L. erythrocarpa* (leaf oil, 18.7%) (Ko et al. 2017), *L. obtusiloba* (leaf oil, 6.8%) (Chung and Moon 2011), and *L. pipericarpa* (leaf oil, 6.1%) (Ali and Jantan 1993). Meanwhile, δ-cadinene from *L. chunii* (flower oil, 9.5%) (Liu et al. 2013), *L. glauca* (fruit oil, 6.2%) (Sun et al. 2023), *L. obtusiloba* (leaf oil, 13.8%) (Yang et al. 2022), and *L. strychnifolia* (leaf oil, 13.8%) (Yan et al. 2009).

Generally, the chemical variations discovered between the *Lindera* species might have possibly relied on the environment in which the plant existed and was collected in addition to seasonal variations at the time. These factors influence the plant's biosynthetic pathways and consequently, the relative proportion of the main characteristic components (Salleh et al. 2016). β-Eudesmol is one of the most studied and major bioactive sesquiterpenes, mainly extracted from *Atractylodes lancea* rhizomes. It has potential antitumor and antiangiogenic activities and is an inhibitor of tumour growth by inhibiting angiogenesis by suppressing CREB activation of the growth factor signalling pathway. It also stimulates neurite outgrowth in rat pheochromocytoma cells with activation of mitogen-activated protein kinases. It may be a promising lead compound for enhancing neural function, and it may

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help to explain the underlying mechanisms of neural differentiation (Acharya et al. 2021).

The results from the microdilution method showed that *Candida albicans* and *Streptococcus mutans* were susceptible to the essential oil with the minimal inhibitory concentration (MIC) value of 250 and 500 µg/mL, respectively. This finding is supported by the previous study that reported the antimicrobial activity of *Lindera* sp. essential oil towards *Candida albicans* (Huong et al. 2023). In addition, the essential oil increased the biofilm of *Candida albicans* by 38.25 ± 0.26%; however, it decreased the biofilm of *Streptococcus mutans* by 47.89 ± 0.07% when treated with 500 µg/mL. In addition, treatment with 250 µg/mL essential oil showed an increased *Candida albicans* biofilm by 81.07 ± 1.46%, however, decreased *Streptococcus mutans* biofilm by 11.32 ± 0.38%. Furthermore, treatment of *Candida albicans* with 500 µg/mL had significantly lower biofilm compared to 250 µg/mL ($p < 0.05$). This finding suggested a higher concentration than 500 µg/mL, the essential oil may have the potential to inhibit the biofilm of *Candida albicans*.

Nevertheless, the effectiveness of essential oils requires a detailed exploration of their mechanism of action towards microbial infections. Perestrelo et al. (2019) reported that the structure and functional groups present in the molecule and its electronegativity play an important role in the activity of compounds against target microorganisms. Thus, the relationship between the activity of compounds and their chemical structures and functional groups, as well as the effect of hydrophobicity and the composition of the lipid membrane, can be considered important factors from the point of view of the selection and application of compounds. Besides, a toxicity study is also required to ensure the safety of the essential oils. Meanwhile, an *in vivo* study is needed to determine the efficacy of the essential oils for oral candidiasis and dental caries prevention in the real environment.

3. Experimental

See Supplementary Material.

4. Conclusion

For the first time, the chemical composition of the essential oil isolated from fresh leaves of *L. subumbelliflora* growing in Malaysia was studied. The essential oil consisted mainly of β-eudesmol (14.6%), *cis*-α-bergamotene (11.0%), α-copaene (8.5%), dodecen-1-ol (8.5%), (*E*)-nerolidol (8.3%), rosifoliol (6.8%), and δ-cadinene (6.2%). These results shed light on the phytochemistry of this unexplored species of the flora of Malaysia. The results also showed that the essential oil inhibited the growth of *Candida albicans* and *Streptococcus mutans* selected strains. In addition, the antibiofilm activity of the essential oil was observed against cariogenic *Streptococcus mutans;* thus, the essential oil may have potential in dental application for caries prevention. Nevertheless, further study is still needed by increasing the cariogenic strains and including *in vivo* studies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Chemical composition of essential oil from *Lindera caesia* Reinw. ex Fern.-Vill. and its antifungal, antibiofilm, and molecular docking studies

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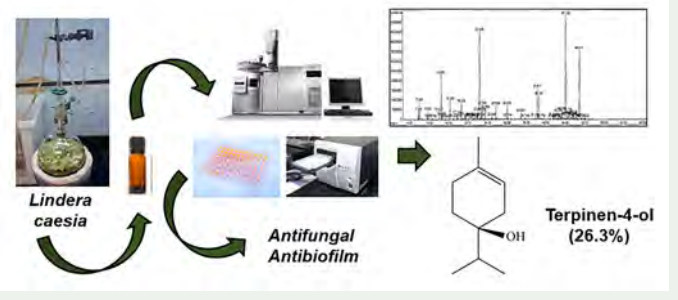
Chemical composition of essential oil from *Lindera caesia* Reinw. ex Fern.-Vill. and its antifungal, antibiofilm, and molecular docking studies

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ABSTRACT

The chemical composition, antifungal, antibiofilm, and molecular docking studies of the essential oil obtained from *Lindera caesia* were investigated. A total of thirty-nine components (96.7%) were identified using gas chromatography (GC-FID) and gas chromatography-mass spectrometry (GC-MS). The major components included terpinen-4-ol (26.3%), *neo*-intermedeol (23.2%), eudesma-4,11-dien-3-one (10.4%), and *o*-cymene (5.3%). The antifungal activity was tested against *Candida albicans* and *Streptococcus mutans* using the broth microdilution assay, whereas the microbial biofilms were determined using a semi-quantitative static biofilm. The essential oil exhibited activity against *C. albicans* (MIC 125 µg/mL) and *S. mutans* (MIC 250 µg/mL), and increased the biofilm of *C. albicans* by 31.25% when treated with 500 µg/mL. The molecular docking study shows *neo*-intermedeol, eudesma-4,11-dien-3-one, α-selinene, and β-selinene as the good candidate to target Erg11 with a binding energy of −7.3 kcal/mol. These findings demonstrated that the essential oil may have potential in dental application for caries prevention.



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1. Introduction

Lindera is one of the genus in Lauraceae family. It consists of over 100 species which can be found all over the world in tropical, subtropical climates, and temperate zones of Asia and Midwestern America. In Malaysia, it is contributing about 213 species from 16 genera (Cao et al. 2016). *Lindera* species are great for ornamental and economical use, as well as for their medicinal and therapeutic benefits to treat a wide range of conditions. In Chinese traditional medicine, the leaves of *L. aggregata* are used to treat stomach-ache, urinary system diseases, and rheumatic pain (Lai et al. 2021). The aerial parts of *L. akoensis* have been used in Taiwanese folk therapy for inflammation (Yang et al. 2019). The flower of *L. pulcherrima* is used to treat intestinal worms and cure sores (Joshi and Mathela 2012).

Essential oils have been utilised for thousands of years for their therapeutic and medical effects. It involves complex mixtures of natural compounds with versatile organic structures representing useful medicinal properties. Essential oils are important natural sources and are used as raw materials for the production of fragrance compounds in cosmetics and as flavouring additives for food and beverages (Salleh et al. 2012, 2016, 2021; Salleh and Ahmad 2016; Azhar et al. 2020; Shakri et al. 2020). Analysis of volatile components from several species of *Lindera* has revealed mostly the presence of monoterpenoids and sesquiterpenoids and displayed various biological activities including anti-allergic, anti-arthritic, antivirus, antibacterial, anticancer, anti-inflammatory, antitumor, and cytotoxicity. The essential oils from *Lindera* species have been broadly studied and investigated, with the most reported species are *L. aggregata*, *L. obtusiloba*, and *L. glauca* (Lv et al. 2022; Huong et al. 2023).

Although many members of the family Lauraceae are renowned for their valuable essential oils, the genus *Lindera* is still poorly explored as far as its essential oil composition is concerned. Therefore, it is interesting to report the essential oil composition of *Lindera caesia* Reinw. ex Fern.-Vill. The native range of this species is West and Central Malaysia. It is a tree and grows primarily in the wet tropical biome. This is the first study of its kind to investigate the chemical composition, antifungal, antibiofilm, and molecular docking studies of *L. caesia* essential oil.

2. Results and discussion

The identified components of the essential oil are listed in Table S1, according to their Kovats index on an HP-5 column. The GC-FID and GC-MS (Figure S1) analysis of the essential oil revealed the presence of 39 chemical components constituting about 96.7%. Oxygenated monoterpenes were the most dominant components found in the essential oil, accounting 39.8% of the total composition. In addition, oxygenated sesquiterpenes were also presented, accounting for 35.9% of the total composition. The most abundant components were terpinen-4-ol (26.3%), *neo*-intermedeol (23.2%), eudesma-4,11-dien-3-one (10.4%), and o-cymene (5.3%). Nevertheless, the abundant levels of terpinen-4-ol in the essential oil of *L. caesia* identified in this study represent the first chemical compositional report for this genus. Likewise, terpinen-4-ol has been identified as the major and common component present in some species of

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the Lauraceae family such as *Cinnamomum illicioides* (bark oil, 10.4%) (Giang et al. 2006), *C. glanduliferum* (bark oil, 7.5%) (Taha and Eldahshan 2017), *C. longepaniculatum* (leaf oil, 8.6%) (Zhang et al. 2022), *Neolitsea variabillima* (leaf oil, 9.3%) (Su et al. 2013), and *Licaria rigida* (bark oil, 10.7%) (da Silva et al. 2013).

The essential oil was also subjected to a preliminary test to verify the biological activity, including antifungal and antibiofilm activities. The results from the microdilution method showed that *C. albicans* and *S. mutans* were susceptible to the essential oil with the MIC value of 125 and 250 µg/mL, respectively. Furthermore, the essential oil increased the biofilm of *C. albicans* by 31.25 ± 0.15%; however, it decreased the biofilm of *S. mutans* by 51.42 ± 0.12% when treated with 500 µg/mL. In addition, treatment with 250 µg/mL essential oil showed an increased *C. albicans* biofilm by 78.25 ± 1.22%, however, decreased *S. mutans* biofilm by 15.85 ± 0.54%. Furthermore, treatment of *C. albicans* with 500 µg/mL had significantly lower biofilm compared to 250 µg/mL ($p < 0.05$). This finding suggested a higher concentration than 500 µg/mL, the essential oil may have the potential to inhibit the biofilm of *C. albicans*. As such, the high quantity of terpinen-4-ol obtained in the essential oil may contribute, at least in part, to the activity ascribed to the plant. In previous reports, terpinen-4-ol has strong antibacterial activity against *S. aureus*, acting in a bactericidal manner. Terpinen-4-ol has a remarkable antibiofilm activity and is able to inhibit biofilm formation even at subinhibitory concentrations. It also has characteristics that suggest it is a good candidate as a drug to treat infections by *S. aureus*, whether isolated or associated with other drugs; it is also able to interfere with *S. aureus*-associated biofilms (Almeida et al. 2020; Cordeiro et al. 2020; Rodrigues et al. 2022).

In this study, a molecular docking study was performed for six major components to assess their interactions with the Erg11 receptor. For the potentially inhibition of Erg11 activity, leading to toxic sterol accumulation and cell death, offering a promising strategy against fungal infections (Lim et al. 2023). The docking score ranges between −5.6 to −7.3 kcal/mol, with *neo*-intermedeol, eudesma-4,11-dien-3-one, β-selinene and α-selinene having the highest (-7.3 kcal/mol), while fluconazole (control) have a score of −7.2 kcal/mol (Figure S2). The docking result is illustrated in Figure S3 demonstrating the interaction of the major components. Based on the binding analysis, all ligand formed an alkyl bond with Ile139 and Lys151 within the range of 4.01 Å − 5.46 and 4.20 Å − 4.32 Å respectively. In addition, for *neo*-intermedeol it also form two unfavourable donor-donor between methyl group of Lys151 and carboxyl group of this ligand at the distance 4.33 and 2.15 Å respectively. This bond occurs when two hydrogen bond donors are in close proximity and cannot form stable hydrogen bonds with the acceptor molecule (Chen et al. 2016). Besides, the hydroxyl group forms a single bond with the imidazole side chain of His468 at a distance of 2.45 Å, while the carboxyl group forms a conventional hydrogen bond with Arg469 at 2.99 Å. In eudesma-4,11-dien-3-one binding analysis, four an alkyl bonds are formed with Ile139 (4.63 Å), Leu307 (4.76 Å), Leu147 (4.99) and Lys151 (4.26 Å). Figure 1 depict the binding conformation of neo-intermedeol and eudesma-4,11-dien-3-one superimposed into the Erg11-fluconazole complex. For carboxyl group of α-selinene and β-selinene, it formed an alkyl interaction with Leu307 at 4.75 and 4.70 Å (Figure S3). Besides, π-alkyl interactions were also formed with His140 at 5.02 and 4.55 Å appropriately. All components formed a Van der Waals interaction with the binding site residue within a

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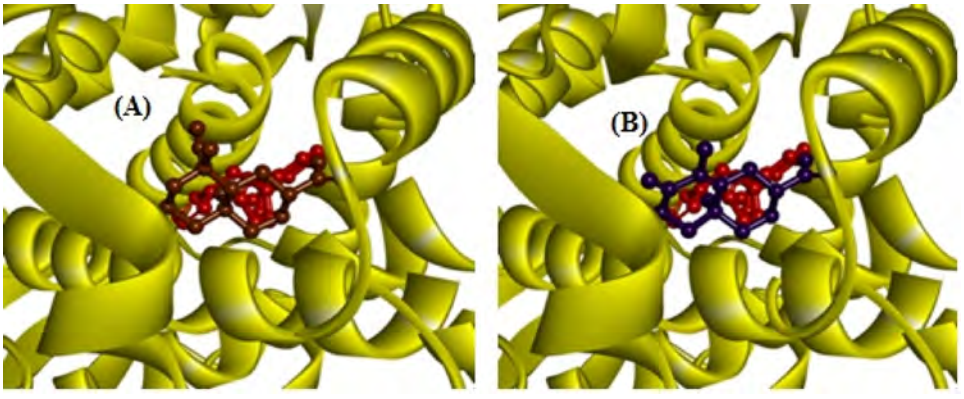


Figure 1. 3D conformation view of neo-intermedeol (**A**) eudesma-4,11-dien-3-one (**B**) superimposed into Erg11-fluconazole complex.

reasonable distance. Our results reveal that despite its high abundance, terpinen-4-ol exhibited a lower docking score of −5.3 kcal/mol compared to the others. The antibiofilm results demonstrated a moderate range of activity, spanning from 15 to 78%. These findings suggest that the inhibitory effect of terpinen-4-ol may not align with its abundance, emphasising the complex nature of the essential oil's antimicrobial properties. In our study, *neo*-intermedeol, eudesma-4,11-dien-3-one, β-selinene, and α-selinene gave the highest binding score, suggesting they can be good inhibitors of Erg11 (Ahmad et al. 2015).

3. Experimental

See Supplementary material.

4. Conclusion

This is the first report on the essential oil composition and biological activities of *L. caesia* grown in Malaysia. A study on the essential oil of *L. caesia* revealed the existence of terpinen-4-ol as a major component. The results also showed that the essential oil inhibited the growth of *C. albicans* and *S. mutans*. In addition, the antibiofilm activity of the essential oil was observed against cariogenic *S. mutans*, while in molecular docking it revealed that neo-intermedeol and eudesma-4,11-dien-3-one have better docking energy than fluconazole (control). Thus, this finding can successfully determine this essential oil may have potential in dental application for caries prevention. Nevertheless, further study is still needed by increasing the cariogenic strains and including *in vivo* studies.

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Disclosure statement

The authors declare that there are no conflicts of interest.

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Review Article

A Review on Chemical Constituents and Pharmacological Action of the Genus *Lindera* (Lauraceae)

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ABSTRACT

The genus *Lindera* consists of approximately 100 species that are widely distributed in tropical and subtropical areas throughout the world. It is represented by widely well-known medicinal and aromatic plants that produce various phytochemicals with potential pharmacological actions. This review attempts to summarize the information on the phytochemicals of *Lindera* species together with their biological properties. The data and information were collected via an electronic search engine which are Scopus, ScienceDirect, Google Scholar, PubMed, and SciFinder. Sesquiterpenes represent the major chemical compounds that have been characterised in *Lindera* species, as well as alkaloids, flavonoids, and phenolics. These compounds were shown to possess anticancer, antifibrotic, anti-inflammatory, antitumor, antioxidant, anti-arthritic, cytotoxic, antiallergic, and antihyperlipidemic properties. The outcome of these studies will further support the therapeutic potential of the genus *Lindera* and provide convincing evidence for its future clinical applications in modern medicine.

Keywords: *Lindera*, Lauraceae, sesquiterpenes, phytochemicals, pharmacology

1. INTRODUCTION

Natural products are chemical substances produced by living organisms, predominantly plants. Medicinal plants have historically been utilized to treat various ailments and are considered potential sources for pharmaceuticals. Initially, the ancient medical is based on empirical observations of herbs and natural remedies, and now natural products have undergone millions of years of evolution and chemical diversification, which has led to a variety of biological activities and drug-like qualities (Maria & Christoph, 2020). According to earlier research, the presence of specific phytochemicals has proven to be an effective treatment for a better quality of life. For instance, *Centella asiatica* leaf contains active ingredients, kaempferol and quercetin that can treat skin damage and improve blood circulation (Gray et al., 2018). In addition, *Marinda citrifolia* has the active compounds,

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scopoletin and rutin, which can act as antioxidant, anticancer, and anti-inflammatory agents (Jamaludin et al., 2021).

Lauraceae family, considered one of the most ancient plant families within the Magnoliidae subclass, predominantly across Southeast Asia, Madagascar, northern South America, and the east coast of Brazil. In Malaysia, it is known as 'medang' that contributes around 213 species from 16 genera, while China hosts 25 genera and 445 species. Identified by specific floral morphology including smooth bark with aromatic sap, plain leaves arranged oppositely, spirally, or alternately, and small, fragrant, trimerous flowers, often with six sepals. Many of its species are utilized for spices, perfume oils, and medicines in traditional practices, such as *Laurus nobilis* for digestive disorders (Alejo Armijo et al., 2017), *Cinnamomum verum* for respiratory and digestive issues (Ranasinghe et al., 2013), and *Persea americana* for topical treatment of skin conditions (Nayak et al., 2008).

The genus *Lindera*, comprising approximately 80-100 species within the Lauraceae family, is distributed worldwide across the tropical, subtropical, and temperate regions of Asia and Midwestern America. *Lindera* species such as *L. aggregate*, *L. akoensis*, and *L. chunii merr* are prevalent in countries like China, Korea, Japan, India, the United States, Nepal, Vietnam, and Malaysia. Known for their aromatic leaves and bark, *Lindera* trees are utilized in traditional medicine, culinary practices, and aromatherapy. Dioecious in nature, *Lindera* species produce small, inconspicuous flowers with six tepals and tiny drupe fruits (Nakamura et al., 2021). With medicinal applications ranging from treating gastrointestinal disorders to respiratory infections, *Lindera* species like *L. radix* and *L. aggregata* hold cultural significance in traditional Chinese medicine for their ability to alleviate discomfort and promote wellness by improving qi circulation and relieving congestion (Cao et al., 2015).

However, further research is necessary to fully explore the medicinal potential of ethnobotanical plants, particularly those within the *Lindera* species, for the development of future herbal medicines and pharmaceuticals.

2. CHEMICAL CONSTITUENTS OF THE GENUS *Lindera*

2.1. Sesquiterpenes

Sesquiterpenes (Figure 1) are found particularly in higher plants and in many other living systems. Numerous plants, including fruits, vegetables, herbs, and spices, contain sesquiterpenes. They are frequently found in plants such as chamomile, ginger, and turmeric (Dhifi et al., 2016). Besides, sesquiterpenes are commonly found in fungi and some marine organisms, and known for their diverse range of biological activities and therapeutic properties. Naturally, they occur as hydrocarbons or in oxygenated forms including lactones, alcohols, acids, aldehydes, and ketones (Lv et al., 2023). According to Scopus, there are about 874 documents that relate to *Lindera* sesquiterpenes since 1964. To date, a total of 362 sesquiterpenes have been reported, mostly isolated from the roots, leaves, flowers, and a few obtained from whole plants. Among them, germacrane-, eudesmane- and lindenane-type sesquiterpenoids account for a fairly large proportion (Feng et al., 2022). Table 1 shows several sesquiterpenes that have been isolated andidentified from various *Lindera* species. Most of the compounds are reported mainly from *L. aggregata*, *L. strychnifolia*, and *L. glauca*. Furthermore, there that were 165 compounds were classify as bisobolane, elemane, eudesme, gemacrane, guaiane, as well as 46 compounds from lindenane and sesquiterpenes dimers.

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Table 1. Sesquiterpenes isolated from several *Lindera* species

Compounds	Species	Part	References
BISOBOLANE			
3-(Hydroxymethyl)-6-(5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)-4-oxocyclohex-2-en-1-yl acetate **(1)**	*L. blume*	Leaves	Ryen et al., 2020
6-(2-Hydroxy-6-methylhept-5-en-2-yl)-3-(hydroxymethyl)-4-oxocyclohex-2-en-1-yl acetate **(2)**	*L. blume*	Leaves	Ryen et al., 2020
ELEMANE			
β -Elemene **(3)**	*L. strychnifolia*	Roots	Lv et al., 2023
Hydroxyisogermafurenolide **(4)**	*L. strychnifolia*	Roots	Gan et al., 2009b
Isogermafurenolide **(5)**	*L. strychinifolia*	Roots	Lv et al., 2023
Isolinderalactone **(6)**	*L. strychnifolia*	Roots	Yen et al., 2016
	L. aggregata	Roots	Yang et al., 2020b
Isogermafurene **(7)**	*L. strychinifolia*	Roots	Lv et al., 2023
EUDESME			
ent-4(15)-Eudesmene-1b,6,α-diol **(8)**	*L. aggregata*	Roots	Yang et al., 2020b
3-Oxo-4, 5αH, 8βH-eudesma- 1,7(11)-dien-8, 12-olide **(9)**	*L. strychinofolia*	Roots	Ohno et al., 2005
3-Oxo-5αH, 8βH-eudesma-1,4(15), 7(11)-trien-8, 12-olide **(10)**	*L. strychinofolia*	Roots	Ohno et al., 2005
8-Hydroxylindestenolide **(11)**	*L. aggregata*	Roots	Sumioka et al., 2011
Atractylenolide III **(12)**	*L. aggregata*	Roots	Gan et al., 2009
Eudesma-4(14),11-diene **(13)**	*L. strychinifolia*	Roots	Liu et al., 2016
Dehydrolindestrenolide **(14)**	*L. aggregata*	Roots	Yang et al., 2020
Hydroxylindestenolide **(15)**	*L. aggregata*	Roots	Li et al., 2002
Lindestrene **(16)**	*L. strychinofolia*	Roots	Liu et al., 2013
Linderagalactone D **(17)**	*L. aggregata*	Roots	Wu et al., 2010
Linderagalactone E **(18)**	*L. aggregata*	Roots	Gan et al., 2009b
Linderaggredin A **(19)**	*L. aggregata*	Aerial	Kuo et al., 2020
Linderolide A **(20)**	*L. aggregata*	Roots	Sumioka et al., 2011
Linderolide C **(21)**	*L. aggregata*	Roots	Sumioka et al., 2011
Linderolide B **(22)**	*L. aggregata*	Roots	Sumioka et al., 2011
Linderolide D **(23)**	*L. aggregata*	Roots	Sumioka et al., 2011
Linderolide E **(24)**	*L. aggregata*	Roots	Sumioka et al., 2011
Linderolide G **(25)**	*L. aggregata*	Roots	Liu et al., 2013
Linderolide H **(26)**	*L. aggregata*	Roots	Liu et al., 2013
Linderolide I **(27)**	*L. aggregata*	Roots	Liu et al., 2013
Linderolide J **(28)**	*L. aggregata*	Roots	Liu et al., 2013
Linderagalactones D **(29)**	*L. aggregata*	Roots	Gan et al., 2009b
Linderagalactones E **(30)**	*L. aggregata*	Roots	Gan et al., 2009b
Lindestrenolide **(31)**	*L. strychinifolia*	Roots	Sumioka et al., 2011
	L. aggregata	Roots	Liu et al., 2013
Hydroxylindestrenolide **(32)**	*L. aggregata*	Roots	Liu et al., 2013
Linerenone **(33)**	*L. communis*	Fruits	Deng et al., 2011
Myrrhalindenane C **(34)**	*L. myrrha*	Roots	Nguyen et al., 2023
Polydactin B **(35)**	*L. communis*	Fruits	Deng et al., 2011
GEMACRANE			
Neosericenyl acetate **(36)**	*L. aggreggata*	Roots	Lv et al., 2023
Linderalactone **(37)**	*L. strychnifolia*	Roots	Li et al., 2002
	L. chunii	Roots	Liu et al., 2013
	L. aggreggata	Roots	Yang et al., 2020

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Linderane **(38)**	*L. aggregata*	Roots	Wu et al., 2010
	L. strychnifolia	Roots	Li et al., 2002
Linderanines A **(39)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanines B **(40)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanines C **(41)**	*L. aggregata*	Roots	Qiang et al., 2011
Lindera dine **(42)**	*L. strychnifolia*	Roots	Qiang et al., 2011
Linderanlide A **(43)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide B **(44)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide C **(45)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide D **(46)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanlide E **(47)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderoline **(48)**	*L. strychnifolia*	Roots	Liu et al., 2013
Linderanine A **(49)**	*L. aggregata*	Roots	Qiang et al., 2011
Linderanine C **(50)**	*L. aggregata*	Roots	Qiang et al., 2011
Eudeglaucone **(51)**	*L. glauca*	Twigs	Yu et al., 2016
Neolinderane **(52)**	*L. strychnifolia*	Roots	Liu et al., 2013
Neolinderalactone **(53)**	*L. strychnifolia*	Roots	Liu et al., 2013
	L. aggregata	Roots	Gan et al., 2009b
Pseudoneolinderane **(54)**	*L. strychnifolia*	Roots	Li et al., 2002
	L. chunii	Roots	Zhang et al., 2002
	L. aggregata	Roots	Liu et al., 2021
Parvigemone **(55)**	*L. aggregata*	Roots	Liu et al., 2016
Neolindenenonelactone **(56)**	*L. aggregata*	Roots	Gan et al., 2009b
GUAIANE			
1,4-Dimethyl-7-ethylazulene **(57)**	*L. strychnifolia*	Roots	Liu et al., 2013
Aciphyllene **(58)**	*L. glauca*	Leaves	Nii et al., 1983
Glaucyl alcohol **(59)**	*L. glauca*	Roots	Nii et al., 1983
Aciphyllic acid **(60)**	*L. glauca*	Roots	Nii et al., 1983
Aciphyllyl alcohol **(61)**	*L. glauca*	Leaves	Nii et al., 1983
Dehydrocostuslactone **(62)**	*L. aggregata*	Roots	Wen et al., 2021
Glaucic acid **(63)**	*L. glauca*	Roots	Nii et al., 1983
Lindenanolides C **(64)**	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolides D **(65)**	*L. aggregata*	Roots	Wen et al., 2021
Linderazulene **(66)**	*L. strychnifolia*	Roots	Lv et al., 2023
LINDENANE			
(1*R*, 3*S*, 4*R*, 5*S*, 8*S*, 10*S*)-4-Hydroxy-1,3-cycloeudesma-7(11)-en-12,8-olide **(67)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 4*R*, 5*R*, 8*S*, 10*S*)-4-Methoxy-1,3-cycloeudesma-7(11)-en-12,8-olide **(68)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 4*R*, 5*R*, 8*S*, 10*S*)-4,8-Dihydroxy-1,3-cycloeudesma-7(11)-en-12,8-olide **(69)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 4*R*, 5*R*, 6*R*, 8*S*, 10*S*)-4,6,8-Trihydroxy-1,3-cyclo-eudesma-7(11)-en-12,8-olide **(70)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 4*R*, 5*R*, 6*R*, 8*S*, 10*S*)-4,8-Dihydroxy-6-acetoxy- 1,3-cycloeudesma-7(11)-en-12,8-olide **(71)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 4*S*, 5*S*, 8*R*, 10*R*)-4-Hydroxy-6-oxo-1,3-cycloeudesma-7(11)-en-12,8-olide **(72)**	*L. strychinifolia*	Roots	Liu et al., 2016
(1*R*, 3*S*, 5*R*, 6*R*, 8*R*, 10*S*)-6-Methoxy-8-hydroxy-1,3-cyclo-eudesma-4(15),7(11)-dien-12,8- olide **(73)**	*L. strychinifolia*	Roots	Liu et al., 2016
6α-Acetyl-lindenanolide B1 **(74)**	*L. aggregata*	Roots	Wen et al., 2021
6α-Acetyl-lindenanolide B2 **(75)**	*L. aggregata*	Roots	Wen et al., 2021
Lindenenyl acetate **(76)**	*L. aggregata*	Roots	Li et al., 2009
Isolinderoxide **(77)**	*L. strychifolia*	Roots	Wen et al., 2021
Lindenene **(78)**	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolide A **(79)**	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolide B1 **(80)**	*L. aggregata*	Roots	Wen et al., 2021
Lindenanolide B2 **(81)**	*L. aggregata*	Roots	Wen et al., 2021
Linderanlide F **(82)**	*L. aggregata*	Roots	Qiang et al., 2011

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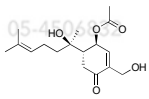
Linderanlide K **(83)**	*L. aggregata*	Roots	Liu et al., 2013
Linderanlide L **(84)**	*L. aggregata*	Roots	Liu et al., 2013
Linderanlide M **(85)**	*L. aggregata*	Roots	Liu et al., 2013
Linderanlide N **(86)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide O **(87)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide P **(88)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide Q **(89)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide R **(90)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide S **(91)**	*L. aggregata*	Roots	Liu et al., 2016
Linderanlide T **(92)**	*L. aggregata*	Roots	Liu et al., 2016
Linderagalactone B **(93)**	*L. aggregata*	Roots	Gan et al., 2009b
Linderagalactone C **(94)**	*L. aggregata*	Roots	Gan et al., 2009b
Linderaggredin B **(95)**	*L. aggregata*	Aerial	Kuo et al., 2020
Linderolide L **(96)**	*L. strychnifolia*	Roots	Liu et al., 2013
Linderolide M **(97)**	*L. strychnifolia*	Roots	Liu et al., 2013
Linderolide N **(98)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide O **(99)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide P **(100)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide Q **(101)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide R **(102)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide S **(103)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide T **(104)**	*L. strychnifolia*	Roots	Cao et al., 2016
Linderolide U **(105)**	*L. aggregata*	Roots	Kim et al., 2021
Linderolide V **(106)**	*L. aggregata*	Roots	Kim et al., 2021
Lindenenol **(107)**	*L. aggregata*	Roots	Liu et al., 2013
	L. strychnifolia	Roots	Li et al., 2002
Myrrhalindenane A **(108)**	*L. myrrha*	Roots	Duong et al., 2023
Myrrhalindenane B **(109)**	*L. myrrha*	Roots	Duong et al., 2023
Strychnilactone **(110)**	*L. aggregata*	Roots	Li et al., 2002
Strychnistenolide **(111)**	*L. aggregata*	Roots	Li et al., 2002
Strychnistenolide 6-O-acetate **(112)**	*L. strychnifolia*	Roots	Liu et al., 2016
SESQUITERPENE DIMERS			
Aggreganoid A **(113)**	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid B **(114)**	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid C **(115)**	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid D **(116)**	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid E **(117)**	*L. aggregata*	Roots	Liu et al., 2019a
Aggreganoid F **(118)**	*L. aggregata*	Roots	Liu et al., 2019a
Linderin A **(119)**	*L. aggregata*	Roots	Wen et al., 2021
Linderin B **(120)**	*L. aggregata*	Roots	Wen et al., 2021
Linderaggrenolide A **(121)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide B **(122)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide C **(123)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide D **(124)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide E **(125)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide F **(126)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide G **(127)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide H **(128)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide I **(129)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide J **(130)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide K **(131)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide L **(132)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide M **(133)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderaggrenolide N **(134)**	*L. aggregata*	Roots	Liu et al., 2021b
Linderanoid A **(135)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid B **(136)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid C **(137)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid D **(138)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid E **(139)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid F **(140)**	*L. aggregata*	Roots	Liu et al., 2021a

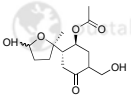
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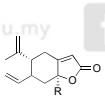
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Linderanoid G **(141)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid H **(142)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid I **(143)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid J **(144)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid K **(145)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid L **(146)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid M **(147)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid N **(148)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderanoid O **(149)**	*L. aggregata*	Roots	Liu et al., 2021a
Lindenaneolide F **(150)**	*L. aggregata*	Roots	Liu et al., 2021a
Linderalide A **(151)**	*L. aggregata*	Roots	Liu et al., 2019a
Linderalide B **(152)**	*L. aggregata*	Roots	Liu et al., 2019a
Linderalide C **(153)**	*L. aggregata*	Roots	Liu et al., 2019a
Linderalide D **(154)**	*L. aggregata*	Roots	Liu et al., 2019a
OTHERS			
10,11-Dihydroxyeremophilan-3-one 11-O-β-D-glucopyranoside **(155)**	*L. strychinifolia*	Roots	Mimura et al., 2009
Alangioside L **(156)**	*L. umbellata*	Stems	Kuroda et al., 2011
Aristofone **(157)**	*L. communis*	Fruits	Deng et al., 2011
Cadinene **(158)**	*L. aggregata*	Seeds	Lv et al., 2023
Cadina-4,10 (15)-diene **(159)**	*L. aggregata*	Seeds	Lv et al., 2023
Dehydrocostuslactone **(160)**	*L. aggregata*	Root	Qiang et al., 2011
Epiglobulol **(161)**	*L. communis*	Fruits	Deng et al., 2011
Linderaggredin C **(162)**	*L. aggregata*	Aerial	Kuo et al., 2020
Linderagalactone A **(163)**	*L. aggregata*	Aerial	Kuo et al., 2020
Pseudoguaianelactones A **(164)**	*L. glauca*	Roots	Ruan et al., 2020
Pseudoguaianelactones B **(165)**	*L. glauca*	Roots	Ruan et al., 2020
Pseudoguaianelactone C **(166)**	*L. glauca*	Roots	Ruan et al., 2020


(1)


(2)

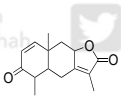

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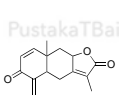

(4) R = OH
(5) R = H


(6)


(7)


(8)

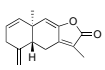

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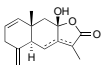

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(11)

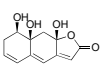

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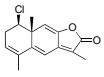

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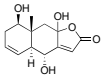

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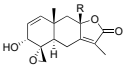

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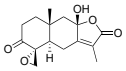

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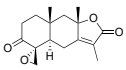

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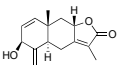

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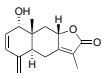

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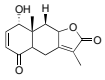

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(21) R = H

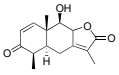

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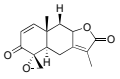

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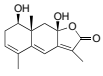

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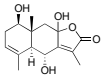

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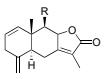

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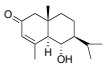

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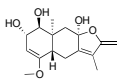

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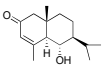

(29)


(30)


(31) R = H
(32) R = OH


(33)

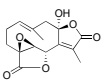

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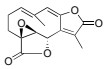

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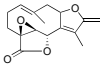

(36)


(37)

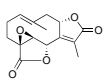

(38)


(39)


(40)


(41)


(42)


(43)

(44)

(45)

(46) R =CH_3
(47) R = Ac

(48)

(49) R = OH
(50) R = H

(51)

(52)

(53)

(54)

(55)

(56)

(57)

(58) R =CH_3
(59) R =CH_2OH
(60) R =COOH

(61)

(62)

(63)

(64) R = α-OH
(65) R = β-OH

(66)

(67) R = H
(68) R = OCH_3

(69)

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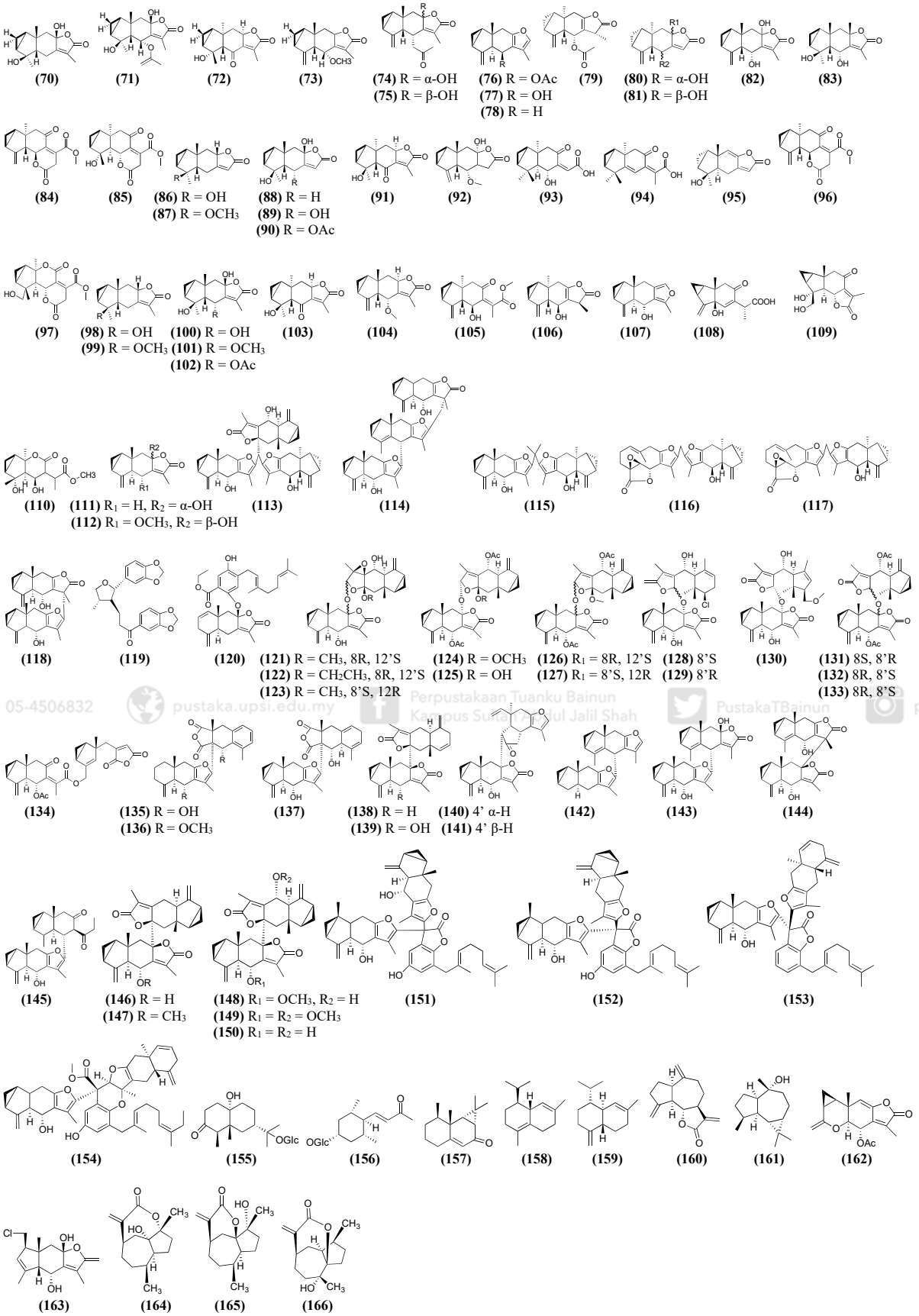


Figure 1. Chemical structures of isolated sesquiterpenes.

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2.2. Alkaloids

Alkaloids are one of the most diverse groups of secondary metabolites found in living organisms and have an array of structure types, biosynthetic pathways, and pharmacological activities. Alkaloids are a group of naturally occurring organic compounds which contain at least one nitrogen atom in an amine-type structure. Alkaloids are divided into several classes based on their sources, pharmacokinetics, and chemical structures such as isoquinoline, quinoline, indole, indolizidine, pyrroloindole, pyrrole and pyrrolidine, imidazole or glyoxaline, pyridine, piperidine, aporphine, pyrrolizidine, tropane, and purine (Azzeme & Zaman, 2019). Several studies on the alkaloids of *Lindera* species (Figure 2) were documented starting from 1994 to 2023. Eight *Lindera* species have been reported on alkaloids which were from *L. aggregata*, *L. glauca*, *L. chunii*, *L. megaphylla*, *L. reflexa*, *L. radix*, *L. myrrha*, and *L. oldhanii* with a total of 65 alkaloids. They were identified as amides, aporphines, benzyl-tetrahydroisoquinolines, bis-benzyltetrahydroisoquinolines, and isoquinolines. These isolated compounds were tabulated in Table 2.

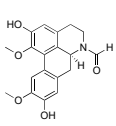
Table 2. Alkaloids isolated from several *Lindera* species

Compounds	Species	Part	References
AMIDES			
Linderaggrine B **(167)**	*L. aggregata*	Roots	Kuo et al., 2020
Northalifoline **(168)**	*L. glauca*	Aerial	Ma et al., 2015
N-*cis*-sinapoyltyramine **(169)**	*L. glauca*	Aerial	Chang et al., 2000
N-*trans*-sinapoyltyramine **(170)**	*L. glauca*	Aerial	Chang et al., 2000
N-*cis*-feruloyltyramine **(171)**	*L. glauca*	Aerial	Chang et al., 2000
N-*trans*-feruloyltyramine **(172)**	*L. glauca*	Aerial	Chang et al., 2000
Squamolone **(173)**	*L. glauca*	Aerial	Chang et al., 2000
Northalifoline **(174)**	*L. glauca*	Aerial	Chang et al., 2000
Thalifoline **(175)**	*L. glauca*	Aerial	Ma et al., 2015
APORPHINE			
7-Oxohernagine **(176)**	*L. chunii*	Roots	Zhang et al., 2002
7-Oxohernangerine **(177)**	*L. chunii*	Roots	Zhang et al., 2002
Hernandonine **(178)**	*L. chunii*	Roots	Zhang et al., 2002
Lindechunine A **(179)**	*L. chunii*	Roots	Zhang et al., 2002
Lycicamine **(180)**	*L. glauca*	Aerial	Chang et al., 2000
Actinodaphnine **(181)**	*L. aggregata*	Roots	Yang et al., 2020
Bulbocapnine **(182)**	*L. aggregata*	Roots	Lv et al., 2023
Hernangerine **(183)**	*L. aggregata*	Roots	Cao et al., 2016
Boldine **(184)**	*L. aggregata*	Roots	Gan et al., 2009a
	L. glauca	Aerial	Chang et al., 2001
D-dicentrine **(185)**	*L. megaphylla*	Roots	Huang et al., 1998
Isoboldine **(186)**	*L. aggregata*	Roots	Ma et al., 2015
Linderaline **(187)**	*L. aggregata*	Roots	Chou et al., 2005
Laetanine **(188)**	*L. glauca*	Aerial	Zhu et al., 2016
	L. reflexa	Roots	Chen et al., 2015
Laurolistine **(189)**	*L. chunii*	Roots	Zhang et al., 2002
Laurotetanine **(190)**	*L. aggregata*	Roots	Gan et al., 2009a
N-methyllaurotetanine **(191)**	*L. aggregata*	Roots	Gan et al., 2009a
	L. chunii	Roots	Zhang et al., 2002
Norboldine **(192)**	*L. aggregata*	Roots	Gan et al., 2009a
Norboldine acetate **(193)**	*L. aggregata*	Roots	Gan et al., 2009a
Norbracteoline **(194)**	*L. glauca*	Aerial	Zhu et al., 2016
	L. reflexa	Roots	Chen et al., 2015
Norisoboldine **(195)**	*L. aggregata*	Roots	Yang et al., 2020
Lindechunine B **(196)**	*L. chunii*	Roots	Zheng et al., 2002
Launobine **(197)**	*L. reflexa*	Roots	Chen et al., 2015
Norisocorydine **(198)**	*L. glauca*	Aerial	Zhu et al., 2016
Hernovine **(199)**	*L. myrrha*	Roots	Phan et al., 1994

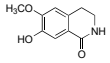
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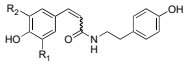
Hernavine **(200)**	*L. myrrha*	Roots	Phan et al., 1994
Hernangerine **(201)**	*L. myrrha*	Roots	Phan et al., 1994
N-Methylhernangerine **(202)**	*L. chunii*	Leaves	Zhang et al., 2002
N-Methylovigerine **(203)**	*L. chunii*	Leaves	Zhang et al., 2002
O-Methylbulbocapnine **(204)**	*L. megaphylla*	Flower	Chen et al., 1995
N-Methylhernovine **(205)**	*L. megaphylla*	Flower	Chen et al., 1995
Secoboldine **(206)**	*L. aggregata*	Roots	Yang et al., 2020
Secolaurolitsine **(207)**	*L. aggregata*	Roots	Yang et al., 2020
Linderine A **(208)**	*L. aggregata*	Roots	Lv et al., 2023
BENZYL TETRAHYDROISOQUINOLINE			
(1*S*)-5′-O-p-Hydroxy benzoyl norreticuline **(209)**	*L. aggregata*	Roots	Yang et al., 2020
Norjuziphine **(210)**	*L. aggregata*	Roots	Yang et al., 2020
Reticuline **(211)**	*L. aggregata*	Roots	Yang et al., 2020
	L. megaphylla	Flower	Chen et al., 1995
Protosinomenine **(212)**	*L. aggregata*	Roots	Yang et al., 2020
Norcinnamolaurine **(213)**	*L. glauca*	Aerial	Zhu et al., 2016
Argemexirine **(214)**	*L. aggregata*	Roots	Lv et al., 2023
Magnocurarine **(215)**	*L. aggregata*	Roots	Gan et al., 2009a
BIS-BENZYL TETRAHYDROISOQUINOLINE			
(1′*S*)-12′-Hydroxyl-linderegatine **(216)**	*L. aggregata*	Roots	Yang et al., 2020
(1*R*, 1′*R*)-11,11′-Biscoclaurine **(217)**	*L. aggregata*	Roots	Yang et al., 2020
Costaricine **(218)**	*L. aggregata*	Roots	Yang et al., 2020
Linderegatine **(219)**	*L. aggregata*	Roots	Zhu et al., 2016
Compounds	**Species**	**Part**	**References**
Lindoldhamine **(220)**	*L. glauca*	Aerial	Zhu et al., 2016
	L. aggregata	Roots	Yang et al., 2020
ISOQUINOLINE			
Demethylcoclaurine-7-O-glucoside **(221)**	*L. aggregata*	Roots	Peng et al., 2020
Karakoramine **(222)**	*L. aggregata*	Roots	Peng et al., 2020
Pallidine **(223)**	*L. aggregata*	Roots	Peng et al., 2020
Salutaridine **(224)**	*L. aggregata*	Roots	Yang et al., 2020
N-Methylflavinantine **(225)**	*L. glauca*	Aerial	Chang et al., 2013
OTHER			
Norcodeine **(226)**	*L. radix*	Roots	Zou et al., 2021
6-O-methyl codeine **(227)**	*L. radix*	Roots	Zou et al., 2021
Boldine n-oxide **(228)**	*L. aggregata*	Roots	Chou et al., 2005
Pronuciferine **(229)**	*L. aggregata*	Roots	Gan et al., 2009
Reticuline n-oxide **(230)**	*L. aggregata*	Roots	Chou et al., 2005
Tetrahydropalmatine **(231)**	*L. radix*	Roots	Zou et al., 2021



(167)



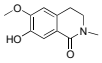
(168)



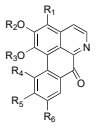
(169) $R_1 = R_2 = OCH_3$, *E*
(170) $R_1 = R_2 = OCH_3$, *Z*
(171) $R_1 = H$, $R_2 = OCH_3$, *E*
(172) $R_1 = H$, $R_2 = OCH_3$, *Z*



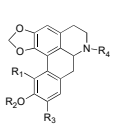
(173)



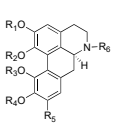
(174) R = CH_3
(175) R = H



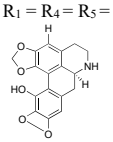
(176) $R_1 = R_6 = H$, $R_2 = R_3 = R_4 = CH_3$, $R_5 = OH$
(177) $R_1 = R_6 = H$, $R_2 = R_3 = CH_2$, $R_4 = OCH_3$, $R_5 = OH$
(178) $R_1 = R_6 = H$, $R_2 = R_3 = R_4 = R_5 = CH_2$
(179) $R_1 = R_4 = OCH_3$, $R_2 = R_3 = CH_2$, $R_5 = OH$, $R_6 = H$
(180) $R_1 = R_4 = R_5 = R_6 = H$, $R_2 = R_3 = CH_3$



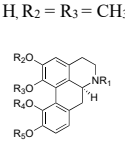
(181) $R_1 = R_4 = H$, $R_2 = CH_3$, $R_3 = OH$
(182) $R_1 = OH$, $R_2 = R_4 = CH_3$, $R_3 = H$
(183) $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$



(184) $R_1 = R_3 = H$, $R_2 = R_4 = R_6 = CH_3$, $R_5 = OH$
(185) $R_1 = R_4 = R_6 = CH_3$, $R_2 = CH_2$, $R_3 = H$, $R_5 = OCH_3$
(186) $R_1 = R_2 = R_4 = R_6 = CH_3$, $R_3 = H$, $R_5 = OH$
(187) $R_1 = R_2 = R_5 = R_6 = H$, $R_3 = R_4 = CH_3$
(188) $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = CH_3$, $R_5 = OCH_3$
(189) $R_1 = R_3 = R_6 = H$, $R_2 = R_4 = CH_3$, $R_5 = OH$
(190) $R_1 = R_2 = R_4 = CH_3$, $R_3 = R_6 = H$, $R_5 = OH$
(191) $R_1 = R_2 = R_4 = R_6 = CH_3$, $R_3 = H$, $R_5 = OH$
(192) $R_1 = R_3 = H$, $R_2 = R_4 = R_6 = CH_3$, $R_5 = OH$
(193) $R_1 = Ac$, $= H$, $R_2 = R_4 = CH_3$, $R_3 = R_6 = H$, $R_5 = OH$
(194) $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_6 = H$, $R_5 = OCH_3$
(195) $R_1 = R_4 = CH_3$, $R_2 = R_3 = R_6 = H$, $R_5 = OH$



(196)



(197) $R_1 = H$, $R_2 = R_3 = R_4 = CH_2$, $R_5 = CH_3$
(198) $R_1 = H$, $R_2 = R_3 = R_4 = R_5 = CH_3$
(199) $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = CH_3$
(200) $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = CH_3$
(201) $R_1 = R_5 = H$, $R_2 = R_3 = CH_2$, $R_4 = CH_3$
(202) $R_1 = R_4 = CH_3$, $R_2 = R_3 = CH_2$, $R_5 = OH$
(203) $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = CH_2$
(204) $R_1 = R_4 = R_5 = CH_3$, $R_2 = R_3 = CH_3$
(205) $R_1 = R_3 = R_4 = CH_3$, $R_2 = R_5 = H$

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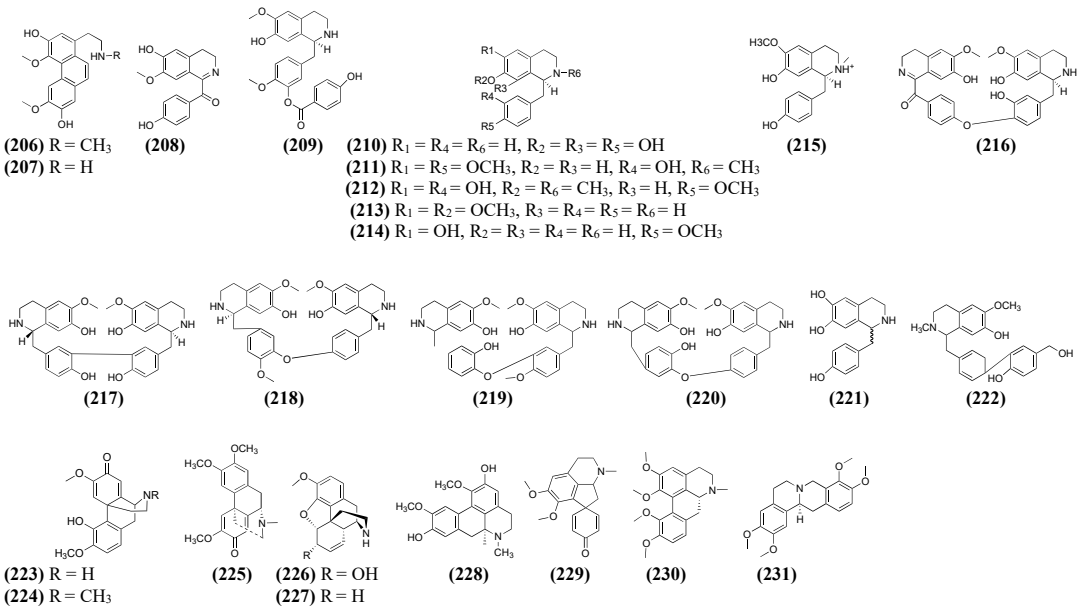


Figure 2. Chemical structures of isolated alkaloids.

2.3. Flavonoids

Flavonoids are divided into several classes based on their sources, pharmacokinetics, and chemical structures such as flavones, flavonols, flavanones, catechins, anthocynidins and isoflavones (Panche et al., 2016). The various classes of flavonoids differ in oxidation level and substitution pattern of the C ring, while the individual compounds within a class differ in the pattern of substitution of A and B rings (Kumar & Pandey, 2013). Several studies on the flavonoids of *Lindera* species (Figure 3) were documented starting from 1985 to 2022. Seven *Lindera* species have been reported with flavonoids which were from *L. aggregata*, *L. erythcarpa*, *L. umbellata*, *L. lucida*, *L. oxyphlla*, *L. glauca*, and *L. obtusiloba.* There were 42 compounds that was classified to flavonoids isolated from *Lindera* species. They were known as chalcones, dihydrochalcones, flavanones, flavonols, and flavones. These isolated compounds were tabulated in Table 3.

Table 3. Flavonoids isolated from several *Lindera* species

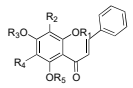
Compounds	Species	Part	References
CHALCONE			
Flavokawain B **(232)**	*L. oxyphlla*	Bark	Hosseinzadeh et al., 2013
Kanakugiol **(233)**	*L. erythrocarpa*	Aerial	Kim et al., 2011
Pedicellin **(234)**	*L. lucida*	Twigs	Leong et al., 1998
Linderachalcone **(235)**	*L. umbellata*	Leaves	Ichino et al., 1989
Neolinderatin **(236)**	*L. umbellata*	Leaves	Ichino et al., 1989
DIHYDROCHALCONE			
3′,5′-Dihydroxy-2′,4′,6′- trimethoxy-dihydrochalcone **(237)**	*L. erythrocarpa*	Leaves	Kim et al., 2011
Dihydrokanakugiol **(238)**	*L. erythrocarpa*	Leaves	Kim et al., 2011
Dihydropashanone **(239)**	*L. erythrocarpa*	Leaves	Kim et al., 2011
Linderatin **(240)**	*L. umbellata*	Leaves	Ichino et al., 1989
Methyllinderatin **(241)**	*L. umbellata*	Leaves	Ichino et al., 1989
Kanakugin **(242)**	*L. erythrocarpa*	Leaves	Kim et al., 2011
Nubigenol **(243)**	*L. aggregata*	Leaves	Zhang et al., 2003
Onysilin **(244)**	*L. oxyphylla*	Bark	Hosseinzadeh et al., 2013
Pinostrobin **(245)**	*L. erythrocarpa*	Leaves	Kim et al., 2011
Pinocembrin **(246)**	*L. oxyphylla*	Bark	Hosseinzadeh et al., 2013

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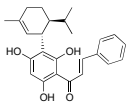
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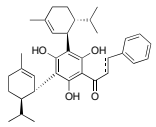
FLAVANONES			
3′-O-methyl-(–)-epicatechin **(247)**	*L. umbellata*	Twigs	Morimoto et al., 1985
3′,4′ -Di-O-methyl-(–)-epicatechin **(248)**	*L. umbellata*	Twigs	Morimoto et al., 1985
5,3′-Di-O-methyl-(–)-epicatechin **(249)**	*L. umbellata*	Twigs	Morimoto et al., 1985
5,7,3′-Tri-O-methyl-(–)-epicatechin **(250)**	*L. umbellata*	Twigs	Morimoto et al., 1985
Catechin **(251)**	*L. umbellata*	Stems	Ichino et al., 1989
	L. aggregata	Stems	Zhang et al., 2003
Epicatechin **(252)**	*L. umbellata*	Stems	Ichino et al., 1989
	L. erythrocarpa	Aerial	Kim et al., 2011
	L. strychnifolia	Stems	Kobayashi et al., 2002
Epigallocatechin **(253)**	*L. aggregata*	Leaves	Zhang et al., 2003
Dihydrokaempferol **(254)**	*L. aggregata*	Leaves	Xiao et al., 2011
Dihydrokaempferol-3-O-l-rhamnoside **(255)**	*L. aggregata*	Leaves	Xiao et al., 2011
Hesperidin **(256)**	*L. aggregata*	Leaves	Xiao et al., 2011
FLAVONE			
5-Hydroxy-6,7,8-trimethoxyflavone **(257)**	*L. lucida*	Twigs	Leong et al., 1998
FLAVONOLS			
Astragaline **(258)**	*L. aggregata*	Leaves	Zhang et al., 2003
Kaempferol **(259)**	*L. nessiana*	Aerial	Chang et al., 2000
Kaempferol-3-O-L-arabinopyranoside **(260)**	*L. glauca*	Aerial	Chang et al., 2000
Kaempferol-3-O-β-d-galactoside **(261)**	*L. aggregata*	Leaves	Chang et al., 2000
Kaempferol-3-O-β-d-galactopyranoside **(262)**	*L. aggregata*	Leaves	Chang et al., 2000
Afzelin **(263)**	*L. aggregata*	Leaves	Luo et al., 2009
Avicularin **(264)**	*L. obtusiloba*	Stems	Lee et al., 2011
Kaempferol-3-O-(2″-O-β-d-glucopyranosyl)-α-l-rhamnopyranoside **(265)**	*L. aggregata*	Leaves	Luo et al., 2009
Isoquercitrin **(266)**	*L. umbellata*	Branches	Lee et al., 2011
Hyperin **(267)**	*L. obtusiloba*	Stems	Lee et al., 2011
Rutin **(268)**	*L. umbellata*	Branches	Zhang et al., 2003b
Kaempferol-3-O-α-d-glucopyranoside **(269)**	*L. glauca*	Aerial	Zhang et al., 2001
Kaempferol-3-O-β-d-xylopyranoside **(270)**	*L. aggregata*	Leaves	Luo et al., 2009
Quercetin **(271)**	*L. aggregata*	Leaves	Zhang et al., 2001
Quercetin-3-O-rhamnoside **(272)**	*L. aggregata*	Leaves	Zhang et al., 2001
Quercetin-3-O-β-d-galacto-pyranoside **(273)**	*L. aggregata*	Leaves	Zhang et al., 2001



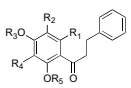
(232) $R_1 = R_3 = CH_3$, $R_2 = R_4 = R_5 = H$
(233) $R_1 = H$, $R_2 = R_4 = OCH_3$, $R_3 = R_5 = CH_3$
(234) $R_1 = R_3 = CH_3$, $R_2 = R_4 = R_5 = H$



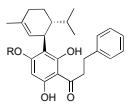
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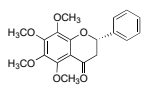
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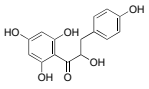
(237) $R_1 = OCH_3$, $R_2 = R_4 = OH$, $R_3 = R_5 = CH_3$
(238) $R_1 = R_5 = H$, $R_2 = OCH_3$, $R_3 = CH_3$, $R_4 = OH$
(239) $R_1 = R_2 = R_4 = OCH_3$, $R_3 = CH_3$, $R_5 = H$



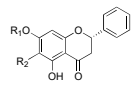
(240) R = H
(241) R = CH_3



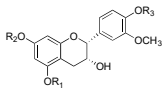
(242)



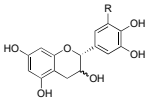
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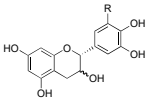
(244) $R_1 = CH_3$, $R_2 = OCH_3$
(245) $R_1 = CH_3$, $R_2 = H$
(246) $R_1 = R_2 = H$



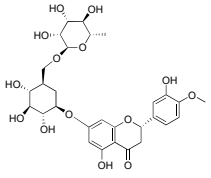
(247) $R_1 = R_2 = R_3 = H$
(248) $R_1 = R_2 = H$, $R_3 = CH_3$
(249) $R_1 = CH_3$, $R_2 = R_3 = H$
(250) $R_1 = R_3 = H$, $R_2 = CH$



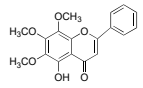
(251) R = H, β-OH
(252) R = H, α-OH
(253) R = OH, α-OH



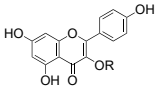
(254) R = H
(255) R = Rhamnosyl



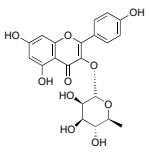
(256)



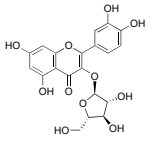
(257)



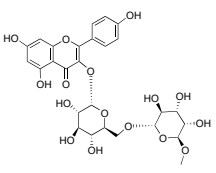
(258) R = Glucopyranosyl
(259) R = H
(260) R = Arabinfuranosyl
(261) R = Galactosyl
(262) R = Galactopyranosyl



(263)



(264)



(265)

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(266) R_1 = OH, R_2 = Glc
(267) R_1 = OH, R_2 = Gal
(268) R_1 = OH, R_2 = Glc (6-1) rha
(272) R = Rhamnosyl
(273) R = Galactopyranosyl

(269) R = Glucopyranosyl
(270) R = Xylopyranosyl
(271) R = H

Figure 3. Chemical structures of isolated flavonoids.

2.4. Phenolics

Phenolic compounds are the most widely distributed secondary metabolites, ubiquitously present in the plant kingdom. They contain benzene rings with one or more hydroxyl substituents, and range from simple phenolic molecules to highly polymerized compounds (Lin et al., 2016). Several studies on the phenolics of *Lindera* species (Figure 4) were documented starting from 2006 to 2021. There were 37 compounds classified to phenolics isolated from *Lindera* species. Overall, four *Lindera* species have been reported with phenolics which were from *L. fruticose*, *L. aggregata*, *L. nacusua*, and *L. obtusiloba.* The most reported phenolic compounds are from *L. aggregata* and *L. obtusiloba*, each with eight reports. Besides, *L. fruticosa* and *L. radix* each with seven reports. The root part is the most common part that contains abundant of phenolic compounds. These isolated compounds as tabulated in Table 4.

Table 4. Phenolics isolated from several *Lindera* species

Compounds	Species	Part	References
β-D-(3,4-Disinapoyl) fructofuranosyl-α-D-(6-sinapoyl) glucopyranoside **(274)**	*L. fruticosa*	Roots	Song et al., 2008
β-D-(3-Sinapoyl) fructofuranosyl-α-D-(6-sinapoyl) glucopyranoside **(275)**	*L. fruticosa*	Roots	Song et al., 2008
p-Hydroxybenzoic acid **(276)**	*L. aggregata*	Roots	Ma et al., 2015
1-O-3-Hydroxyphenyl-4,5-dimethoxy-(6′-O-3″,5″-dimethoxygalloyl)-β-d-glucopyranoside **(277)**	*L. nacusua*	Bark	Lei et al., 2017
1-O-3-Hydroxyphenyl-4,5-dimethoxy-(6′-O-vanilloyl)-β-d-glucopyranoside **(278)**	*L. nacusua*	Bark	Lei et al., 2017
1-O-3-Hydroxyphenyl-5- methoxyphenol-(6′-O-vanilloyl)-β-d-glucopyranoside **(279)**	*L. nacusua*	Bark	Lei et al., 2017
4,6-Dihydroxy-2- methoxyphenyl-1-O- β-D-glucopyranoside **(280)**	*L. obtusiloba*	Stems	Choi et al., 2013
6′-O-Vanilloyltachioside **(281)**	*L. aggregata*	Roots	Ma et al., 2015
6-Hydroxy-4-methoxyphenol 1-O-β-d-(6′-O- syringoyl) glucopyranoside **(282)**	*L. nacusua*	Bark	Lei et al., 2017
2-Methoxy-3,4- methylenedioxybenzophenone **(283)**	*L. fruticosa*	Roots	Song et al., 2006
(*S*)-2-Methoxy-3,4-methylenedioxybenzhydryl alcohol **(284)**	*L. fruticosa*	Roots	Song et al., 2008
3-Hydroxy-5-methoxybiphenyl **(285)**	*L. fruticosa*	Roots	Song et al., 2008
3,5-Dimethoxybiphenyl **(286)**	*L. fruticosa*	Roots	Song et al., 2008
1-Methoxy-2,5,7-trihydroxyxanthone **(287)**	*L. fruticosa*	Roots	Song et al., 2006
1,7-Dihydroxyxanthone **(288)**	*L. fruticosa*	Roots	Song et al., 2006
Benzyl 2-hydroxy-6-methoxybenzoate **(289)**	*L. fruticosa*	Roots	Song et al., 2006
Tyrosol **(290)**	*L. aggregata*	Roots	Ma et al., 2015
2-(4-Hydroxy-3-methoxyphenyl)-ethanol **(291)**	*L. aggregata*	Roots	Ma et al., 2015
2-(4-Hydroxy-3,5-dimethoxyphenol)-ethanol **(292)**	*L. aggregata*	Roots	Ma et al., 2015
2,6-Dimethoxy-p-benzoquinone **(293)**	*L. aggregata*	Roots	Ma et al., 2015
2,6-Dimethoxy-4-hydroxyphenyl-1-O-β-D-glucopyranoside **(294)**	*L. obtusiloba*	Stems	Choi et al., 2013
4,6-Dihydroxy-2-methoxyphenyl-1-O-β-D-glucopyranoside	*L. obtusiloba*	Stems	Choi et al., 2013

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(295)			
Isotachioside **(296)**	*L. obtusiloba*	Stems	Choi et al., 2013
Koaburaside **(297)**	*L. obtusiloba*	Stems	Choi et al., 2013
Tachioside **(298)**	*L. obtusiloba*	Stems	Choi et al., 2013
Cryptochlorogenic acid **(299)**	*L. radix*	Roots	Zou et al., 2021
3-Hydroxy-1-(4-hydroxyphenyl)propan-1-one **(300)**	*L. aggregata*	Roots	Ma et al., 2015
4-Hydroxy-3-methoxy acetophenone **(301)**	*L. aggregata*	Roots	Ma et al., 2015
3-(3,4-Dihydroxyphenyl)propionic acid **(302)**	*L. glauca*	Aerial	Chang et al., 2000
Ferulic acid **(303)**	*L. radix*	Roots	Zou et al., 2021
Erigeside C **(304)**	*L. obtusiloba*	Stems	Choi et al., 2013
Neochlorogenic acid **(305)**	*L. radix*	Roots	Zou et al., 2021
Protocatechualdehyde **(306)**	*L. radix*	Roots	Zou et al., 2021
Salidroside **(307)**	*L. radix*	Roots	Zou et al., 2021
	L. obtusiloba	Stems	Choi et al., 2013
Syringic acid **(308)**	*L. radix*	Roots	Zou et al., 2021
Vanillic acid **(309)**	*L. aggregata*	Roots	Ma et al., 2015

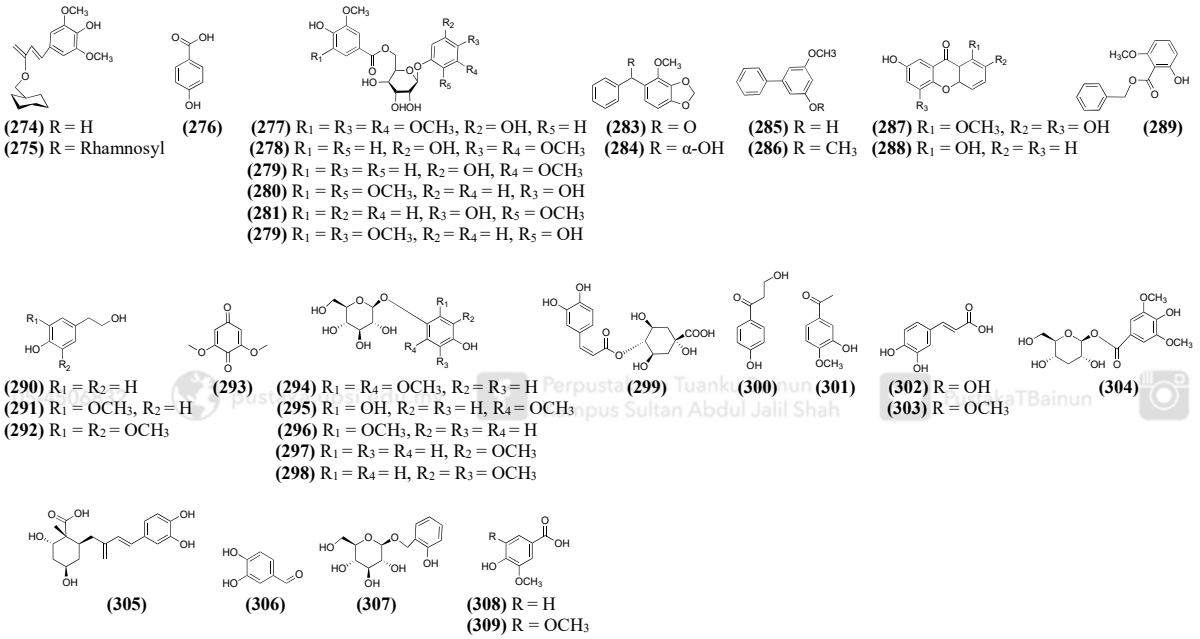


Figure 4. Chemical structures of isolated phenolics.

2.5. Miscellaneous Constituents

Another secondary metabolite compounds that have been identified from *Lindera* species are anthraquinones, butanolides, benzoids, benzoids glycosides, lignans, lucidones, steroids, and tannins (Figure 5). These compounds are tabulated in Table 5.

Table 5. Miscellaneous isolated from several *Lindera* species

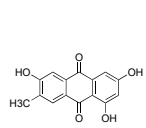
Compounds	Species	Part	References
ANTHRAQUINONES			
Demethylmacrosporine I **(310)**	*L. nacusua*	Bark	Wei et al., 2016
Emodin-6-O-β-D-glucopyranoside **(311)**	*L. nacusua*	Bark	Wei et al., 2016
BUTENOLIDES			
(2*Z*,3*R*,4*S*)-2-(dodec-11-ynylidene)- 3-h-ydroxy-4-methylbutanolide **(312)**	*L. nacusua*	Bark	Wei et al., 2016
Majorenolide **(313)**	*L. akoensis*	Roots	Chang et al., 2008
Majorynolide **(314)**	*L. akoensis*	Roots	Chang et al., 2008
Majoranolide **(315)**	*L. akoensis*	Roots	Chang et al., 2008

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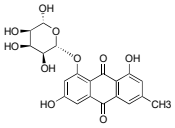
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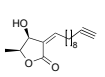
Obtusilactone **(316)**	*L. akoensis*	Roots	Chang et al., 2008
Isoobtusilactone **(317)**	*L. akoensis*	Roots	Chang et al., 2008
Obtusilactone A **(318)**	*L. obtusiloba*	Roots	Kwon et al., 2000
Isoobtusilactone A **(319)**	*L. obtusiloba*	Roots	Kwon et al., 2000
Secoaggregatalactone A **(320)**	*L. aggregata*	Roots	Lin et al., 2007
Litsenolide **(321)**	*L. nacusua*	Bark	Lei et al., 2017
BENZENOIDS			
Linderagatin A **(322)**	*L. aggregata*	Roots	Ma et al., 2015
Linderagatin B **(323)**	*L. aggregata*	Roots	Ma et al., 2015
BENZENOIDS GLYCOSIDE			
6′-O-vanilloyl-5-hydroxy-2,3-dimethoxyphenol 1-O-β-d-glucopyranoside **(324)**	*L. aggregata*	Roots	Kuo et al., 2020
LIGNANS			
rel-(2α,3β)-7-O-methylcedrusin **(325)**	*L. aggregata*	Roots	Ma et al., 2015
Lyoniresinol **(326)**	*L. aggregata*	Roots	Ma et al., 2015
Evofolin B **(327)**	*L. aggregata*	Roots	Ma et al., 2015
Reflexanbene A **(328)**	*L. reflexa*	Leaves	Fu et al., 2022
Reflexanbene C **(329)**	*L. reflexa*	Leaves	Fu et al., 2022
LUCIDONES			
Linderone A **(330)**	*L. oxyphylla*	Bark	Hosseinzadeh et al., 2013
Lucidone **(331)**	*L. erythrocarpa*	Fruits	Kim et al., 2011
Methyllinderone **(332)**	*L. erythrocarpa*	Fruits	Kim et al., 2011
Methyllucidone **(333)**	*L. erythrocarpa*	Fruits	Kim et al., 2011
Linderaspirone **(334)**	*L. aggregata*	Roots	Wang et al., 2010
STEROIDS			
β-Sitosterol **(335)**	*L. glauca*	Stem	Huh et al., 2011
7-Ketositosterol **(336)**	*L. glauca*	Stem	Huh et al., 2011
7β-Hydroxysitosterol **(337)**	*L. glauca*	Stem	Huh et al., 2011
β-Sitosteryl-D-glucoside **(338)**	*L. glauca*	Stem	Huh et al., 2011
β-Sitostenone **(339)**	*L. glauca*	Stem	Huh et al., 2011
Stigmasterol **(340)**	*L. communis*	Wood	Tsai et al., 2002
Daucosterol **(341)**	*L. glauca*	Stem	Huh et al., 2011
TANNINS			
Epicatechin-(4β-8,2-O-7)-epicatechin **(342)**	*L. aggregata*	Roots	Zhang et al., 2003c
Epicatechin-(4β-8,2-O-7)-catechin **(343)**	*L. aggregata*	Roots	Zhang et al., 2003c
Epicatechin-(4β-8)-catechin **(344)**	*L. aggregata*	Roots	Zhang et al., 2003c
Procyanidin B1 **(345)**	*L. aggregata*	Roots	Zhang et al., 2003c
Procyanidin B2 **(346)**	*L. aggregata*	Roots	Zhang et al., 2003c
Procyanidin B3 **(347)**	*L. aggregata*	Roots	Zhang et al., 2003c
Procyanidin B4 **(348)**	*L. aggregata*	Roots	Zhang et al., 2003c
Proanthocyanidins **(349)**	*L. aggregata*	Roots	Zhang et al., 2003c
Cinnamtannin B1 **(350)**	*L. glauca*	Stem	Huh et al., 2011
Cinnamtannin B2 **(351)**	*L. glauca*	Stem	Huh et al., 2011



(310)



(311)



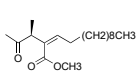
(312)



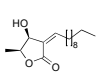
(313) R = CH_2 = CH
(314) R = C = CH
(315) R = CH_2CH_3



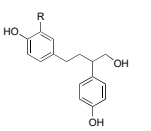
(316) $R_1 = (CH_2)_9OCH_2$, R_2 = H
(317) $(CH_2)_9CH_3$
(318) $R_1 = (CH_2)_{12}CH_3$, R_2 = H
(319) R_1 = H, $R_2 = (CH_2)_{12}CH_3$



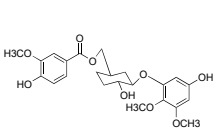
(320)



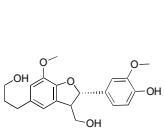
(321)



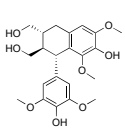
(322) R = H
(323) R = OCH_3



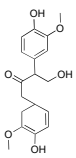
(324)



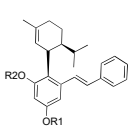
(325)



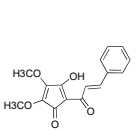
(326)



(327)



(328) $R_1 = R_2$ = H
(329) $R_1 = R_2 = CH_3$



(330)

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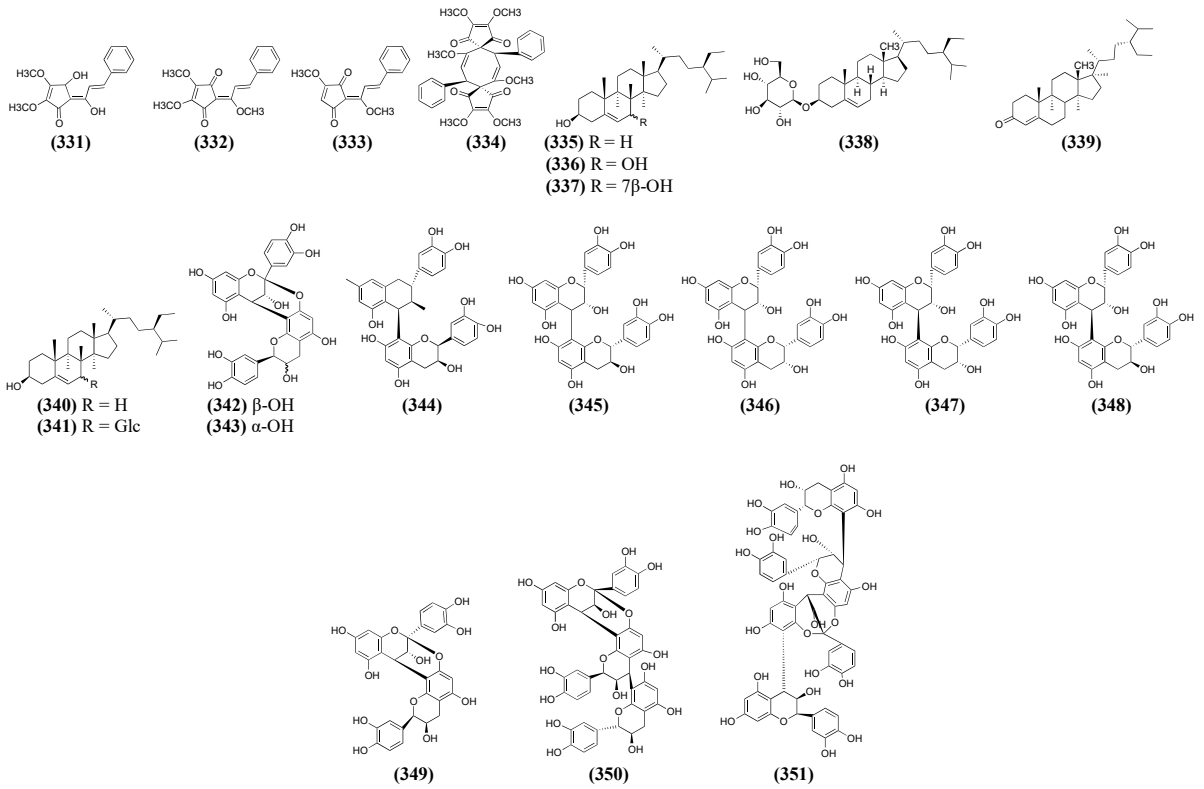


Figure 5. Chemical structures of miscellaneous constituents.

3. PHARMACOLOGICAL ACTION

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Numerous biologically active compounds have been isolated from *Lindera* species previously by several researchers. Sesquiterpenes, flavonoids, phenolics, and alkaloids are among the compounds which reported mainly on anticancer, antifibrotic, anti-inflammatory, antitumor, antioxidant, anti-arthritic, cytotoxic, anti-allergic, and antihyperlipidemic properties. Isolinderalactone **(6)** has been reported to inhibit antitumor, anticancer, and anti-inflammatory activities. Chuang et al. (2018) discovered that isolinderalactone was able to trigger apoptosis or programmed cell death in a variety of cancer cells, including breast cancer cells and lung cancer cells. Fu et al. (2022) was found that isolinderalactone have a strong inhibitory effect on tumor cell lines MGC803 and SMMC-7721 with IC_{50} values 2.65 and 4.13 μM, respectively. Kwak et al. (2022) managed to discover isolinderalactone to exhibit human-resistant colorectal cancer (CRC) cells with IC_{50} value 7.80 μM. Besides, isolinderalactone was also able to inhibit the expression of multiple genes involved in tumour growth and angiogenesis, which it can lead the formation of new blood vessels that can give nutrition to the tumours. In alkaloid type, the most reported compound was norisoboldine **(195)**. Norisoboldine **(195)** helps by preventing the release of cytokines that promote inflammation. In addition, it has been demonstrated that norisoboldine prevents the synthesis of prostaglandin E2 (PGE2) and nitric oxide (NO), both are essential for the inflammatory response. Additionally, Yang et al. (2020) reported the compound induced production of nitric oxide by lipopolysaccharide in RAW 264.7 cells (IC_{50} value 9.6 μM) as well as vascular endothelial growth factor (VEGF)-induced endothelial cell migration (IC_{50} value 15.1 μM) (Lu et al., 2013). In flavonoids type, quercetin-3-*O*-rhamnosides **(272)** are the most reported compound that can act as an antioxidant agent. September-Malaterre et al. (2022) was reported, the compound can control the activities of superoxide dismutase (SOD) and glutathione (GSH). In addition, it is also found extremely effective at increasing the body's

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antioxidant capacity by controlling and regulating glutathione levels (Xu et al., 2019). Koaburaside **(297)** is one of the most reported compounds in phenolic type with mainly for antiallergic effect. Moreover, there were other biological activities of phytochemicals from *Lindera* species that have been reported as described in Table 6.

Table 6. Biological activities of several *Lindera* phytochemicals

Compounds	Species	Biological activities
SESQUITEPENOIDS		
Isolinderalactone **(6)**	*L. aggregata*	**Anticancer**: Exhibited human resistant colorectal cancer (CRC) cells with IC_{50} value 7.80 μM (Kwak et al., 2022) **Antitumor**: Exhibited in breast cancer cell lines by lowering the cell proliferation to the concentration of 30-100 μM (Yen et al., 2015) **Antitumor**: Exhibited in human ovarian cancer (OC) cells and inhibit several cancer cell line growth by reducing mitochondrial superoxide and cell proliferation with a dose concentration of 5-50 μM for 24 h (Rajina et al., 2020) **Anti-inflammatory**: Inhibit the invasion and migration of A549 cancer cells by involving the inhibition of MMP-2 and β-catenin protein expression with the range dose concentration 1-10 μM for 24–48 h (Chuang et al., 2018)
	L. reflexa	**Anticancer**: Strong inhibitory effect on tumor cell lines MGC803 and SMMC-7721 with IC_{50} values 2.65 and 4.13 μM, respectively (Fu et al., 2019)
	L. strychnifolia	**Antitumor**: Decreased G2/M phase cell cycle arrest and reactive oxygen species (ROS) generation triggered apoptotic cell death of colorectal cancer (CRC) cells with a dose concentration of 3-9 μM (Kwak et al., 2022)
Linderalactone **(37)**	*L. aggregate*	**Anticancer**: Strong inhibition in the proliferation of lung cancer cells A-549 with IC_{50} value 15 μM (Deng et al., 2019) **Anti-inflammatory**: Exhibited liver protection by reducing swelling with EC_{50} value 67.0 μM (Gan et al., 2009b)
Lindenene **(78)**	*L. communis*	**Anticancer**: Showed significant activity against H460, ES2, and DU145 cancer cells with IC_{50} value 2.1, 2.8, and 3.0 μg/mL, respectively (Deng et al., 2011)
Lindera aggrenolide H **(128)**	*L. aggregate*	**Anticancer**: Exhibit significant transforming growth factor-β inhibitory activity with IC_{50} value 25.9 μM (Liu et al., 2021b)
Linderanoid E **(139)**	*L. aggregate*	**Anticancer**: Induced TGF-*β* smad2 phosphorylation at a concentration of 25 μM and have low activity against A549 cells with IC_{50} value 49.9 μM (Liu et al., 2021a)
Linderalide D **(154)**	*L. aggregata*	**Anticancer**: Moderate NF-κB inhibitory activity with the inhibitory rate reaching almost 40% at a concentration of 50 μM with IC_{50} value 18.0 (Liu et al., 2019a)
Lindera aggrenolide I **(129)**	*L. aggregata*	**Anticancer**: Transforming growth factor-β inhibitory activity with IC_{50} value 21.5 μM (Liu et al., 2021b)
(1*R*,3*S*,4*R*,5*R*,8*S*,10*S*)-4-Methoxy-1,3-cycloeudesma-7(11)-en-12,8-olide **(68)**	*L. strychinifolia*	**Anti-inflammatory: St**rongly inhibit lipopolysaccharide-stimulated nitric oxide production in murine RAW 264.7 macrophage cells, with IC_{50} value of 6.3 μM (Liu et al., 2016)
(1*R*,3*S*,4*R*,5*R*,8*S*,10*S*)-4,8-Dihydroxy-1,3-cycloeudesma-7(11)-en-12,8-olide **(69)**	*L. strychinifolia*	**Anti-inflammatory:** Strongly inhibit lipopolysaccharide-stimulated nitric oxide production in murine RAW 264.7 macrophage cells, with IC_{50} value of 6.3 of 9.6 μM (Liu et al., 2016)
Linderane **(38)**	*L. aggregata*	**Anti-inflammatory:** Showed activity against H_2O_2-

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		induced oxidative damage on HepG2 cells with EC_{50} value of 167.0 (Gan et al., 2009b) **Anti-inflammatory**: Exhibit liver protection by reducing swelling with EC_{50} value 98.0 µM (Gan et al., 2009b)
Linderagalactone D **(17)**	*L. aggregata*	**Anti-inflammatory**: Exhibit of H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 67.5 µM (Gan et al., 2009b)
Linderolide C **(21)**	*L. aggregata*	**Anti-inflammatory**: Exhibited in LPS-induced RAW264.7 macrophage cells with IC_{50} value 37.8 µM (Sumioka et al., 2011)
Linderagalactone E **(18)**	*L. aggregata*	**Anti-inflammatory**: Exhibit of H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 42.4 µM (Gan et al., 2009b)
Hydroxylindestenolide **(15)**	*L. aggregata*	**Anti-inflammatory**: Exhibit of H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value of 42.4 µM (Gan et al., 2009b)
8-Hydroxy-lindestenolide **(11)**	*L. aggregata*	**Anti-inflammatory**: Exhibit of H_2O_2-induced oxidative damage on HepG2 cells with EC_{50} value 67.5 µM (Gan et al., 2009b)
Linderolide D **(23)**	*L. aggregata*	**Anti-inflammatory**: Exhibited in LPS-induced RAW264.7 macrophage cells with IC_{50} value 38.7 µM (Sumioka et al., 2011)
Linderolide E **(24)**	*L. strychinifolia*	**Anti-inflammatory: S**howed strong activity towards nitric oxide production in RAW264.7 cells with IC_{50} value 18.3 µM (Sumioka et al., 2011)
Linderaggredin A **(19)**	*L. aggregata*	**Anti-inflammatory**: Exhibited human neutrophils with IC_{50} value 7.45 µM (Kuo et al., 2020)
Linerenone **(33)**	*L. communis*	**Anti-inflammatory**: Significant activity against H460, ES2, and DU145 cancer cells with IC_{50} values 2.1, 2.8, and 3.0 µg/mL, respectively (Deng et al., 2011)
Linderaggredin C **(162)**	*L. aggregata*	**Anti-inflammatory**: Inhibit the superoxide anion generation in human neutrophils with IC_{50} value 7.45 µM (Kuo et al., 2020)
Linderolide O **(99)**	*L. aggregata*	**Anti-inflammatory**: Exhibited by reducing redness, swelling, and pain in the body parts with IC_{50} value 6.3 µM (Lv et al., 2023)
Linderolide P **(100)**	*L. aggregata*	**Anti-inflammatory**: Exhibited by reducing redness, swelling, and pain in the body parts with IC_{50} value 9.6 µM (Lv et al., 2023)
3-Oxo-4, 5αH, 8βH-eudesma- 1,7(11)-dien-8, 12-olide **(9)**	*L. aggregata*	**Antitumor**: Showed strong activity against non-small cell lung cancer (A549) with IC_{50} value 7.2 µM (Ohno et al., 2005)
Eudeglaucone **(51)**	*L. glauca*	**Anti-neuroinflammatory**: Inhibited nitric oxide production by lipopolysaccharide with IC_{50} value 15.9 µM (Yu et al., 2016)
Linderagalactone E **(18)**	*L. aggregata*	**Cytotoxicity**: Active in HepG2 cells with IC_{50} value 67.5 µM (Gan et al., 2009b)
ALKALOIDS		
Norisoboldine **(195)**	*L. aggregata*	**Anti-arthritic**: Strong agents in the development of Treg cells through promoting fatty acid oxidation with IC_{50} value 10 µM (Wei et al., 2015)
D-dicentrine **(185)**	*L. megaphylla*	**Antitumor:** Exhibited hepatoma, melanoma, lung/colon carcinoma, oesophageal carcinoma, lymphoma, and leukaemia cell lines with IC_{50} value range of 0.41-29.04 µM (Huang et al., 1998)
Isoboldine **(186)**	*L. aggregata*	**Anti-inflammatory**: Reducing the expression of bone matrix-degrading enzymes with IC_{50} value 6.8 µM (Lv et al., 2023)

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Norboldine **(192)**	*L. aggregata*	**Anticancer**: Exhibited BxPC-3 pancreatic cancer cell with IC_{50} value 27.0 µM (Zahari et al., 2014) **Anti-inflammatory**: Inhibited lipopolysaccharide (LPS)-stimulated nitric oxide production in murine RAW 264.7 macrophage cells with IC_{50} value 9.6 µM (Yang et al., 2020)
N-methyl-laurotetanine **(191)**	*L. aggregata*	**Anti-inflammatory**: Inhibit the superoxide anion generation in human neutrophils with IC_{50} value 8.36 µM (Kuo et al., 2020)
Boldine **(184)**	*L. aggregata*	**Anti-inflammatory**: Induced production of NO by lipopolysaccharide in RAW 264.7 cells with IC_{50} value 8.7 µM (Yang et al., 2020) **Anti-inflammatory**: Reducing the expression of bone matrix-degrading enzymes with IC_{50} value 9.5 µM (Lv et al., 2023)
Lindera aggrine B **(167)**	*L. aggregata*	**Anti-inflammatory**: Exhibited superoxide anion generation in human neutrophils with IC_{50} value 9.2 µM (Kuo et al., 2020)
Laurolistine **(189)**	*L. aggregata*	**Cytotoxic**: Exhibited human colon carcinoma (HCT-116) cell line with IC_{50} value 27.1 µM (Yang et al., 2019)
Costaricine **(218)**	*L. aggregata*	**Cytotoxic**: Exhibited human colon carcinoma (HCT-116) cell line with IC_{50} value 51.4 µM (Yang et al., 2020)
Norisoboldine **(195)**	*L. aggregata*	**Anti-inflammatory**: Induced production of NO by lipopolysaccharide in RAW 264.7 cells with IC_{50} value 7.8 µM (Yang et al., 2020) **Anti-inflammatory**: Inhibit vascular endothelial growth factor (VEGF)-induced endothelial cell migration with IC_{50} value 15.1 µM (Lu et al., 2013) **Anti-inflammatory**: Increase the Treg cells in $CD4^+$ T cells and decrease Th17 cells, thus it can help in preventing autoimmune disease with IC_{50} value 18.4 µM (Lv et al., 2015)
FLAVONOIDS		
Flavokawain B **(234)**	*L. oxyphylla*	**Anticancer**: Strong activity in MCF-7 human breast adenocarcinoma cells with inhibition of 79.7% (Hosseinzadeh et al., 2013) **Anti-inflammatory**: Acts on DPPH radical scavenging activity with IC_{50} value 8.5 ± 0.004 µg/mL (Hosseinzadeh et al., 2013)
Avicularin **(264)**	*L. erythrocarpa*	**Anti-inflammatory:** Reduced releasing of LDH in H9c2 cells with IC_{50} value 0.7 µM (Kim et al., 2011)
Quercetin **(271)**	*L. erythrocarpa*	**Anti-inflammatory:** Reduced releasing of LDH in H9c2 cells with IC_{50} value 22.3 µM (Kim et al., 2011)
	L. aggregata	**Antivirus**: Interact and target the S2 domain in SARS-CoV-2 spike proteins with IC_{50} value 93.0 µM (Kumar & Pandey, 2013)
Quercetin-3-O-rhamnoside **(272)**	*L. aggregata*	**Antioxidant**: Strong antioxidant capacity and modulation of the Nrf-2 pathway with IC_{50} value 7.5 µM (Haque et al., 2020)
Kaempferol **(259)**	*L. neesiana*	**Antivirus**: Act as a 3C protease (3Cpro) inhibitor against enterovirus A71 with IC_{50} value 85.0 µM (Adhikari et al., 2019)
PHENOLICS		
2,6-Dimethoxy-4-hydroxyphenyl-1-O-ß-D-gluco-pyranoside **(294)**	*L. obtusiloba*	**Anti-allergic**: Inhibit histamine release and proinflammatory cytokine production in mast cells with inhibition 68.1% (Choi et al., 2013) **Anti-allergic**: Highly suppressed release of histamine

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		from mast cells with IC_{50} value 10.80 μM (Haque et al., 2023)
Koaburaside **(297)**	*L. obtusiloba*	**Anti-allergic**: Inhibit histamine release and proinflammatory cytokine production in mast cells with inhibition 66.9% (Choi et al., 2013) **Anti-allergic**: Highly suppressed release of histamine from mast cells with IC_{50} value 9.0 μM (Haque et al., 2023)
1-Methoxy-2,5,7-trihydroxyxanthone **(287)**	*L. fruticose*	**Antioxidant**: Moderate to low-density lipoprotein activity with IC_{50} value 25.5 μM (Song et al., 2006)
3-Hydroxy-5-methoxybiphenyl **(285)**	*L. fruticose*	**Antioxidant**: Moderate to low-density lipoprotein activity with IC_{50} value 15.5 μM (Song et al., 2006)
3,5-Dimethoxy-biphenyl **(286)**	*L. fruticose*	**Antioxidant**: Moderate to low-density lipoprotein activity with IC_{50} value 48.1 μM (Song et al., 2006)
MISCELLANEOUS		
Epicatechin **(342)**	*L. erythrocarpa*	**Anti-inflammatory:** Reduced releasing of LDH in H9c2 cells with IC_{50} value 0.7 μM (Kim et al., 2011)
Proanthocyanidins **(349)**	*L. aggregata*	**Antivirus**: Inhibited HIV-1 integrase with IC_{50} value 5.2 to 31.3 μM (Zhang et al., 2003c)
Cinnamtannin B1 **(350)**	*L. glauca*	**Antioxidant**: Inhibit low-density lipoprotein properties with IC_{50} value 2.0 mg/mL (Huh et al., 2014)
Cinnamtannin B2 **(351)**	*L. glauca*	**Antioxidant**: Inhibit low-density lipoprotein properties with IC_{50} value 1.1 mg/mL (Huh et al., 2014)
Procyanidin B1 **(345)**	*L. aggregata*	**Antioxidant**: Inhibitory activities against HIV-1 integrase with IC_{50} value 25.3 μM (Zhang et al., 2003c)
Procyanidin B2 **(346)**	*L. aggregata*	**Antioxidant**: Inhibitory activities against HIV-1 integrase with IC_{50} value 27.1 μM (Zhang et al., 2003c)
Litsenolide **(321)**	*L. nacusua*	**Antitumor**: Moderate against HL-60 and MCF-3 cell lines with respective IC_{50} values of 20.9 and 17.7 μM (Lei et al., 2017)
Reflexanbene A **(328)**	*L. reflexa*	**Cytotoxic**: Moderate against MGC803 and SMMC-7721 cell lines with IC_{50} values 29.6 and 34.3 μM, respectively (Fu et al., 2019)
Reflexanbene C **(329)**	*L. reflexa*	**Cytotoxic**: Moderate against MGC803 and SMMC-7721 cell lines with IC_{50} values 47.5 and 54.9 μM, respectively (Fu et al., 2019)

4. CONCLUSION

Numerous biologically active compounds have been isolated from *Lindera* species previously by several researchers. Sesquiterpenes, flavonoids, phenolics, and alkaloids are among the compounds which reported mainly on anticancer, antifibrotic, anti-inflammatory, antitumor, antioxidant, anti-arthritic, cytotoxic, anti-allergic, and antihyperlipidemic properties. Future studies related to ethnopharmacological research should focus on exploring the traditional uses of *Lindera* species among different locations. These studies should also compile information about their formulation and mode of administration in traditional medicine, which we found lacking in most of the reviewed literature. On the other hand, scientific studies should focus on bioassay-guided drug discovery based on the existing traditional knowledge. Mechanism-based *in vitro* and *in vivo* studies should be performed to understand the underlying mechanisms linked to ethnopharmacological uses.

Declaration of Interest
The authors hereby declare that there is no conflict of interest.

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