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An Update Review of the *Litsea genus*

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Abstract: The *Litsea genus* from the Lauraceae family is widely distributed in Asia and America's tropic and subtropic regions and is used to heal illnesses and as sustenance. Several *Litsea* species were gathered, and their pharmacological effects were studied in this review of phytochemical substances. This literature review updated the phytochemical components and pharmacological function of *Litsea* plants. The reference articles have DOI and were found using the Scopus database, which guarantees their legitimacy and verifiable content. At least 70 articles from the past 10 years were used in this literature analysis. This investigation revealed that several *Litsea* species included high alkaloids, lactones, sesquiterpenes, flavonoids, lignans, and volatile oil, among other structurally diverse ones generated by *Litsea* plants. The substances, extract, and essential oils have a variety of functions, including an antibacterial, antioxidant, antidiabetic, and neuroprotective effect. To fully under Litsea's antidiabetic drug mechanism, more research was necessary.

Keywords: Litsea; phytochemical compounds; pharmacological activities.

1. Introduction

Approximately 132 species of the *Litsea genus*, which belongs to the Lauraceae family, may be found in Asia and North America [1]. The genus, which is primarily found in tropical and subtropical areas, has been used as a traditional medicine to treat a variety of conditions, including arthritic conditions, diabetes, edema, colds, dyspepsia, cardiovascular, gastroenteritis, and more. Alkaloids, lactones, sesquiterpenes, flavonoids, lignans, and volatile oil are among the structurally varied substances that *Litsea* plants produce, according to some studies [2–5].

Due to its pharmacological action and widespread usage in traditional medicine, *Litsea* species, including *Litsea cubeba* and *Litsea coreana* are among the most well-known plants in the genus [6,7]. An earlier study examined the chemical and pharmacological properties of *Litsea* plants [1,8]. Given that there are still a significant number of *Litsea* plants that have not been further studied, this review encourages more research on this genus.

2. Materials and Methods

Data in this article were obtained from international scientific journals in Scopus, PubMed, Science Direct, and Elsevier portal, published in the last 12 years, including 20 articles in the last 2 years.

3. Results and Discussion

3.1. Phytochemical compounds of the Litsea genus.

The *Litsea* plants are the largest genus in the tribe of the Lauraceae family and contains diverse and biologically active chemical constituent. Secondary metabolites such as alkaloids have been isolated from *Litsea* plants and serve as useful taxonomic markers for the genus. Approximately 63 alkaloids have been isolated from the *Litsea* plant, and among them are boldine and laurolitsine, the most commonly found in the various genus *Litsea* [9]. These natural products and their derivatives can be a guide in the development of potential therapies for various diseases [10]. Recently, the pharmacologically active phytochemicals from various *Litsea* species have been studied (Table 1, Figure 1).

Butanolides and butenolactones were also the most representative group of secondary metabolites present in the *Litsea* . Several butanolides have been isolated from the heartwood of *Litsea glutinosa* such as (3R,4S,5S)-2-hexadecyl-3-hydroxy-4-methylbutanolide and litsealactones C-G [11]. Licunolides A and B from the roots of *Litsea acuminata* have been reported from butanolides constituent [12].

To date, monoterpenes, sesquiterpenes, diterpenoids, and triterpenoids have been reported in *Litsea* plants. Sesquiterpenes were detected in almost all parts, especially in twigs and leaves. Most of the monoterpene constituents in *L. cubeba* were oxygenated [13]. Afterward, megastigmane O-glucopyranosides were isolated for the first time from *L. glutinosa* [14]. Diterpenes are rarely found in *Litsea* species, cubelin has been found in the methanolic extract of *L. cubeba* fruits [15]. Meroterpenoids such as panamonon A and B have been exposed from the leaves and twigs of *Litsea panamonja* [16]. Three new guaiane-type sesquiterpenoids and a monoterpenoid, lancilimbnoid C, D, E, and (4R,5R)-4,5-dihydroxy-4-isopropyl-3-methyl-cyclohex-2-en-1-one was obtained for the first time from *Litsea lancilimba* Merr[17].

Flavonoids and their derivatives were also major components of the *Litsea genus*. The rare flavonoid pinocembrin chalcone and kaempferol 3,4`-di-O-L-rhamnopyranoside were isolated from *Litsea fruticosa* (Hemsl.) [9]. Amides were obtained from several *Litsea* species, such as N-feruloyltyramine and N-trans-3,4-methylenecinnamoyl-3-methoxytyramine have been presented from *Litsea greenmaniana* Allen [18].

The new neolignans and oxyneolignan biseugenol A and B were isolated from the bark of *Litsea costalis* (Nees) Kosterm. These compounds exhibited a fairly potent anticancer effect on cell lines and antioxidant (2,2-diphenyl-1-picrylhydrazyl (DPPH)) [19]. The presence of the essential oil was one of the characteristic chemosystematics features of *Litsea* species. Most species of the *Litsea genus* produce an essential oil that can be extracted from different parts of the plant, including the fruit, leaf, stem, root, and flower, with significant diversity in composition and yield. *L. cubeba* is one of the most important medicinal plants of the Lauraceae family. Its essential oil was extracted from fresh fruits of the plant by distillation, and it has a clear oily flavor [13].

The composition and yields of these essential oils can differ with harvesting seasons and geographical sources. The main components of the fruit oil *L. cubeba* from Nanto, Taiwan were found to be geranial (37,16%), neral (28,29%) D-limonen (22,90%) and β-myrcene (2,06%)[20]. Aldehydes (citral, citral isomer, citronellal, and citronellal isomer) were the main components of *L. cubeba* oil from Guangzhou - China, comprising approximately 70% of the composition. Alcohols (linalool, terpineol, 2,7-dimethyl-2,7-octanediol, and farnesol)

accounted for approximately 4%. Alkenes (limonene, sabinene, 1R-α-pinene, 4-methyl-1,4-hepta-diene, β-pinene and farnesene) accounted for approximately 23% [21].

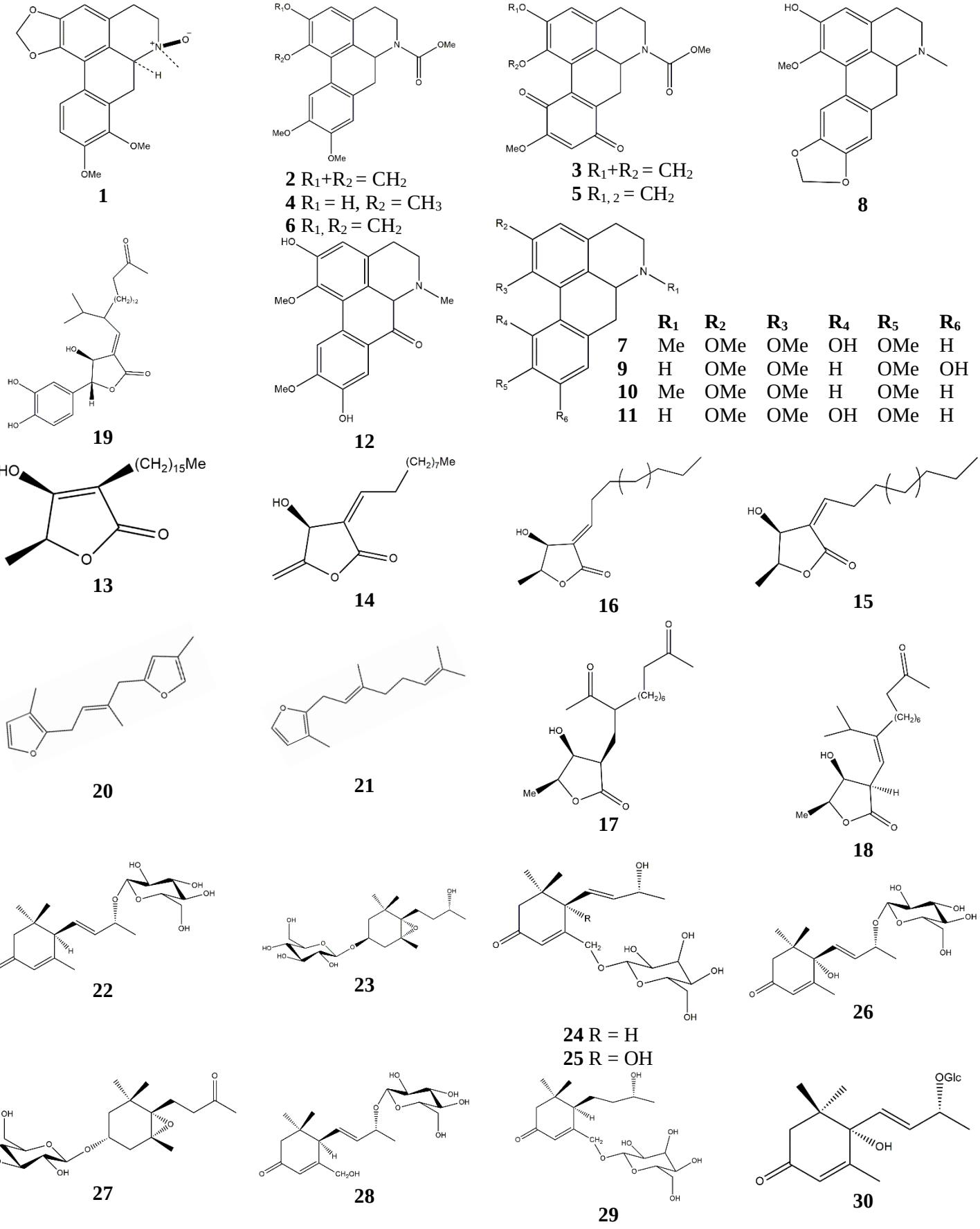
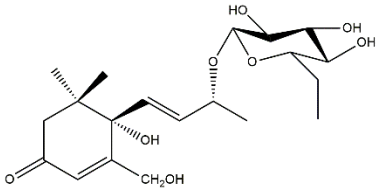


Figure 1. Chemical structure of compounds isolated from Litsea.



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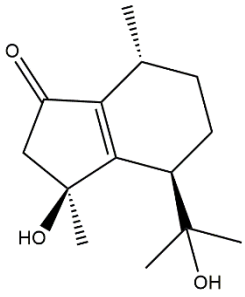

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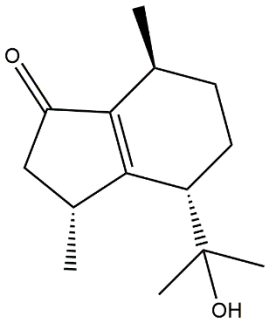

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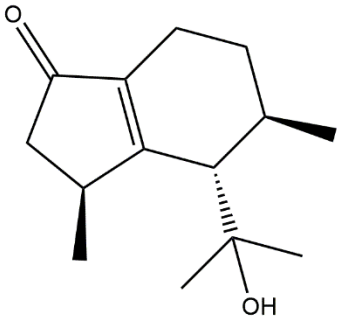

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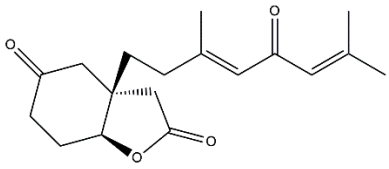

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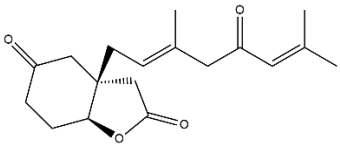

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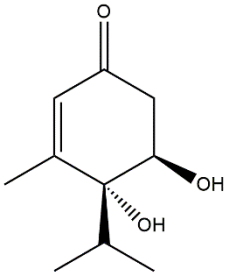

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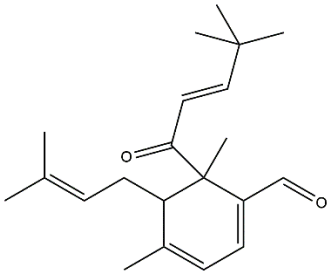

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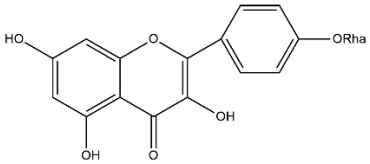

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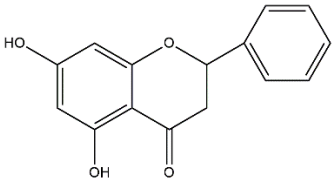

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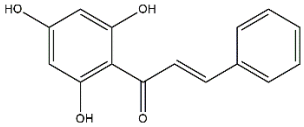

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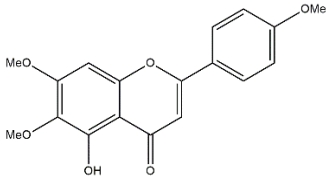

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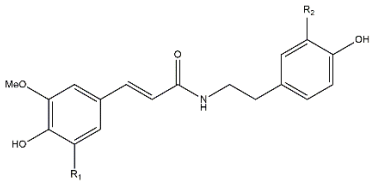
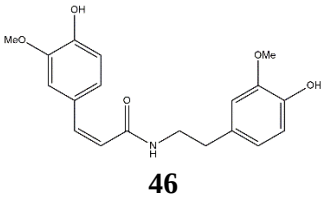


44 R_1=H, R_2=H

45 R_1=OMe, R_2=H



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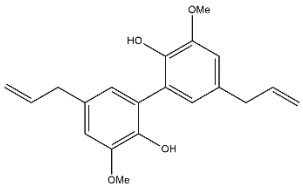

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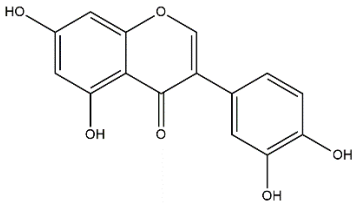

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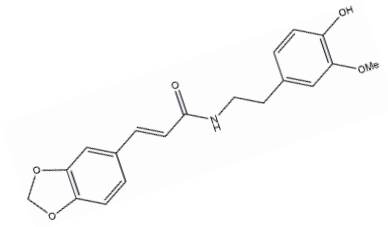

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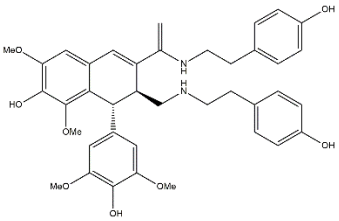

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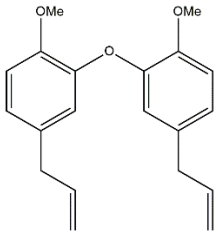

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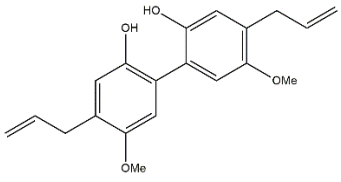

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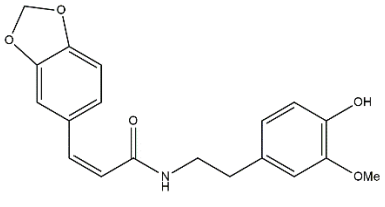

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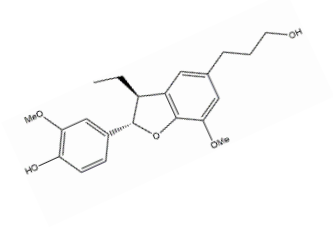

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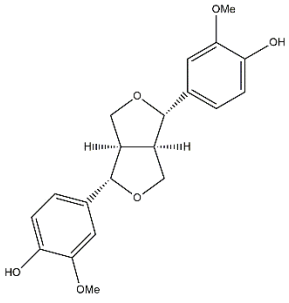

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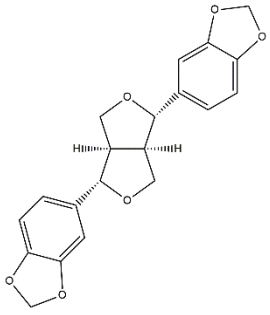

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Figure 1. (Continued)

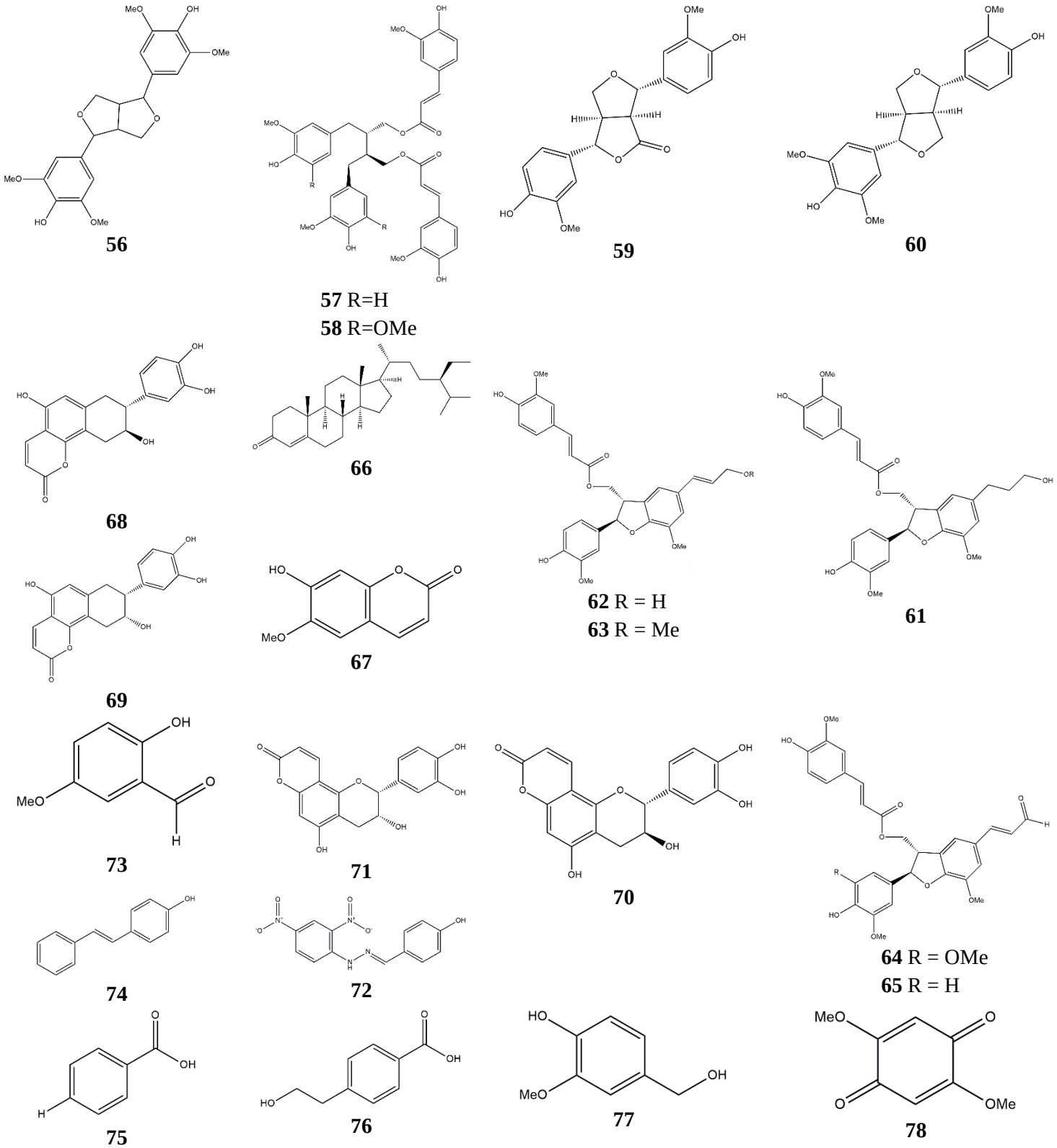
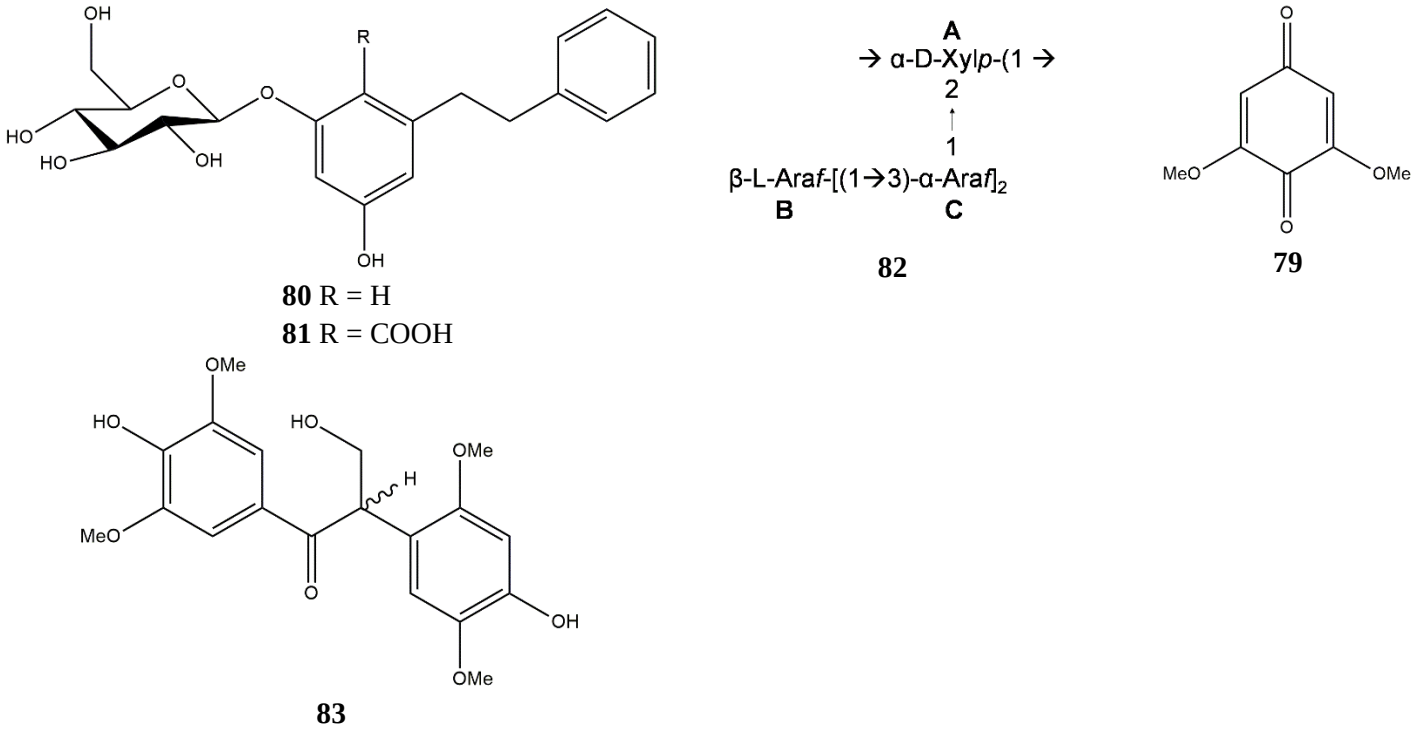


Figure 1. (Continued)

The main constituents of *L. cubeba* from Guangxi - China, were found to be E-citral (geranial) (27.49%), Z-citral (neral) (23.57%), and D-limonene (18.82%) followed by β-thujene (3.34%), β-pinene (2.85%), α-pinene (2.57%), 6-methyl-5-hepten-2-one (2.40%) and linalool (2.36%) [22]. Thus citral and its isomers, neral (cis) and geranial (trans), were the main components that accounted for approximately 70% of the total *L. cubeba* essential oil composition [23].



80 R = H
81 R = COOH
82
79

83

Figure 1. (Continued)

Essential oil from the leaves and fruits of *L. cubeba* was collected from Northeast India and analyzed by GC and GC-MS. Sabinene was the main component of two leaves oils (LC1 and LC2), with α-pinene, terpinen-4-ol, α-terpineol and myrcene being significant compounds in the LC1 oil and 1,8-cineole and α-pinene as the most important compounds in LC2. Citronellol and citronellal were the main components in the fruit oils of LC3 and LC4, accounting for 70% and 10% of the total oil composition, respectively. Geranial (c. 44%) and neral (c. 40%) were the main components of LC5, but citronellal accounted for only approximately 3% [24].

The compositional pattern of essential oil from five *Litsea* plants in Vietnam was reported. The leaves oil of *Litsea helferi* Hook.f. was rich in limonene (17.5%), β-caryophyllene (14.2%), bicyclogermacrene (13.1%), bicycloelemene (12.4%) and α-phellandrene (8.0%). The main constituents of *Litsea ferruginea* Liou. Leaves oil was dominated by monoterpenes comprising of sabinene (34.5%), α-pinene (10.1%), γ-terpinene (7.8%), limonene (6.9%), and terpinen-4-ol (6.6%). The significant constituents of the leaves oil from *Litsea verticillata* Hance were also monoterpenes compound represented by linalool (23.4%), α-pinene (26.1%), and β-pinene (11.7%). In addition, the monoterpene hydrocarbons (*E*)-β-ocimene (57.4%), along with α-pinene (7.8%) and β-pinene (7.3%), were the main constituent in the leaves oil of *L. glutinosa* (Lour.) C. B. Rob. The main compounds in the leaves, stem, fruits, and roots oils of *L. cubeba* (Lours.) Pers. were (*Z*)-citral 32.9-66.1%), sabinene (1.4-4.2%), limonene (7.0-13.6%) and linalool (1.9-9.5%) [25].

Many other compounds have been obtained from *Litsea* species. Two flavanocoumarins, isophyllocoumarin and apiphyllocoumarin were isolated from the leaves of *L. coreana* [26]. Two dihydrostilbenoid glycoside, 5-(2-phenylethyl)-3-hydroxyphenol-1-*O*-β-D-glucopyranoside and 6-(2-phenylethyl)-2,4-dihydroxy benzoic acid-2-*O*-β-D-glucopyranoside, were isolated from the leaves of *L. coreana* [24,27]. A benzoic acid derivative termed eusmoside C was obtained from the heartwoods of *L. glutinosa* [11]. A new water-

soluble polysaccharide, arabinoxylan, from the green leaves of *L. glutinosa* was found to contain xylose and arabinose in a molar ratio of nearly 1:3 [27].

Table 1. Phytochemical compounds.

No.	Compounds	*Litsea* plants	Ref
	Alkaloid		
1	(+)-9-methoxyisolaurenine-*N*-oxide	*L. cubeba*	[28]
2	(+)-*N*-(methoxylcarbonyl)-*N*-norglaucine	*L. cubeba*	[28]
3	(+)-*N*-(methoxylcarbonyl)-*N*-norbulbodione	*L. cubeba*	[28]
4	(+)-*N*-(methoxylcarbonyl)-*N*-nordicentrin	*L. cubeba*	[28]
5	(+)-*N*-(methoxylcarbonyl)-*N*-norisocorydione	*L. cubeba*	[28]
6	(+)-*N*-(methoxylcarbonyl)-*N*-norpredicentrine	*L. cubeba*	[28]
7	Isocorydine	*L. greenmaniana*	[29]
8	Isodomesticine	*L. greenmaniana*	[29]
9	Laurotetanine	*L. greenmaniana*	[29]
10	*N*-methyllaurotetanine	*L. greenmaniana*	[29]
11	Norisocorydine	*L. greenmaniana*	[29]
12	2,9-dihydroxy-1,10-dimethoxy-4,5-dihydro-7-oxoaporphine	*L. greenmaniana*	[29]
	Butanolides and Butenolactones		
13	(3*R*,4S,5S)-2-hexadecyl-3-hydroxy-4-methylbutanolide	*L. glutinosa*	[11]
14	Isolancifolide	*L. acuminata*	[12]
15	Licunolides A	*L. acuminata*	[12]
16	Licunolides B	*L. acuminata*	[12]
17	Litsealactone C	*L. glutinosa*	[11]
18	Litsealactone D	*L. glutinosa*	[11]
19	Litsealactone G	*L. glutinosa*	[11]
20	Longifolin	*L. acuminata*	[12]
21	Sesquirose furan	*L. acuminata*	[12]
	Sesquiterpenes		
22	(6R,7E,9*R*)-9-hydroxy-megastigma-4,7-dien-3-one 9-O-β-D-glucopyranoside	*L. glutinosa*	[14]
23	Alangionoside E	*L. glutinosa*	[14]
24	Apocynoside I	*L. glutinosa*	[14]
25	Apocynoside II	*L. glutinosa*	[14]
26	Blumenol C Glucoside	*L. glutinosa*	[14]
27	Euodionoside A	*L. glutinosa*	[14]
28	Euodionoside F	*L. glutinosa*	[14]
29	Euodionoside G	*L. glutinosa*	[14]
30	Roseoside	*L. glutinosa*	[14]
31	Spinoside A	*L. glutinosa*	[14]
32	Lancilimbnoid C	*L. lancilimba*	[17]
33	Lancilimbnoid D	*L. lancilimba*	[17]
34	Lancilimbnoid E	*L. lancilimba*	[17]
	Diterpenoids		
35	Cubelin [(+)-6-(4-hydroxy-4-methyl-2-pentenoyl)-4,6-dimethyl-5-(3-methyl-2-butenyl)-1,3-cyclohexadienecarbaldehyde]	*L. cubeba*	[15]
	Monoterpenoids		
36	(4*R*,5*R*)-4,5-dihydroxy-4-isopropyl-3-methyl-cyclohex-2-en-1-one	*L. lancilimba*	[17]
	Meroterpenoids		
37	Panamonone A	*L. panamonja*	[16]
38	Panamonone B	*L. panamonja*	[16]
	Flavonoids		
39	Kaempferol 3,4'-di-O-β-D-xylopyranoside	*L. fruticosa*	[9]
40	Pinocembrin	*L. guatemalensis*	[30]
41	Pinocembrin chalcone	*L. fruticosa*	[9]
42	Salvigenin	*L. cubeba*	[31]
43	5,7,3',4'-tetrahydroxy-isoflavone	*L. guatemalensis*	[30]
	Amides		
44	*N*-feruloyltyramine	*L. greenmaniana*	[18]
45	*N*-feruloyl-3-methoxytyramine	*L. cubeba*	[31]
46	3-methoxy-N-sinapoyltyramine	*L. cubeba*	[31]
47	*N*-trans-3,4-methylenecinnamoyl-3-methoxytyramine	*L. greenmaniana* *L. cubeba*	[18] [31]
48	1,2-dihydro-6,8-dimethoxy-7,1-(3,5-dimethoxy-4-hydroxyphenyl)-*N*1, *N*2-bis-[2-(4-hydroxyphenyl)ethyl]-2,3-naphthalene dicarboxamide	*L. cubeba*	[32]
49	*N*-cis-3,4-methylenedioxycinnamoyl-3-methoxytyramine	*L. cubeba*	[31]
	Lignans		
50	Dihydrodehydroconiferyl alcohol	*L. greenmaniana*	[18]
51	Eugenol	*L. cubeba*	[11]
52	Biseugenol A	*L. costalis*	[19]

No.	Compounds	*Litsea* plants	Ref
53	Biseugenol B	*L. costalis*	[19]
54	(+)-sesamin	*L. greenmaniana*	[18]
55	(+)-pinoreinol	*L. greenmaniana*	[18]
56	syringaresinol	*L. cubeba*	[31]
57	9-9'-O-di-(*E*)-feruloyl-(+)-secoisolariciresinol	*L. cubeba*	[31]
58	9-9'-O-di-(*E*)-feruloyl-5,5'-(+)-dimethoxysecoisolariciresinol	*L .cubeba*	[31]
59	Balanophonin B	*L .cubeba*	[31]
60	(+)-medioresinol	*L. cubeba*	[31]
61	(−)-(7*R*,8*S*)-9-O-(*E*)-feruloyl-4,9,9'-trihydroxy-3',3-dimethoxy-4',7-epoxy-8,5'-neolignan	*L. cubeba*	[33]
62	(−)-(7*R*,8*S*,7'*E*)-9-O-(*E*)-feruloyl-4,9,9'-trihydroxy-3,3'-dimethoxy-4',7-epoxy-8,5'-neolignan-7'-ene	*L. cubeba*	[33]
63	(−)-(7*R*,8*S*,7'*E*)-9-O-(*E*)-feruloyl-4,9-dihydroxy-3,3',9'-trimethoxy-4',7-epoxy-8,5'-neolignan-7'-ene	*L. cubeba*	[33]
64	(−)-(7*R*,8*S*,7'*E*)-9-O-(*E*)-feruloyl-4,9-dihydroxy-3,5,3'-trimethoxy-4',7-epoxy-8,5'-neolignan-7'-ene-9'-al	*L. cubeba*	[33]
65	(−)-(7*R*,8*S*,7'*E*)-9-O-(*E*)-feruloyl-4,9-dihydroxy-3,3'-dimethoxy-4',7-epoxy-8,5'-neolignan-7'-ene-9'-al	*L. cubeba*	[33]
	Steroid		
66	B-sitostenone	*L. cubeba*	[32]
	Other compounds		
67	Scopoletin	*L. guatemalensis*	[30]
68	Isophyllocoumarin	*L. coreana*	[26]
69	Isoepiphyllocoumarin	*L. coreana*	[26]
70	Phyllocoumarin	*L. coreana*	[26]
71	Epiphyllocoumarin	*L. coreana*	[26]
72	p-hydroxybenzaldehyde	*L. greenmaniana*	[18]
73	5-methoxy-2-hydroxy benzaldehyde	*L. costalis*	[19]
74	(*E*)-4-styrylphenol	*L. costalis*	[19]
75	Benzoic acid	*L. greenmaniana*	[18]
76	4-hydroxy ethylbenzoate	*L. greenmaniana*	[18]
77	4-hydroxy-3-methoxy-benzyl alcohol	*L. greenmaniana*	[18]
78	2,5-dimethoxy-p-benzoquinone	*L. cubeba*	[32],
79	2,6-dimethoxy-p-benzoquinone	*L. cubeba*	[31,32]
80	5-(2-phenylethyl)-3-hydroxyphenol-1-O-β-D-glucopyranoside	*L. coreana*	[32]
81	6-(2-phenylethyl)-2,4-dihydroxy benzoic acid-2-O-β-D-glucopyranoside	*L. coreana*	[34]
82	Arabinoxylan	*L. glutinosa*	[34]
83	Cubebanone	*L. cubeba*	[27] [31]

3.2. Pharmacological activities of Litsea genus.

The *Litsea* plants were reported to have several pharmacological properties as anticancer, anti-inflammatory, antimicrobial, insecticidal, antioxidant, antidiabetic, antiviral, hepatoprotective, neuropharmacological, cytotoxic, and other pharmacological activities [1,2].

3.2.1. Anticancer activities.

The vapor of volatile oil compounds obtained from *L. cubeba* seeds was reported to kill human NSCLC cells, A549, via induction of apoptosis and cell cycle arrest [35]. Alkaloids were isolated from the bark of *L. cubeba* and determined *in vitro* activities with regard to BGC-823 cells (human gastric carcinoma), HepG2 cells (human hepatocellular carcinoma), MCF-7 cells (human breast cancer), SGC-7901 cells (human gastric adenocarcinoma), using revised MTT (3-(4,5-dimethylthiazol-2yl)2,5-diphenyltetrazolium bromide) method. The result showed that the alkaloids (+)-N-(methoxylcarbonyl)-N-norbulbodine and (+)-N-(methoxylcarbonyl)-N-norisocorydione with two carbonyl groups at C-8 and C-11 exhibited the most potent cytotoxic effect on all tested tumor cell lines, with IC_{50} values of 9.54-12.22 and 9.83-11.96 μM, respectively, meanwhile, (+)-N-(methoxylcarbonyl)-N-norglaucine, (+)-N-(methoxylcarbonyl)-N-nordicentrin and (+)-N-(methoxylcarbonyl)-N-norpredicentrine showed a moderate cytotoxic effect on six tumor cell lines [28].

Another report from a chemical constituent from *L. cubeba*, such as salvigenin, balanophonin B and other compounds were found to significantly inhibit the growth of the HePG2 cell line with IC_{50} values of 10.0-48.2 µM using the MTT method [31]. Cubelin from *L. cubeba* fruit could induce apoptosis in HeLa cells by activating the apoptotic caspase cascade with etoposide (VP-16) as the positive control [15]. The cytotoxicity result showed that biseugenol A and B as well as 5-methoxy-2-hydroxy benzaldehyde demonstrated excellent and high *in vitro* cytotoxic effect against HepG2, PC-3 and MCF-7 with IC_{50} values of 18 ± 2.1, 1.1 ± 0.19 and 28 ± 2 µM, respectively [19]. The Furano sesquiterpenes longifolin and sesquirosefuran demonstrated significant cytotoxic effects on HeLa cell lines *in vitro* with an IC_{50} value of 0.21 and 0.36 µg/mL, respectively. The number of furan rings might affect the cytotoxic effect on the HeLa cells [12]. The alkaloid boldine potently inhibited the viability of the human invasive breast cancer cell lines MDA-MB-231 (48-h IC_{50} 46.5 ± 3.1 µg/mL) and MDA-MB-468 (48-h IC_{50} 50.8 ± 2.7 µg/mL) [36]. These reported that boldine could be potentially used to treat breast cancer. Boldine and laurolitsine also showed cytotoxic activity in Hep-2 tumor cells [10]. A cell-based high-throughput screening was performed for ethanolic extract of L. glutinosa (ZK-06), L. monopetala (ZK-07), and L. garrettii (ZK-08) using a stable ARE luciferase reporter cell line derived from human breast cancer MDA-MB-231 cells. ZK-08 potently increased the ARE luciferase by more than threefold compared to the control treated with nontoxic doses. ZK-06 and ZK-07 presented moderate inductions of ARE luciferase activity (two- to threefold). Further studies expressed the Nrf2-dependent cytoprotective effect of ZK-08 on H_2O_2 [37].

The antitumor activities of arabinoxylan were tested against MDA-MB-231 and MCF-7 cells. Arabinoxylan exhibited significant antiproliferation activities in a concentration-dependent manner on two cell lines. At the concentration of 400 µg/mL, the inhibition rates of arabinoxylan on MDA-MB-231 reached 42.71%. These results indicated that polysaccharides might have potential antitumor effects [38]. MGN-3/BioBran (a type of arabinoxylan) has been reported to possess a potent anticancer effect by inhibiting inflammation, induction of apoptosis, and suppressing cancer cell proliferation [39].

3.2.2. Anti-inflammatory activities.

Litsea plants have been traditionally used in herbal medicine to treat inflammation, including gastroenterology, edema, and rheumatoid arthritis. *L. cubeba*, *L. glutinosa*, *L. akoensis*, *L. japonica*, and *L. guatemalensis* have been assessed for their anti-inflammatory effects, with various other *Litsea* plants requiring investigation [31,40]. Lin *et al*. reported that the root extract of *L. cubeba* could significantly attenuate adjuvant arthritis (AA) in rats with Freund's complete adjuvant (CFA)-induced arthritis (AA): this effect may be attributed to the action of alkaloids, a major constituent in this species [41]. Further study exposed the effect of the total flavonoid of *L. coreana* (TFLC) on CFA-induced arthritis in rats. TFLC (100, 200 mg/kg i.g x 10 days) could significantly reduce secondary paw swelling and the serum levels of TNF-α and IL-1β. Histopathological data revealed that TFLC treatment improved the morphologic changes in articular cartilages and synovium. In an anti-inflammatory activity test, the crude methanol extract of *L. glutinosa* leaves showed significant ($p<0.001$) therapeutic potential at doses of 250 and 500 mg/kg body weight (1.51 ± 0.04 and 1.47 ± 0.03 mm paw edema, respectively), with ketorolac reducing edema by 1.64 ± 0.05 mm after 3 h of carrageenan injection [42].

The anti-inflammatory effects of *L. japonica* fruits extract were investigated using LPS-stimulated Raw264.7 cells. Both the 30% EtOH extract and the CH_2Cl_2 fraction (LJM) showed significant inhibitory effects on the production of COX-2/PGE_2, NO/iNOS, and pro-inflammatory cytokines (IL-1, IL-6, and TNF-α). LJM exhibit an optimal combination of anti-inflammatory effects and low cytotoxicity: the latter effects are caused by the inhibition of nuclear factor kappa B (NF-κB) and JNK/p38 MAPK signaling in LPS-induced macrophages by molecular profiling [43]. In a later study, the anti-osteoarthritic effect of 70% ethanol extract of *L. japonica* (LJFE) was evaluated in a rat model of osteoarthritis (OA) induced monosodium iodoacetate. Compared with the OA control group, treatment with high doses of LJFE (100 and 200 mg/kg) led to a > 80% inhibition of the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). LJFE inhibited the loss of the lateral and medial subchondral bone of the knee and tibiae as the expression of inflammatory markers such as IL-6, IL-1β and TNF-α in the serum, which in turn reduced the expression of biomarkers associated with OA, such as MMPs and TIMPs in the cartilage [44]. Five new sesquineolignans were isolated from an ethyl acetate extract of the twigs of *L. cubeba* and showed moderate inhibitory effects against LPS-induces NO production in RAW264.7 macrophages, with IC_{50} values of 16.2, 20.2, 22.1, 15.1, and 16.6 μmol/L, respectively [33].

3.2.3. Antimicrobial activities

Several extracts and phytochemicals from *Litsea* species have demonstrated antibacterial, antifungal, and antimicrobial activities against numerous pathogenic strains. Essential oils from the leaves and fruits of *L. cubeba* were evaluated for their antimicrobial effect on *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger*. All microbial strains were found to be sensitive to the cytotoxic effect of the essential oils being studied. Leaves and fruit oils showed different levels of inhibition depending on their particular chemical composition [24]. The antibacterial effect and kinetics of L. cubeba oil on E. coli were studied by the toxic food method at both a MIC of 0.124% (v/v) and at a minimum bactericidal concentration (MBC). The *L. cubeba* oil showed a moderate antibacterial effect on *E. coli* with antibacterial and rapid bactericidal effects. The presence of aldehydes accounted for its antibacterial effects (approximately 70% of the total composition), with the minor components producing a synergistic antibacterial effect [21]. The antimicrobial activity of *Litsea resinosa* and *L. elliptica* were evaluated by agar well diffusion assay and mycelial radial growth assay. Essential oils from the root of both species showed significant antifungal activities with inhibition rates of 80.11% and 66.85%, respectively [45]. Recently *L. cubeba* essential oils' antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported. The destructive effect of LCEO on MRSA cytomembrane was acquired by TEM test and subsequently validated through qualitative and quantitative investigation of biological macromolecules and intracellular enzyme leakage during LCEO treatment. Furthermore, LCEO may impair MRSA respiratory metabolism and reduce HMO key regulator enzyme activity. Finally, the main component of LC-EO, citral, could further form the chimera with the DNA of MRSA to inhibit its biological activity [46].

The antibacterial activity of LCEO was adequate to eliminate *S. aureus* biofilm. The bacterial density inside the biofilm decreased by 75.89% after 4 hours of treatment with 2 mg/mL LC-EO. The adherence of *S. aureus* was attenuated during LCEO treatment, and the transcription level of ica operon genes (biofilm formation-related) was inhibited to varied

degrees [47]. Another antibacterial activity from LCEO against *E. coli* O15:H17 has been reported. The LCEO could effectively inhibit the growth of *E. coli* O15:H17, and its MIC was 0.5 mg/mL [48]. The antimicrobial activity of *L. cubeba* essential oil against *A. flavus*, *F. graminearum*, *A. ochraceus*, and *F. moniloforme* was indicated by the MICs value of 183.11 µg/mL for all toxin-producing fungi. The MICs of L. cubeba essential oil as fungicides against the four indicator strains indicated their ability to inhibit [49].

3.2.4. Antioxidant activities.

Various *Litsea* extracts were investigated for their free radical scavenging activities. The compounds biseugenol A-B and 5-methoxy-2-hydroxybenzaldehyde isolated from the bark of *L. costalis* were screened for DPPH radical scavenging activity; the results revealed the excellent 2,2-diphenyl-1-picrylhydrazyl (DPPH) activity of biseugenol A with an IC_{50} value of 4.77 ± 0.006% µg/mL and that of biseugenol B and 5-methoxy-2-hydroxybenzaldehyde with IC_{50} values of 41.92 ± 0.02 and 17 ± 0.03 [19]. The methanol extract of the root and stem of *L. elliptica* and *L. resinosa* exhibited high antioxidant activity with regard to DPPH radicals with EC_{50} values of 23.99, 41.69, 11.22, and 33.48 mg/L, respectively, comparable to standard butylated hydroxytoluene [45]. The methanolic extracts of the *L. elliptica* leaves expressed antioxidant activities against DPPH, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and ferric-reducing ion antioxidant power (FRAP) due to the existing phenolic and flavonoids compounds. Both young and mixed *L. elliptica* leaves had high antioxidant capacities (QEAC = 55.34 ± 3.81 and 12.06 ± 0,90 mg QEAC/g dry sample) [50]. Hawk tea had widely used as herbal tea in Southwest China, extracted from *L. coreana* Levl. var. lanuginose. The polysaccharides of hawk primary leaves tea exhibited higher antioxidant activities than other polysaccharides. The polysaccharides from high primary hawk tea might have potential applications in the food industry [5]. Hawk tea was typically divided into three types based on the harvest period: hawk bud (HB) tea, hawk primary (HP) leaves tea, and hawk mature (HM) leaves tea. The contents of total flavonoids, vitamin C and carbohydrates in hawk bud tea infusion (HBI) were higher than those in the primary hawk leaves tea infusion (HPI) and hawk mature leaves tea infusion (HMI). HPI had a higher proportion of total polyphenols and exhibited the strongest DPPH radical scavenging activity and ferric-reducing power, whereas HBI more effectively protected against erythrocyte hemolysis. The bioactive constituents and antioxidant activities of hawk tea infusions were significantly affected by the degree of maturity of the raw material [51]. The antioxidant activity of *Litsea glaucescens* Kunth had been reported by the presence of phenolic compound from methanolic extract of *L. glaucescens* leaves [52].

3.2.5. Antidiabetic activities.

Litsea japonica is an endemic plant that grows in the southern regions of Korea and Japan and was consumed as a vegetable. Mounting evidence indicated that advanced glycation end products (AGEs) contributed to the pathogenesis of diabetic nephropathy. The extract of *L. japonica* (LJE) reduced the development of diabetic nephropathy by inhibiting the accumulation of AGEs in db/db mice after administration of LJE (100 or 250 mg/kg per day) to diabetic mice for 12 weeks. Moreover, LJE treatment restored the loss of nephrin, an important slit diaphragm component in the kidneys [53]. Other studies reported that LJE inhibited the expression of vascular endothelial growth factor (VEGF) in the retina and

produces a preventive effect on diabetic retinopathy on oral administration of LJE (100 and 250 mg/kg) once a day for 12 weeks. LJE exhibited a 2.9-fold higher inhibitory effect on AGE formation than did aminoguanidine (AG) (IC_{50} 62.40 µg/mL, a well-known glycation inhibitor) and a 168-fold higher inhibitory effect on cross-linking if AGE-bovine serum albumin (BSA) with collagen (IC_{50} 17.38 µg/mL) than AG (IC_{50} 2.92 µg/mL). LJE treatment blocked the diabetes-induced breakdown of the blood-retine barrier (BRB), decreased the retinal VEGF expression in db/db mice, and inhibited the degradation of occludin, an important tight junction protein [54]. Further study elucidated the mechanism underlying the protective effect of LJE in model diabetic db/db mice. LJE significantly reduced the expression levels of AGEs and their receptors (RAGE) in the neural retinas of the db/db mice, markedly inhibited the apoptosis of retinal ganglion cells, and suppressed the activation of NF-κB [55]. Moreover, LJE inhibited the aldose reductase activity in rat lens *in vitro* in a dose-inhibited manner (IC_{50} 13.53 ± 0.74 µg/mL and the lenticular sorbitol accumulation and lens architectural changes in db/db mice. LJE may be beneficial in the treatment of diabetes-induced lens opacification [56].

Treatment with a methanolic fraction of *L. cubeba* (LCMF) (200, 400, and 800 mg/kg) for 28 days significantly reduced blood glucose levels in male Wistar rats. Decreased in VLDL cholesterol levels was shown by LCMF (400 mg/kg) and metformin control by 21.9% and 30%, respectively. Experimentation on diabetic model rats revealed potent antidiabetic and antihyperlipidemic activities of fruits of *L. cubeba*. Metabolic profiling of LCMS showed the presence of a major bioactive principle that might synergistically act against diabetic complications. Network pharmacological analysis showed the interaction of these active molecules with several potential disease target proteins associated with diabetes and interconnected via several cellular signaling pathways [57].

Boldine was a potent antioxidant found in *Litsea* and other plants, with several health-promoting properties such as anti-inflammatory, antitumor, antidiabetic, and cytoprotective activities. Treatment with boldine (50 mg/kg/day) was found to prevent renal alterations in rats with streptozotocin-induced diabetes, such as hyperglycemia, hypertension, and renal damage. It also diminished the harmful effects of the increased oxidative stress and pro-inflammatory state in diabetes by exerting an antioxidative effect maintaining cellular homeostasis by preventing the opening of hemichannels and keeping cells coupled to each other [58]. Boldine exhibited a significant endothelial protective effect in animal models of hypertension and diabetes mellitus. It interfered with the oxidative stress-mediated signaling pathway to prevent endothelial dysfunctions associated with hypertension and diabetes mellitus [59].

3.2.6. Hepatoprotective activities.

Flavonoids are the main chemical constituents responsible for their antioxidant property. Treatment with total flavonoid of *L. coreana* (TFLC) (200 and 400 mg/kg) inhibited the expression of transforming growth factor-beta1 and increased the expression of peroxisome proliferator-activated receptor-gamma, proving the ability of TFLC to ameliorate liver injury and provided protection against liver fibrosis in rats. The protective effects of TFLC on the alcoholic fatty liver (AFL) in rats were also evaluated [60]. In addition, a study for the preventive effects of hawk tea *in vivo* on hepatic damage induced by carbon tetrachloride (CCl_4) in Sprague Dawley (SD) rats. Varying concentrations of hawk tea significantly decreased the serum levels of aspartate transaminase (AST) and alanine transaminase (ALT and LDH compared with silymarin) $p<0.05$). The 400 mg/kg hawk tea-treated group showed significantly decreased mRNA and protein expression levels of iNOS, COX-2, TNF-α, and IL-

1β compared with the control group: this dose also prevented CCl_4-induced hepatic damage *in vivo*. These results suggested that hawk tea was potentially beneficial in treating or preventing hepatic damage [61].

3.2.7. Neuropharmacological activities.

Based on several behavioral analyses, the *L. cubeba* essential oil (LCEO) was found to show neuropharmacological activity in ICR mice. Oral administration of 100, 300, and 500 mg/kg of LCEO significantly prolonged pentobarbitone-induced sleeping time in mice by 20.0%, 110.8%, and 159.6%, respectively. In a tail-flick test, LCEO exhibited potent anxiolytic activity after treating mice with 500 mg/kg of LCEO, compared to 90 mg/kg of the positive control acetaminophen. Thus, LCEO showed a potent effect on the central nervous system of mice, which was consistent with its traditional use as an analgesic [20]. The neuroprotective effect of total flavonoid from *L. coreana* (TFLC) was evaluated in a rat model of focal cerebral ischemia/reperfusion by oral administration of TFLC (25, 50, and 100 mg/kg). Treatment with TFLC significantly decreased the neurological deficit scores, infarct volume, and histological damage in a dose-dependent manner. The protective effect at a high dose (100 mg/kg) was similar to those of the positive control edaravone on cerebral ischemia/reperfusion injury. TFLC exerted neuroprotective effects on focal cerebral ischemia/reperfusion injury in rats, which can be attributed to its antioxidant activities[62]. The essential oil of *L. glaucescens* showed antidepressant-like activity at doses of 100 and 300 mg/kg with several behavioral models in mice, including the forced swimming, open-field, rotarod, traction performance, elevated plus maze and exploratory cylinder tests. As active principles of the essential oil, β-pinene and linalool decreased the spontaneous locomotor activity of mice in the open-field test due to their sedative effect. This indicated that the essential oil was superior to the two active compounds [63]. The fruit of *Litsea lancilimba* Merr. yielded 20 recognized sesquiterpens and four previously unidentified sesquiterpenes. The neuroprotective effects of each substance against H_2O_2-induced SH-SY5Y cell injury were examined. Five substances showed equivalent neuroprotective efficacy to the effective Trolox at 50 μM [64].

3.2.8. Toxicity studies.

Cytotoxicity study of methanolic extract of mixed-leaves *L. elliptica* had significantly higher cytotoxicity than the young-leaf against A549 lung cancer cell line at the 24 and 48 h treatment periods [39]. The essential oil of *L. cubeba* fruits showed strong contact toxicity in adult cigarette beetles (*Lasioderma serricorne*) and the booklice (*Liposcelis bostrychophila*), with LD_{50} values of 27.33 μg/adult and 71.56 μg/cm^2, respectively, as well as strong fumigant toxicity against the two stored product insect with LC_{50} values of 22.97 and 0.73 mg/L, respectively, compared with the positive control pyrethrins (LD_{50} 18.72 μg/cm^2) and dichlorvos (LC_{50} 1.35 μg/L). Citral and linalool, the two primary constituents of the essential oil, showed stronger contact toxicity against *L. serricone* and *L. bostrycophila* (16.54, 18.04 mg/L air and 0.14, 0.71 mg/L air, respectively) [22]. Female SD rats were used to test the oral gavage method for acute and subacute toxicities of *L. elliptica* essential oil. The *L. elliptica* essential oil was administered in doses ranging from 500 to 4000 mg/kg (single dose) for the acute toxicity study, and in doses 125, 250 and 500 mg/kg for the subacute toxicity test for 25 consecutive days. The *L. elliptica* essential oil caused dose-dependent adverse behavior and mortality in the acute toxicity study with a medial lethal dose value of 3488.86 mg/kg and an acute non-

observed adverse effect level of 500 mg/kg. The subacute toxicity study on *L. elliptica* essential oil did not reveal an alteration in body weight and consumption of food and water[65].

3.2.9. Other activities.

For decades, there have been several herbs that are attributed to have anti-osteoporotic effects; however the candidate genes involved in it remained unknown. Changani and Parikh reported that methanolic extract of *L. glutinosa* showed upregulation and down-regulation of various crucial genes that are involved in some decisive pathways of osteoblast proliferation and differentiation. *L. glutinosa* also suppressed the genes which are involved in apoptosis in Saos-2-cells [66]. *L. cubeba* essential oils (LCEO) were studied for their *Vibrio parahaemolyticus* inhibition and anti-biofilm ability. *V. parahaemolyticus* is a common pathogen in seafood. The results showed that the MIC value of the LCEO was 1.024 µg/mL. Moreover, LCEO inhibited growth and promoted the removal of biofilms by reducing the content of hydrophobic and extracellular polysaccharides on the cell surface[67]. The acaricidal activity of the essential oils from *L. cubeba* has been reported that LCEO (diluted both in DMSO and in ethanol) only gave rise to more than 99% mortality at concentrations of 10 mg/mL [68]. Laurolitsine presented a significant inhibitory effect on type I HIV integrase with an IC_{50} value of 16.3 mM [10]. These findings supported the potential of *Litsea* plants to serve as leads in the discovery of new anti-HIV agents. Docking studies and molecular dynamics simulation for SARS-Cov2 nsp12 have been carried out on several metabolites from *Litsea* plants. After molecular docking and molecular dynamic simulation, dankasterone B from *Litsea hypophaea* was one of the other potent metabolites. Dankasterone B had high binding energy and maximum number in clusters. Dankasterone B is recommended as a candidate for further experimental studies for the study of COVID-19 [69].

4. Conclusions

There is a wide variety of plants in the genus Litsea. The *Litsea genus* has been the subject of recent research over the past ten years, and this work has yielded a variety of data to determine their phytochemical constituents and pharmacological actions. The corresponding bioactive substances may be used to treat conditions like diabetes, cancer, and HIV. However, more research needs to be done on some *Litsea* plants to uncover previously unknown bioactive substances and improve the data on their pharmacological activity. Research specifically on *Litsea* to understand how its chemical component works as an antidiabetic agent.

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Conflicts of Interest

The authors reported no potential conflict of interest.

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