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Research Progress on the Chemical Constituents and Pharmacological Activity of *Litsea cubeba* (Lour) Pers

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Abstract: *Litsea cubeba*, a deciduous shrub belonging to the Lauraceae family, has a variety of medicinal properties, and its fruit, leaves, roots, and bark are used for treating conditions such as spleen-stomach deficiency, dysphagia, and unidentified tumors. The main chemical components of *Litsea cubeba* are alkaloids, flavonoids, lignans, terpenes, and their glycosides, with aporphine alkaloids being the most characteristic. Recent studies have demonstrated that *Litsea cubeba* has a wide variety of pharmacological activities, including antitumor, antioxidant, antimicrobial, anti-inflammatory, and hypoglycemic effects. This article summarizes the chemical composition and pharmacological activities of *Litsea cubeba* and explores their mechanisms of action, providing a reference for the development and utilization of the *Litsea cubeba* chemical components.

Key words: Lauraceae; *Litsea cubeba;* chemical composition; biological activity.

1. Introduction

Litsea cubeba (Lour) Pers (Lauraceae) is also known as Shan Ji Jiao, Shan Cang Zi, and Bi Cheng Qie. It is a deciduous shrub or small tree distributed mainly in Chinese provinces south of the Yangtze River, as well as in various countries in Southeast Asia [1]. According to statistics, forests of wild *Litsea cubeba* cover approximately 14 400 hectares in China, accounting for 0.04% of the total economic forest area in the country [2]. In recent years, with breakthroughs in breeding and seedling propagation techniques such as tissue culture and artificial cutting [3-5], many provinces such as Fujian, Hunan, Sichuan, Guizhou, and Jiangxi have cultivated large areas of *Litsea cubeba* forests [6], providing sufficient raw materials for the development and utilization of *Litsea cubeba*. The entire plant has medicinal properties, and the roots and rhizomes are used in the traditional Chinese medicine "douchijiang" which is used for dispelling wind and cold, calming liver wind, reducing swelling, and for the treatment rheumatism and pain [7]. The fruit, leaves, and branches of *Litsea cubeba* contain a variety of essential oils, with the oil obtained from the fruit being the main source of commercially available *Litsea cubeba* essential oil [8]. These rich resources and medicinal properties of *Litsea cubeba* have attracted the attention of researchers at home and abroad, resulting in the appearance of

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numerous studies. *Litsea cubeba* essential oil is widely used in the medical, food, and chemical industries due to its antibacterial, antioxidant, anti-inflammatory, insecticidal, and antitumor properties [9-14]. It is also used as an important raw material for food preservatives and fresh-keeping agents, with good prospects for further development [6]. While there are many reports of the efficacy and utilization of *Litsea cubeba* essential oil in the literature [8,11,15-16], there have been few investigations of its non-oil components [17]. Therefore, the present article provides a comprehensive review of the non-volatile oil components and pharmacological activities of *Litsea cubeba*, to provide a reference for the further development and utilization of the medicinal properties of *Litsea cubeba*.

2. Chemical Composition Studies

To date, 150 non-volatile oil components have been isolated and identified from the *Litsea cubeba* plant, including alkaloids, lignans, flavonoids, and others.

2.1 Alkaloids

Litsea cubeba is rich in alkaloids, and 40 isoquinoline alkaloids (**1-40**) and 14 amide alkaloids (**41-54**) have been identified. Most alkaloids have been isolated from ethanol extracts of its branches, roots, or mixed bodies. The most abundant of the isoquinoline alkaloids are aporphine alkaloids with biphenyl structures. These aporphine alkaloids have a structural skeleton as well as significant biological activities, as shown by the Taiwanese researcher S. S. Lee [18] and others, who have shown that they are characteristic components of *Litsea cubeba*. Aporphine alkaloids are characterized by a variety of substituents that can easily form different oxidation states, with differences in configuration differences centered on C-6a. The aporphine alkaloids have various N-substituents, including N-H, N-CH3, C=N, N-COOCH3, and charged N double-substituted types (compounds **16**, **18**, **19**). C-1, C-2, C-9, and C-10 are easily substituted by hydroxyl or methoxy groups. Compounds **24** and **26** can further oxidize C-1 and C-2 to form 1,2-methylene dioxy ring structures, while compounds **15** and **36** have the same structures at C-9 and C-10. Several compounds undergo oxidation of their C and D rings leading to the introduction of carbonyl groups and are thus classified as oxidized aporphine alkaloids (compounds **17, 26-28, 36**).

Compounds **41-48** belong to the phenolic amide alkaloids, with the core structure formed by a hydroxycinnamic acid and amine combination. Compounds **41** and **46**, as well as compounds **43** and **47**, are cis-trans isomers. Compounds **49-54** represent the diphenylamide alkaloids with the core structure formed by the lignan. The specific structures are shown in Table 1 and Figure 2.

Aporphine alkaloids have a variety of pharmacological activities, the most significant of which is their anti-tumor activity (Figure 1). They have been shown to inhibit the growth of various cancer cell lines, including A549 lung cancer cells, human leukemia HL-60 cells, the breast cancer cell line MCF-7, the liver cancer cell line HepG-2, HCT-116 human colon cancer cells, and the melanoma cell line B16F10, making the study of these alkaloids a hotspot in research on antitumor drugs. Studies have shown that aporphine alkaloids from *Litsea cubeba* have a relatively flat structure that allows them to insert into the DNA double strand, binding efficiently to the target site of DNA topoisomerase II (TopoII) to form a complex that is difficult to dissociate. This competitive binding inhibits the catalytic activity of TopoII, resulting in antitumor activity. Further investigation has shown that the oxidized apomorphine structure binds more effectively to DNA where it is more likely to form a planar structure, leading to stronger anticancer activity. This is seen with the carbonyl structures at the C-8 and C-11 positions of alkaloids **26** and **27**, and these alkaloids have been found to have significantly greater toxicity to tumor cells compared with other alkaloid derivatives [19-20]. In addition, the presence of a 1,2-methylenedioxy substitution on the A-ring of aporphine alkaloids enhances the cytotoxicity of the parent nucleus [21], seen in compounds **19**, **24**, and **26**. Other isoquinoline alkaloids also exhibit antitumor activities. B. Tang et al. [22] evaluated the cytotoxicity of alkaloid **38** against HL-60 and MCF-7 cells using MTT assays, observing good cytotoxicity with IC_{50} values of 18.1 and 15.0 μM, respectively.

Studies have shown that aporphine alkaloids have anti-inflammatory and analgesic effects [23]. Their mechanism of action may be to inhibit the cyclooxygenase-2 (COX-2) pathway of

arachidonic acid. Specifically, N-H aporphine alkaloids with one methoxy group substitution are highly effective COX-2 inhibitors. A study by S. Y. Zhang et al. [24] showed that compounds **1** and **2** displayed specific anti-inflammatory activity against mouse microglial cells (BV-2) in vitro, with IC_{50} values of 85.1 and 112.1 μmol·L^{-1}, respectively. Compounds **9** and **40** showed moderate inhibition of NO production in mouse macrophages (RAW 264.7), with IC_{50} values of 13.3 and 26.3 μmol·L^{-1}, respectively, while the positive control quercetin had an IC_{50} value of 5.4 μmol·L^{-1}. The highest inhibition rate of NO generation for compounds **2-6** was 19.4% at a concentration of 40 μmol·L^{-1}. Q. Guo et al. [25] found that compounds **5, 15**, and **20** also significantly inhibited NO production in BV-2 cells, with IC_{50} values of 50.4, 40.6, and 33.6 μM, respectively.

T. C. Chi et al. [26] investigated the effects of compounds **1** and **3** on a rat model of diabetes and showed that compound **1** may exert hypoglycemic effects by regulating the insulin signaling pathway. Both compounds were found to be effective through a non-insulin-dependent mechanism.

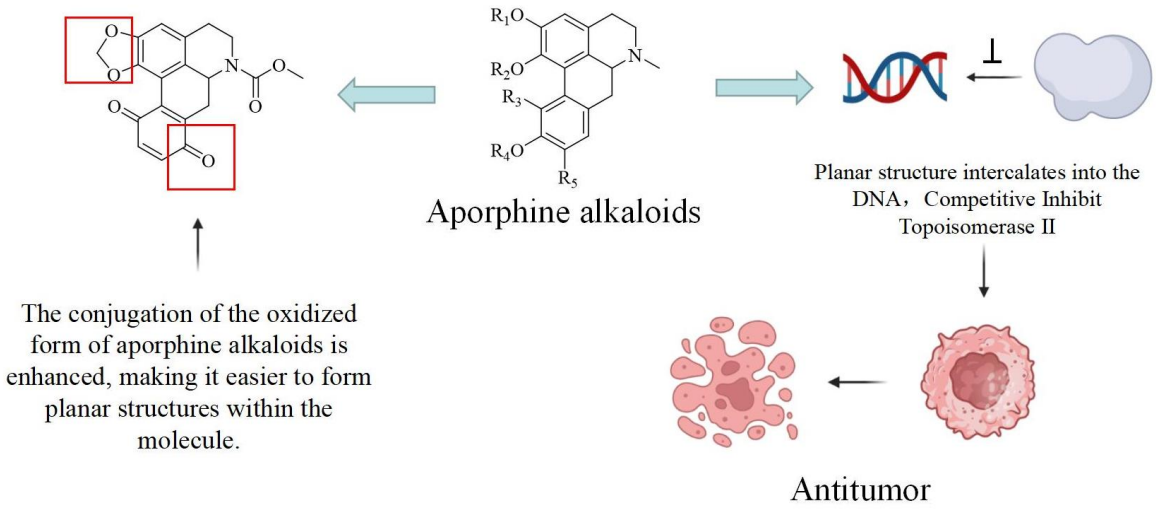


Figure 1. Antitumor pathway of aporphine alkaloids

Table 1. Alkaloids in plants of *Litsea cubeba* (Lour) Pers.

No	Compounds	Formula	Part	Ref.
1	boldine	$C_{19}H_{21}NO_4$	Aerial, Branches	[18,27]
2	isoboldine	$C_{19}H_{21}NO_4$	Aerial, Branches	[18,27]
3	N-methyllaurotetanine	$C_{20}H_{23}NO_4$	Roots, Branches	[25,28]
4	N-methyllindcarpine	$C_{19}H_{21}NO_4$	Branches	[18]
5	isocorydine	$C_{20}H_{23}NO_4$	Aerial	[25,27]
6	Lirioferine	$C_{20}H_{23}NO_4$	Aerial, Branches	[18,27]
7	norisoboldine	$C_{18}H_{19}NO_4$	Aerial	[27]
8	Lorisocorydine	$C_{19}H_{21}NO_4$	Branches	[18]
9	laurolitsine	$C_{18}H_{19}NO_4$	Branches	[18]
10	laurotetanine	$C_{19}H_{21}NO_4$	Roots, Branches	[18,28]
11	norlirioferine	$C_{19}H_{21}NO_4$	Aerial	[27]
12	nilsonirine	$C_{19}H_{21}NO_4$	Aerial	[27]
13	muricinine	$C_{18}H_{19}NO_4$	Aerial	[27]
14	(+)-norcorydine	$C_{19}H_{21}NO_4$	Roots	[25]
15	isodomesticine	$C_{19}H_{19}NO_4$	Branches	[18,25]
16	xanthoplanine	$C_{21}H_{26}ClNO_8$	Branches	[29]

17	atheroline	$C_{19}H_{15}NO_5$	Roots	[28]
18	(+)-isoboldineβ-N-oxide	$C_{19}H_{21}NO_5$	Aerial	[27]
19	(+)-8-methoxyl-isolaurenineN-oxide	$C_{20}H_{21}NO_5$	Barks	[30]
20	(+)-N-(methoxycarbonyl)- N-norboldine	$C_{20}H_{21}NO_6$	Aerial	[25,27]
21	(+)-N-(methoxycarbonyl)-N-norglaucine	$C_{22}H_{25}NO_6$	Barks，Roots	[30,31]
22	(+)-N-(methoxycarbonyl)-N-norlauroscholtzine	$C_{21}H_{19}NO_6$	Roots	[31]
23	N-(methoxycarbonyl)-N-norisoboldine	$C_{21}H_{19}NO_6$	Aerial	[27]
24	(+)-N-(methoxylcarbonyl)-N-nordicentrin	$C_{21}H_{21}NO_6$	Barks	[30]
25	(+)-N-(methoxycarbonyl)-N-norpredicentrine	$C_{21}H_{19}NO_6$	Barks	[30]
26	(+)-N-(methoxylcarbonyl)-N-norbulbodione	$C_{20}H_{19}NO_7$	Barks	[30]
27	(+)-N-(methoxycarbonyl)-N-norisocorydione	$C_{21}H_{23}NO_7$	Barks	[30]
28	glaziovine	$C_{18}H_{19}NO_3$	Branches	[18]
29	(-)-magnocurarine	$C_{19}H_{24}ClNO_7$	Branches	[29]
30	(-)-oblongine	$C_{19}H_{24}ClNO_8$	Branches	[29]
31	(-)-8-O-methyloblongine	$C_{20}H_{26}ClNO_7$	Branches	[29]
32	reticuline	$C_{18}H_{21}NO_2$	Aerial	[27]
33	N-methylcoclaurine	$C_{19}H_{23}NO_4$	Aerial	[27]
34	(-)-litcubinine	$C_{19}H_{22}ClNO_8$	Branches	[32]
35	(-)-litcubine	$C_{18}H_{20}ClNO_8$	Branches	[32]
36	oxonantenine	$C_{19}H_{17}NO_5$	Fruits	[33]
37	litebamine	$C_{20}H_{21}NO_4$	Trunks	[34]
38	N-methoxycarbonyl-norjuziphine	$C_{19}H_{21}NO_5$	Leaves	[22]
39	7-*β*-D-glucopyranosyloxythalifoline.	$C_{17}H_{24}NO_8$	Branches	[38]
40	berberine	$C_{20}H_{18}NO_4$	Branches	[24]
41	N-feruloyl-3-methoxytyramine	$C_{19}H_{21}NO_5$	Roots	[37]
42	N-trans-coumaroyltyramine	$C_{17}H_{17}NO_3$	Branches，Roots	[35,36]
43	N-trans-feruloyltyramine	$C_{18}H_{19}NO_4$	Branches，Roots	[35,36]
44	N-trans-sinapoyltyramine	$C_{19}H_{21}NO_5$	Branches	[39]
45	N-trans sinapyl -3-methoxy tyramine	$C_{20}H_{23}NO_6$	Branches	[37]
46	cis-N-feruloyl-3-methoxytyramine	$C_{19}H_{21}NO_5$	Roots	[37]
47	N-cis-ferulictyramine	$C_{18}H_{19}NO_4$	Roots	[37]
48	N-cis-cinnamyltyramine	$C_{17}H_{17}NO_2$	Roots	[37]
49	cubebamineA	$C_{38}H_{40}N_2O_{10}$	Roots	[35]
50	1, 2-dihydro-6, 8-dimethyl oxygen-7-1-(3,5 -dimethoxy-4-hydroxyphenyl)-N^1,N^2-double-[2-(4-hydroxyphenyl)ethyl]-2,3-naphthalene-amide	$C_{39}H_{49}N_2O_{10}$	Branches, Roots	[36]
51	1,2-dihydro-6,8-dimethoxy-7-hydroxy-1-(3,5-dimethoxy- 4-hydroxyphenyl)-N^1,N^2-bis-[2-(4-hydroxypeenyl)ethyl]-2,3-naphthalene dicarboxamide	$C_{38}H_{40}N_2O_{10}$	Roots	[40]
52	(−)-(7′*R*,8′*S*)-N^1-[2-(4-hydroxyphenyl)-ethyl]-N^2-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]-4,4′-dihydroxy-3,5,3′,5′-tetramethoxy-2,7′-cyclolignan-7-en-9,9′-diamide.	$C_{39}H_{42}N_2O_{11}$	Roots	[40]
53	(−)-(7′*R*,8′*S*)-N[1]-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]-N[2]-[2-(4-hydroxyphenyl)-ethyl]-4,4′-dihydroxy-3,5,3′,5′-tetramethoxy-2,7′-cyclolignan-7-en-9,9′-diamide.	$C_{39}H_{42}N_2O_{11}$	Branches	[40]
54	(-)-(7′*R*,8′*S*)-N-[2-(4-hydroxyphenyl)-ethyl]-4,4′,9′-trihydroxy-3,5,3′,5′-tetramethoxy-2,7′-cyclolignan-7-en-9-amide.	$C_{30}H_{33}NO_9$	Branches	[40]

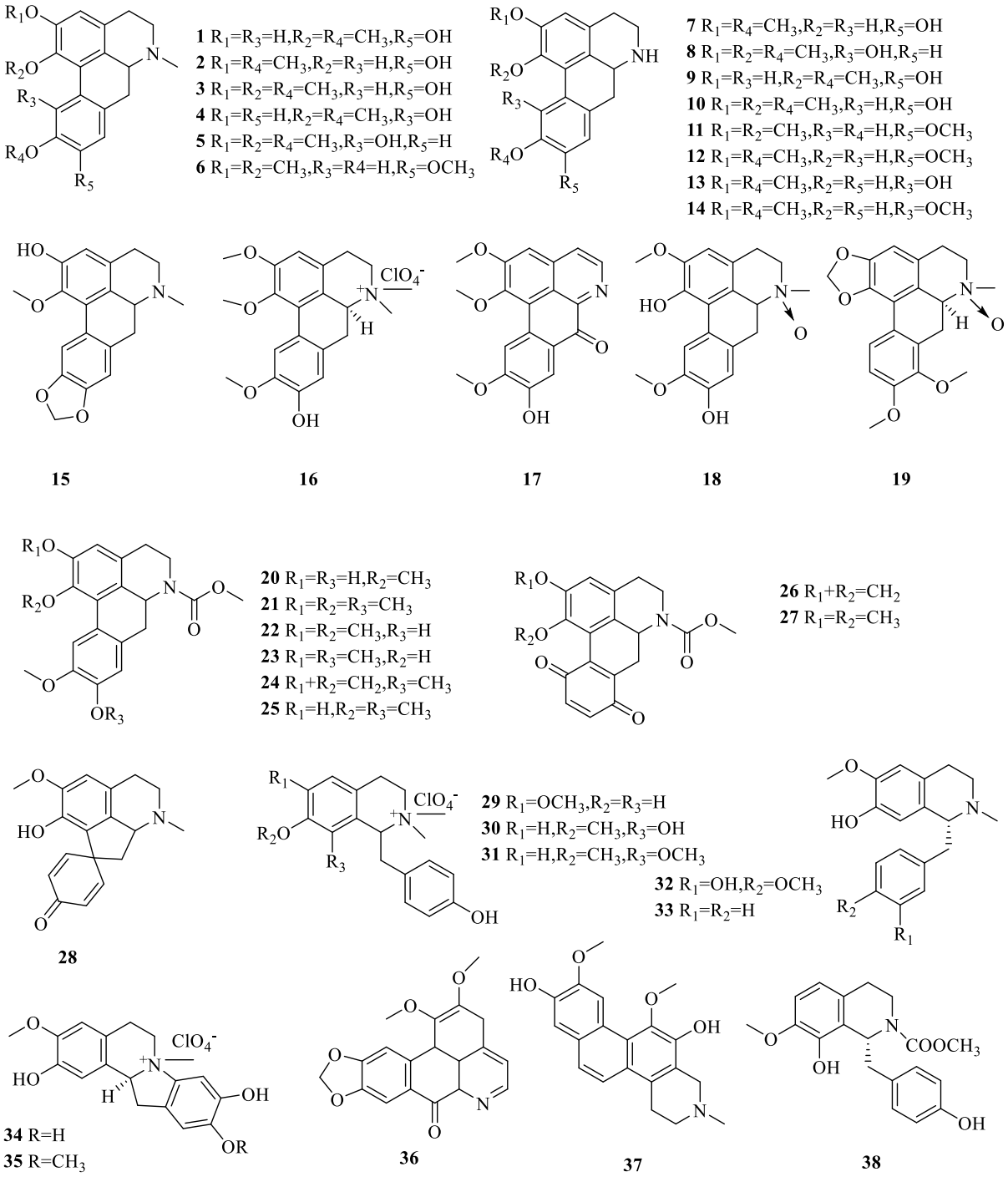


Figure 2. The structures of alkaloids from *Litsea cubeba* (Lour) Pers.

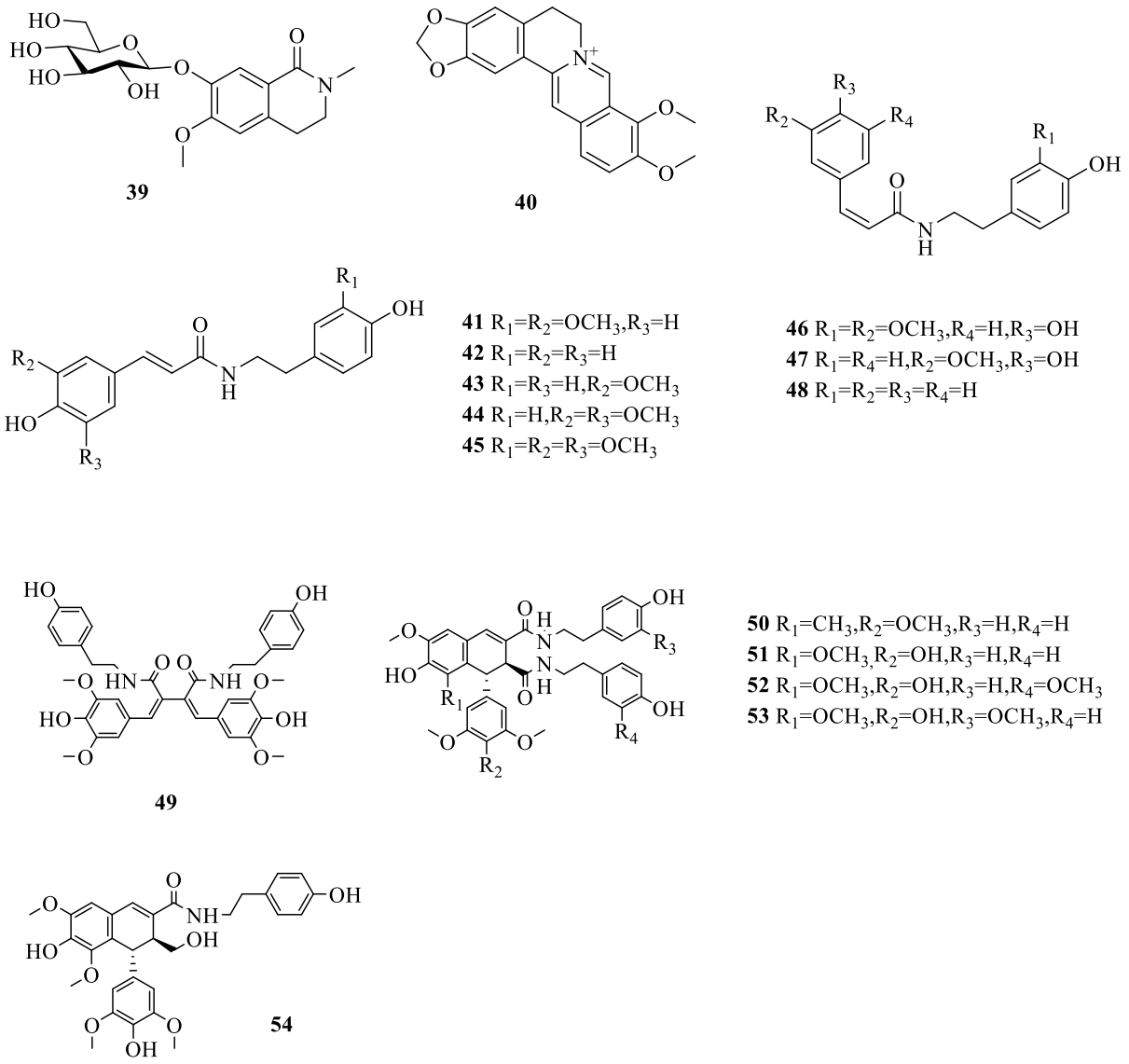


Figure 2. The structures of alkaloids from *Litsea cubeba* (Lour) Pers. (continued..)

2.2. Lignan Compounds

Thirty-one lignan compounds have been isolated from the branches and roots of *Litsea cubeba*. These include the dibenzylbutane (**55-59**, **81-83**), dibenzylbutyrolactone (**67-69**, **79-80**), tetrahydrofuran (**60-66**, **71-72**, **78-80**), and Eupromete benzofuran-type lignans (**70**, **73-77**, **84-85**), which were isolated for the first time from *Litsea cubeba*. Compounds **73-85** are lignan glycosides, in which the glycosidic bond is usually connected to the benzene ring; however, in compounds **73**, **77**, and **85**, the glycosidic bond is in a specific position, connected to the methyl group (C-9) of the benzofuran ring. The details are shown in Table 2 and Figure 4.

X. T. Li et al. [40] reported that compounds **60** and **62-64**, which are 7',9-epoxy-lignans with feruloyl or cinnamoyl groups, exhibited IC_{50} values below 20 μM against the human lung cancer cell line NCI-H1650. On the other hand, the dibenzylbutyrolactone lignans **67-69** were cytotoxic to the HCT-116 and A2780 cell lines, with IC_{50} values ranging from 0.28 to 18.47 μM. These findings highlight the importance of the presence of a feruloyl or cinnamoyl moiety at C-9' and/or C-7 ketone in 7',9-epoxy-lignans in their structure-activity relationships. (Figure 3)

A study by L. Y. Wang et al. [38] found that compounds **74**, **76**, **82**, and **84-86**, at concentrations of 10 μM, reduced acetaminophen-induced injury to HepG2 cells by 30.5%-46.0%. Additionally, compounds **74** and **141** showed moderate inhibitory activities against histone deacetylase 1 (HDAC1), with IC_{50} values of 3.6 μM and 4.6 μM, respectively. Q. Guo et al. [25] found that compound **70** significantly inhibited NO production in Bv-2 cells.

Table 2. Lignans in plants of *Litsea cubeba* (Lour) Pers.

No.	Compounds	Formula	Part	Ref.
55	(+)-(8*S*,8′*S*)-9-O-(*E*)-cinnamoylsecoisolariciresinol	$C_{31}H_{36}O_{10}$	Branches	[40]
56	(+)-(8*S*,8′*S*)-9-O-(*E*)-feruloyl-5,5′-dimethoxysecoisolariciresinol.	$C_{32}H_{38}O_{11}$	Branches	[40]
57	(+)-(8*S*,8′*S*)-9-O-(*E*)-feruloyl-secoisolariciresinol	$C_{32}H_{34}O_{12}$	Branches	[40]
58	(+)-9,9′ -O-di-(*E*)-feruloyl-5,5 *O* -dimethoxy secoisolariciresinol	$C_{43}H_{49}O_{14}$	Branches	[40]
59	(+)-9,9′-O-di-(*E*)-feruloylsecoisolariciresinol	$C_{42}H_{47}O_{13}$	Branches	[40]
60	(+)-(8*R*,7′*S*,8′*R*)-9′-O-(*E*)-feruloyl-5,5′-dimethoxylariciresinol-7-one	$C_{32}H_{34}O_{12}$	Branches	[40]
61	(+)-(8*R*,7′*S*,8′*R*)-9′-O-(*E*)-cinnamoyl-5,5′-dimethoxylariciresinol	$C_{33}H_{38}O_{12}$	Branches	[40]
62	9′-O-(*E*)-feruloyl-5,7,5′-trimethoxy-lariciresinol	$C_{33}H_{38}O_{12}$	Branches	[40]
63	(+)-9′-O-(*E*)- feruloyl-5,5′-dimethoxylariciresinol	$C_{32}H_{36}O_{11}$	Branches	[40]
64	(+)-9′-O-(*E*)-feruloyl-5′-methoxylariciresinol	$C_{31}H_{34}O_{10}$	Branches	[40]
65	(+)-5,5′-dimethoxylariciresinol	$C_{22}H_{28}O_8$	Branches	[40]
66	(+)-5′-methoxylariciresinol	$C_{21}H_{26}O_7$	Branches	[40]
67	arctigenin	$C_{21}H_{24}O_6$	Branches	[40]
68	matairesino	$C_{20}H_{22}O_6$	Branches	[40]
69	(7*E*,8′*R*)-didehydroarctigenin	$C_{21}H_{22}O_6$	Branches	[40]
70	litsecols B	$C_{31}H_{32}O_{10}$	Roots	[25]
71	(-)-divanillyltetrahydrofuranferulate	$C_{30}H_{32}O_8$	Branches	[39]
72	(+)-9′-O-(*E*)-feruloyl-5,5′-dimethoxylariciresinol	$C_{32}H_{38}O_{11}$	Branches	[39]
73	(7*S*,8*R*)-dehydrodiconiferinol-4,9'-diO-*β*-D-glucopyranoside		Branches	[41]
74	(7*S*,8*R*)-5-methoxy dihydrodehydrodiguaiacylol-4-O-*β*-D-glucopyranoside	$C_{27}H_{36}O_{12}$	Branches	[41]
75	(7*S*,8*R*)-urolignoside	$C_{26}H_{34}O_{11}$	Branches	[41]
76	(7*R*,8*S*)-dihydrodeguaiacylol-4'-O-*β*-D-glucopyranoside	$C_{26}H_{34}O_{11}$	Branches	[41]
77	(7*S*, 8*R*) - two hydrogen to the two guaiac wood base alcohol-9-O-beta-D-pyran glucose base (1→2) -O-beta-D-pyran glycosidase	$C_{33}H_{46}O_{15}$	Branches	[41]
78	lanicepside A	$C_{26}H_{34}O_{12}$	Branches	[41]
79	Arhanoid-4-O-*β*-D-glucopyranoside	$C_{26}H_{32}O_{11}$	Branches	[41]
80	tyraxjaponoside B	$C_{27}H_{34}O_{11}$	Branches	[41]
81	(+)Candlewoodresinphenol-9'-O-*β*-D-glucopyranoside	$C_{28}H_{38}O_{13}$	Branches	[41]
82	(+)-(7*R*,8*S*)-4,7,9,4′,9′-pentahydroxy-3,5,3′,5′-tetramethoxy-9′a-homo-8,4′-oxyneolignan-4-O-*β*-D-glucopyranoside	$C_{29}H_{42}O_{14}$	Branches	[38]
83	(-)-(7*S*,8*R*,7′*E*)-4,7,9,4′,9′-pentahydroxy-3,5,3′,5′-tetramethoxy-8,4′-oxyneolignan-7′-ene-4,9′-di-O-*β*-D-glucopyranoside	$C_{34}H_{48}O_{19}$	Branches	[38]
84	(-)-(7*S*,8*R*,7′*E*)-4,9,9′-trihydroxy-3,5,3′,5′-tetramethoxy-4′,7-epoxy-8,3′-neolignan-7′-ene-4,9′-di-O-*β*-D-glucopyranoside	$C_{33}H_{44}O_{17}$	Branches	[38]
85	(7*S*,8*R*)-4,9'di-*β*-D-glucopyranosyloxydehydrodiconiferyl alcohol	$C_{32}H_{42}O_{16}$	Branches	[38]
86	(-)-(7*S*,8*R*)-4,9,9′-trihydroxy-3′,5-dimethoxy-4′,7-epoxy-8,3′-neoligan-9-O-[*α*-L-rhamnopyranosyl(1→6)]-*β*-D-glucopyranoside	$C_{32}H_{44}O_{15}$	Branches	[38]

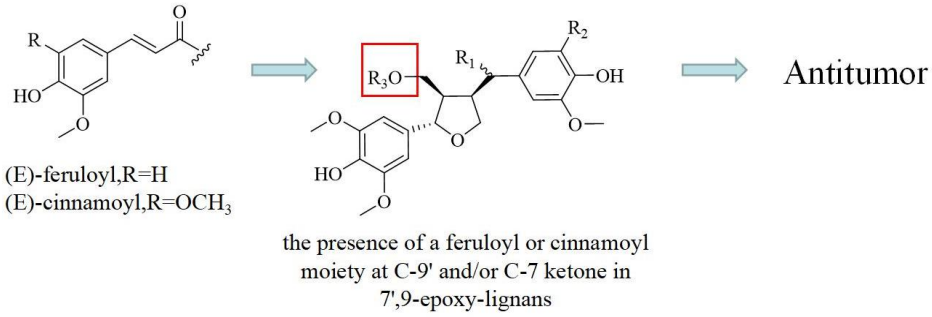
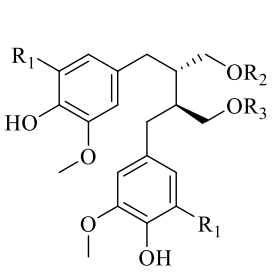
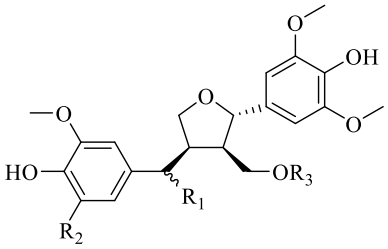


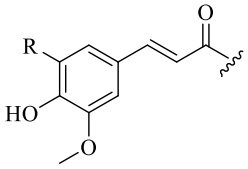
Figure 3. Antitumor structure-activity of lignans



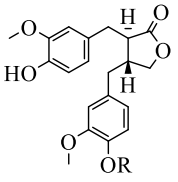
55 R_1= R_3=H, R_2=(*E*)-cinnamoyl
56 R_1=OCH_3, R_2=(*E*)-feruloyl, R_3=H
57 R_1=R_3=H, R_2=(*E*)-feruloyl
58 R_1=OCH_3, R_2=R_3=(*E*)-feruloyl
59 R_1=H, R_2=R_3=(*E*)-feruloyl



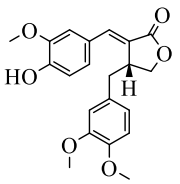
60 R_1=O‖, R_2=OCH_3,R_3=(*E*)-feruloy
61 R_1=H, R_2=OCH_3, R_3=(*E*)-cinnamoyl .
62 R_1=OCH_3,R_2=OCH_3,R_3=(*E*)-feruloyl
63 R_1=H, R_2=OCH_3,R_3=(*E*)-feruloyl
64 R_1=R_2=H,R_3=(*E*)-feruloyl
65 R_1=R_3=H,R_2=OCH_3
66 R_1=R_2=R_3=H



(*E*)-feruloyl,R=H
(*E*)-cinnamoyl,R=OCH_3



67 R=CH_3
68 R=H



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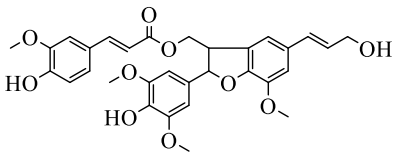

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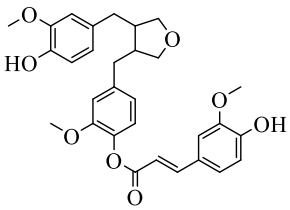

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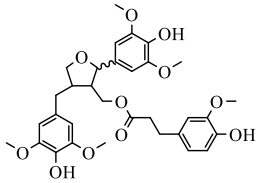

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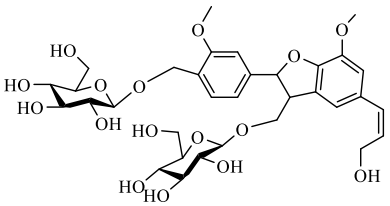

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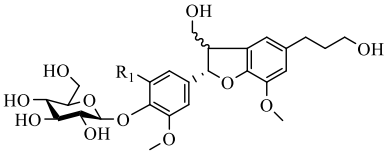
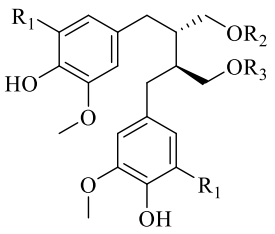
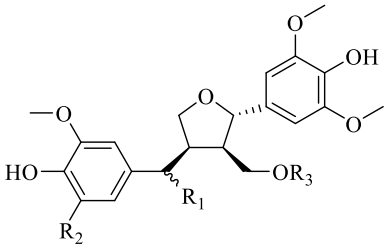


74 R_1=OCH_3
75 R_1=H(7*S*,8*R*)
76 R_1=H(7*R*,8*S*)

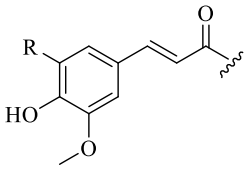
Figure 4. The structures of lignans from *Litsea cubeba* (Lour) Pers.



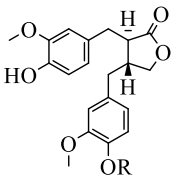
55 R_1= R_3=H, R_2=(*E*)-cinnamoyl
56 R_1=OCH_3, R_2=(*E*)-feruloyl, R_3=H
57 R_1=R_3=H, R_2=(*E*)-feruloyl
58 R_1=OCH_3, R_2=R_3=(*E*)-feruloyl
59 R_1=H, R_2=R_3=(*E*)-feruloyl



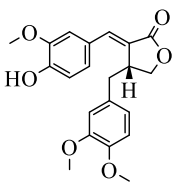
60 R_1=O‖, R_2=OCH_3,R_3=(*E*)-feruloy
61 R_1=H, R_2=OCH_3, R_3=(*E*)-cinnamoyl .
62 R_1=OCH_3,R_2=OCH_3,R_3=(*E*)-feruloyl
63 R_1=H, R_2=OCH_3,R_3=(*E*)-feruloyl
64 R_1=R_2=H,R_3=(*E*)-feruloyl
65 R_1=R_3=H,R_2=OCH_3
66 R_1=R_2=R_3=H



(*E*)-feruloyl,R=H
(*E*)-cinnamoyl,R=OCH_3



67 R=CH_3
68 R=H



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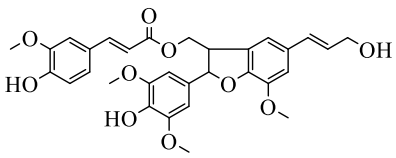

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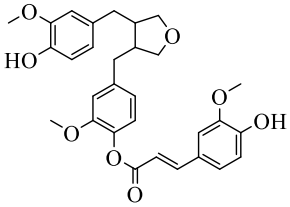

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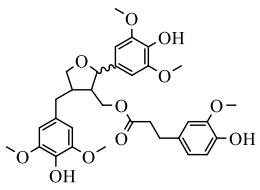

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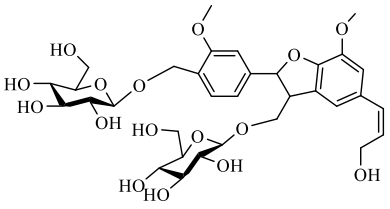

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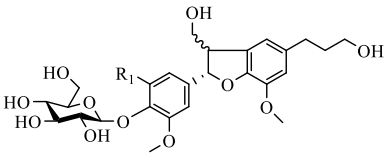


74 R_1=OCH_3
75 R_1=H(7*S*,8*R*)
76 R_1=H(7*R*,8*S*)

Figure 4. The structures of lignans from *Litsea cubeba* (Lour) Pers . (continued..)

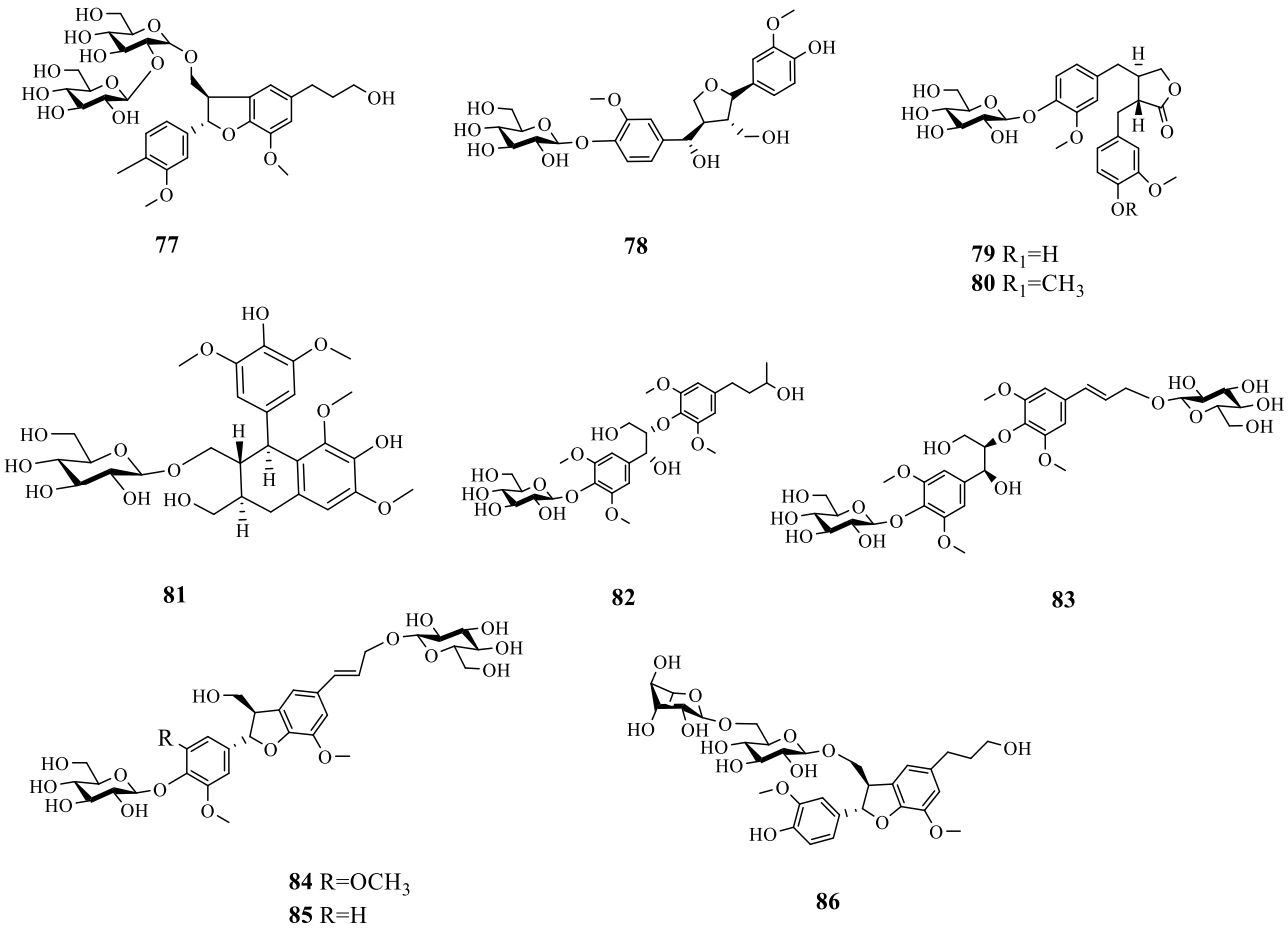


Figure 4. The structures of lignans from *Litsea cubeba* (Lour) Pers . (continued..)

2.3. Terpenes and Their Glycosides

Seven monoterpenes (**87-93**) and one sesquiterpene (**94**) have been isolated from *Litsea cubeba*. The remaining compounds were terpene glycosides (**95-103**). It is worth noting that compounds **99-103** are monoterpenoid glycosides, and compounds **100-102** have two glycosidic bonds, forming a linkage between a monoterpenoid and another monosaccharide. Terpenoid compounds are relatively scarce in the non-volatile oil fraction of the plant extracts and most exist in the form of terpenoid glycosides. The details are shown in Table 3 and Figure 5.

Terpenoid compounds also exhibit specific activities, with compound **98** showing selective cytotoxicity against A549 and HCT-8 cells, with IC_{50} values of 8.9 and 9.6 μM, respectively [42]. Compound **103** has been found to reduce NO production in Bv-2 cells significantly [25].

Table 3. Terpenoids in plants of *Litsea cubeba* (Lour) Pers.

No	Compounds	Formula	Part	Ref.
87	litsecols A	$C_{10}H_{20}O_3$	Roots	[25]
88	(6*R*)-3,7-dimethyl-7-hydroxy-2-octen-6-olide	$C_{10}H_{16}O_3$	Fruits	[33]
89	6,7-dihydroxy-3,7-dimethyl-oct-2-enoicacid	$C_{10}H_{18}O_4$	Roots	[36]
90	bakuchiol	$C_{18}H_{24}O$	Branches	[37]
91	Δ^3,2-hydroxybakuchiol	$C_{18}H_{24}O_2$	Branches	[37]
92	8*β*-hydroxy-4,7,7-trimethyl-1,6-dioxaspiro[4,4] non-3-en-2-one	$C_{10}H_{16}O_4$	Branches	[37]
93	8*α*-hydroxy-4,7,7-trimethyl-1,6-dioxaspiro[4,4] non-3-en-2-one	$C_{10}H_{16}O_4$	Branches	[37]
94	(+) -arturmerone	$C_{15}H_{20}O$	Branches	[37]
95	staphylionoside D	$C_{18}H_{30}O_8$	Branches	[41]
96	Ethoyl-9-O-*β*-D-glucopyranoside	$C_{19}H_{30}O_8$	Branches	[41]
97	Dihydroethoxyl-9-O-*β*-D-glucopyranoside	$C_{20}H_{34}O_7$	Branches	[41]
98	(1*S*,3*S*,5*R*,6*S*)-11-O-*β*-D-glucopyranosyl-14-oxo-dihydrophaseate	$C_{21}H_{30}O_{11}$	Branches	[42]
99	(6*R*,3*E*)-1-O-*β*-D-glucopyranosyl-6,7-dihydroxy-3,7-dimethyl-2-octenoate	$C_{16}H_{28}O_9$	Branches	[42]
100	(-)-1-O-{6-O-[(6*R*,3*E*)-6,7-dihydroxy-3,7-dimethyl-2-octenoyl]}-*β*-D-glucopyranosyl-2-methoxyhydroquinone	$C_{23}H_{34}O_{11}$	Branches	[38]
101	(+)-(2*R*,3*S*)-catechin7-{6-O-[(6*R*,2*E*)-8-hydroxy-2,6-dimethyl-2-octenoyloxy]}-*β*-D-glucopyranoside	$C_{31}H_{40}O_{13}$	Branches	[38]
102	(+)-(7*S*,8*S*)-guaiacylglycerol-8-{6-O-[(2*E*)-6-hydroxy-2,6-dimethylocta-2,7-dienoyloxy]}-*β*-D-glucopyranoside	$C_{26}H_{38}O_{12}$	Branches	[38]
103	icariside B6	$C_{19}H_{32}O_7$	Roots	[25]

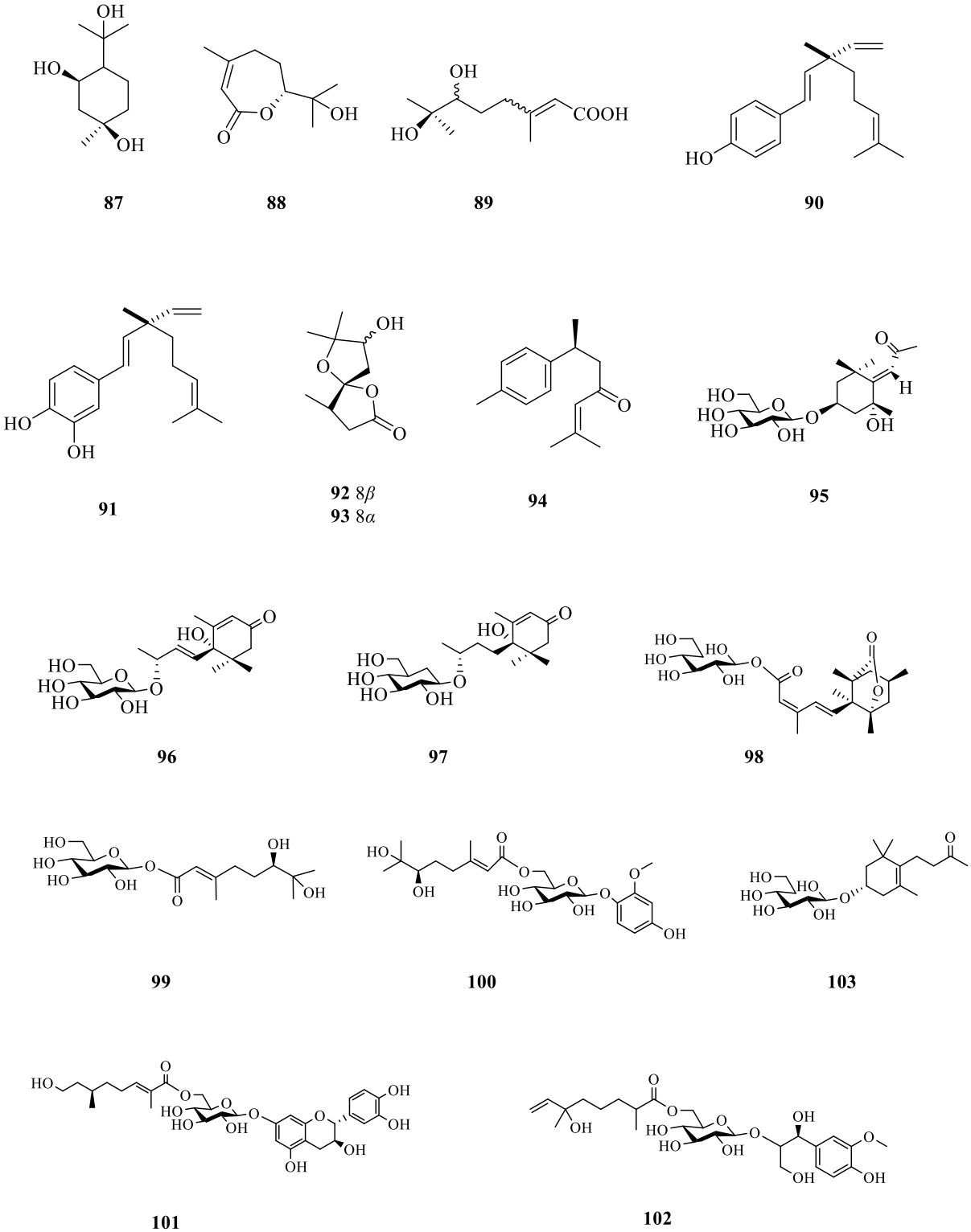


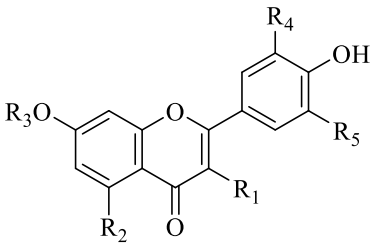
Figure 5. The structures of terpenoids from *Litsea cubeba* (Lour) Pers.

2.4. Flavonoids

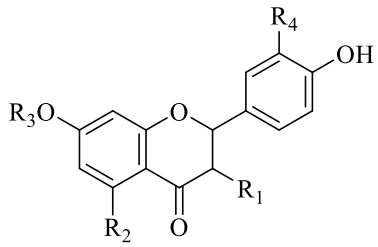
Flavonoid compounds have also been isolated and identified from *Litsea cubeba*. These include flavones (**104-107**,**110-113**) and dihydroflavones (**108-109**,**114**). Common substituents were found at positions 3, 5, 7, 3', 4', and 5', with common groups such as hydroxyls, glucose (Glc), arabinose (Ara), and rhamnose (Rha), while the sugar moiety is generally substituted at positions 3 and 7. The details are shown in Table 4 and Figure 6.

Table 4. Flavonoids in plants of *Litsea cubeba* (Lour) Pers.

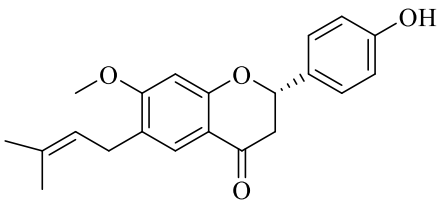
NO.	Compounds	Formula	Part	Ref.
104	quercetin	$C_{15}H_{10}O_7$	Roots	[36]
105	luteolin	$C_{15}H_{10}O_6$	Roots	[36]
106	apigenin7-O-*β*-D-glucopyranoside	$C_{21}H_{22}O_{10}$	Roots	[36]
107	luteolin7-O-*β*-D-glucopyranoside	$C_{21}H_{22}O_{11}$	Roots	[36]
108	(+) -catechin-7-O-*β*-D-glucopyranoside	$C_{21}H_{24}O_{11}$	Branches	[41]
109	3'-methoxy epicatechin 7-O-*β*-D-glucopyranoside	$C_{23}H_{28}O_{11}$	Branches	[41]
110	Kaempferol-3-O-*β*-D-glucopyranoside (1→2) -O-*β*-D-galactopyranoside-7-O-*α*-L-rhamnoside	$C_{33}H_{40}O_{20}$	Branches	[41]
111	Quercetin-3-O-alpha-L-rhamnose base (1→6)-O-beta-D-pyran glucose base (1→3) -O-alpha L-rhamnose base (1→2)-O-beta-D-pyran glycosidase	$C_{33}H_{40}O_{21}$	Branches	[41]
112	kaempferitrin	$C_{27}H_{30}O_{14}$	Branches	[41]
113	quercetin3-O-*β*-D-glucopyranosyl(1→2)-α-L-arabifuranosyl-7-O-*α*-L-rhamnopyranoside	$C_{32}H_{38}O_{19}$	Branches	[38]
114	bavachinin	$C_{21}H_{22}O_4$	Branches	[37]



104 R_1=R_2=R_4=OH,R_3=R_5=H
105 R_1=R_3=R_5=H,R_2=R_4=OH
106 R_1=R_4=R_5=H,R_2=OH,R_3=Glc
107 R_1=R_2=R_4=OH,R_3=Glc.R_5=H
110 R_1=OGlc(1→2)Rha,R_2=OH,R_3=Glc,R_4=R_5=H
111 R_1=ORha(1→6)Glc(1→3)Rha,R_2=R_4=OH,R_3=R_5=H
112 R_1 =ORha,R_2=OH,R_3=Rha,R_4=R_5=H
113 R_1=OAra(1→2)Glc,R_2=R_5=OH,R_3=Rha,R_4=H



108 R_1=R_2=R_4=OH,R_3=Glc
109 R_1=OH,R_2=R_4=OCH_3,R_3=Glc



114

Figure 6. The structures of flavonoids from *Litsea cubeba* (Lour) Pers.

2.5. Other Compounds

Other compounds isolated from the roots, branches, and fruit of *Litsea cubeba* mainly include small amounts of phenylpropanoids, fatty acids, sterides, and organic acids. The structures are shown in Table 5 and Figure 7.

The sterides (**134-139**) have been found to have specific pharmacological activity. Q. Guo. et al. [25] found that the steroid compounds **137** and **138** exhibited significant neuroprotective effects

against oxidative damage induced by hydrogen peroxide in rat PC12 pheochromocytoma cells. Compound **139** also inhibits NO production in Bv-2 cells, with an IC_{50} value of 22.5 μM

Table 5. Other compounds in plants of *Litsea cubeba* (Lour) Pers.

No	Compounds	Formula	Part	Ref.
115	ferulaicacid	$C_{10}H_{10}O_4$	Roots	[36]
116	trans-3,4,5-trimethoxylcinnamylalcohol	$C_{12}H_{14}O_5$	Fruits	[33]
117	vanillicacid	$C_8H_8O_4$	Fruits	[33]
118	protocatechuic acid	$C_7H_6O_4$	Branches	[37]
119	ω-hydroxypropioguaiacone	$C_{10}H_{12}O_4$	Branches	[37]
120	3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone	$C_{11}H_{14}O_5$	Branches	[37]
121	vanillin	$C_8H_8O_3$	Branches	[37]
122	p-hydroxy benzaldehyde	$C_7H_6O_2$	Branches	[37]
123	p-hydroxyacetophenone	$C_8H_8O_2$	Branches	[37]
124	litseacubebicacid	$C_9H_{14}O_3$	Fruits	[33]
125	4, 4-dimethyl-1, 7-opimelic acid	$C_9H_{16}O_4$	Branches	[39]
126	fumaricaid	$C_4H_4O_4$	Branches	[39]
127	(-)-tephrosin	$C_{23}H_{22}O_7$	Fruits	[43]
128	lignocericacid	$C_{24}H_{48}O_2$	Roots	[28]
129	palmiticacid	$C_{16}H_{32}O_2$	Roots	[36]
130	isolinderanolide	$C_{22}H_{38}O_3$	Branches	[37]
131	Secosubamolide A	$C_{23}H_{42}O_4$	Branches	[37]
132	2,5-dimethoxy-p-benzoquinone	$C_8H_8O_4$	Branches	[35]
133	2,6-dimethoxy-p-benzoquinone	$C_8H_8O_4$	Branches	[35]
134	β-sitostenone	$C_{29}H_{48}O$	Branches	[35]
135	β-sitosterol	$C_{29}H_{50}O$	Roots,Branches,Fruits	[28]
136	*β*-daucosterol	$C_{35}H_{60}O_6$	Roots	[28]
137	stigmast-5-ene-3*β,* 7*α*-diol	$C_{29}H_{50}O_2$	Roots	[25]
138	stigmast-5-ene-3*β*, 7*β*-diol	$C_{29}H_{50}O_2$	Roots	[25]
139	3*β*-hydroxystigmast-5-ene-7-one	$C_{29}H_{48}O_2$	Roots	[25]
140	alaschanisoside A	$C_{21}H_{32}O_{10}$	Branches	[41]
141	syringin	$C_{17}H_{24}O_9$	Branches	[41]
142	psoralenoside	$C_{18}H_{22}O_8$	Branches	[41]
143	isonsoralenoside	$C_{18}H_{24}O_8$	Branches	[41]
144	scopolin	$C_{16}H_{18}O_9$	Branches	[41]
145	2, 6-dimethoxy-4-hydroxyphenol-1-O-*β*-D-glucopyranoside	$C_{14}H_{20}O_9$	Branches	[41]
146	3-hydroxy-4, 5-dimethoxyphenol-*β*-D-glucopyranoside	$C_{14}H_{20}O_9$	Branches	[41]
147	2-(3, 4-dihydroxyphenyl) -ethyl-*β*-D-glucopyranoside	$C_{14}H_{20}O_8$	Branches	[41]
148	2-(4-hydroxyphenyl) -ethyl-*β*-D-glucopyranoside	$C_{14}H_{20}O_7$	Branches	[41]
149	2,6-dimethoxy-4-propionylphenyl-O-[*α*-L-rhamnopyranosyl(1→6)]-*β*-D-glucopyranoside	$C_{23}H_{34}O_{13}$	Branches	[38]
150	6'-O-vanilloylisotachioside	$C_{21}H_{24}O_{11}$	Roots	[25]

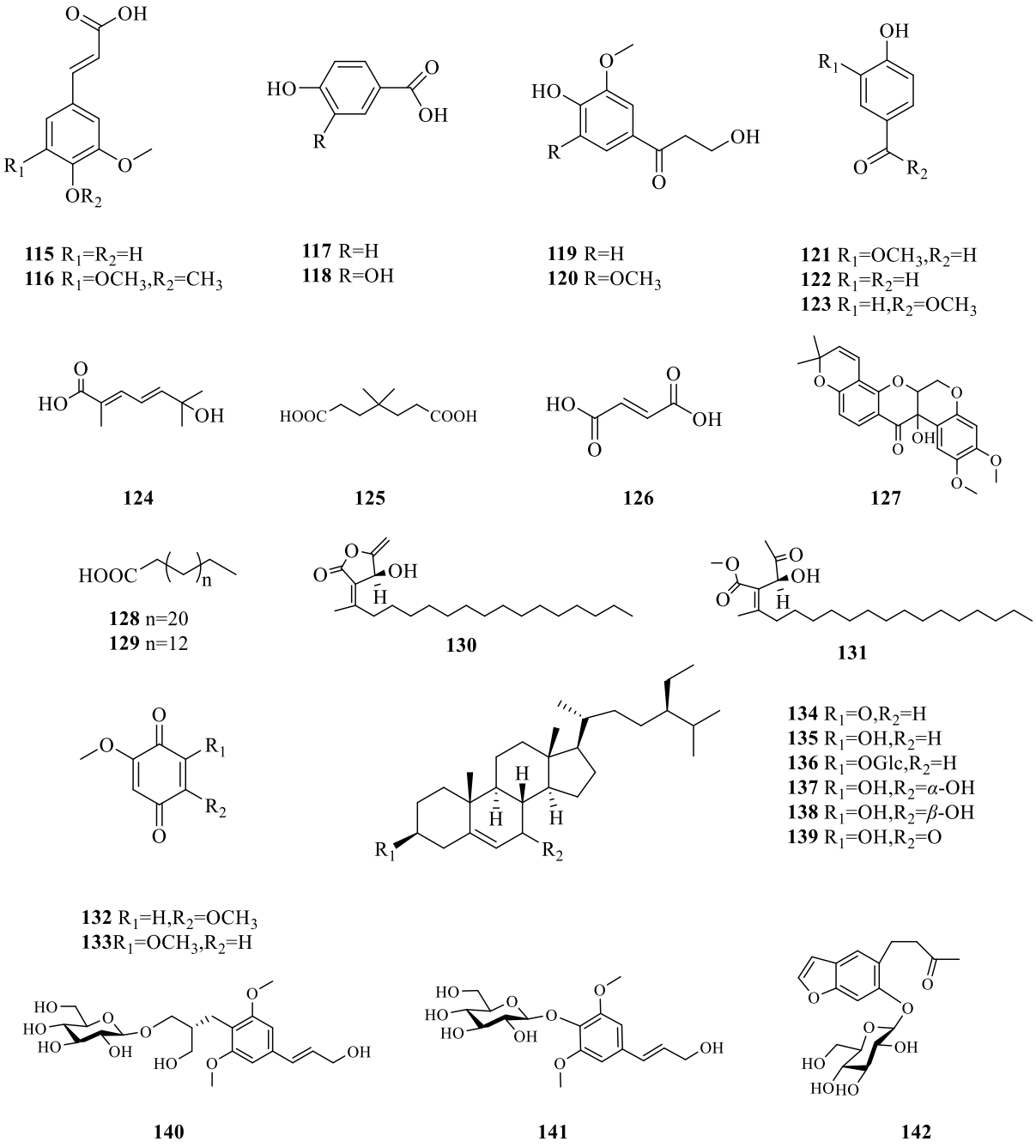


Figure 7. The structures of other compounds from *Litsea cubeba* (Lour) Pers.

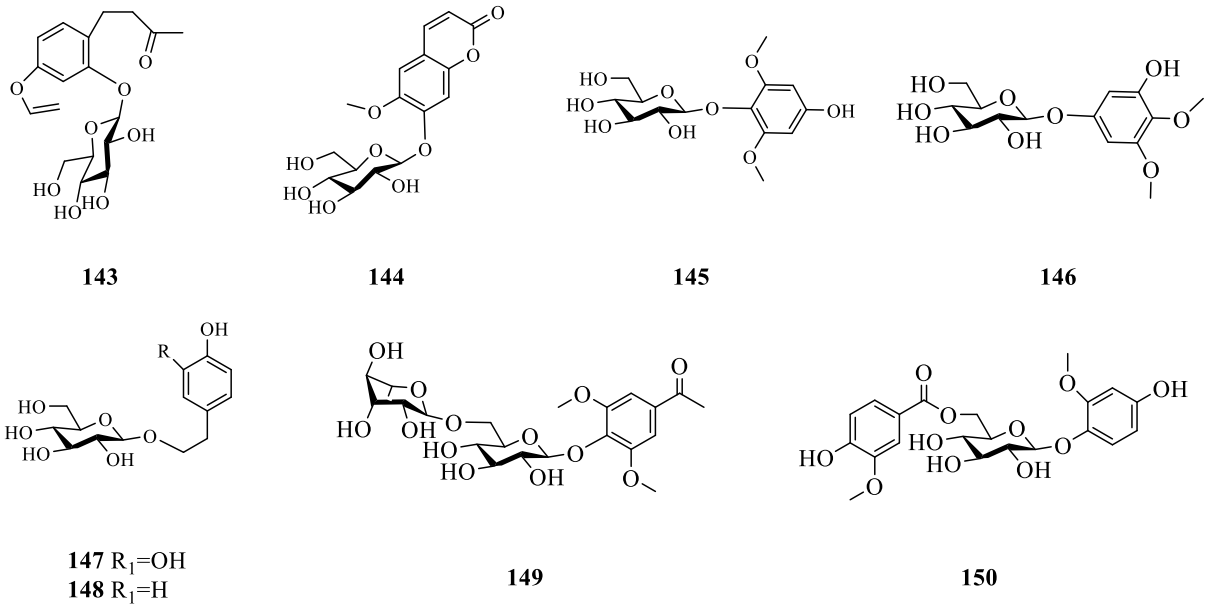


Figure 7. The structures of other compounds from *Litsea cubeba* (Lour) Pers. (continued..)

3. Conclusion

The medicinal properties of *Litsea cubeba* have attracted extensive attention worldwide, leading to substantial research in the field of plant chemistry and biology. Numerous unique compounds with significant pharmacological activities have been isolated from *Litsea cubeba*, holding potential for the further development of new drugs. However, research on the non-volatile components of *Litsea cubeba* is limited, with most studies focusing solely on the essential oils. Therefore, there is a need to expand the scope of research on the active constituents of *Litsea cubeba* and further explore its pharmacological actions.

Compounds derived from *Litsea cubeba* have been shown to have various significant properties. This is especially true of the alkaloids and lignans. Alkaloids are present in high concentrations and have been shown to have a variety of pharmacological effects such as hypoglycemic, anti-inflammatory, and anticancer activities, with aporphine alkaloids being representative examples. However, most compounds have only been studied in terms of their effects on cells in vitro, and the mechanisms underlying their actions remain unclear. Consequently, it is essential to focus on the main direction of medicinal research on *Litsea cubeba* and employ modern pharmacological and pharmacodynamic methods to investigate the mechanisms of action. Moreover, corresponding pharmacological evaluations should be conducted on the specific chemical constituents of *Litsea cubeba* to fully realize the medicinal value of the plant.

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