e-ISSN:2321-6182
p-ISSN:2347-2332

Research and Reviews: Journal of Pharmacognosy and Phytochemistry

Phytochemicals and Biological Activities of the Genus *Cinnamomum*

Jie Zhao*, Jin-shuo Ma
School of Pharmacy, Xinxiang Medical University, Xinxiang, 453003, China

Review Article

Received date: 21/07/2015
Accepted date: 25/12/2015
Published date: 03/01/2016

***For Correspondence**

Jie Zhao, School of Pharmacy, Xinxiang Medical University, Xinxiang, China; Tel: +86-0373-3831879

E-mail: zhzijie820@163.com

Keywords: *Cinnamomum;* Phytochemicals; Bioactivities.

ABSTRACT

The genus *Cinnamomum* has been reviewed for its chemical constituents and biological activities including traditional importance of some common species. The plants of this genus contain butanolides, cinnamaldehyde and its analogues, diterpenoids, lignans and others. The aim of the present paper is to review the comprehensive knowledge of the plants of this genus including the traditional uses, chemistry, and pharmacology.

INTRODUCTION

The genus *Cinnamomum* (Lauraceae) comprises of about 250 species, which occur in Eastern Asia, Australia, and archipelago of Pacific Ocean [1]. It is acknowledged worldwide as an important genus because of its beneficial uses of the essential oils produced by the barks, in particular, cinnamon (*C. verum* syn. *C. zeylanicum*), cassia (Chinese cassia, *C. cassia* syn. *C. aromaticum*; Indonesian cassia, *C. burmannii*; and Indian cassia, largely *C. tamala*), and camphor (*C. camphora*), and will be of interest to research scientists [2-4]. *Cinnamomum cassia* is the most famous one, scheduled as cortex cinnamomi in the Chinese pharmacopoeia [5], which is used for treating dyspepsia, gastritis, blood circulation disturbances, and inflammatory diseases. Its extracts contain several active components such as essential oils (cinnamaldehyde, cinnamic alcohol, cinnamic acid, and coumarin), tannin, mucus, and carbohydrates [6]. The main constituents of *C. cassia* bark oil are cinnamaldehyde. It is used mainly in medicine, foods and cosmetics [7], and is employed in aromatherapy as a rub to promote blood circulation. It also contains both anti-fungal and anti-bacterial principles that can be used to prevent food spoilage due to bacterial contamination [8].

A number of plants in the genus *Cinnamomum* are sources of secondary metabolites with interesting chemical structures and significant bioactivities.

In this article, due to the wide variety of chemical constituents, we aim at providing an overview of the phytochemical progress and listing the compounds isolated from *Cinnamomum* over the period from 1980 to 2014 in worldwide distribution. The biological activities of the crude extracts and isolated compounds of this genus are also included. This review is intended to compile the constituents, verify their bioactivities, indicate potential leads for future drug design, and thus, provide a reference for further research and the application of *Cinnamomum*.

CHEMICAL CONSTITUENTS

A total of 127 chemical constituents have been obtained from the genus *Cinnamomum*

Over the past three decades, including butanolides (1-19), cinnamaldehyde and its analogues (20-55), diterpenoids (56-75), dibenzocycloheptanoids (76-87), Lignans (88-100), flavonoids (101-116), as well as others (117-127), their structures are shown below, and their names and the corresponding plant sources are compiled in **Table 1.** These new compounds are discussed in view of the structural feature as follows.

e-ISSN:2321-6182
p-ISSN:2347-2332

Table 1. Chemical Constituents of plants from the genus *Cinnamomum.*

No.	Compound class and name	Source	Ref.
	Butanolides		
1	Kotomolide A	*C. kotoense*	[9]
2	Isokotomolide A	*C. kotoense*	[9]
3	Obtusilactone A	*C. kotoense*	[9]
4	Isoobtusilactone A	*C. kotoense*	[9]
5	Subamolide D	*C. subavenium*	[11]
6	Subamolide E	*C. subavenium*	[11]
7	Linderanolide B	*C. subavenium*	[11]
8	Isolinderanolide B	*C. subavenium*	[11]
9	Tenuifolide A	*C. tenuifolium.*	[12]
10	Isotenuifolide A	*C. tenuifolium.*	[12]
11	Kotomolide B	*C. kotoense*	[9]
12	Subamolide C	*C. subavenium*	[10]
13	Tenuifolide B	*C. tenuifolium*	[12]
14	Subamolide A	*C. subavenium*	[10]
15	Subamolide B	*C. subavenium*	[10]
	Secobutanolide		
16	Secokotomolide A	*C. kotoense*	[9]
17	Secosubamolide	*C. subavenium*	[10]
18	Secosubamolide A	*C. subavenium*	[11]
19	Secotenuifolide A	*C .tenuifolium.*	[12]
	Cinnamaldehyde and its analogues		
20	Cinnamaldehyde	*C .cassia*	[13]
21	2-methoxycinnamaldehyde	*C. cassia*	[13]
22	2-hydroxycinnamaldehyde	*C. cassia*	[13]
23	Coniferaldehyde	*C. cassia*	[13]
24	Cassiferaldehyde	*C. cassia*	[13]
25	Cinnamic acid	*C. cassia*	[13]
26	Cinnamic alcohol	*C. cassia*	[13]
27	o-coumaric acid	*C. cassia*	[13]
28	Rosavin	*C. cassia*	[13]
29	Cinnacasolide A	*C. cassia*	[14]
30	Dihydomelilotoside	*C. cassia*	[13]
31	Methyl dihydromelilotoside	*C. cassia*	[13]
32	Dihydrocinnacasside	*C. cassia*	[13]
33	4-hydroxy-3-methoxyphenethyl butyrate	*C. reticulatum*	[15]
34	4-hydroxy-3-methoxyphenethyl hexyrate	*C. reticulatum*	[15]
35	4-hydroxy-3-methoxyphenethyl pentadecyrate	*C. reticulatum*	[15]
36	4-hydroxy-3-methoxyphenethyl stearate	*C. reticulatum*	[15]
37	4-hydroxy-3-methoxyphenethyl heneicosyrate	*C. reticulatum*	[15]
38	p-hydroxybenzoic acid	*C. burmanii*	[16]
39	Syringic acid	*C. burmanii*	[16]
40	Vanillic acid	*C. burmanii*	[16]
41	Protocatechuic acid	*C. burmanii*	[16]
42	Kobusinol B	*C. zeylanicum*	[17]
43	Caffeic acid	*C. zeylanicum*	[17]
44	Cinnamic acid	*C. zeylanicum*	[17]
45	Ferulic acid	*C. zeylanicum*	[17]
46	Eugenol	*C. zeylanicum*	[17]
47	Icariside DC	*C. cassia*	[13]
48	Cinnacassiol	*C. cassia*	[13]
49	cinnacasolideb	*C. cassia*	[14]
50	Cinnacasolide C	*C. cassia*	[14]
51	Cinnacasside A	*C. cassia*	[18]
52	Cinnacasside B	*C. cassia*	[18]

53	Cinnacasside C	*C. cassia*	[18]
54	Cinnacasside D	*C. cassia*	[18]
55	Cinnacasside E	*C. cassia*	[18]
	Diterpenes		
56	Cinnzeylanine	*C. cassia*	[19]
57	Cinnzeylanol	*C. cassia*	[19]
58	Anhydrocinnzeylanine	*C. cassia*	[19]
59	Anhydrocinnzeylanol	*C. cassia*	[19]
60	Cinncassiol A	*C. cassia*	[19]
61	Cinncassiol A-19-O-β-D-glucopyranoside	*C. cassia*	[19]
62	Cinncassiol B	*C. cassia*	[20]
63	Cinncassiol B-19-O-β-D-glucopyranoside	*C. cassia*	[20]
64	Cinncassiol C1	*C. cassia*	[21]
65	Cinncassiol C1-19-O-β-D-glucopyranoside	*C. cassia*	[22]
66	Cinncassiol C2	*C. cassia*	[22]
67	Cinncassiol C3	*C. cassia*	[22]
68	Cinncassiol D1	*C. cassia*	[23]
69	Cinncassiol D1-19-O-β-D-glucopyranoside	*C. cassia*	[23]
70	Cinncassiol D2	*C. cassia*	[23]
71	Cinncassiol D2 -19-O-β-D-glucopyranoside	*C. cassia*	[23]
72	Cinncassiol D3	*C. cassia*	[23]
73	Cinncassiol D4	*C. Cassia*	[24]
74	Cinncassiol D4-19-O-β-D-glucopyranoside	*C. Cassia*	[24]
75	Cinncassiol E	*C. Cassia*	[25]
	Dibenzocycloheptanoids		
76	Tenuifolin	*C. tenuifolium.*	[27]
77	Reticuol	*C. macrostemon*	[26]
78	Subamol	*C. subavenium*	[28]
79	Burmanol	*C. burmanii*	[16]
80	9,12-di-O-methylsubamol	*C. subavenium*	[29]
81	(aR)- and (aS)-Subavenoside A	*C. subavenium*	[29]
82	(aR)- and (aS)-Subavenoside B	*C. subavenium*	[29]
83	(aR)- and (aS)-Subavenoside C	*C. subavenium*	[29]
84	(aR)- and (aS)-Subavenoside D	*C. subavenium*	[29]
85	(aR)- and (aS)-Subavenoside E	*C. subavenium*	[29]
86	(aR)- and (aS)-Subavenoside F	*C. subavenium*	[29]
87	(aR,7R)-Dihydrisosubamol	*C. subavenium*	[29]
	Lignans		
88	Lyomresmol 3α-O-β-D-glucopyranoside	*C. Cassia*	[30]
89	(+)-syringaresinol	*C. burmanii*	[16]
90	(+)-yangambin	*C. burmanii*	[16]
91	(+)-sesamin	*C. subavenium*	[9]
92	Pluviatilol	*C. subavenium*	[9]
93	Clemaphenol A	*C. subavenium*	[9]
94	Cinbalansan	*C. balansae*	[31]
95	Secoisolariciresinol	*C. osmophloeum*	[32]
96	Secoisolariciresinol diferuloyl esters	*C. osmophloeum*	[32]
97	9,9′-di-*O*-feruloyl-(+)-5,5′-dimethoxy secoisolariciresinol	*C. osmophloeum*	[32]
98	(−)-lyoniresinol	*C. osmophloeum*	[32]
99	(7′*S*,8′*R*,8*R*)-lyoniresinol-9-*O*-(*E*)-feruloyl ester	*C. osmophloeum*	[32]
100	(7′*S*,8′*R*,8*R*)-lyoniresinol-9,9′-di-*O*-(*E*)-feruloyl ester	*C. osmophloeum*	[32]
	Flavonoids		
101	Kaempferol	*C. osmophloeum*	[33]
102	Kaempferol-3-*O*-α-L-rhamnopyranoside	*C. osmophloeum*	[33]

103	Kaempferol-7-O-α-L- rhamnopyranoside	*C. osmophloeum*	[33]
104	Kaempferol-3-O-α-L-rhamnopyranoside-7-O-α-L-rhamnopyranoside	*C. osmophloeum*	[33]
105	Kaempferol-3-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranoside	*C. osmophloeum*	[33]
106	Kaempferitrin	*C. osmophloeum*	[34]
107	Kaempferol 3-O-β-D-glucopyranosyl-(1→4)- α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside	*C. osmophloeum*	[34]
108	Kaempferol 3-O-β-D-apiofuranosyl-(1→2)- α-L-arabinofuranosyl-7-O-α-L-rhamnopyranoside	*C. osmophloeum*	[34]
109	Kaempferol 3-O-β-D-apiofuranosy-(1→4)- α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside	*C. osmophloeum*	[34]
110	Quercetin	*C. zeylanicum*	[35]
111	Quercetin-3-O-α-L-rhamnopyranoside	*C. zeylanicum*	[35]
112	rutin	*C. zeylanicum*	[35]
113	(-)-epicatechin	*C. Cassia*	[36]
114	(-)-epicatechin-3-O-β-D-glucopyranoside	*C. Cassia*	[36]
115	(-)-epicatechin-8-C-β-D-glucopyranoside	*C. Cassia*	[36]
116	(-)-epicatechin-6-C-β-D-glucopyranoside	*C. Cassia*	[36]
	others		
117	N-trans-feruloylmethoxytyramine	*C. reticulatum*	[37]
118	N-cis-feruloylmethoxytyramine	*C. reticulatum*	[37]
119	Cinnaretamine	*C. reticulatum*	[37]
120	ethyl 3,5-dihydroxy-4-nitrobenzoate	*C. tenuifolium*	[38]
121	Subamone	*C. subavenium*	[39]
122	Reticuone	*C. reticulatum*	[40]
123	Cinnakotolactone	*C. kotoense*	[41]
124	Cinnamophilin D	*C. philippinense*	[42]
125	2,3-dihydro-6,6-dimethylbenzo-[b][1,5]dioxocin-4(6H)-one	*C. tenuifolium*	[43]
126	Urolignoside	*C. zeylanicum*	[35]
127	Cinnamtannin B-1	*C. zeylanicum*	[35]

Butanolides

In the course of screening for the chemotaxonomy and biologically active metabolites from Formosan Lauraceous plants, Chen and co-workers analyzed several *Cinnamomum* plants. Three new butanolides, kotomolide A (**1**), isokotomolide A (**2**), and kotomolide B (**11**), were from the leaves of *C. kotoense* [9].

Subamolides A-C (14-15, 12), and new secobutanolides, secosubamolide (17), were isolated from the stems of *C. subavenium* [10]. Subamolide D (5) and subamolide E (6), and a new secobutanolide, secosubamolide A (18), were isolated from the leaves of *C. subavenium* [11]. Tenuifolide A (9), isotenuifolide A (10), and tenuifolide B (13), a new secobutanolide, secotenuifolide A (19) were isolated from the stems of *C. tenuifolium* [12]. Compounds 1-10 have the same hydroxy-γ-methylene-α, β-unsaturated-γ-lactone skeleton. Compounds 16-19 belong to the class of secobutanolides.

Cinnamaldehyde and its Analogues

A methanol extract of the twigs of *C. cassia* was found to possess inhibitory activity against tyrosinase. Purification of the MeOH extract afforded four new phenolics, cassiferaldehyde (24), icariside DC (47), cinnacassinol (48), and dihydrocinnacasside (32), together with 10 known compounds (20-23, 25-28, 30-31)[13]. Later, cinnacasolide A–C (29, 49-50) were isolated from the same plant [14]. Two n-hexane and $CHCl_3$ extractions of the stems of *C. reticulatum* afforded a mixture of 4-hydroxy-3-methoxyphenethyl derivatives (33–37). Compounds 35-37 were new compounds [15]. P-hydroxybenzoic acid (38), syringic acid (39), vanillic acid (40), protocatechuic acid (41) and kobusinol B (42) were isolated from stems of *C. burmanii* [16]. Caffeic acid (43), cinnamic acid (44), ferulic acid (45) and eugenol (46) were purified from n-hexane and ethyl acetate fraction of the stem bark of *C. zeylanicum* [17]. Cinnacassides A–E (51–55), five novel glycosides with a unique geranylphenylacetate carbon skeleton, was isolated from the stem bark of *Cinnamomum cassia*. Each of the cinnacassides A–D possesses one of the four stereoisomers in the aglycone. Their structures were established by extensive spectroscopic analysis and chemical and chiroptical methods [18].

Diterpenoids

The structures of twenty diterpenoids (56-75), isolated from the fraction exhibiting anti-complement activity of the water extractive of *Cinnamomi Cortex*, have been characterized by means of chemical, spectral and X-ray crystallographic analyses [19-25]. These diterpenes so far obtained from *Cinnamomi Cortex* can be classified into four groups. Cinnzeylanine (56) [19], cinnzeylanol (57) [19], cinncassiol B (62) [20] and cinncassiol B-19-O-β-D-glucopyranoside (63) [20] belong to the ketal type. Anhydrocinnzeylanine (58) [19], anhydrocinnzeylanol (59) [19], cinncassiol A (60) [19] and cinncassiol A-19-O-β-D-glucopyranoside (61) [19] belong to the lactone type. Cinncassiol C1 (64) [21], cinncassiol C1-19-O-β-D-glucopyranoside (65) [22], cinncassiol C2 (66) [22] and cinncassiol C3 (67) [22] belong to the diketone type. Compounds 68-74 [23,24] were the novel pentacyclic diterpene consisting of three five-numbered rings and two six-numbered ones, and its skeleton corresponds to a migrated form from the C5-C6 into C5-C1 bond in the ketal-type diterpene. D-glucosyl moiety of compounds 61, 63, 65, 69, 71 and 74 are linked to the C-19 hydroxy group of diterpenes and is β-configuraticn.

Dibenzocycloheptanoids

Chen's group found reticuol (77) in *C. macrostemon* and *C. reticulatum* [26], separated tenuifolin (76) from *C. tenuifolium* [27], isolated subamol (78) from *C. subavenium* [28] and also separated burmanol (79) from *C. burmanii* [16]. Those *dibenzocycloheptanoids* which might exist in *Cinnamomum* plant specially. Five dibenzocycloheptatrienes (80−82, 84, and 85) and one dibenzocycloheptadiene (87) were isolated from the leaves of *C. subavenium*. The glycosides 81−86, named (aR)- and (aS)-Subavenoside A-F, comprise two diastereomers because of the chiral glycosyl moiety and the axial chirality of the biphenyl system[29].

Lignans

Lyomresmol 3α-O-β-D-glucopyranoside (88) and (+)-syringaresinol (89) had been obtained from the dried bark of *C. cassia* [30]. Four lignans, (+)-sesamin (91), (+)-syringaresinol(89), pluviatilol(92), and clemaphenol A(93), were isolated from the leaves of *C. kotoense* [16]. (+)-Syringaresinol (89), (+)-yangambin (90) and (+)-sesamin (91) were isolated from the stems of *C. burmanii* [16]. A new cyclobutane lignan, named cinbalansan (94), was isolated from the leaves of *C. balansae* [31], The structure of cinbalansan was shown to be 1β, 2β, 3α, 4α-1,2-dimethyl-(3,4-dimethoxyphenyl) cyclobutane by a combination of ^{1}H-, ^{13}C-NMR, and NOE-experiments and by direct analysis of the ^{1}H-NMR spectrum by the method of X-ray. Three novel lignan esters, one dibenzylbutane-type ligan ester [9, 9′-di-O-feruloyl-(+)-5, 5′-dimethoxy secoisolariciresinol (97)] and two cyclolignan esters [(7′S, 8′R, 8-lyoniresinol-9-O-(E)-feruloyl ester (99) and (7′S, 8′R, 8R)-lyoniresinol-9,9′-di-O-(E)-feruloyl ester (100)], and three known lignans(compounds 95-96, 98) from the heartwood and roots of *C. osmophloeum* [32].

Flavonoids

Six flavonoids, including kaempferol (101), kaempferol 3-O-α-L-rhamno-pyranoside (102), kaempferol 7-O-α-L-rhamnopyranoside (103), kaempferol 3-O-α-L-rhamnopyrano-side-7-O-α-L-rhamnopyranoside (104), kaempferol 3-O-α-L-rhamnopyranosyl-(1→2)- α-L-rhamno-pyranoside (105), were isolated from *C. osmophloeum* [33].

Kaempferitrin (106), kaempferol 3-O-β-D-glucopyranosyl-(1→4)- α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside(107), kaempferol 3-O-β-D- apiofuranosyl-(1→2)- α-L-arabinofuranosyl-7-O-α-L-rhamnopyranoside (108), and kaempferol 3-O-β-D-apiofuranosy-(1→4)- α-L-rhamnopyranosyl-7-O-α-L-rhamno-pyranoside (109) were isolated from the leaves of *C. osmophloeum*, a Taiwan endemic tree [34].

Quercetin-3-O-α-L-rhamnopyranoside (110) and rutin (111) were isolated from the water extract of cinnamon fruits of *C. zeylanicum* [35].

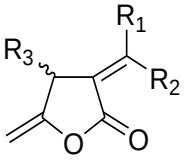
A chemical examination of the bark of *C. cassia* has led to the isolation of three flavan-3-ol glucoside (114-116) and (-)-epicatechin (113) [36].

Others

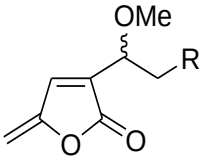
Three amides, N-transferuloylmethoxytyramine (117), N-cis-feruloylmethoxytyr amine (118) and cinnaretamine (119), were isolated and identified from *C. reticulatum* [37]. One new nitrobenzoate, ethyl 3,5-dihydroxy-4-nitrobenzoate (120) was isolated from leaf extract of *C. tenuifolium* [38]. This is the first report of *Cinnamomum* metabolites with a nitro benzenoid derivative. Two novel *Cinnamomum* normonoterpenoids, subamone (121) has been isolated from *C. subavenium* [39], reticuone (122) has been isolated from *C. reticulatum* Hay [40]. A new C19 γ-lactone, cinnakotolactone (123), was isolated from the n-hexane layer of the leaf extracts of *C. kotoense* [41]. Cinnamophilin D (124) was isolated from the leaves of *C. philippinense* [42]. One novel benzodioxocinone, 2, 3-dihydro-6,6-dimethylbenzo-[b][1,5] dioxocin-4(6H)-one (125) was isolated from the leaves' extract of *C. tenuifolium* [43].

Two phenolic derivatives, urolignoside (126) and cinnamtannin B-1 (127), were isolated from the water extract of cinnamon fruits of *C. zeylanicum* [35] **(Figure 1).**

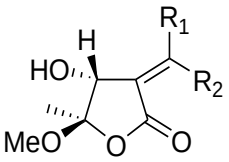
Figure 1: Chemical Constituents of Plants from the Genus *Cinnamomum*.



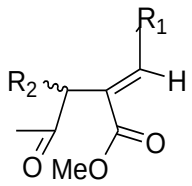
1 R_1=H, R_2=$(CH_2)_6CH_3$, R_3=βOH
2 R_1=$(CH_2)_6CH_3$, R_2=H, R_3=βOH
3 R_1=H, R_2=$(CH_2)_{12}CH_3$, R_3=βOH
4 R_1=$(CH_2)_{12}CH_3$, R_2=H, R_3=βOH
5 R_1=H, R_2=$(CH_2)_9CH_3$, R_3=αOH
6 R_1=$(CH_2)_9CH_3$, R_2=H, R_3=αOH
7 R_1=H, R_2=$(CH_2)_{12}CH_3$, R_3=αOH
8 R_1=$(CH_2)_{12}CH_3$, R_2=H, R_3=αOH
9 R_1=H, R_2=$(CH_2)_{25}CH_3$, R_3=βOH
10 R_1=$(CH_2)_{25}CH_3$, R_2=H, R_3=βOH



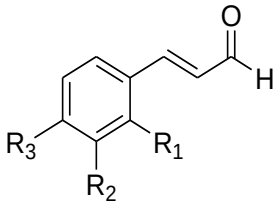
11 R=$(CH_2)_{16}CH_3$
12 R=$(CH_2)_{12}CH_3$
13 R=$(CH_2)_{17}CH_3$



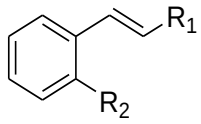
14 R_1=H, R_2=$(CH_2)_{12}CH_3$
15 R_1=$(CH_2)_{12}CH_3$, R_2=H



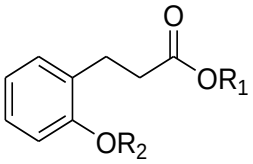
16 R_1=$(CH_2)_{11}CH_3$, R_2=αOH
17 R_1=$(CH_2)_{11}CH_3$, R_2=βOH
18 R_1=$(CH_2)_{13}CH_3$, R_2=βOH
19 R_1=$(CH_2)_{22}CH_3$, R_2=αOH



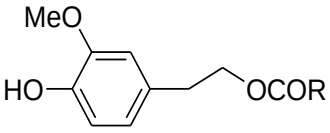
	R_1	R_2	R_3
20	H	H	H
21	OMe	H	H
22	OH	H	H
23	H	OMe	OH
24	OMe	OH	H



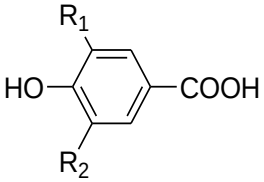
	R_1	R_2
25	COOH	H
26	OH	H
27	COOH	OH
28	CH_2OGlc-Ara	H
29	CH_2OH	OGlc-Api



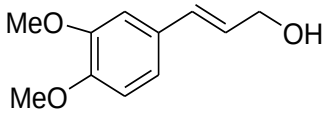
	R_1	R_2
30	H	Glc
31	Me	Glc
32	Glc	H



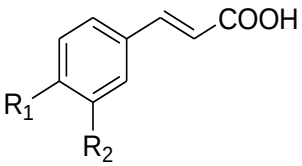
33 R=$(CH_2)_2CH_3$
34 R=$(CH_2)_4CH_3$
35 R=$(CH_2)_{13}CH_3$
36 R=$(CH_2)_{16}CH_3$
37 R=$(CH_2)_{19}CH_3$



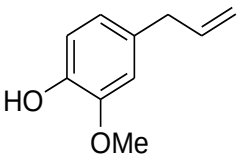
38 R_1=H, R_2=H
39 R_1=OCH_3, R_2=OCH_3
40 R_1=H, R_2=OCH_3
41 R_1=H, R_2=OH



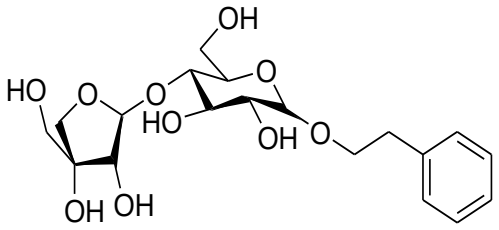
42



43 R_1=R_2=OH
44 R_1=R_2=H
45 R_1=OCH_3, R_2=OH



46



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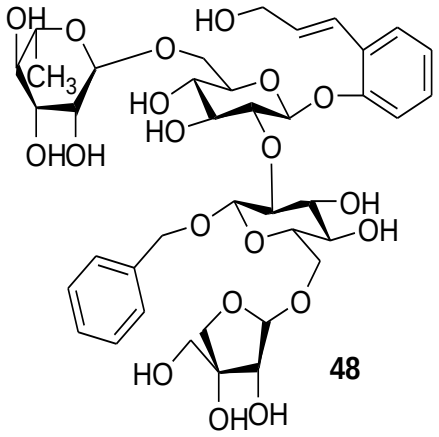

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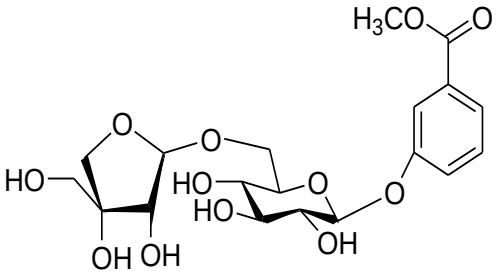

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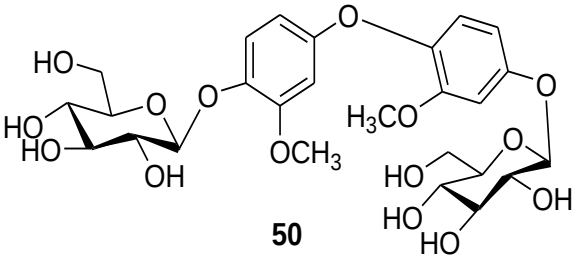

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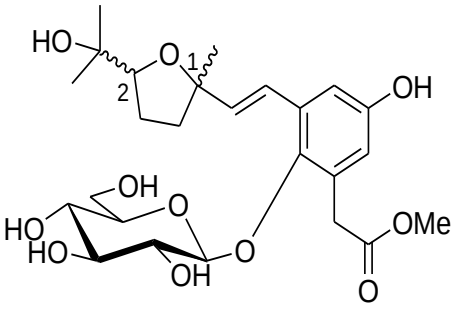
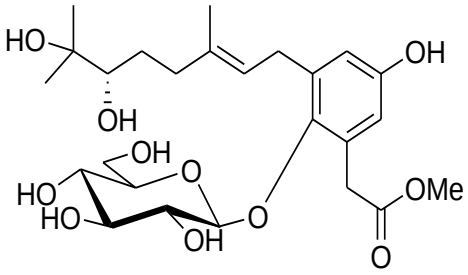
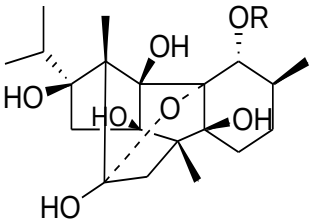


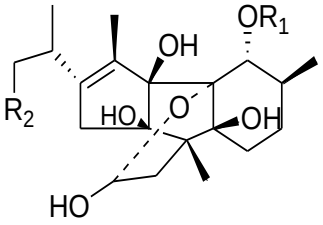
51 1S, 2S
52 1R, 2R
53 1S, 2R
54 1R, 2S



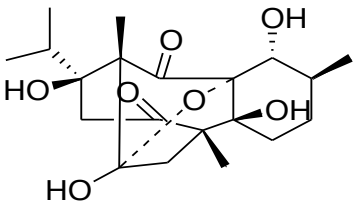
55



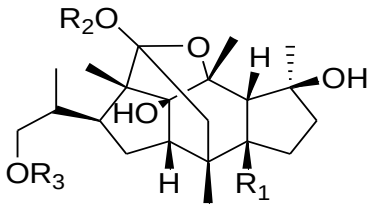
56 R=OH
57 R=H



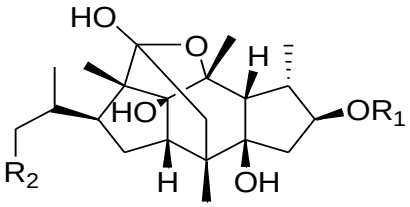
58 R_1=Ac, R_2=H
59 R_1=R_2=H
60 R_1=H, R_2=OH
61 R_1=H, R_2= -O-β-D-Glc.pyr



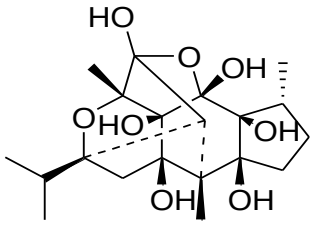
67



68 $R_1=R_2=R_3=H$
69 $R_1=R_2=H, R_3=^{-}\beta$-D-Glc.pyr
70 $R_1=OH, R_2=R_3=H$
71 $R_1=OH, R_2=H, R_3=^{-}\beta$-D-Glc.pyr



72 $R_1=H, R_2=OH$
73 $R_1=R_2=H$
74 $R_1=^{-}\beta$-D-Glc.pyr, $R_2=H$



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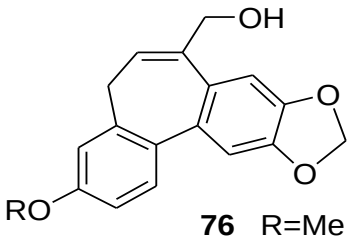
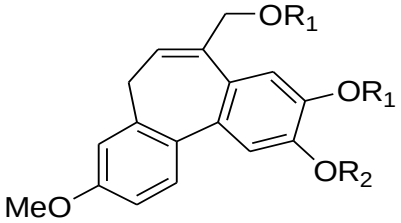
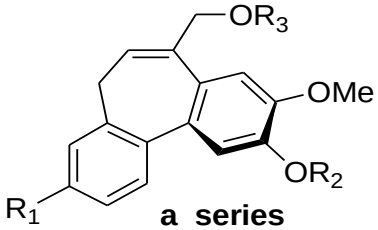


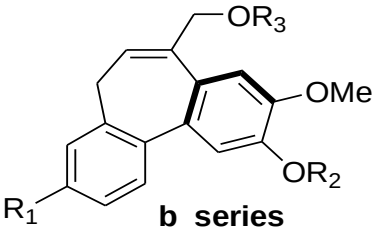
76 R=Me
77 R=H



78 $R_1=R_2=H$
79 $R_1=H, R_2=Me$
80 $R_1=Me, R_2=H$

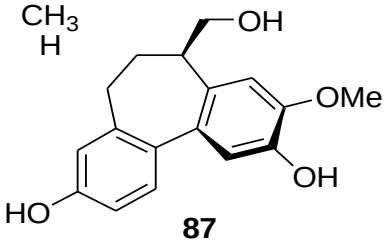


a series

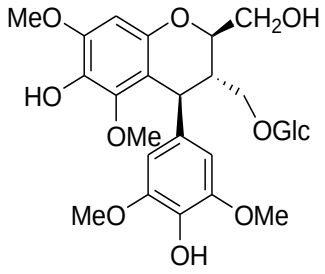


b series

	R_1	R_2	R_3
81a/**81**b	H	H	Glc
82a/**82**b	OCH_3	H	Glc
83a/**83**b	OH	H	Glc
84a/**84**b	H	Glc	H
85a/**85**b	OCH_3	Glc	CH_3
86a/**86**b	OH	Rha	H



87



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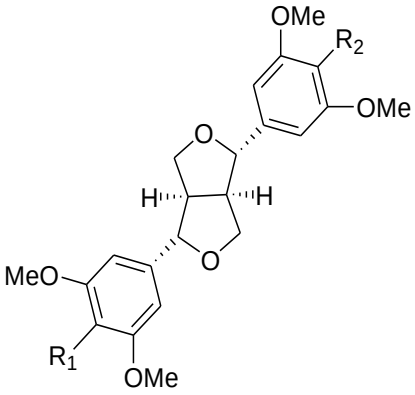
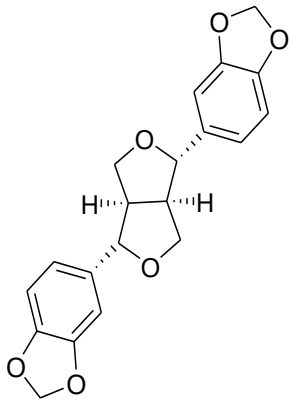


89 R_1=OH, R_2=OH
90 R_1=OMe, R_2=OMe



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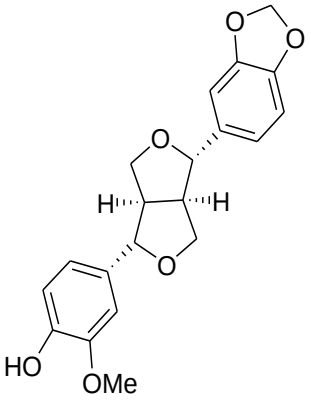

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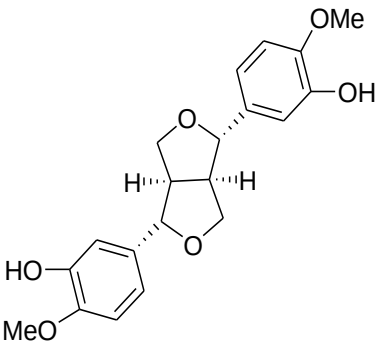
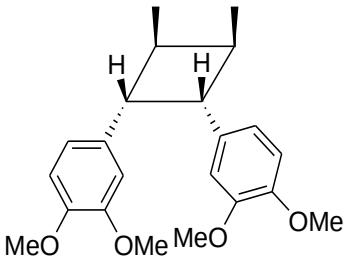


93



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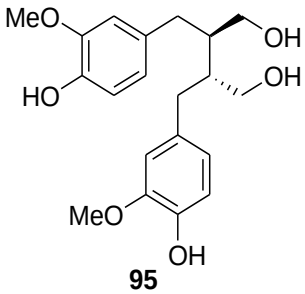

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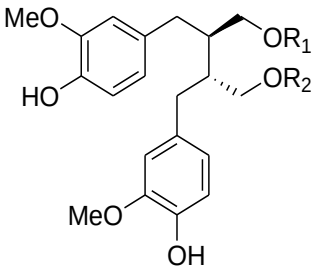
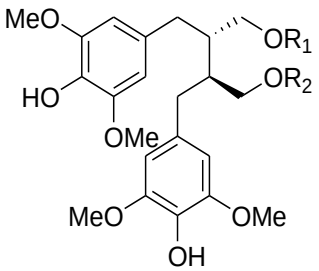
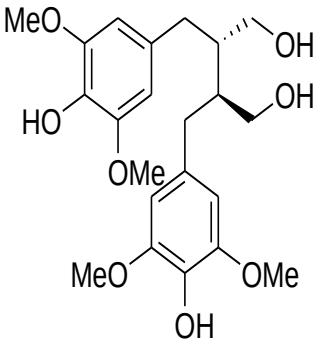


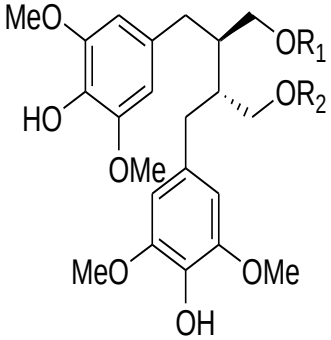
96 R_1=R_2=feruloyl



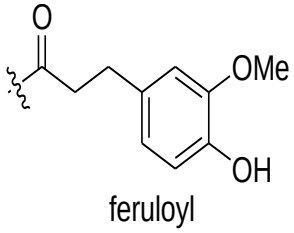
97 R_1=R_2=feruloyl



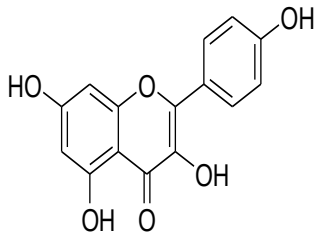
98



99 R_1=feruloyl, R_2=H
100 R_1=R_2=feruloyl



feruloyl



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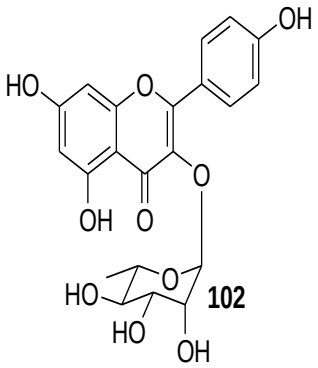

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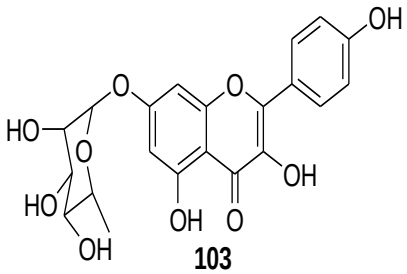

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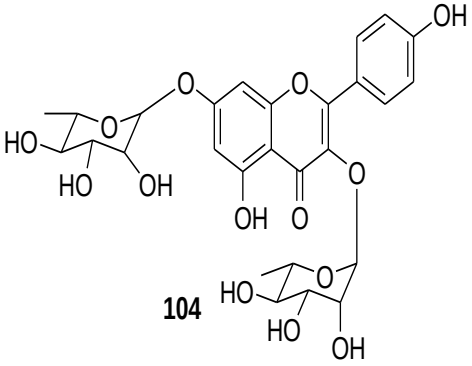

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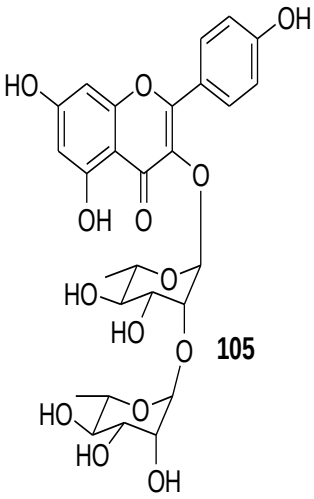

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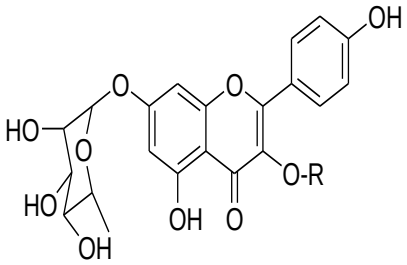
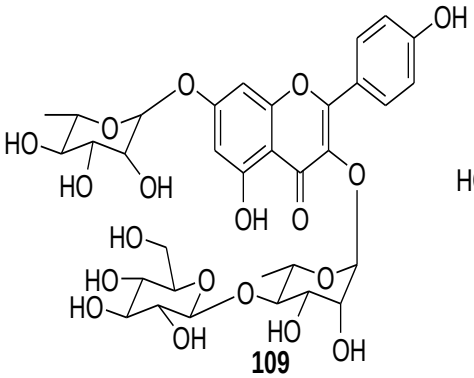


106 R=Rra
107 R=Ara$^{6}\rightarrow_{1}$Api
108 R=Rha$^{4}\rightarrow_{1}$Api



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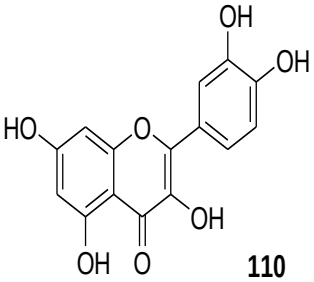

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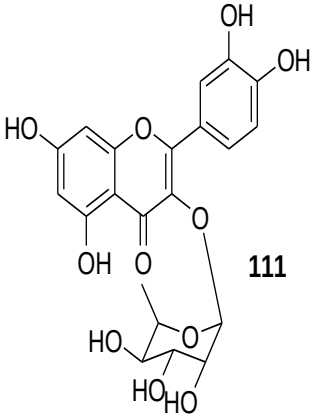

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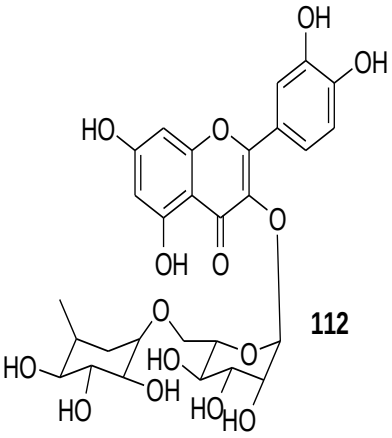

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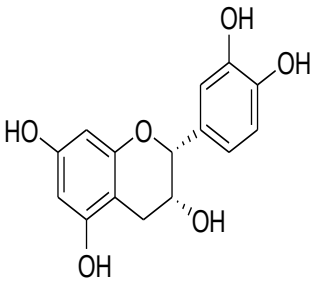

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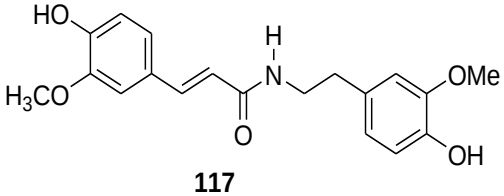

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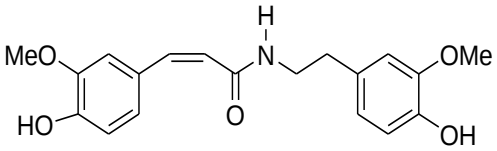

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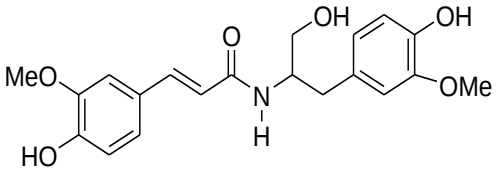
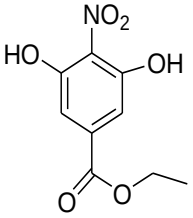


119



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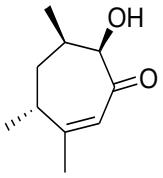

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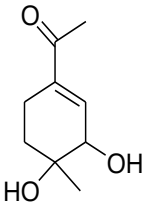

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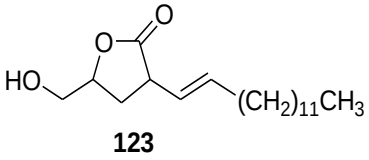
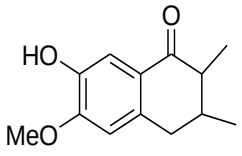
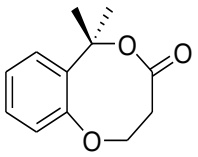


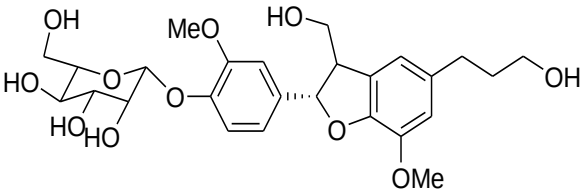
123



124



125



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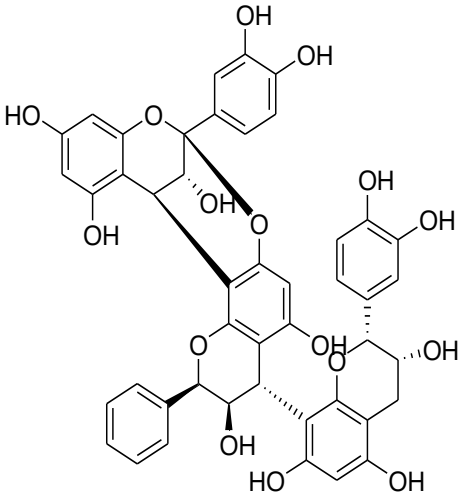

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e-ISSN:2321-6182
p-ISSN:2347-2332

BIOACTIVITIES

The traditional medicinal applications of the *Cinnamomum* species have inspired many pharmacological investigations. The secondary metabolites from genus *Cinnamomum* possess various biological properties, which were mainly *cytotoxicity*, anti-inflammatory, antioxidant, NF-κB inhibitory and tyrosinase inhibition activity.

Cytotoxicity

Secokotomolide A (16), isolated from the leaves of *C. kotoense*, was found to induce significant cell death in the human HeLa cell line. Apoptotic-related DNA damage can be positively related to the dose of secokotomolide A [9].

Propidium iodide staining and flow cytometry were used to evaluate DNA damage of the treated SW480 cells, and it was found that five new butanolides and one secobutanolide, subamolides A-E (14-15, 12, 5-6) and secosubamolide (17) caused DNA damage in a dose-dependent manner after 24 h of treatment. At a 100 μM concentration, all compounds induced significant damage to DNA. The order of potency in inducing DNA damage was observed to subamolide E (6) > subamolide D (5) > subamolide B (15) > subamolide A (14) > secosubamolide (17) > subamolide C (12) [10-12].

Isoobtusilactone A (4), a constituent isolated from the leaves of *C. kotoense*, was investigated the anticancer effect on human non-small cell lung cancer (NSCLC) A549 cells. Isoobtusilactone A was found to induce the arrest of G2-M phase, induce apoptosis, increase sub-G1, and inhibit the growth of these cells. Further investigation revealed that isoobtusilactone A's blockade of the cell cycle was associated with increased levels of p21/WAF1, $p27^{kip1}$, and p53 [44].

A new secobutanolide, secotenuifolide A (19) was discovered to induce apoptotic-related DNA damage, increase sub-G1 cells, and inhibit the growth of human prostate cancer cells, DU145 [12].

(7′*S*, 8′*R*, 8*R*)-lyoniresinol-9,9′-di-O-(*E*)-feruloyl ester (100) from *C. osmophloeum* has strong activities against human liver cancer (HepG2 and Hep3B) and oral cancer (Ca9-22) cells, with IC_{50} values of 7.87, 4.31, and 2.51 μg/mL [32].

Subamone (121) was demonstrated to have cytotoxicity against A549, DU145 and LNCaP cell line (pIC_{50} was: 2.24±0.03, 2.42±0.01 and 7.01±0.04, respectively). Subamone was also found to be significantly active against LNCaP cell line (prostate cancer epithelial cell) [39].

Antioxidant Activity

Kaempferol-7-O-α-L-rhamnopyranoside (103) was also isolated from the antioxidative BuOH fraction of *C. osmophloeum*, and showed 26.9 μM and 68.1 μM of EC_{50} values in 1-diphenyl-2-picrylhydrazyl (DPPH) and Superoxide radical scavenging assay (NBT assay), respectively[33].

The antioxidant activities of compounds 41, 111-112 were screened for their antioxidative potential using β-carotenelinoleate and DPPH model systems. All of the compounds showed antioxidant and radical scavenging activities. Cinnamtannin B-1(127) showed the highest activity followed by rutin (112) and quercetin-3-O-α-L-rhamnopyranoside (111), as in the case of β-carotene antioxidant activity assay [35].

Anti-inflammatory Activity

Four kaempferol glycosides, compounds 105-108 inhibited lipopolysaccharide (LPS) and interferon (IFN)-γ-induced nitric oxide (NO), and cytokines [tumor necrosis factor TNF-α and interleukin IL-12] in a dose-dependent manner. The concentration of 50% inhibition (IC_{50}) of NO by compounds 105, 106, 107 were 40, 15, 20 μM, respectively. In parallel, these concentrations were approximately in a similar manner to that observed for TNF-α and IL-12 production. However, compound 109 inhibited NO and cytokines production by 30% at 100 μM concentration. On the other hand, compounds 106 and 107 showed no inhibitory effect on the production of NO from macrophages, when inducible NO synthase was already expressed by the stimulation with LPS and IFN-γ [34].

NF-κB Inhibitory Activity

Trans-cinnamaldehyde (20) and 2-methoxycinnamaldehyde (21) were identified as NF-κB inhibitors from *C. cassia* with IC_{50} values of 43 μM and 31 μM, respectively. As a positive control, caffeic acid phenethyl ester (CAPE) showed an IC_{50} value of 2 μM on NF-κB transcriptional activity. Both compounds 20 and 21 inhibited LPS–induced DNA binding activity of NF-κB in addition to NF-κB transcriptional activity [45].

Tyrosinase Inhibition

In the course of a program to screen for tyrosinase inhibitors from plants, Ngoc *et al* found that a MeOH extract of the twigs of *C. cassia* exhibited a strong inhibitory activity (>85% inhibition at 100 μg/mL). Cinnamaldehyde and its analogues (compounds 20-25, 27, 30-32 and 47-48) showed strong inhibitory activity against tyrosinase, with IC_{50} values ranging from 0.24 to 0.94 mM [13].

CONCLUSIONS

In this review, we summarize the secondary metabolites reported from *Cinnamomum* species as well as their biological

activities. All the information showed that *Cinnamomum* is a promising and rich source for natural products with chemical and pharmacological diversity. The competitive results stimulate us to get a better understanding of *Cinnamomum* species from the phytochemical and pharmacological viewpoints and to elucidate the chemical composition of substances responsible for the pharmacological activities.

ACKNOWLEDGEMENT

This work was supported by Scientific Research Fund of Xinxiang Medical University grants [2013QN121].

REFERENCES

1. Li X, Bai P. Flora Reipublicae Popularis Sinicae. Science Press, Tomus, 1982; 31:509.
2. Huang TC, In Flora of Taiwan; Huang TC, Hsieh C, Boufford DE, Kuoh CS, Ohashi H, et al. [2ndedn], National Science Council of the Republic of China. Taipei, 2003; 437.
3. Kuo YH, Shue MJ. New Esters, 2-(4-Hydroxy-3-Methoxyphenyl)Ethyl Hexa- and Octacosanoates from the Leaves of *Cinnamomum Reticulatum* Hay. Journal of the Chinese Chemical Society. 1991; 38(1): 65-69.
4. Fang Q, Yongheng T, Xiaofeng X. Comparison Study on the Quality of Cortex Cinnamomi from Genuine Producing Areas,GAP Planting Base and Commercial Markets. Trad Chin Drug Res Clin Pharmacol. 2007; 18249.
5. Ravindran PN, Nirmal-Babu K, Shylaja M. In Cinnamon and Cassia. Hardman R. The Genus Cinnamomum. Medicinal and Aromatic Plantsd Industrial Profiles. CRC, Washington DC. 2004; 36.
6. He ZD, Qiao CF, Han QB. Authentication and Quantitative Analysis on the Chemical Profile of Cassia Bark (Cortex Cinnamomi) by High-Pressure Liquid Chromatography. J Agric Food Chem. 2005; 53(7): 2424-2428.
7. Bown D. The Royal Horticultural Society Encyclopedia of herbs and their uses. Dorling Kindersley Ltd. London. 1995; 424.
8. Huang DF, Xu JG, Liu JX, Zhang H, Hu QP. Chemical constituents, antibacterial activity and mechanism of action of the essential oil from *Cinnamomum cassia* bark against four food-related bacteria. Microbiol. 2014; 83(4): 357-365.
9. Chen CH, Lo WL, Liu YC, Chen CY. Chemical and Cytotoxic Constituents from the Leaves of *Cinnamomum kotoense*. J Nat Prod .2006; 69(6): 927-933.
10. Chen CY, Chen CH, Wong CH, Liu YW, Lin YS, et al. Cytotoxic Constituents of the Stems of *Cinnamomum subavenium*. J Nat Prod. 2007; 70(1): 103-106.
11. Kuo SY, Hsien TJ, Wang YD, Lo WL, Hsui YR, et al. Cytotoxic Constituents from the Leaves of *Cinnamomum subavenium*. Chem Pharm Bull. 2008; 56(1): 97-101.
12. Lin RJ, Cheng MJ, Huang JC, Lo WL,Yeh YT, et al. Cytotoxic Compounds from the Stems of *Cinnamomum tenuifolium*. J Nat Prod. 2009; 72(10): 1816-1824.
13. Ngoc TM, Lee I, Ha DT, Kim HJ, Min BS, et al. Tyrosinase-Inhibitory Constituents from the Twigs of *Cinnamomum cassia*. J Nat Prod. 2009; 72(6):1205-1208.
14. Ngoc TM, Khoi NM, Ha DT, Nhiem NX, Tai BH, et al. Xanthine oxidase inhibitory activity of constituents of *Cinnamomum cassia* twigs. Bioorg. Med Chem Lett. 2012; 22(14): 4625-4628.
15. Lin IJ, Lo WL, Chiac YC, Huang LY, Cham TM, et al. Isolation of new esters from the stems of *Cinnamomum Reticulatum Hay*. Nat Prod Res. 2010; 24(8): 775-780.
16. Chen CY, Hong ZL, Yang WL, Wu MH, Huang JC, et al. A novel homosesquiterpenoid from the stems of *Cinnamomum burmanii*. Nat Prod Res. 2012; 26(13): 1218-1223.
17. Shahwara D, Raza MA, Shafiq-Ur-Rehman MA, Abbasi; Atta-Ur-Rahman. An investigation of phenolic compounds from plant sources as trypsin inhibitors. Nat Prod Res. 2012; 26(12): 1087-1093.
18. Liao SG, Yuan T, Zhang C, Yang SP, Wua Y, et al. Cinnacassides A–E, five geranylphenylacetate glycosides from *Cinnamomum cassia*. Tetrahedron. 2009; 65(4): 883-887.
19. Yagi A, Tokubuchl N, Nohara T, Nonaka G, Nishioka I, et al. The Constituents of *Cinnamomi Cortex*. I. Structures of Cinncassiol A and Its Glucoside. Chem Pharm Bull. 1980; 28(9): 1432-1436.
20. Nohara T, Tokubuchi N, Kuroiwa M, Nishioka I. The Constituents of *Cinnamomi Cortex* III Structures of Cinncassiol B and Its Glucoside. Chem Pharm Bull. 1980; 28(9): 2682-2686.
21. Nohara T, Tokubuchi N, Kuroiwa M, Nishioka I, Cinncassiol C. A novel type of diterpene from *Cinnamomi Cortex*. Chem Pharm Bull. 1980; 28(6): 1969-1970.
22. Kashiwada Y, Nohara T, Tomimatsuand T, Nishioka I. The Constituents of *Cinnamomi Cortex* IV. Structures of Cinncassiol C_1 Glucoside, C_2 and C_3.Chem Pharm Bull. 1981; 29: 2686-2688.

23. Nohara T, Kashiwada Y, Murakami K, Tomimatsuand T, Yagi A, et.al Constituents of *Cinnamomi Cortex*. V. Structures of Five Novel Diterpenes, Cinncassiols D_1, D_1 Glucoside, D_2, D_2 Glucoside and D_3. Chem Pharm Bull. 1981; 29: 2451-2459.

24. Nohara T, Tokubuchi N, Kuroiwa M, Nishioka I. Two novel diterpenes from bark of *Cinnamomum cassia*. Phytochemistry.1982; 21(8): 2130-2132.

25. Nohara T, Tokubuchi N, Kuroiwa M, Nishioka I. Cinncassiol E, A diterpene from the bark of *Cinnamomum cassia*. Phytochemistry. 1985; 24(8): 1849-1850.

26. Chen HL, Yang WL, Li YP, Kang YF, Wu HM, et al. A novel homosesquiterpene from *Cinnamomum macrostemon Hayata*. Journal of Medicine and Medical Sciences. 2012; 3(2): 90-92.

27. Lin RJ, Cheng MJ, Huang JC, Lo WL, Yeh YT, et al. Cytotoxic Compounds from the Stems of *Cinnamomum tenuifolium*. J Nat Prod. 2009; 72(10):1816-1824.

28. Chen CY, Yang WL, Hsui YR. A novel sesquiterpenoid from the roots of *Cinnamomum subavenium*. Nat Prod Res. 2010; 24(5): 423-427.

29. Lin HC, Lee SS. Dibenzocycloheptanoids from the Leaves of *Cinnamomum subavenium*. J Nat Prod. 2012; 75(10): 1735-1743.

30. Miyamura M, Nohara T, Tomimatsu T, Nishiokat I. Seven aromatic compounds from bark of *Cinnamomum cassia*. Phytochemistry, 1983, 22(22): 215-218.

31. Cuong NM, Taylor W, Sung TV. A New Cyclobutane Lignan from *Cinnamomum Balansae*. Nat Prod Let. 2006; 15(5): 331-338.

32. Chen TH, Huang YH, Lin JJ, Liau BC, Wan SY, et al. Cytotoxic Lignan Esters from *Cinnamomum osmophloeum*. Planta Med. 2010; 76(6): 613-619.

33. Chen CY, Hsieh SL, Hsieh MM, Hsieh SF, Hsieh TJ. Substituent Chemical Shift of Rhamnosides from the Stems of *Cinnamomum osmophleum*. The Chinese Pharmaceutical Journal. 2004; 56(3): 141-146.

34. Fang SH, Rao YK, Tzeng YM. Inhibitory effects of flavonol glycosides from *Cinnamomum osmophloeum* on inflammatory mediators in LPS/IFN-γ-activated murine macrophages. Bioorg Med Chem. 2005; 13(7): 2381-2388.

35. Jayaprakasha GK, Ohnishi-Kameyama, M, Ono H, Yoshida M, Jaganmohan Rao L. Phenolic Constituents in the Fruits of *Cinnamomum zeylanicum* and Their Antioxidant Activity. J Agric Food Chem. 2006; 54(5): 1672.

36. Mokimoto S, Nonaka GI, Nishioka I. Tannins and Related Compounds. XXXVIII: Isolation and Characterization of Flavan-3-ol Glucosides and Procyanidin Oligomers from Cassia Bark: *Cinnamomum cassia* BLUME. Chem Pharm Bull. 1986; 34(2): 633.

37. Chen CY, Yeh HC. A new amide from the stems of *Cinnamomum reticulatum* Hay. Nat Prod Res. 2011; 25(1): 26-30.

38. Cheng MJ, Yeh YT, Wang CJ, Chen CY. Isolation of a nitrobenzoate from the leaves of *Cinnamomum tenuifolium*. Nat Prod Res. 2010; 25(2): 118-122.

39. Lin RJ, Lob WL, Wang YD, Chen CY. A novel cytotoxic monoterpenoid from the leaves of *Cinnamomum subavenium*. Nat Prod Res. 2008; 22(12): 1055-1059.

40. Cheng MJ, Lob WL, Tseng WS, Yehc HC, Chen CY. A novel normonoterpenoid from the stems of *Cinnamomum reticulatum* Hay. Nat Prod Res. 2010; 24(8):732-736.

41. Yang SS, Hou WC, Huang LW, Lee TH. A new γ-lactone from the leaves of *Cinnamomum kotoense*. Nat Prod Res.2006; 20(13): 1246.

42. Cheng MJ, Yeh YT, Wang CJ, Chen CY. A new 3, 4-dihydronaphthalen-1(2H)-one from the leaves of Cinnamomum *philippinense*. Nat Prod Res. 2012; 26(15):1433-1435.

43. Chen HL, Kuo SY, Li YP, Kang YF, Yeh YT, et al. A new benzodioxocinone from the leaves of *Cinnamomum tenuifolium*. Nat Prod Res. 2012; 26(20):1881-1886.

44. Lin RJ, Cheng MJ, Huang JC, Lo WL, Yeh YT, et al. Anticancer Activity of Isoobtusilactone A from *Cinnamomum kotoense*: Involvement of Apoptosis, Cell-Cycle Dysregulation, Mitochondria Regulation, and Reactive Oxygen Species. J Nat Prod .2008; 71(6): 933-940.

45. Reddy AM, Seo JH, Ryu SH, Kim YS, Kim YS, et al. Cinnamaldehyde and 2-Methoxycinnamaldehyde as NF-κB Inhibitors from *Cinnamomum cassia*. Planta Med. 2004; 70(9): 823-827.