MS Editions

Blacpma

BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
19 (6): 527 - 541 (2020)
© / ISSN 0717 7917 / **www.blacpma.ms-editions.cl**

Revisión / Review

Lindera aggregata (Sims) Kosterm: Review on phytochemistry and biological activities

[*Lindera agreggata* (Sims) Kosterm: revisión de su fitoquímica y actividades biológicas]

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Abstract: The genus *Lindera* consists of approximately 100 species that are widely distributed in tropical and subtropical areas throughout the world. Most *Lindera* plants, particularly *Lindera aggregata* is a well-known traditional Chinese medicine that has important medicinal value and health benefits. Contemporary chemical and pharmacological studies have shown that *L. aggregata* are a source of structurally diverse molecules having pharmacological potential. In an effort to promote research on *L. aggregata* and develop therapeutic and pharmacological products, this review describes the structural diversity of its components and pharmacological and biological significance of *L. aggregata*. This review is based on a literature analysis of scientific journals from electronic sources, such as Science Direct, PubMed, Google Scholar, Scopus and Web of Science. Thus, with the growing interest in traditional medicine and botanical drugs worldwide, *L. aggregata* will increasingly capture chemists' and pharmacologists' attention because they produce diverse and structurally novel compounds having pharmacological significance.

Keywords: Lauraceae; *Lindera aggregata*; Phytochemistry; Sesquiterpenoid; Alkaloid; Phenolic.

Resumen: El género *Lindera* consta de aproximadamente 100 especies que están ampliamente distribuidas en áreas tropicales y subtropicales en todo el mundo. La mayoría de las plantas de *Lindera*, particularmente *Lindera aggregata*, es parte conocida de la medicina tradicional china con un importante valor medicinal y beneficios para la salud. Estudios químicos y farmacológicos contemporáneos han demostrado que *L. aggregata* es una fuente de moléculas estructuralmente diversas que con potencial farmacológico. En un esfuerzo por promover la investigación sobre *L. aggregata* y desarrollar productos terapéuticos y farmacológicos, esta revisión describe la diversidad estructural de sus componentes y la importancia farmacológica y biológica de *L. aggregata*. Esta revisión se basa en un análisis de literatura de revistas científicas de fuentes electrónicas, como Science Direct, PubMed, Google Scholar, Scopus y Web of Science. Por lo tanto, con el creciente interés en la medicina tradicional y las drogas botánicas en todo el mundo, *L. aggregata* captará cada vez más la atención de los químicos y farmacólogos debido a que producen compuestos diversos y estructuralmente novedosos que tienen importancia farmacológica.

Palabras clave: Lauraceae; *Lindera aggregata*; Fitoquímica; Sesquiterpenoide; Alcaloide; Fenólico

Recibido | Received: April 19, 2020
Aceptado | Accepted: May 8, 2020
Aceptado en versión corregida | Accepted in revised form: May 12, 2020
Publicado en línea | Published online: November 30, 2020
Este artículo puede ser citado como / This article must be cited as: WMNHW Salleh. 2020. *Lindera aggregata* (Sims) Kosterm: Review on phytochemistry and biological activities. **Bol Latinoam Caribe Plant Med Aromat** 19 (6): 527 – 541. **https://doi.org/10.37360/blacpma.20.19.6.37**

INTRODUCTION

For centuries, botanical remedies have been used for human disease management because plants contain multitude of novel components of diverse therapeutic value. The Lauraceae family is by far the largest family of the order Laurales with about 50 genera and over 2000 species distributed throughout tropical to subtropical latitudes especially in Southeast Asia and tropical America (Van der Werff & Richter, 1996; Salleh *et al*., 2015). Most of the plants of this family and particularly genus *Lindera* are of great interest to pharmacists as preliminary pharmacological studies proved that these plants have the efficient medicinal potential for the treatment of broad-spectrum health disorders (Cao *et al*., 2016). The genus *Lindera* consists of approximately 100 species that are widely distributed in tropical, subtropical, and temperate zones of Asia and Midwestern America (Tsui, 1987). *Lindera* plants are rich in essential oils and are used for producing spices, fragrances, and building timber. It also reported that the plants are appropriate for manufacturing soaps and lubricants (Flora of China Editorial Committee, 2010).

Lindera aggregata (Sims.) Kosterm. (Lauraceae) (**Figure No. 1**) is an important medicinal plant, widely distributed in China, Japan, Taiwan, and Southeast Asia (Li, 1984). In China, it is locally known as *Wu Yao*, while in Japan known as *Uyaku*. *L. aggregata* is an evergreen shrub or small tree that is widely distributed and common across the eastern moist subtropical evergreen broadleaved forests (Wang *et al*., 2007). Some isolated outposts have also been reported from Vietnam and the Philippines and the species is sometimes cultivated outside its native range. The plant grows on sunny mountain slopes, in sparse forests and thickets at elevations between 200 and 1,000 m. It is dioecious, produces entomophilous flowers and fleshy drupes that are putatively dispersed by birds (Hirayama *et al*., 2004). The Flora of China and The Plant List recognize two varieties which are *L. aggregata* var. *hemsleyana* (Diels) S.S.Ying and *L. aggregata* var. *playfairii* (Hemsl.) H.B. Cui (The Flora of China, 2010; The Plant List, 2010). Previous phytochemical investigations revealed that sesquiterpenoids are the main secondary metabolites isolated from this plant.

Due to its diverse applications, wide attention has been paid by scientific communities and plenty of investigations on bioactive constituents and pharmacological activities have been conducted. At this time, we summarize research findings on phytochemistry and their pharmacological activities. This highlights the current status and likely future directions that will provide a representative overview of this medicinal plant. The scientific databases: Google Scholar, Web of Science, PubMed, and Scopus were utilized to gather all relevant information from literature articles.

Figure No. 1
***Lindera aggregata* (Sims.) Kosterm.**

Traditional uses

There is a long history of using *L. aggregata* in traditional Chinese medicine for the treatment of various diseases. *L. aggregata* extracts is usually used for treating urinary system diseases such as enuresis and urinary stones. Besides, it has pronounced effects on chronic gastritis and rheumatoid arthritis (Zhang & Wang, 2000). In addition, mashed leaves of *L. aggregata* are beneficial for treating mastitis, acute cellulitis, and carbuncles (Chou *et al*., 2000). Fresh cut leaves of *L. aggregata* stir-fried in rice wine show the therapeutic effect on rheumatoid arthritis. In addition, *L. aggregata* extracts are used in Japan to treat stroke and cholera (Han *et al*., 2008).

PHYTOCHEMISTRY

A review of the literature revealed that few phytochemical studies have been carried out on *L. aggregata*. The studies have reported the presence of several classes of secondary metabolites including sesquiterpenoids, amides, alkaloids, flavonoids, procyanidins, lignans, benzenoids, butenolides, phenolics, and essential oils. The isolated phytochemicals are tabulated in **Table No. 1**.

Table No. 1
Phytochemicals isolated from *Lindera aggregata*

No	Constituents	Parts	References
	SESQUITERPENOIDS		
1	Aggreganoid A	Roots	Liu *et al*., 2009a
2	Aggreganoid B	Roots	Liu *et al*., 2009a
3	Aggreganoid C	Roots	Liu *et al*., 2009a
4	Aggreganoid D	Roots	Liu *et al*., 2009a
5	Aggreganoid E	Roots	Liu *et al*., 2009a
6	Aggreganoid F	Roots	Liu *et al*., 2009a
7	Linderalide A	Roots	Liu *et al*., 2009b
8	Linderalide B	Roots	Liu *et al*., 2009b
9	Linderalide C	Roots	Liu *et al*., 2009b
10	Linderalide D	Roots	Liu *et al*., 2009b
11	Linderanlide A	Root tubers	Qiang *et al*., 2011
12	Linderanlide B	Root tubers	Qiang *et al*., 2011
13	Linderanlide C	Root tubers	Qiang *et al*., 2011
14	Linderanlide D	Root tubers	Qiang *et al*., 2011
15	Linderanlide E	Root tubers	Qiang *et al*., 2011
16	Linderanlide F	Root tubers	Qiang *et al*., 2011
17	Linderanine A	Root tubers	Qiang *et al*., 2011
18	Linderanine B	Root tubers	Qiang *et al*., 2011
19	Linderanine C	Root tubers	Qiang *et al*., 2011
20	(+)-Linderadine	Root tubers	Qiang *et al*., 2011
21	ent-4(15)-Eudesmene-1β,6α-diol	Root tubers	Qiang *et al*., 2011
22	Dehydrocostuslactone	Root tubers	Qiang *et al*., 2011
23	Linderagalactone A	Root tubers	Gan *et al*., 2009a
24	Linderagalactone B	Root tubers	Gan *et al*., 2009a
25	Linderagalactone C	Root tubers	Gan *et al*., 2009a
		Roots	Wu *et al*., 2010
26	Linderagalactone D	Root tubers	Gan et al., 2009a
		Roots	Wu *et al*., 2010
27	Linderagalactone E	Root tubers	Gan *et al*., 2009a
28	3-Eudesmene-1β,11-diol	Root tubers	Gan *et al*., 2009a
29	Hydroxylindestenolide	Root tubers	Gan *et al*., 2009a
		Leaves	Zhang *et al*., 2001
		Root tubers	Qiang *et al*., 2011
		Roots	Wu *et al*., 2010
		Roots	Ma *et al*., 2015
30	Dehydrolindestrenolide	Leaves	Zhang *et al*., 2001
31	Strychnistenolide	Root tubers	Gan *et al*., 2009a
32	Hydroxyisogermafurenolide	Root tubers	Gan *et al*., 2009a
33	Atractylenolide III	Root tubers	Gan *et al*., 2009a
34	Linderane	Root tubers	Gan *et al*., 2009a
		Roots	Cheng *et al*., 2007
		Roots	Wu *et al*., 2010
		Root tubers	Qiang *et al*., 2011
35	Neolinderalactone	Root tubers	Gan *et al*., 2009a
		Roots	Wu *et al*., 2010
36	Neolindenenonelactone	Roots	Cheng *et al*., 2007
37	Isolinderalactone	Roots	Cheng *et al*., 2007
38	Linderalactone	Roots	Cheng *et al*., 2007
		Root tubers	Gan *et al*., 2009a

		Root tubers	Qiang *et al*., 2011
		Leaves	Zhang *et al*., 2001
39	8-Hydroxylindestenolide	Roots	Cheng *et al*., 2007
40	bi-Linderone	Roots	Wang *et al*., 2010a
		Roots	Chen *et al*., 2018
41	epi-bi-linderone	Roots	Chen *et al*., 2018
42	(±)-Linderaspirone A	Roots	Wang *et al*., 2010b
		Roots	Chen *et al*., 2018
43	(±)-Lindepentone A	Roots	Chen *et al*., 2018
44	Lindoxepines A	Roots	Chen *et al*., 2018
45	Lindoxepines B	Roots	Chen *et al*., 2018
46	(+)-Demethoxy-epi-bi-linderone	Roots	Chen *et al*., 2018
47	(-)-Demethoxy-epi-bi-linderone	Roots	Chen *et al*., 2018
48	Methyllinderone	Roots	Chen *et al*., 2018
49	Methyllucidone	Roots	Chen *et al*., 2018
	AMIDES AND ALKALOIDS		
50	(+)-Norboldine acetate	Roots	Gan *et al*., 2009b
51	(+)-Norboldine	Roots	Gan *et al*., 2009b
		Roots	Han *et al*., 2008
52	(+)-Boldine	Roots	Gan *et al*., 2009b
		Roots	Chou *et al*., 2005
		Roots	Han *et al*., 2008
		Roots	Ma *et al*., 2015
		Roots	Yang *et al*., 2020
53	(+)-Laurotetanine	Roots	Gan *et al*., 2009b
		Roots	Yang *et al*., 2020
54	(+)-N-methyllaurotetanine	Roots	Gan *et al*., 2009b
		Roots	Ma *et al*., 2015
		Roots	Yang *et al*., 2020
55	(+)-Reticuline	Roots	Gan *et al*., 2009b
		Roots	Chou *et al*., 2005
		Roots	Gan *et al*., 2008
		Roots	Han *et al*., 2008
		Roots	Yang *et al*., 2020
56	(-)-Pronuciferine	Roots	Gan *et al*., 2009b
		Roots	Chou *et al*., 2005
57	Pallidine	Roots	Gan *et al*., 2009b
		Roots	Chou *et al*., 2005
		Roots	Gan *et al*., 2008
58	Linderaline	Roots	Chou *et al*., 2005
59	Protosinomenine	Roots	Chou *et al*., 2005
60	Laudanosoline 3′,4′-dimethyl ether	Roots	Chou *et al*., 2005
61	Norisoboldine	Roots	Chou *et al*., 2005
		Roots	Yang *et al*., 2020
62	Linderagatine	Roots	Gan *et al*., 2008
		Roots	Han *et al*., 2008
		Roots	Yang *et al*., 2020
63	Lindera aggrine A	Roots	Kuo *et al*., 2014
		Roots	Ma et al., 2015
64	N-trans-feruloyltyramine	Roots	Ma et al., 2015
65	N-cis-feruloyltyramine	Roots	Ma *et al*., 2015
66	N-trans-feruloylmethoxytyramine	Roots	Ma *et al*., 2015
67	(+)-Isoboldine	Roots	Ma *et al*., 2015

		Roots	Yang *et al*., 2020
68	Thalifoline	Roots	Ma *et al*., 2015
69	Northalifoline	Roots	Ma *et al*., 2015
70	Yuzirine	Roots	Ma *et al*., 2015
71	(1′S)-12′-Hydroxyl-linderegatine	Roots	Yang *et al*., 2020
72	(1S)-5′-O-p-Hydroxybenzoyl norreticuline	Roots	Yang *et al*., 2020
73	(1R, 1′R)-11,11′-Biscoclaurine	Roots	Yang *et al*., 2020
74	Costaricine	Roots	Yang *et al*., 2020
75	Actinodaphnine	Roots	Yang et al., 2020
76	Laurolitsine	Roots	Yang *et al*., 2020
77	Norjuziphine	Roots	Yang *et al*., 2020
78	Reticuline n-oxide	Roots	Yang *et al*., 2020
79	Boldine n-oxide	Roots	Yang *et al*., 2020
80	N-methyllaurotetanine n-oxide	Roots	Yang *et al*., 2020
81	Salutaridine n-oxide	Roots	Yang *et al*., 2020
82	Lindoldhamine	Roots	Yang *et al*., 2020
83	Secolaurolitsine	Roots	Yang *et al*., 2020
84	Secoboldine	Roots	Yang *et al*., 2020
	FLAVONOIDS		
85	Quercetin	Leaves	Xiao *et al*., 2011
86	Quercetin-3-O-α-D-arabinofuranoside	Leaves	Xiao *et al*., 2011
87	Quercetin-3-O-α-D-glucopyranoside	Leaves	Xiao *et al*., 2011
88	Quercetin-3-O-α-L-rhamnopyranoside	Leaves	Han *et al*., 2008
89	Quercitrin	Leaves	Xiao *et al*., 2011 Xu *et al*., 2017
90	Kaempferol	Leaves	Xiao *et al*., 2011
91	Kaempferol-3-O-L-rhamnoside	Leaves	Xiao *et al*., 2011
92	Kaempferol-3-O-D-glucopyranoside	Leaves	Xiao *et al*., 2011
93	Dihydrokaempferol-3-O-L-rhamnoside	Leaves	Xiao *et al*., 2011
	PROCYANIDINS		
94	Procyanidin B1	Leaves	Zhang *et al*., 2003
95	Cinnamtanin B1	Leaves	Zhang *et al*., 2003
96	Cinnamtannin B2	Leaves	Zhang *et al*., 2003
	LIGNANS		
97	rel-(2α,3β)-7-O-methylcedrusin	Roots	Ma *et al*., 2015
98	(-)-Lyoniresinol	Roots	Ma *et al*., 2015
99	Evofolin B	Roots	Ma *et al*., 2015
	BENZENOIDS		
100	Linderagatin A	Roots	Ma *et al*., 2015
101	Linderagatin B	Roots	Ma *et al*., 2015
	BUTENOLIDE		
102	Secoaggregatalactone A	Leaves	Lin *et al*., 2007
	PHENOLICS		
103	3-Hydroxy-1-(4-hydroxyphenyl)propan-1-one	Roots	Ma *et al*., 2015
104	p-Hydroxybenzoic acid	Roots	Ma *et al*., 2015
105	4-Hydroxy-3-methoxy acetophenone	Roots	Ma *et al*., 2015
106	Methyl 3,5-dimethoxy-4-hydroxybenzoate	Roots	Ma *et al*., 2015
107	Vanillic acid	Roots	Ma *et al*., 2015
108	Tyrosol	Roots	Ma *et al*., 2015
109	2-(4-Hydroxy-3-methoxyphenyl)-ethanol	Roots	Ma *et al*., 2015
110	2-(4-Hydroxy-3,5-dimethoxyphenol)-ethanol	Roots	Ma *et al*., 2015
111	2,6-Dimethoxy-p-benzoquinone	Roots	Ma *et al*., 2015

112	6′-O-Vanilloyltachioside	Roots	Ma *et al*., 2015
	OTHERS		
113	(-)-Boscialin	Roots	Ma *et al*., 2015
114	Methyl dihydrophaseate	Roots	Ma *et al*., 2015

Sesquiterpenoids

A total of forty-nine sesquiterpenoids (**1-49**), including dimeric and trimeric sesquiterpenoids have been reported phytochemically from *L. aggregata*. The chemical structures are shown in **Figure No. 2**. Liu *et al*. (2009a) were successfully isolated and characterized six unprecedented sesquiterpenoid trimmers and dimers, aggreganoids A-F (**1-6**) from the ethanolic extract of the roots of *L. aggregata*. These compounds represent a new class of oligomeric sesquiterpenoids featuring the connection between different or identical sesquiterpenoid monomers via a carbon bridge. The new linkage pattern of these compounds is not only crucial for the chemical diversity and biosynthesis of oligomeric sesquiterpenoids, but also the chemotaxonomic studies on genus *Lindera*. In the same year, the authors also managed to isolate four disesquiterpenoid-geranylbenzofuranone conjugates, linderalides A-D (**7-10**) from the same part. These compounds represent the first examples of disesquiterpenoid-geranylbenzofuranone hybrids directly linked by two C−C bonds. Another compound was linderalide D (**10**), which bears an unprecedented carbon skeleton featuring an unusual linearly 6/6/5/6/6 pentacyclic ring system fused by a sesquiterpenoid unit and a geranylbenzofuranone moiety.

In another study, Chen *et al*. (2018) were reported a novel skeleton of 3,5-dioxocyclopent-1-enecarboxylate, known as (±)-lindepentone A (**43**), together with an unprecedented oxepine-2,5-dione derivative skeleton, lindoxepines A-B (**44-45**). The authors also suggest that compound (**44-45**) might be the key intermediates for the synthesis of *Lindera* cyclopentenediones. Besides, Qiang *et al.* (2011) have successfully isolated six new sesquiterpenoids, known as linderanlide A-F (**11-16**) from the root tubers part. Linderanlide A (**11**) is a C-8 epimer of linderanine C (**19**). Meanwhile, Wang *et al.* (2010a) reported the isolation of a racemate, bi-linderone (**40**) from the roots part. The compound represents the first member of an unprecedented class of spirocyclopentene diones. Although it shares its structural features with the cyclopentenedione derivative methyl-linderone (**48**), it has a backbone with 34 carbon atoms that includes a unique spiro ring, which is unprecedented in the field of natural products. In the meantime, the authors also managed to isolate a pair of natural windmill-shaped enantiomers, known as (±)-linderaspirone A (**42**). The biogenetic route to linderaspirone A (**42**) was proposed to be a formation by a [4+4] cycloaddition from the monomer methyl linderone (**48**). Furthermore, Gan *et al.* (2009a) were reported the identification of five new sesquiterpene lactones, named as linderagalactones A-E (**23-27**) from the roots part. In addition, Cheng *et al*. (2007) were managed to characterize a new sesquiterpene, neolindenenonelactone (**35**), along with linderane (**34**), isolinderalactone (**37**), linderalactone (**38**), and 8-hydroxylindestenolide (**39**).

Amides and alkaloids

Thirty-five alkaloids including amides (**50-84**) were successfully identified from the roots of *L. aggregata*. The chemical structures are shown in **Figure No. 3**. Gan *et al.* (2009b) was reported the isolation of new alkaloid, (+)-norboldine acetate (**50**) together with (+)-norboldine (**51**), (+)-boldine (**52**), (+)-laurotetanine (**53**), (+)-*N*-methyllaurotetanine (**54**), (+)-reticuline (**55**), (-)-pronuciferine (**56**), and pallidine (**57**) from the roots of *L. aggregata*. A year before, the authors also reported a novel bisbenzylisoquinoline alkaloid, linderegatine (**62**), as well as two known isoquinoline alkaloids reticuline (**55**) and pallidine (**57**) from the same part (Gan *et al*., 2008).

Another study, Chou *et al.* (2005) was successfully identified a new aporphinoid alkaloid, named as linderaline (**58**), along with eight known isoquinoline alkaloids, identified as pallidine (**57**), protosinomenine (**59**), laudanosoline 3′,4′-dimethyl ether (**60**), boldine (**52**), norisoboldine (**61**), norboldine (**51**), pronuciferine (**56**), and reticulline (**55**) from the ethanol extract of the dried roots part. In addition, Kuo *et al.* (2014) managed to isolate a new β-carboline alkaloid, linderaggrine A (**63**) from the roots part of *L. aggregata*. β-Carboline alkaloids are a prevalent class of biologically active natural products and this is the first report from this plant. Recently, Yang *et al.* (2020) were successfully

characterized three new benzylisoquinoline alkaloids, (1′*S*)-12′-hydroxyl-linderegatine (**71**), (1*S*)-5′-*O*-*p*-hydroxybenzoyl norreticuline (**72**), and (1*R*,1′*R*)-11,11′-biscoclaurine (**73**), along with eighteen known compounds.

Flavonoids

Nine flavonoids (**85-93**) have been isolated from the leaves of *L. aggregata*. The chemical structures are shown in **Figure No. 4**. Xiao *et al*. (2011) successfully characterized eight known flavonoids, identified as quercetin (**85**), quercetin-3-O-α-D-arabinofuranoside (**86**), quercetin-3-O-α-D-glucopyranoside (**87**), quercetin-3-O-L-rhamnopyranoside (**88**), kaempferol (**90**), kaempferol-3-O-L-rhamnoside (**91**), kaempferol-3-O-D-glucopyranoside (**92**), and dihydrokaempferol-3-O-L-rhamnoside (**93**). Compounds (**91-93**) were isolated for the first time from this species. Meanwhile, quercitrin (**89**) and their pharmacokinetics studies have been described by Xu *et al*. (2017).

Miscellaneous compounds

In addition to the above-mentioned phytochemicals, some other constituents such as procyanidins (**94-96**), lignans (**97-99**), benzenoids (**100-101**), butenolide (**102**), and phenolics (**103-112**) were also identified from the leaves and roots of *L. aggregata*. The chemical structures are shown in **Figure No. 5**. Ma *et al.* (2015) managed to isolate two new benzenoids, identified as linderagatin A and B (**100-101**), together with three known lignans, *rel*-(2α,3β)-7-O-methylcedrusin (**97**), (-)-lyoniresinol (**98**), and evofolin B (**99**) from the roots part.

Additionally, the authors also managed to characterize ten known phenolic compounds, which were identified as 3-hydroxy-1-(4-hydroxyphenyl)-propan-1-one (**103**), *p*-hydroxybenzoic acid (**104**), 4-hydroxy-3-methoxy acetophenone (**105**), methyl 3,5-dimethoxy-4-hydroxybenzoate (**106**), vanillic acid (**107**), tyrosol (**108**), 2-(4-hydroxy-3-methoxyphenyl)-ethanol (**109**), 2-(4-hydroxy-3,5-dimethoxyphenol)-ethanol (**110**), 2,6-dimethoxy-*p*-benzoquinone (**111**), and 6′-O-vanilloyltachioside (**112**). Meanwhile, Lin *et al.* (2007) were successfully isolated a new secobutanolide, secoaggregatalactone A (**102**) from the leaves part. Moreover, three procyanidins were reported by Zhang *et al.* (2003), characterized as procyanidin B1 (**94**), cinnamtanin B1 (**95**), and cinnamtannin B2 (**96**).

Essential oils

Three studies have been reported on the essential oil of *L. aggregata*. Analysis of the root tubers oil of *L. aggregata* led to the identification of α-longifolene (15.13%), bornyl acetate (11.49%), and α-eudesmol (9.14%) as the major components (Du *et al*., 2003). In another study, the leaves oil-rich of sesquithuriferol (35.90%), 14-oxy-α-muurolene (16.45%) and 1,8-cineole (5.34%) (Fu *et al*., 2009). Nevertheless, lindene (19.21%), linderene (16.83%), bornyl acetate (8.26%) and linderene acetate (8.17%) were main constituents of the essential oil of *L. aggregata* roots from Jiangxi Province while that from Fujian Province contained β-phellandrene (16.23%) followed by lindene (14.90%), linderene (12.83%), and linderene acetate (9.29%) (Wu *et al*., 2010). The above findings suggested that the essential oil content of *L. aggregata* and its composition showed considerable variations and maybe due to plant origin, ecological and climatic conditions as well as storage duration of medicinal herbs.

Biological activities

The literature study reveals the need for a thorough investigation of the pharmacological characteristics of the extracts and isolated compounds from *L. aggregata*. The biological activities including antihyperlipidemic, anti-inflammatory, cytotoxicity, insecticidal, antiulcer, hepatoprotective, gastrointestinal, and mutagenicity have been reported in some works.

Urox is an herbal formulation containing concentrated extracts of *L. aggregata* root, *Crataeva nurvala* stem bark, and *Equisetum arvense* stem, have well established traditional uses and reported safe for human consumption (Deshpande *et al*., 1982). Besides, Schoendorfer *et al.* (2018) demonstrated viability of this herbal combination to serve as an effective treatment, with minimal side-effects, based on results of the treatment of symptoms of overactive bladder and urinary incontinence.

In addition, the extracts have been used traditionally to treat some types of ailments have not been investigated for their biological activities at all. Thus, this is an opportunity to find new pharmacological properties from this species, not to mention promising sources for drugs. Furthermore, their toxicity has not been studied. The information on the qualification of the extracts is very important to be applied as drugs.

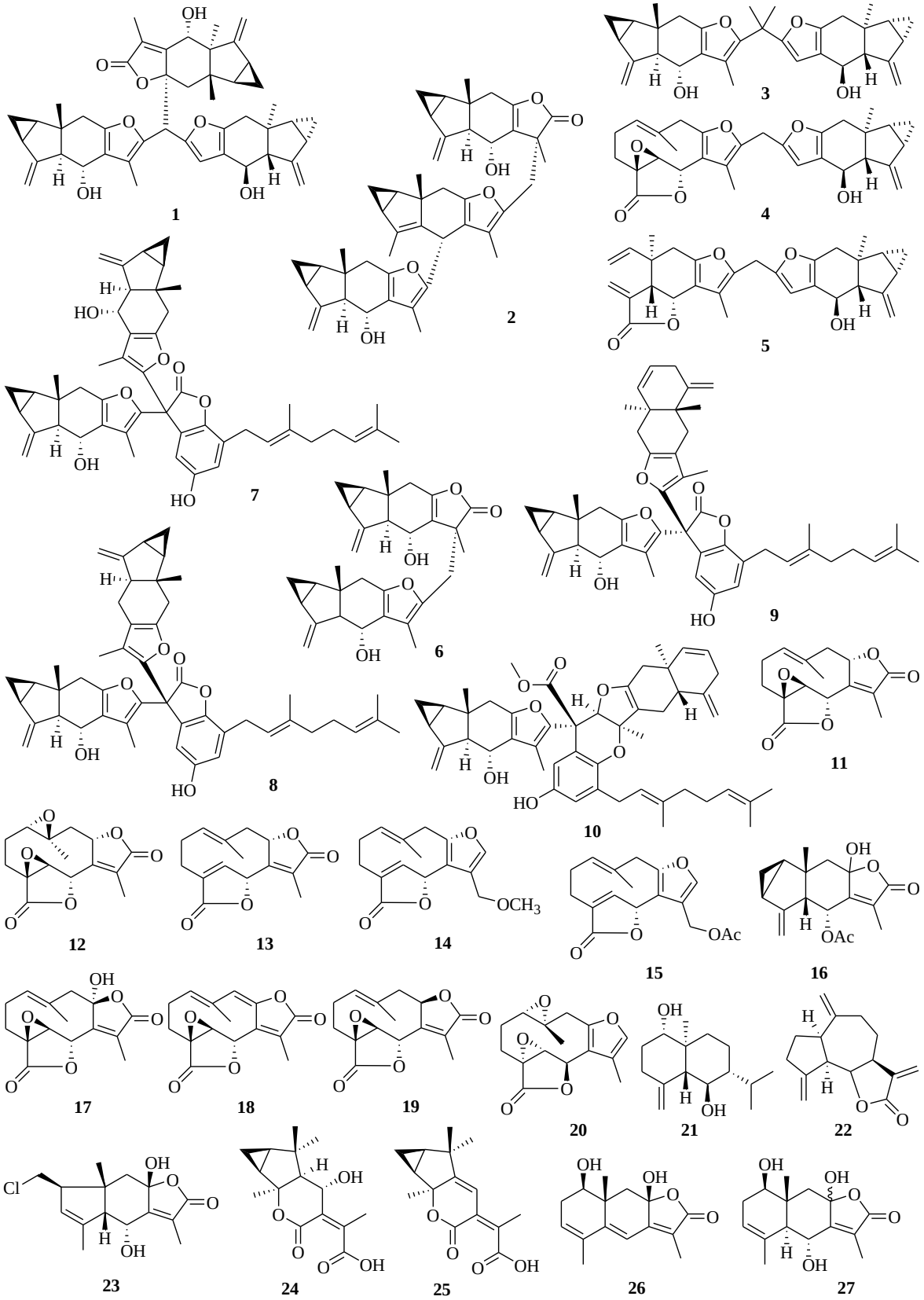


Figure No. 2
Chemical structures of sesquiterpenoids

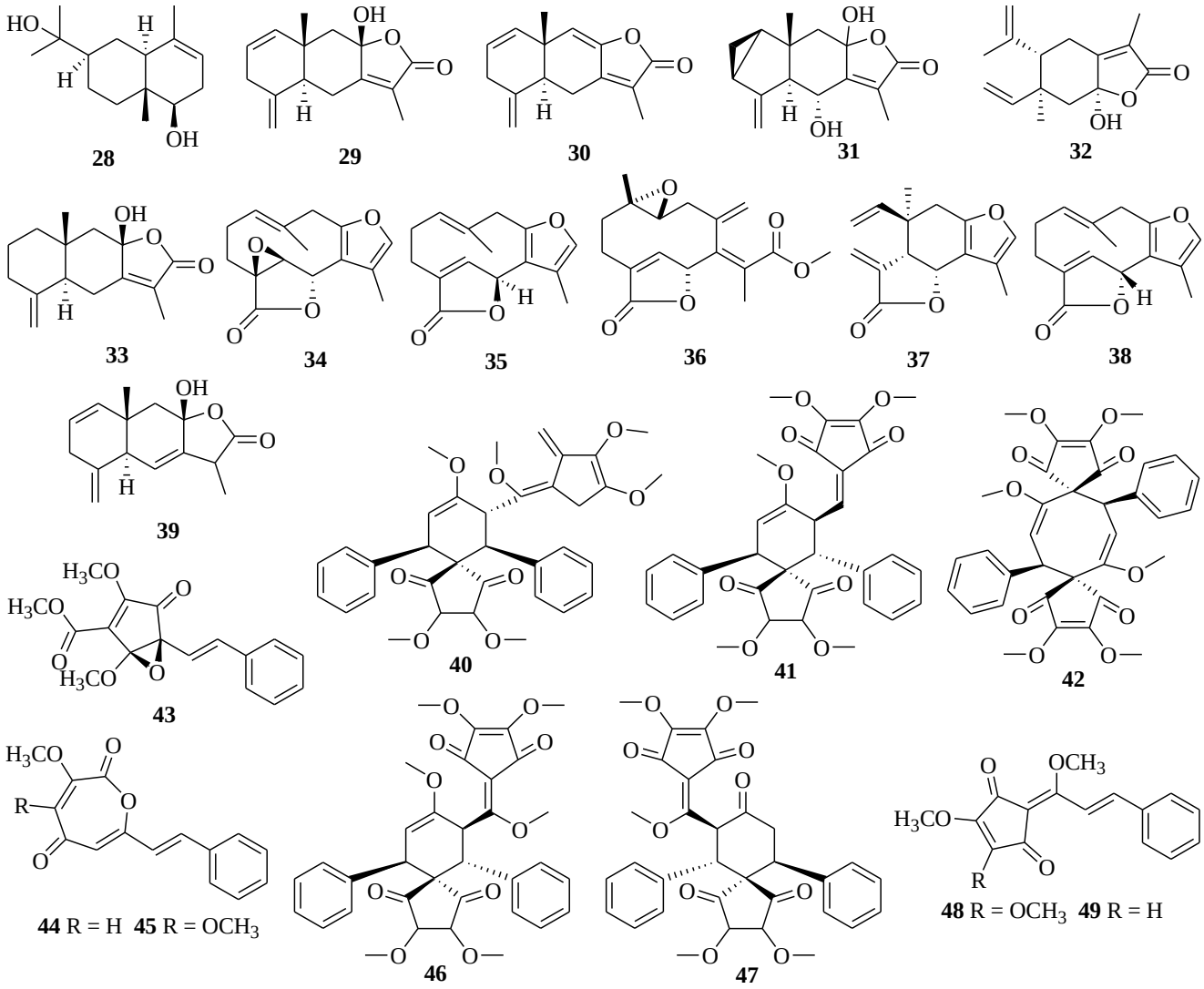


Figure No. 2 (continue)
Chemical structures of sesquiterpenoids

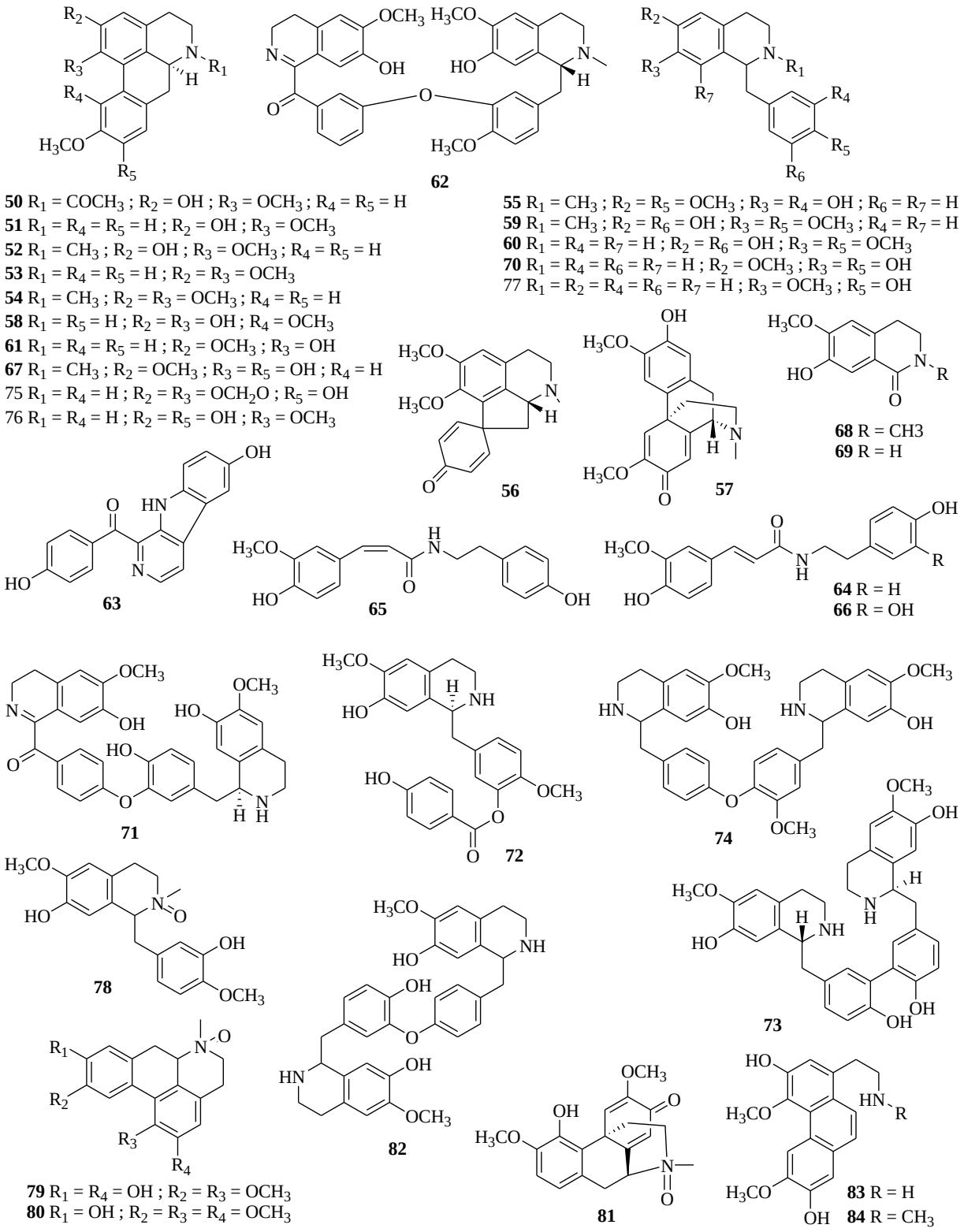
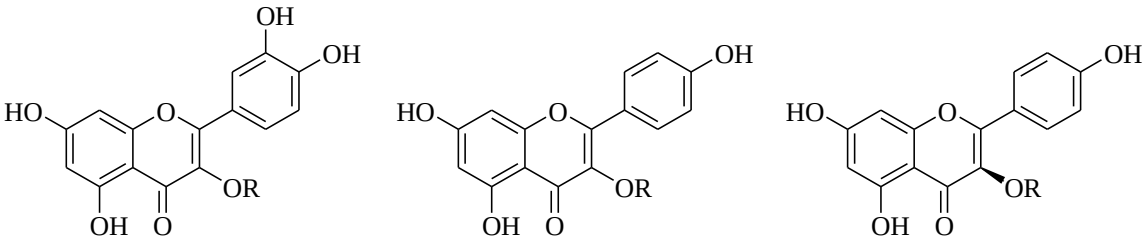


Figure No. 3
Chemical structures of amides and alkaloids



85 R = H
86 R = arabinofuranosyl
87 R = glucopyranosyl
88 R = rhamnopyranosyl
89 R = rhamnosyl

90 R = H
91 R = rhamnosyl
92 R = glucopyranosyl

93 R = rhamnosyl

Figure No. 4
Chemical structures of flavonoids

Antihyperlipidemic

The aqueous leaves extract of *L. aggregata* showed significantly reduced serum triglyceride (TG), alanine aminotransferase level (ALT), but elevated faecal TG in normal mice. It also remarkably lowered serum total cholesterol (TC), TG, low-density lipoprotein (LDL), N-HDL, ALT, hepatic lipid/glucose (GLU), apolipoprotein B (APOB), hepatic GLU and increased serum high-density lipoprotein (HDL), apolipoprotein A1 (APOA-I), faecal TG levels in hypercholesterolemic (HCL) mice. These results revealed that the extract treatment regulated the disorders of the serum lipid and liver function, reduced hepatic GLU contents both in normal and HCL mice (Zhu *et al*., 1998; Wang *et al*., 2020).

Anti-inflammatory

Aggreganoid A (**1**) was reported to inhibit the TGF-β induced Smad2 protein phosphorylation in a dose-dependent manner in A549 cells, and suggested to have potential as TGF-β inhibitor. However, no significant activity of aggreganoids A-F (**1-6**) was reported against A549 and SH-SY5Y cell lines (Liu *et al*., 2009a). Meanwhile, linderaspirone A (**42**) was found markedly elevated phosphorylation of InsR, Akt, and GSK-3β under insulin-resistant condition (Wang *et al*., 2010b). Furthermore, norisoboldine (**61**) and boldine (**52**) showed inhibitory activities on nitric oxide production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells, with IC_{50} values of 37.8 and 38.7 μM, respectively (Yang *et al*., 2020).

Cytotoxicity

(+)-Norboldine (**51**) showed weak activity against the mouse lymphocytic leukemia L1210 cell line with LC_{50} value 1.1×10^{-4} mol/L (Gan *et al*., 2009b). **S**ecoaggregatalactone A (**102**) was found to exhibit noticeable cytotoxicity (EC_{50} of 6.61 μg/mL) against the human hepatoma cell line (HepG2 cell line). The authors suggested that the compound induced significant apoptotic cell death through the activation of caspase-8, Bid, and caspase-3, leading to cleavage of PARP and causing DNA fragmentation (Lin *et al*., 2007). In another study, costaricine (**74**) and laurolitsine (**76**) showed cytotoxic activities against human colon carcinoma cell line (HCT-116) with IC_{50} values of 51.4 and 27.1 μM against human cancer cell line (HCT-116), respectively (Yang *et al*., 2020).

Insecticidal

The essential oil of *L. aggregata* was found to possess insecticidal activity against two-grain storage insects, *Sitophilus zeamais* and *Tribolium castaneum* with LC_{50} values of 61.65 and 18.47 μg/adult, respectively. In addition, the oil showed pronounced fumigant toxicity against *Sitophilus zeamais* and *Tribolium castaneum* which gave LC_{50} values of 23.04 and 14.69 mg/L air, respectively (Liu *et al*., 2016).

Antiulcer

Zhu *et al.* (1998) were reported the antiulcer action of the extract of the root of *L. aggregata* against the ethanol-induced ulceration model in rats. The extract was found to produce strong local gastric protective effects and mild systemic effects against ethanol-induced ulcer formation. The protective effect may be mediated by endogenous prostaglandins and regulation of the vagus nerve.

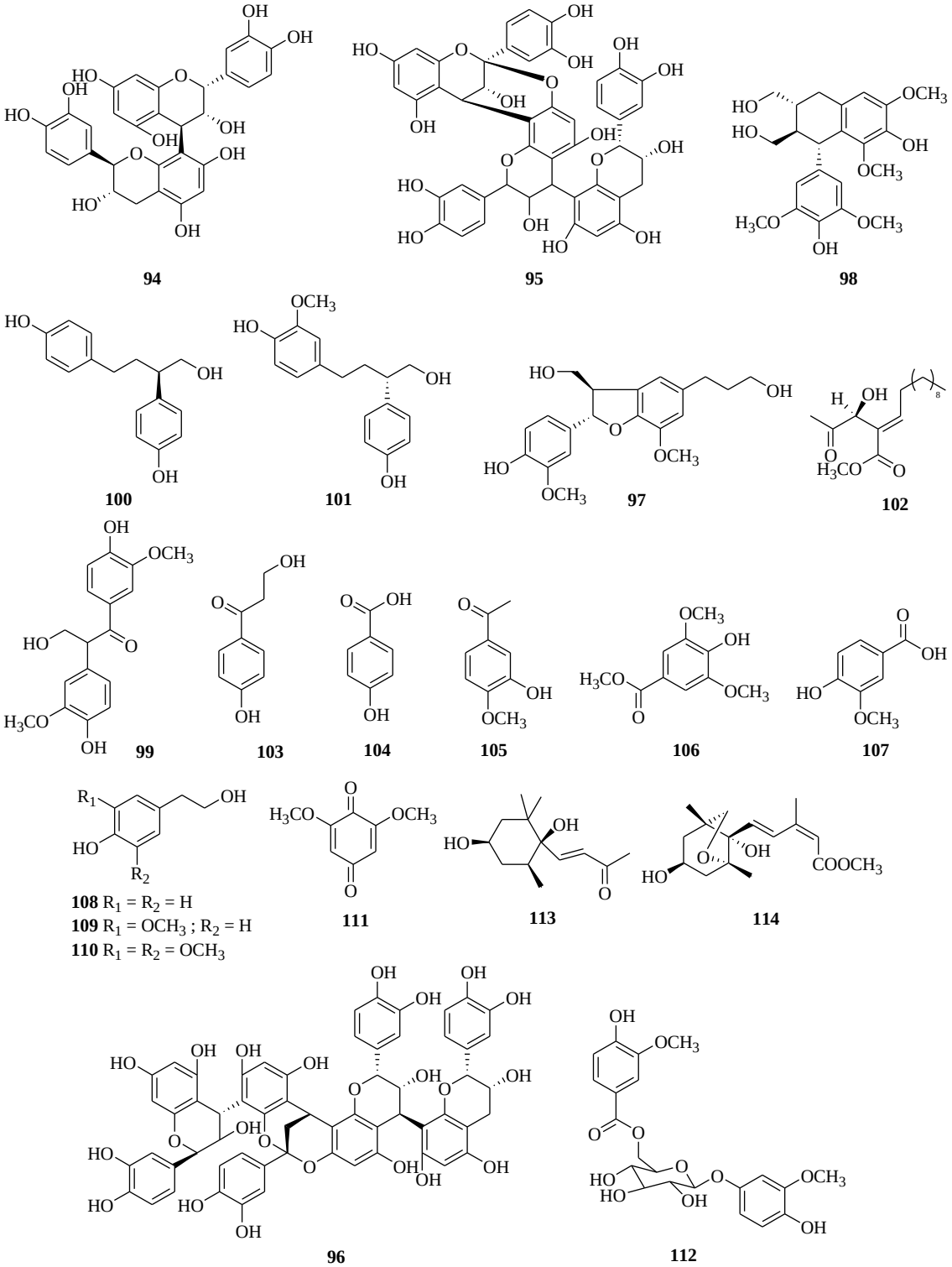


Figure No. 5
Chemical structures of miscellaneous compounds

Hepatoprotective

Linderagalactone E (**27**), linderane (**34**), hydroxylindestenolide (**29**), and linderalactone (**38**) have shown hepatoprotective activity against H_2O_2-induced oxidative damages on HepG2 cells with EC_{50} values of 67.5, 167.0, 42.4, and 98.0 μM, respectively (Gan *et al*., 2009a).

Gastrointestinal

It has been documented that *L. aggregata* extract can regulate gastric motility and the essential oil fraction was able to increase the contraction of the intestines, so it can be used as a carminative to treat abdominal distension (Li, 1992).

Mutagenicity

The ethanolic *L. aggregata* roots extract showed a significant inhibitory mutagenicity effect on the 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]-indole (Trp-P-1) by the Ames assay (Niikawa *et al*., 1995).

CONCLUSION

Until now, significant progress has been witnessed in phytochemistry and pharmacology of *L. aggregata*. Thus, some traditional uses have been well supported and clarified by modern pharmacological studies. Moreover, *L. aggregata* also showed therapeutic potential in the treatment of cardiac, renal, cystic and rheumatic diseases. But present findings are still insufficient that cannot satisfactorily explain some mechanisms of action. More well-designed studies *in vitro*, especially *in vivo*, are required to establish links between the traditional uses and bioactivities, discover new skeletons and activity molecules, as well as ensure safety before clinical use. We hope that the information discussed here could make people more aware of *L. aggregata* and can be beneficial for further research.

ACKNOWLEDGMENTS

This research was supported by the Ministry of Education (MOE) through the Fundamental Research Grant Scheme for Research Acculturation of Early Career Researchers (FRGS-RACER/1/2019/STG01/UPSI/1). The authors also would like to thank the Department of Chemistry, Faculty of Science and Mathematics, UPSI for research facilities.

REFERENCES

Cao Y, Xuan B, Peng B, Li C, Chai X, Tu P. 2016. The genus *Lindera*: a source of structurally diverse molecules having pharmacological significance. **Phytochem Rev** 15: 869 - 906. **https://doi.org/10.1007/s11101-015-9432-2**

Chen L, Liu B, Deng JJ, Zhang JS, Li W, Ahmed A, Yin S, Tang GH. 2018. *Lindera* cyclopentenedione intermediates from the roots of *Lindera aggregata*. **RSC Adv** 8: 17898 - 17904. **https://doi.org/10.1039/C8RA03094D**

Cheng XL, Ma SC, Wei F, Wang GL, Xiao XY, Lin RC. 2007. A new sesquiterpene isolated from *Lindera aggregata* (Sims) Kosterm. **Chem Pharm Bull** 55: 1390 - 1392. **https://doi.org/10.1248/cpb.55.1390**

Chou GX, Noerio N, Ma CM, Wang ZT, Hattori M, Xu LS, Xu GJ. 2000. Seven new sesquiterpene lactones from *Lindera aggregata*. **J China Pharm Univ** 31: 333 - 340.

Chou GX, Norio N, Ma CM, Wang ZT, Masao H. 2005. Isoquinoline alkaloids from *Lindera aggregata*. **Chinese J Nat Med** 3: 272 - 275.

Deshpande P, Sahu M, Kumar P. 1982. *Crataeva Nurvala* Hook and Forst (Varuna)-the ayurvedic drug of choice in urinary disorders. **Indian J Med Res** 76: 46 - 53.

Du ZQ, Xia HL, Jiang HX, Zhang BF, Meng F. 2003. Composition of *Lindera aggregata* essential oil determined by GC-MS. **Chinese Trad Herbal Drugs** 34: 308 - 310. **https://doi.org/10.1080/0972060X.2014.960275**

Flora of China Editorial Committee. 2010. Flora of China. Science Press, Beijing, China.

Fu J, Li JM, Chen SY, Yao XL, Wang Q. 2009. Study on chemical constituents of *Lindera aggregata* essential oil. **Chinese Trad Herbal Drugs** 40: 112 - 114.

Gan L, Zhao X, Yao W, Wu L, Li L, Zhou C. 2008. A novel bisbenzylisoquinoline alkaloid from *Lindera aggregata*. **J Chem Res** 5: 285 - 286. **https://doi.org/10.3184/030823408X320674**

Gan LS, Zheng YL, Mo JX, Liu X, Li XH, Zhou CX. 2009a. Sesquiterpene lactones from the root tubers of *Lindera aggregata*. **J Nat Prod** 72: 1497 - 1501. **https://doi.org/10.1021/np900354q**

Gan LS, Yao W, Mo JX, Zhou CX. 2009b. Alkaloids from *Lindera aggregata*. **Nat Prod Commun** 4: 43 - 46. **https://doi.org/10.1177/1934578X0900400111**

Han Z, Zheng Y, Chen N, Luan L, Zhou C, Gan L, Wu Y. 2008. Simultaneous determination of four alkaloids in *Lindera aggregata* by ultra-high-pressure liquid chromatography-tandem mass spectrometry. **J Chromatogr A** 1212: 76 - 81. **https://doi.org/10.1016/j.chroma.2008.10.017**

Hirayama D, Itoh A, Yamakura T. 2004. Implications from seed traps for reproductive success, allocation and cost in a tall tree species *Lindera erythrocarpa*. **Plant Species Biol** 19: 185 - 196. **https://doi.org/10.1111/j.1442-1984.2004.00114.x**

Kuo PC, Li YC, Hwang TL, Ma GH, Yang ML, Lee EJ, Wu TS. 2014. Synthesis and structural characterization of an anti-inflammatory principle purified from *Lindera aggregata*. **Tetrahedron Lett** 55: 108 - 110. **https://doi.org/10.1016/j.tetlet.2013.10.126**

Li GX. 1992. Pharmacology, toxicity and clinic of traditional chinese medicine. Tianjin Science and Technique Translation Publishing House, Tianjin, China.

Li XW. 1984. In Chinese Flora (Zhongguo Zhiwu Zhi). Science Press, Beijing, China.

Lin CT, Chu FH, Chang ST, Chueh PJ, Su YC, Wu KT, Wang SY. 2007. Secoaggregatalactone-A from *Lindera aggregata* induces apoptosis in human hepatoma Hep G2 cells. **Planta Med** 73: 1548 - 1553. **https://doi.org/10.1055/s-2007-993739**

Liu X, Yang J, Fu J, Yao XJ, Wang JR, Liu L, Jiang ZH, Zhu GY. 2009a. Aggreganoids A-F, Carbon-bridged sesquiterpenoid dimers and trimers from *Lindera aggregata*. **Org Lett** 21: 5753 - 5756. **https://doi.org/10.1021/acs.orglett.9b02166**

Liu X, Yang J, Yao XJ, Yang X, Fu J, Bai LP, Liu L, Jiang ZH, Zhu GY. 2009b. Linderalides A-D, Disesquiterpenoid-geranylbenzofuranone conjugates from *Lindera aggregata*. **J Org Chem** 84: 8242 - 8247. **https://doi.org/10.1021/acs.joc.9b00522**

Liu ZL, Chu SS, Jiang CH, Hou J, Liu QZ, Jiang GH. 2016. Composition and insecticidal activity of the essential oil of *Lindera aggregata* root tubers against *Sitophilus zeamais* and *Tribolium castaneum*. **J Essent Oil Bear Pl** 19: 727 - 733. **https://doi.org/10.1080/0972060X.2014.960275**

Ma GH, Lin CW, Hung HY, Wang SY, Shieh PC, Wu TS. 2015. New benzenoids from the roots of *Lindera aggregata*. **Nat Prod Commun** 10: 2131 - 2133. **https://doi.org/10.1177/1934578X1501001229**

Niikawa M, Wu AF, Sato T, Nagase H, Kito H. 1995. Effects of Chinese medicinal plant extracts on mutagenicity of TRP-P-1. **Nat Med** 49: 329 - 331.

Qiang Y, Yang ZD, Yang JL, Gao K. 2011. Sesquiterpenoids from the root tubers of *Lindera aggregata*. **Planta Med** 77: 1610 - 1616. **https://doi.org/10.1055/s-0030-1270922**

Salleh WMNHW, Ahmad F, Khong HY, Zulkifli RM. 2015. A review on phytochemistry and pharmacology of the genus *Beilschmiedia* (Lauraceae). **Trop J Pharm Res** 14: 2139 - 2150.

Schoendorfer N, Sharp N, Seipel T, Schauss AG, Ahuja KDK. 2018. Urox containing concentrated extracts of *Crataeva nurvala* stem bark, *Equisetum arvense* stem and *Lindera aggregata* root, in the treatment of symptoms of overactive bladder and urinary incontinence: A phase 2, randomised, double-blind placebo controlled trial. **BMC Complement Altern Med** 18: 42 - 52. **https://doi.org/10.1186/s12906-018-2101-4**

The Flora of China, 2010. Volume 4. Piperaceae. **http://www.efloras.org**

The Plant List, 2010. Version 1. **http://www.theplantlist.org**

Tsui HB. 1987. A study on the system of *Lindera*. **J Grad Sch Chin Acad Sci** 25: 167 - 171.

Van der Werff H, Richter HG. 1996. Toward an improved classification of Lauraceae. **Ann Miss Bot Gard** 83: 409 - 418.

Wang F, Gao Y, Zhang L, Liu JK. 2010a. Bi-linderone, a highly modified methyl-linderone dimer from *Lindera aggregata* with activity toward improvement of insulin sensitivity in vitro. **Org Lett** 12: 2354 - 2357. **https://doi.org/10.1021/ol1007247**

Wang F, Gao Y, Zhang L, Bai B, Hu YN, Dong ZJ, Zhai QW, Zhu HJ, Liu JK. 2010b. A pair of windmill-shaped enantiomers from *Lindera aggregata* with activity toward improvement of insulin sensitivity. **Org Lett** 12: 3196 - 3199. **https://doi.org/10.1021/o11011289**

Wang J, Wang F, LixiaYuan Wu Y, Peng X, Kai G, Zhu S, Liu Y. 2020. Aqueous extracts of *Lindera aggregate* (Sims) Kosterm. leaves regulate serum/hepatic lipid and liver function in normal and hypercholesterolemic mice. **J Pharmacol Sci** 143: 45 - 51. **https://doi.org/10.1016/j.jphs.2020.01.009**

Wang XH, Kent M, Fang XF. 2007. Evergreen broad-leaved forest in Eastern China: Its ecology and conservation and the importance of resprouting in forest restoration. **Forest Ecol Manag** 245: 76 - 87. **https://doi.org/10.1016/j.foreco.2007.03.043**

Wu Y, Zheng Y, Liu X, Han Z, Ren Y, Gan L, Zhou C, Luan L. 2010. Separation and quantitative determination of sesquiterpene lactones in *Lindera aggregata* (Wu-yao) by ultraperformance LC-MS/MS. **J Separat Sci** 33: 1072 - 1078. **https://doi.org/10.1002/jssc.200900768**

Xiao M, Cao N, Fan JJ, Shen Y, Xu Q. 2011. Studies on flavonoids from the leaves of *Lindera aggregata*. **J Chinese Med Mat** 34: 62 - 64.

Xu B, Chen M, Han H, Xu X, Tian J. 2017. Pharmacokinetics and bioavailability of quercitrin in *Lindera aggregata* leaf extract in rats. **Latin Amer J Pharm** 36: 495 - 501.

Yang JJ, Chen Y, Guo ML, Chou GX. 2020. Chemical constituents from the roots of *Lindera aggregata* and their biological activities. **J Nat Med** 74: 441 - 447.

Zhang CF, Sun QS, Wang ZT, Chou GX. 2001. Studies on constituents of the leaves of *Lindera aggregata* (Sims) Kosterm. **China J Chinese Mat Med** 26: 765 - 767.

Zhang CF, Sun QS, Wang ZT, Masao H, Supinya T. 2003. Inhibitory activities of tannins extracted from stem of *Lindera aggregata* against HIV-1 integrase. **Chinese Pharm J** 38: 911 - 914.

Zhang CF, Wang ZT. 2000. An advance in the study on medicinal plant of *Lindera*. **J Shenyang Univ Tech** 17: 230 - 234.

Zhu M, Luk CT, Lew TH. 1998. Cytoprotective effect of *Lindera aggregata* roots against ethanol-induced acute gastric injury. **Pharm Biol** 36: 222 - 226. **https://doi.org/10.1076/phbi.36.3.222.6349**