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Lindera aggregata (Sims) Kosterm: a systematic review of its traditional applications, phytochemical and pharmacological properties, and quality control

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Abstract

Lindera aggregata (Sims) Kosterm (LA), a traditional medicinal herb, has long been used as a regulator of 'Qi' (vital energy) in China, for treating chest and abdominal pain, bladder deficiency, hernia, bladder cold, dysmenorrhea, and frequent enuresis and urination. This article describes a systematic review of botanical characteristics, traditional applications, and phytochemical, pharmacological, pharmacokinetic, and toxicological properties of LA through the collation and discussion of literature from several databases, namely Elsevier, Web of Science, SciFinder, PubMed, CNKI, ScienceDirect, and Google Scholar, as well as Master's theses and Doctoral dissertations. To date, over 166 chemical components have been isolated from LA, including alkaloids, sesquiterpenoids, flavonoids, cyclopentanedione derivatives and enantiomers of ketone derivatives, disesquiterpenoid-geranylbenzofuranone conjugates, benzenoids, and benzenoid glycosides. Crude extracts of LA and its purified compounds are used for treating inflammation, tumor, hyperlipidemia, alcoholic liver disease, diarrhea, abdominal pain, and antibiotics; these extracts and compounds possess broad pharmacological properties with anti-inflammatory activity, liver protection effects, antitumor effects, lipid lowering effects, antibacterial and analgesic effects, and kidney protection activity. Additional studies are needed to confirm the relationship between the traditional effects of LA and modern pharmacological research. Hence, we suggest that future investigations on LA should focus on modern pharmacological research to confirm or support its traditional application.

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Introduction

The genus *Lindera* includes over 100 species and contains shrubs and evergreen or deciduous trees that are intermittently scattered in tropical, subtropical, and temperate Asia as well as the Midwest[1]. Among them, *Lindera aggregata* (Sims) Kosterm (LA) is an frequently used medicinal herb found in the south of the Yangtze River basin, China[2]. It is a popular herb in East Asia and is extensively used in Japan and China. Its tuberous root, named 'Wuyao' in traditional Chinese medicine (TCM), is a commonly used TCM in China, which can regulate 'Qi' (vital energy) and relieve pain, warm the kidneys, and dissipate cold. It is clinically used for chest and abdominal pain, asthma and cough, bladder deficiency, nocturnal enuresis, frequent urination, hernia-associated pain, menstrual cold abdominal pain, and other symptoms[3]. The tuberous roots of LA possess many biological activities, including hepatoprotective effect, anti-inflammatory activity, antitumor effect, anti-hyperlipidemia effect, analgesic effect, protection of the liver and kidney, bacteriostatic effect, anti-rheumatic effect, diarrhea improvement, and blood stasis improvement. Phytochemical investigations conducted to date have revealed that LA is enriched with phytochemicals such as sesquiterpenoids, alkaloids, flavonoids, cyclopentanedione derivatives, enantiomers of ketone derivatives, disesquiterpenoid-geranylbenzofuranone conjugates, benzenoids, benzenoid glycosides, and others. However, to date, bioactivity studies have been conducted for a limited number of these compounds; moreover, there is a lack of sufficient analysis and comprehensive discussion of their structures in other studies. LA is effective in mitigating various inflammations; however, the safety and toxicity of the chemical constituents in its extracts are yet to be defined. Regarding pharmacological aspects, critical pharmacological evaluations of their relationship with traditional applications of LA are lacking. Furthermore, the quality standards of LA have been poorly studied, and it remains unclear whether the availability of taproot of LA has been adopted.

The present systematic review describes the latest as well as comprehensive literature assessment of LA by presenting its botanical characteristics, traditional applications, phytochemical and pharmacological properties, possible molecular mechanisms, and safety. This article demonstrates the traditional applications of LA in disease treatment through research on phytochemistry and pharmacology. The information summarized in this article provides a direction for future clinical trials of LA bioactive compounds and helps to develop new drugs containing this compound.

Materials and methods

All data regarding LA were collected by searching online databases, including Google Scholar, Web of Science, Springer, ScienceDirect, SciFinder, PubMed, and Baidu Scholar. We also

searched the library for classical books on Chinese herbal medicines, locally published magazines, Master's theses, and Doctoral dissertations. The key words included *Lindera aggregata* (Sims) Kosterm (LA), secondary metabolites, biological activity, phytochemistry, ethnobotanical survey, pharmacology, safety, medicinal uses, toxicology, quality control, and other corresponding words. We verified the alias of LA through The Plant List (available at: www.theplantlist.org) and obtained relevant information.

Botany

Lindera aggregata (Sims) Kosterm. (Fig. 1) (named 'Wuyao' in China, and '*Lindera strychinifolia* Vill.' in Japan), is a plant of *Lindera* in *Lauraceae*. Based on 'The Plant List', *Lindera aggregata* (Sims) Kosterm. is the most accepted name for this plant, and the remaining five synonyms are *Laurus aggregata* Sims, *Daphnidium strychnifolium* Siebold & Zucc., *Lindera eberhardtii* Lecomte, *Lindera aggregata* var. *aggregata*, and *Lindera strychnifolia* (Siebold & Zucc.) Fern. -Vill. LA is not only distributed in East Asia such as China and Japan but also in Southeast Asia such as the Philippines. Although we searched the relevant literature, the data regarding the distribution of LA in Japan and the Philippines could not be obtained[4]. LA is mainly distributed in 18 provinces in China, including Zhejiang, Jiangxi, Hunan, Gansu, Taiwan, Yunnan, Shaanxi, Sichuan, Guizhou, Hainan, Chongqing, Guangdong, Guangxi, Henan, Hubei, Anhui, Fujian, and Jiangsu provinces. The areas with LA abundance are centered in Taizhou, Zhejiang Province, including Xianxialing Mountains and Kuochang Mountains and their surrounding areas[3]. Figure 2 shows the geographical distribution of LA in China.

LA grows in the forest or forest edge on sunny hillsides, wilderness, and foothills[4]. LA can grow well in areas with an altitude of 800–1,200 m, annual sunlight duration of 1,100–1,300 h, and annual rainfall of 1,000–1,200 mm[5]. LA is an evergreen shrub with a height of 4–5 m. The root is 8 cm in length, fusiform, 2.5 cm in diameter, and brown yellow or brown black in color. Young branches are covered densely with yellow silky hairs, and they become glabrous at maturity. The terminal bud is oblong. The leaves are ovate and elliptic or nearly round, 2.7–5 (–7) cm long and 1.5–4 cm wide, with caudal or acuminate apex and round base. The lower part is densely covered with brown pubescence when young and then falls off; there are small pits on both sides, with three veins. The middle vein and the first opposite side vein are often concave at the top. Petiole length is 0.5–1 cm; umbrella is axillary, without peduncle, often 6–8 order, with short branches, seven flowers per inflorescence; pedicel pilose; perianth segments nearly equal in length, white pilose, inner surface glabrous. The male flower perianth segment is about 4 mm long. The filaments are sparsely pilose, and the base of the third round of filaments has two broad reniform stalked glands. The pistil is degenerate. The female perianth segment is about 2.5 mm long; the ovary is oval and covered with brown pubescence; the stigma is capitate; the staminodes are long strip, sparsely pilose; and the base of the third round of filaments has two stalked glands. The fruit is ovoid or nearly spherical, 0.6–1 cm long (www.iplant.cn).

Traditional applications

The medicinal application of LA was first recorded first in Kaibao Herbology (《开宝本草》), which dates to the Song dynasty (A.D. 973–974). LA has also been mentioned in several traditional texts on herbal medicine, such as the Illustrated Canon of Herbology (《本草图经》) (Song dynasty, A.D. 1061), Compendium of Herbology (《本草纲目》) (Ming dynasty, A.D. 1552–1578), Ben Cao Yuan Shi (《本草原始》) (Ming dynasty, A.D. 1612), and Southern Yunnan Materia Medica (《滇南本草》) (Ming dynasty, A.D. 1436). LA has been widely applied for treating chest and abdominal pain, dyspnea, bladder deficiency, enuresis and frequent urination, bladder cold, hernia, dysmenorrhea and other diseases. As a traditional medicine for regulating 'Qi', LA has a soothing 'Qi' effect, relieves pain, warms the kidneys, and dissipates cold. However, the mechanism underlying some of these traditional effects of LA remain unclear.

LA has many folk names, including *Pangqi*, *Aizhang*, *Tiantaiwuyao*, *Baibeishu*, *Niuyanzhang*, *Diaozhang*, *Baiyecai*, and *Xiangyeshu*[6]. The tuberous roots of LA taste hot, bitter, cool, and slightly mild, and they are nontoxic. According to the TCM, the components of the tuberous roots reach the lung, spleen, kidney, and bladder channels, wherein they tonify the spleen, warm the kidneys, replenish 'Qi', relieve pain, and prevent nocturnal enuresis. In TCM, LA tuberous roots are commonly

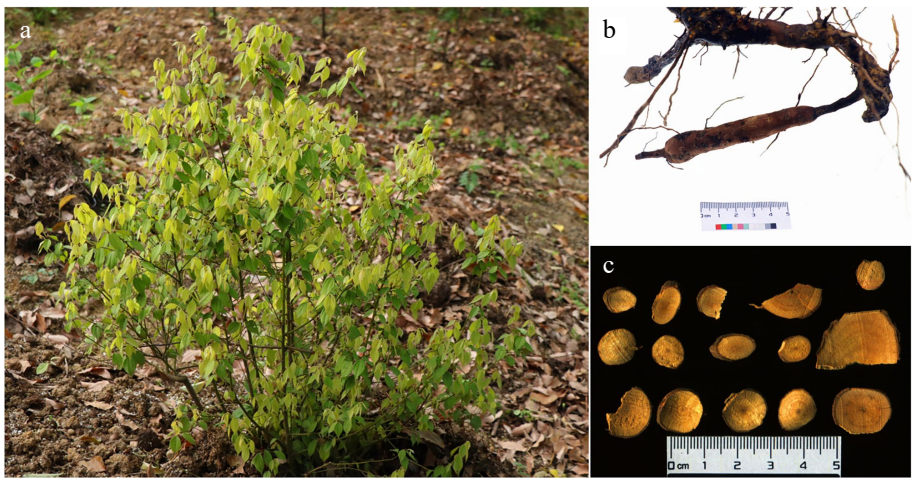

Fig. 1 (a) Whole plant, (b) medicinal portion, and (c) commercial herbal pieces of *Lindera aggregata*.

Fig. 2 General geographical distribution of *Lindera aggregata* in China.

applied to cure various kidney-related diseases and 'Qi' deficiency, including nocturnal enuresis, hernia, menstrual abdominal pain, chest and abdominal pain, cold condensation, stagnation of 'Qi', and some chronic inflammatory diseases. The theory in TCM believes that 'Qi' (气) is the combination of matter and function[7]. When various pathogenic factors act on the human body, it can lead to various systemic or regional diseases by affecting the body's 'Qi' dynamic and 'Qi' transformation[8]. 'Qi' stagnation is an important factor in the formation of blood stasis. In cold coagulation 'Qi' stagnation blood stasis syndrome rats, essential oil of LA can effectively improve TCM syndrome score and hemorheology, play the role of vascular endothelial cell protection and improve blood hypercoagulability in rats with cold coagulation, 'Qi' stagnation, and blood stasis syndrome, and its mechanism is associated with the regulation of the NO-sGC-cGMP signaling pathway[9]. LA exerts a potential positive influence on cardiovascular diseases; hence, further detailed studies are required on its bioactive monomer compounds, molecular mechanisms, as well as clinical efficacy to prove the underlying mechanism.

Regarding the medicinal parts of LA, the records in the herbal literature are not only limited to the root, but also the leaves, fruits, seeds, and bark of LA[4]. LA have been used in over 525 classic formulations for treating diseases (https://db.yaozh.com, last access date: May 03, 2023). Examples of classic and TCM formulations containing LA are listed in Table 1. The table shows empirically effective prescriptions obtained from the clinical practice of TCM. The research on the modern clinical application of LA is mainly focused on the application of '*Tiantai Wuyao San*', '*Si Mo Tang*', '*Nuan Gan Jian*', '*Bai He Tang*', '*Wu Yao Tang*', and '*Suo Quan Wan*'[10]. '*Tiantai Wuyao San*' can be used to treat gastritis, gastric ulcer, prostatitis, chronic appendicitis, and other diseases[11]. '*Si Mo Tang*' oral liquid is effective for curing functional dyspepsia, which can reduce the symptom score and improve the patient's quality of life[12]. People used '*Nuan Gan Jian*' to treat chronic orchitis caused by

Table 1. Examples of traditional Chinese medicine prescriptions containing *Lindera aggregata*.

Preparation name	Composition	Role of LA in prescription	Traditional and clinical uses	References
Suo Quan Wan	*Lindera aggregata*, *Alpinia oxyphylla*, *Dioscorea polystachya*	Leading role	Treatment of nocturnal enuresis and frequent urination caused by kidney deficiency	Weishi Jiacangfang (《魏氏家藏方》)
Tiantai Wuyao San	*Lindera aggregata*, *Aucklandia costus*, *Foeniculum vulgare*, *Citrus reticulata*, *Alpinia officinarum*, *Areca catechu*, *Melia azedarach*, *Croton tiglium*	Leading role	Treat small intestinal hernia, reduce abdominal pain and induce testicles	Sheng Ji Zong Lu (《圣济总录》)
Wu Yao Tang	*Lindera aggregata*, *Cyperus rotundus*, *Aucklandia costus*, *Angelica sinensis*, *Glycyrrhiza uralensis*	Leading role	Treatment of irregular menstruation, dysmenorrhea, premenstrual syndrome, chronic pelvic inflammatory disease, chronic hepatitis, hyperplasia of mammary glands, and chronic gastritis	Ji Yin Gangmu (《济阴纲目》)
Wu Mo Yin Zi	*Lindera aggregata*, *Aquilaria sinensis*, *Areca catechu*, fruit of *Citrus aurantium*, *Aucklandia costus*	Leading role	Relieve depression, treat anger and convulsion	Yifang Jijie (《医方集解》)
Zheng Qi Tian Xiang San	*Lindera aggregata*, *Cyperus rotundus*, *Citrus reticulata*, *Perilla frutescens*, *Zingiber officinale*	Leading role	Treat menstrual irregularities, chest and side pain	Yixue Gangmu (《医学纲目》)
Wu Yao San	*Lindera aggregata*, *Cyperus rotundus*, *Alpinia officinarum*, *Paeonia lactiflora*	Leading role	Reconcile milk to treat children's night crying	Therapeutics of Children's Disease (《小儿药证直诀》)
Jia Wei Wu Yao Tang	*Lindera aggregata*, *Cyperus rotundus*, *Amomum villosum*, *Aucklandia costus*	Leading role	Promote blood circulation, regulate menstruation, and relieve pain	Ji Yin Gangmu (《济阴纲目》)
Bai He Tang	*Lilium brownii* var. *viridulum*, *Lindera aggregata*	Supporting role	Treatment of heartache and epigastric pain	Shifang Kuoge (《时方歌括》)
Bu Xin Tang	*Angelica sinensis*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Corydalis yanhusuo*, *Lindera aggregata*, *Paeonia* × *suffruticosa*, *Polygala tenuifolia*, (*Poria cocos Schw.*), *Dimocarpus longan*	Supporting role	Treatment of heartache and limb chills	Yu An (《玉案》)
Si Mo Tang	*Panax ginseng*, *Areca catechu*, *Aquilaria sinensis*, *Lindera aggregata*	Supporting role	Treatment of chest tightness and anorexia	Ji Sheng Fang (《济生方》)
Tong Yu Jian	*Angelica sinensis*, *Carthamus tinctorius*, *Crataegus pinnatifida*, *Lindera aggregata*, *Citrus reticulata*, *Cyperus rotundus*, *Alisma plantago-aquatica*	Supporting role	Activating blood circulation and removing blood stasis, promoting "Qi" and relieving pain	Complete Collection of Jingyue's Treatise (《景岳全书》)
Nuan Gan Jian	*Angelica sinensis*, *Lycium chinense*, (*Poria cocos Schw.*), *Foeniculum vulgare*, *Cinnamomum cassia*, *Lindera aggregata*, *Aquilaria sinensis*	Supporting role	Treat liver and kidney colds, abdominal pain, and hernia	Complete Collection of Jingyue's Treatise (《景岳全书》)
Ai Fu Nuan Gong Wan	*Ambrosia artemisiifolia*, *Cyperus rotundus*, *Cinnamomum cassia*, *Angelica sinensis*, *Paeonia lactiflora* Pall. *Phlomoides umbrosa* (Turcz.) Kamelin & Makhm., *Lindera aggregata*, *Morinda officinalis*, *Kadsura heteroclita*	Supporting role	Treatment of menstrual irregularity and dysmenorrhea	Shenshi Zhen Sheng Shu (《沈氏尊生书》)
Liu Mo Tang	*Aquilaria sinensis*, *Aucklandia costus*, *Areca catechu*, *Lindera aggregata*, fruit of *Citrus aurantium*, *Rheum palmatum*	Supporting role	Treatment of bloating and constipation	Zhengzhi Zhunshen (《证治准绳》)

liver and kidney deficiency and 'Qi' stagnation of lower energizer[13]. '*Tiantai Wuyao San*', '*Suo Quan Wan*' and '*Suo Quan Wan*' are classical Chinese formulations described in several ancient books. LA in these therapies is frequently combined with other medicinal plants, for example, *Alpinia oxyphylla*, *Zingiber officinale*, *Perilla frutescens*, *Ligusticum chuanxiong*, *Citrus reticulata*, and *Aucklandia costus*. Here, we clarify the clinical efficacy of LA combined with other TCMs. To treat superficial gastritis, the author combined 10 to 12 g of LA with 15 to 25 g of *Taraxacum mongolicum* and used 20 to 30 g of roasted *Astragalus membranaceus* var. *mongholicus* with 10 to 15 g of LA to treat the symptoms of urinary incontinence[14]. In current research, the high dose of *Alpinia oxyphylla*-LA combination has a better effect on improving the damage of animal kidney tissue, thus indicating that the treatment of DN (diabetic nephropathy) by *Alpinia oxyphylla*-LA combination is related to the protective effect of regulating cell autophagy in podocytes in mice with diabetic nephropathy[15]. To study the volatile oil of drug pair, researchers separately analyzed the volatile oil of *Aucklandia costus*-LA combination, *Zingiber officinale*-LA combination, *Citrus reticulata*-LA combination, *Ligusticum chuanxiong*-LA combination and *Perilla frutescens*-LA combination[16–20]. However, the potential mechanisms underlying the possible associations and synergistic effects among the bioactive components of LA and other medicinal plants remain unclear and require further investigations.

Because of its important medicinal value and extensive pharmacological effects, LA has attracted increasing attention in

China. LA is distributed in many regions in China, of which the quality produced in Tiantai, Zhejiang Province is the best. It is called 'Tai Wuyao' and is considered the region with LA abundance[21]. However, the germplasm resources of LA in different regions are mixed, and the content of medicinal components in the germplasm varies greatly in different regions, which severely affects the stability of the quality of LA and has become the bottleneck of standardized cultivation (GAP) of LA and large-scale promotion of fine varieties (lines)[22]. Regarding the use of LA medicinal parts, only the best processing techniques can enable the effective ingredients of LA to play a better role in practical application[23]. The protocol of LA processing, i.e., stir-frying until slightly yellow, was recorded in Boji Fang (《博济方》) (Song dynasty, A.D. 1047) and Puji Fang (《普济方》) (Ming dynasty, A.D. 1390). Later, during the rule of Qing Dynasty (A.D. 1636–1912), roasting with wine was recorded in herbal preparation (《本草备要》) (A.D. 1694). Together with other traditional processing methods, such as stir-frying with either ginger, brine, or wheat bran, roasting with vinegar is also the most popular traditional method in Henan, Hubei, Fujian, and other provinces[3]. The best vinegar roasting method involves moistening 100 g root for 90 min and baking for 2 h at 60 °C with 20 g vinegar[24].

Phytochemical properties

Phytochemical analyses of LA have shown the presence of several phytochemicals, for example, sesquiterpenoids, alkaloids, flavonoids, cyclopentanedione derivatives and enantiomers of ketone derivatives, disesquiterpenoid-geranylbenzofuranone conjugates, benzenoids, benzenoid glycosides, and others. Based on the current research, most chemical compounds are derived from LA roots, and the study of the chemical composition of fruits deserves additional investigations. Alkaloids and sesquiterpenoids are the most important bioactive components in LA. Many investigations have been performed on the types of sesquiterpenoids and alkaloids isolated from LA roots. The medicinal organs of LA are also worthy of further investigations. All compounds identified in *L. aggregata* are summarized and shown in Table 2, and the corresponding structures are shown in Figs 3–7.

Sesquiterpenes

Sesquiterpene is the main chemical component of LA. Eighty-eight sesquiterpenoid compounds have been derived from LA, which include linderaggredin A—D **1**—**4**[25], linderanlide A—F **5**—**10,** sesquiterpenoids(6)—(15) **11**—**19**[26], neolindenenone-lactone **20**[27], linderagalactones A—E **21—25**[28], linderanoid A—O **26**—**40**[29], linderaggrenolide A—N **41**—**54**[30], aggreganoid A—F **55—60**[31], linderolide G—M **61**—**67**, lindestrenolide **68**, shizukanolide **69**, chloranthalactone D **70**, lindenene **71**, lindenenol **72**, lindenonolide H **73**, lindenanolide A **74**, lindestrene **75**, 8-hydroxyisogermafurenolide **76**, linderane **77**[32], dehydrolindestrenolide II **78**, hydroxylinderstrenolide III **79**, linderalactone IV **80**, ^{6}-acetyl-lindenanolide B-1I **81**, ^{6}-acetyl-lindenanolide B-2I **82**[33], lindenanolide H **83**, lindenanolide A **84**, atractylenolide III **85**[34], linderin A **86**, and linderin B **87**[35]. Sesquiterpenes were mostly isolated from roots and a small amount of them were detected in leaves. Following additional studies, a growing number of new sesquiterpenoids have been discovered, including sesquiterpene dimer, oxygen-conjugated sesquiterpene dimer, and oligomeric sesquiterpene.

Table 2. The main compounds isolated from *Lindera aggregata*.

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
Sesquiterpenes	Linderaggredin A **1**	Whole plants	Chromatography, 1H NMR spectrum, HSQC NMR spectral, HMBC spectral, NOESY spectra	Methanol extract	Kuo et al.[25]
	Linderaggredin B **2**	Whole plants	Chromatography, 1H NMR spectrum, HSQC NMR spectral, HMBC spectral, NOESY spectra	Methanol extract	Kuo et al.[25]
	Linderaggredin C **3**	Whole plants	Chromatography, 1H NMR spectrum, HSQC NMR spectral, HMBC spectral, NOESY spectra	Methanol extract	Kuo et al.[25]
	Linderaggredin D **4**	Whole plants	Chromatography, 1H NMR spectrum, HSQC NMR spectral, HMBC spectral, NOESY spectra	Methanol extract	Kuo et al.[25]
	Linderanlide A **5**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Linderanlide B **6**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Linderanlide C **7**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Linderanlide D **8**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Linderanlide E **9**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Linderanlide F **10**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral, CC	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (6) **11**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (7) **12**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (8) **13**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (9) **14**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (10) **15**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (11) **16**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]

(to be continued)

Table 2. (continued)

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
	Sesquiterpenoids (13) **17**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (14) **18**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Sesquiterpenoids (15) **19**	Roots	UV, IR, NMR, HR-ESI-MS, and CD spectra, CD spectral	Ethanol extract	Qiang et al.[26]
	Neolindenenonelactone **20**	Roots	Fast atom bom-bardment mass spectroscopy, one-dimensional nuclear magnetic resonance spectroscopy, two-dimensional-nuclear magnetic resonance spectroscopy, ilica gel column chromatography,TLC	EtOH extract	Cheng et al.[27]
	Linderagalactones A **21**	Roots	HRESIMS, 2D NMR, ECD spectra, HMBC spectrum, NOESY spectrum, silica gel GF254 plates, C18 reversed-phase silica gel, TLC	EtOH extract	Gan et al.[28]
	Linderagalactones B **22**	Roots	HRESIMS, 2D NMR, ECD spectra, HMBC spectrum, NOESY spectrum, silica gel GF254 plates, C18 reversed-phase silica gel, TLC	EtOH extract	Gan et al.[28]
	Linderagalactones C **23**	Roots	HRESIMS, 2D NMR, ECD spectra, HMBC spectrum, NOESY spectrum, silica gel GF254 plates, C18 reversed-phase silica gel, TLC	EtOH extract	Gan et al.[28]
	Linderagalactones D **24**	Roots	HRESIMS, 2D NMR, ECD spectra, HMBC spectrum, NOESY spectrum, silica gel GF254 plates, C18 reversed-phase silica gel, TLC	EtOH extract	Gan et al.[28]
	Linderagalactones E **25**	Roots	HRESIMS, 2D NMR, ECD spectra, HMBC spectrum, NOESY spectrum, silica gel GF254 plates, C18 reversed-phase silica gel, TLC	EtOH extract	Gan et al.[28]
	Linderanoid A **26**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid B **27**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid C **28**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid D **29**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid E **30**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid F **31**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid G **32**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid H **33**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid I **34**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid J **35**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid K **36**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid L **37**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid M **38**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid N **39**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderanoid O **40**	Roots	UV spectra, ECD spectra, NMR Spectrum	Ethanol extract	Liu et al.[29]
	Linderaggrenolide A **41**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	LinderaggrenolideB **42**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide C **43**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide D **44**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide E **45**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide F **46**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide G **47**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Linderaggrenolide H **48**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]

(to be continued)

Table 2. (continued)

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
	Lindera aggrenolide I **49**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Lindera aggrenolide J **50**	Roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Lindera aggrenolide K **51**	roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Lindera aggrenolide L **52**	roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Lindera aggrenolide N **53**	roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Lindera aggrenolide N **54**	roots	NMR spectra, UV spectra, ECD spectra, HRESIMS, Silica gel column chromatography, thin layer chromatography	EtOH extract	Liu et al.[30]
	Aggreganoid A **55**	\	IR spectrum, NMR spectra, ECD spectra	EtOH extract	Liu et al.[31]
	Aggreganoid B **56**	\	NMR spectra	EtOH extract	Liu et al.[31]
	Aggreganoid C **57**	\	positive HR-ESIMS spectrum, NMR spectra, ECD spectra	EtOH extract	Liu et al.[31]
	Aggreganoid D **58**	\	NMR spectra	EtOH extract	Liu et al.[31]
	Aggreganoid E **59**	\	NMR spectra	EtOH extract	Liu et al.[31]
	Aggreganoid F **60**	\	NMR spectra	EtOH extract	Liu et al.[31]
	Linderolide G **61**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide H **62**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide I **63**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide J **64**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide K **65**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide L **66**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderolide M **67**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindestrenolide **68**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Shizukanolide **69**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Chloranthalactone D **70**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindenene **71**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindenenol **72**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindenonolide H **73**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindenanolide A **74**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Lindestrene **75**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	8-hydroxyisogermafurenolide **76**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Linderane **77**	Roots	UV spectra, IR spectra, CD spectra, NMR spectra, EI-mass spectra, CC, TLC	Methanol extract	Liu et al.[32]
	Dehydrolindestrenolide II **78**	Leaves	NMR spectra, TLC, Silica gel column chromatography	Ethanol extract	Zhang et al.[33]
	Hydroxylinderstrenolide III **79**	Leaves	NMR spectra, TLC, Silica gel column chromatography	Ethanol extract	Zhang et al.[33]
	Linderalactone IV **80**	Leaves	NMR spectra, TLC, Silica gel column chromatography	Ethanol extract	Zhang et al.[33]
	^{6}-acetyl lindenanolide B^{-1} I **81**	Leaves	NMR spectra, TLC, Silica gel column chromatography	Ethanol extract	Zhang et al.[33]
	^{6}-acetyl lindenanolide B^{-2} I **82**	Leaves	NMR spectra, TLC, Silica gel column chromatography	Ethanol extract	Zhang et al.[33]
	Lindenanolide H (2) **83**	Leaves	TLC, HPLC, NMR spectra	Ethanol extract	Sun et al.[34]
	Lindenanolide A (3) **84**	Leaves	TLC, HPLC, NMR spectra	Ethanol extract	Sun et al.[34]
	Atractylenolide III(4) **85**	Leaves	TLC, HPLC, NMR spectra	Ethanol extract	Sun et al.[34]
	Linderin A **86**	Roots	IR spectra, NMR spectra, HR-ESI-MS, Thin-layer chromatography, silica gel G precoated plates	Ethanol extract	Wen et al.[35]

(to be continued)

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Table 2. (continued)

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
	Linderin B **87**	Roots	IR spectra, NMR spectra, HR-ESI-MS, Thin-layer chromatography, silica gel G precoated plates	Ethanol extract	Wen et al.[35]
Alkaloid	Lindera aggrine B **88**	Whole plants	Chromatography, 1H NMR spectrum, NOESY spectra	Methanol extract	Kuo et al.[25]
	(1′S)-12′-hydroxyl-linderegatine **89**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	(1S)-5′-O-p-hydroxybenzoyl norreticuline **90**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	(1R, 1′R)-11,11′-biscoclaurine **91**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Costaricine **92**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	N-methyllauro-tetanine **93**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Laurotetanine **94**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Actinodaphnine **95**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Isoboldine **96**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Laurolitsine **97**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Norisoboldine **98**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Boldine **99**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Norjuziphine **100**	Roots	UV, spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Reticuline **101**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Reticuline n-oxide **102**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Boldine n-oxide **103**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	N-methyllaurotetanine n-oxide **104**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Salutaridinen-oxide **105**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Linderegatine **106**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Lindoldhamine **107**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Secolaurolitsine **108**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	Secoboldine **109**	Roots	UV spectra, HRESIMS spectra, Waters HPLC column, NMR spectroscopy, ECD spectra, Thin-layer chromatography, Silica gel column chromatography	EtOH extract	Yang et al.[36]
	(+)-norboldine acetate **110**	Roots	2D NMR spectra, 1H NMR spectra, IR spectra, NMR spectra, RP-18 column	EtOH extract	Gan et al.[37]
	(+)-norboldine **111**	Roots	2D NMR spectra, 1H NMR spectra, IR spectra, NMR spectra, Silica gel column chromatography	EtOH extract	Gan et al.[37]
	(+)-boldine **112**	Roots	2D NMR spectra, IR spectra, NMR spectra, RP-18 column	EtOH extract	Gan et al.[37]
	(+)-laurotetanine **113**	Roots	2D NMR spectra, IR spectra, NMR spectra, Silica gel column chromatography	EtOH extract	Gan et al.[37]

(to be continued)

Table 2. (continued)

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
	(+)-N-methyllaurotetanine**114**	Roots	2D NMR spectra, IR spectra, NMR spectra, Silica gel column chromatography	EtOH extract	Gan et al.[37]
	(+)-reticuline **115**	Roots	2D NMR spectra, IR spectra, NMR spectra, Silica gel column chromatography	EtOH extract	Gan et al.[37]
	(−)-pronuciferine **116**	Roots	2D NMR spectra, IR spectra, NMR spectra, Silica gel column chromatography	EtOH extract	Gan et al.[37]
	Pallidine **117**	Roots	2D NMR spectra, IR spectra, NMR spectra, RP-18 column	EtOH extract	Gan et al.[37]
	Demethylcoclaurine-7-o- glucoside **118**	Roots	\	Methanol extract	Peng et al.[38]
	Coclaurine **119**	Roots	\	Methanol extract	Peng et al.[38]
	Magnocurarine **120**	Roots	\	Methanol extract	Peng et al.[38]
	Boldine **121**	Roots	\	Methanol extract	Peng et al.[38]
	Reticuline **122**	Roots	\	Methanol extract	Peng et al.[38]
	Hernangerine **123**	Roots	\	Methanol extract	Peng et al.[38]
	N-methyllaurotetanine**124**	Roots	\	Methanol extract	Peng et al.[38]
	Karakoramine **125**	Roots	\	Methanol extract	Peng et al.[38]
Flavonoids	Quercetin **126**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Quercetin-3-O-rhamnoside **127**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Kampferol-3-O-L-arabinopyranoside **128**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Quercetin-3-O-β-D-galactopyranoside **129**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Isorhamnetin-3-O-[β-D-glucopyranosy-l (6→1)- rhamno-side]**130**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Kampferol-3-O-α-glicurinoside **131**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[39]
	Nubigenol **132**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[40]
	Kaempferol-3-O-(6″-trans-p-coumaroyl)-β-D-glucopyranoside **133**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[40]
	Chrysoeriol-7-β-D-glucopyranoside **134**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[40]
	Rutin **135**	Leaves	Infrared spectrum, NMR spectra, TLC	Ethanol extract	Zhang et al.[40]
	Kaempferol-3-O-L-rhamnoside **136**	Leaves	NMR spectra, TLC	Ethanol extract	Xiao et al.[41]
	Kaempferol **137**	Leaves	NMR spectra, TLC	Ethanol extract	Xiao et al.[41]
	Dihydrokaempferol-3-O-L-rhamnoside **138**	Leaves	NMR spectra, TLC	Ethanol extract	Xiao et al.[41]
	Quercetin **139**	Leaves	NMR spectra, TLC	Ethanol extract	Xiao et al.[41]
	Kaempferol-3-O-D-glucopyranoside **140**	Leaves	NMR spectra, TLC	Ethanol extract	Xiao et al.[41]
	Avicularin **141**	Leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Afzelin **142**	Leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Dihydrokaempferol **143**	Leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Astragaline **144**	Leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Kaempfero-l3-O-β-D-xylopyranoside **145**	Leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Juglalin **146**	leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]
	Kaempfero-l3-O-(2″-O-β-D-glucopyranosyl)-α-L-rhamnopyranoside **147**	leaves	NMR spectra, TLC	Ethanol extract	Luo et al.[42]

Table 2. (continued)

Class	Compounds	Part of the plant	Chromatographic methods	Type of extract	Reference
Cyclopentenedione derivatives	(±)-lindepentone A **148**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Lindoxepine A **149**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Lindoxepine B **150**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Epi-bi-linderone **151**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Bi-linderone **152**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Linderaspirone A **153**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Methyllinderone **154**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	Methyllucidone (a pair of cis–trans isomers, 9a and 9b) **155**	Roots	NMR spectra, ESIMS, HRESIMS, Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
Enantiomers of ketone derivatives	(+)-demethoxy-epi-bi-linderone (4a) **156**	Roots	NMR spectra, ESIMS, HRESIMS,Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
	(-)-demethoxy-epi-bi-linderone (4b) **157**	Roots	NMR spectra, ESIMS, HRESIMS,Silica gel column chromatography, High performance liquid chromatography	EtOAc extract	Chen et al.[45]
Disesquiterpenoid–geranylbenzofuranone conjugates	Linderalide A **158**	Roots	UV spectra, CD spectra, NMR spectra, Waters XBridge C18 (5 μm, 250 × 10 mm^2, i.d.) columns, Siliabond C18 ODS column, Silica gel column chromatography	Ehanol extract	Liu et al.[46]
	Linderalide B **159**	Roots	UV spectra, CD spectra, NMR spectra, Waters XBridge C18 (5 μm, 250 ×10 mm^2, i.d.) columns, Siliabond C18 ODS column, Silica gel column chromatography	Ehanol extract	Liu et al.[46]
	Linderalide C **160**	Roots	UV spectra, CD spectra, NMR spectra, Waters XBridge C18 (5 μm, 250 ×10 mm^2, i.d.) columns, Siliabond C18 ODS column, Silica gel column chromatography	Ehanol extract	Liu et al.[46]
	Linderalide D **161**	Roots	UV spectra, CD spectra, NMR spectra, Waters XBridge C18 (5 μm, 250 ×10 mm^2, i.d.) columns, Siliabond C18 ODS column, Silica gel column chromatography	Ehanol extract	Liu et al.[46]
Benzenoids and	linderagatin A **162**	Roots	1D (1H, 13C) spectra, 2D NMR (COSY, NOESY, HSQC and HMBC) spectra, ECD spectra, CC, TLC	MeOH extracts	Ma et al.[47]
	linderagatin B (1-2) **163**	Roots	1D (1H, 13C) spectra, 2D NMR (COSY, NOESY, HSQC and HMBC) spectra, ECD spectra, CC, TLC	MeOH extracts	Ma et al.[47]
benzenoid glycoside	6′-O-vanilloyl-5-hydroxy-2,3-dimethoxyphenol 1-O-β-D-gluco-pyranoside **164**	Whole plants	Chromatography, 1H NMR spectrum, HMBC spectral, HSQC NMR spectral	Methanol extract	Kuo et al.[25]
Others	9,9′-dihydroxy-3,4-methylenedioxy-3′-methoxy [7-O-4′,8-5′]Lignans **165**	Leaves	TLC, HPLC, NMR spectra	Ethanol extract	Sun et al.[34]
	Hernangerine **166**	Roots	TLC, NMR spectra	Ethanol extract	Zhu et al.[48]

'\' Denotes no useful information found in the study.

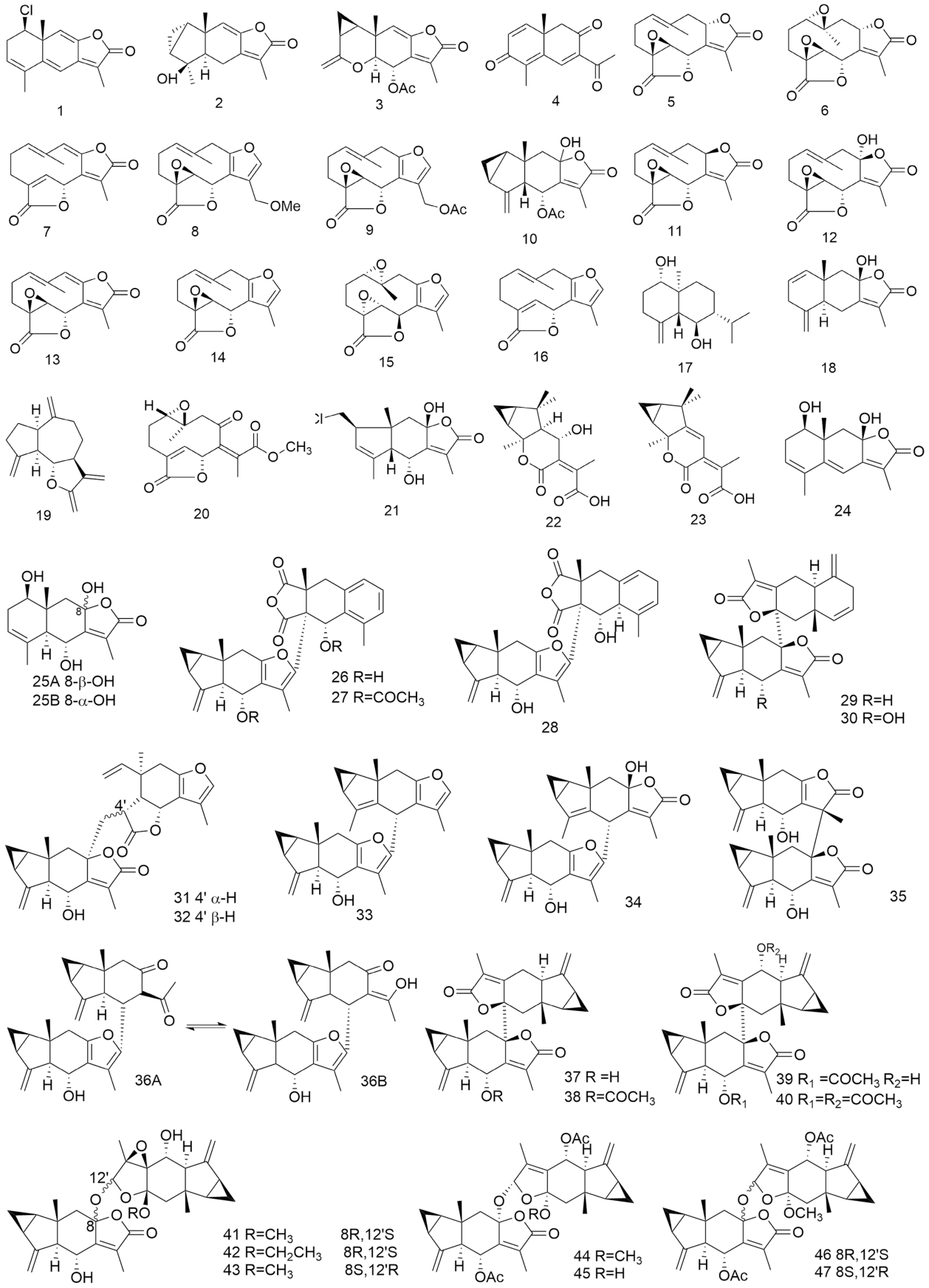

Fig. 3 (to be continued)

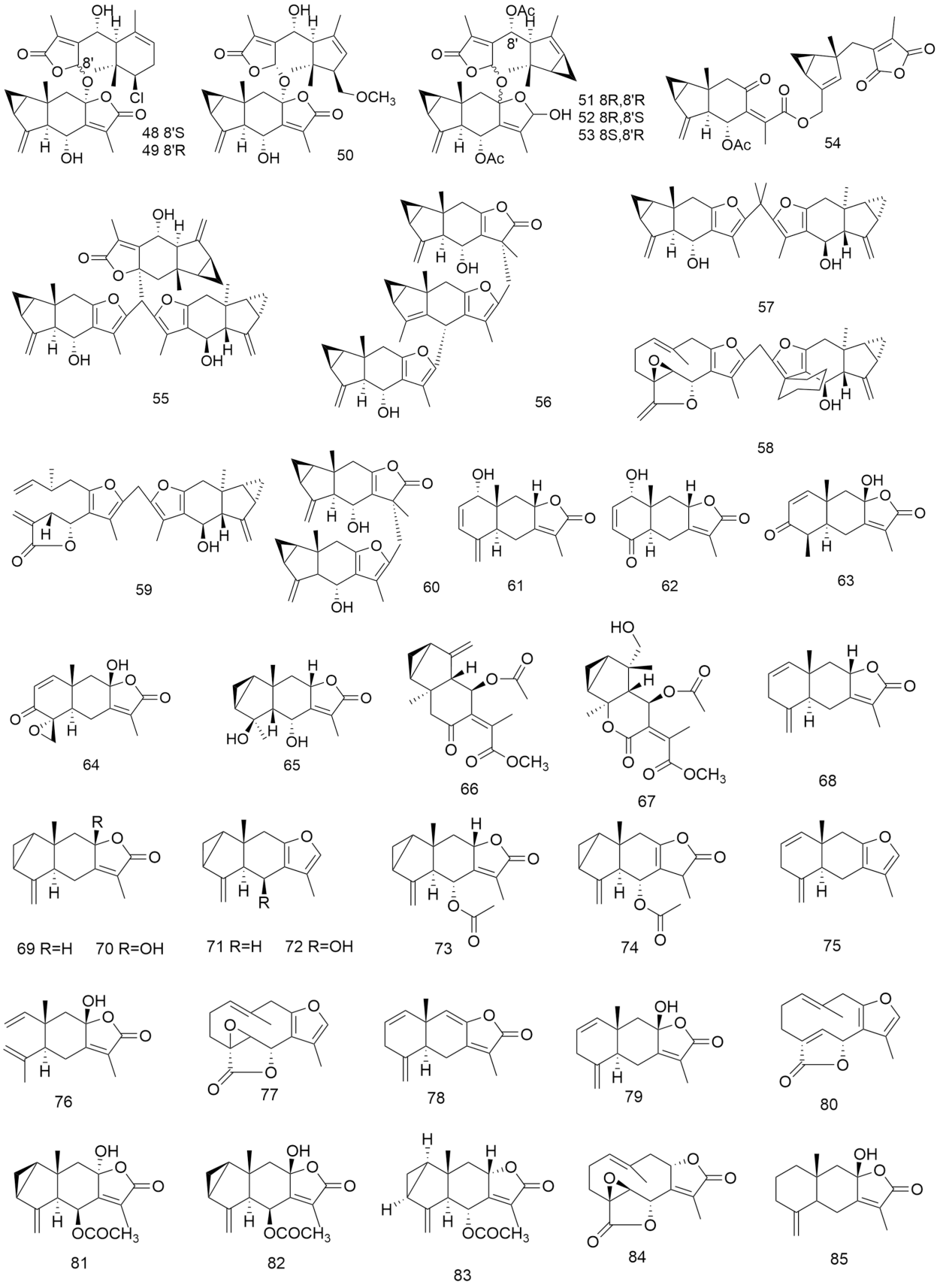

Fig. 3 (to be continued)

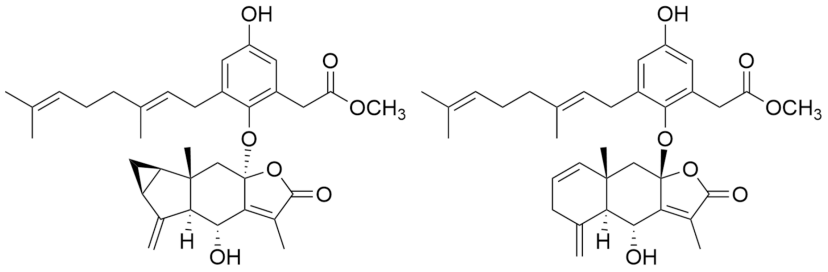

Fig. 3 Structures of sesquiterpenoids (1–87) isolated from *Lindera aggregata*.

Pharmacological studies have confirmed that sesquiterpenes have antitumor activity, antioxidant activity, hypoglycemic activity, liver protection, and other effects[3]. The chemical structures of these sesquiterpenoids are shown in Fig. 3.

Alkaloids

Alkaloids are the important active components of LA. Thirty-eight alkaloid compounds, including isoquinoline alkaloids, benzylisoquinoline alkaloids, and other types, have been detected in LA through NMR and TLC, including linderaggrine B **88**[25], (1′S)-12′-hydroxyl-linderegatine **89**, (1S)-5′-O-p-hydroxy-benzoyl-norreticuline **90**, (1R, 1′R)-11,11′-biscoclaurine **91**, costaricine **92**, N-methyllauro-tetanine **93**, laurotetanine **94**, actinodaphnine **95**, isoboldine **96** laurolitsine **97**, norisoboldine **98**, boldine **99**, norjuziphine **100**, reticuline **101**, reticulinen-oxide **102**, boldinen-oxide **103**, N-methyllaurotetaninen-oxide **104**, salutaridinen-oxide **105**, linderegatine **106**, lindoldhamine **107**, secolaurolitsine **108**, secoboldine **109**[36], (+)-norboldine acetate **110**, (+)-norboldine **111**, (+)-boldine **112**, (+)-laurotetanine **113**, (+)-N-methyllaurotetanine **114**, (+)-reticuline **115** (+)-pronuciferine **116**, pallidine **117**[37], demethylcoclaurine-7-o-glucoside **118**, coclaurine **119**, magnocurarine **120**, boldine **121**, reticuline **122**, hernangerine **123**, (+)-N-methyllaurotetanine **124**, and karakoramine **125**[38]. Alkaloids from LA exhibit anti-inflammatory and analgesic effects[3]. The chemical structures of these alkaloids are shown in Fig. 4.

Flavonoids

Flavonoids are the main compounds isolated from the leaves of LA, and to date, 22 flavones have been identified , including quercetin **126**, quercetin-3-O-rhamnoside **127**, kampferol-3-O-L-arabinopyranoside **128**, quercetin-3-O-β-D-galactopyranoside **129**, isorhamnetin-3-O-[β-D-glucopyranosy-l (6→1)-rhamno-side] **130**, kampferol-3-O-α-glicurinoside **131**[39], nubigenol **132**, kaempferol-3-O-(6″-trans-p-coumaroyl)-β-D-glucopyranoside **133**, chrysoeriol-7-β-D-glucopyranoside **134**, rutin **135**[40], kaempferol-3-O-L-rhamnoside **136**, kaempferol **137**, dihydrokaempferol-3-O-L-rhamnoside **138**, quercetin **139**, kaempferol-3-O-D-glucopyranoside **140**[41], avicularin **141**, afzelin **142**, dihydrokaempferol **143**, astragaline **144**, kaempfero-l3-O-β-D-xylopyranoside **145**, juglalin **146**, and kaempfero-l3-O-(2″-O-β-D-glucopyranosyl)-α-L-rhamnopyranoside **147**[42]. The total flavones in the leaves of LA have antioxidant effects[43]. Quercetin-3-O-α-L-rhamnopyranoside (Ql) is a flavonoid derived from LA leaves and has antioxidant activity[44]. The chemical structures of0 these flavonoids are shown in Fig. 5.

Cyclopentanedione derivatives and enantiomers of ketone derivatives

Ten cyclopentenedione derivatives and new bi-linderone derivative enantiomers, including (±)-lindepentone A **148**, lindoxepine A **149**, lindoxepine B **150**, epi-bi-linderone **151**, bi-linderone **152**, linderaspirone A **153**, methyllinderone **154**, methyllucidone **155** (a cis–trans isomer pair, 9a and 9b), (+)-demethoxy-epi-bi-linderone (4a) **156**, and (–)-demethoxy-epi-bi-linderone (4b) **157** have been identified from LA[45]. The chemical structures are shown in Fig. 6.

Disesquiterpenoid–geranylbenzofuranone conjugates

Four disesquiterpenoid–geranylbenzofuranone conjugates, namely linderalide A **158**, linderalide B **159**, linderalide C **160**, and linderalide D **161**[46], have been determined from LA roots. The chemical structures of these sesquiterpenoids are shown in Fig. 7.

Benzenoids and benzenoid glycosides

Two benzenoids, linderagatin A **162** and linderagatin B (1-2) **163**[47], and one benzenoid glycoside, 6′-O-vanilloyl-5-hydroxy-2,3-dimethoxyphenol 1-O-β-D-gluco-pyranoside **164**[25] were isolated from LA. The chemical structures of these benzenoids and benzenoid glycosides are shown in Fig. 7.

Others

One lignan, 9,9'-dihydroxy-3,4-methylenedioxy-3'-methoxy [7-O-4',8-5'] lignan **165**[34], as well as other compounds such as hernangerine **166**[48] were detected in LA. The chemical structures are shown in Fig. 7.

Pharmacological activities

LA exhibits several pharmacological effects such as hepatoprotective effect, anti-inflammatory activity, antitumor activity, antihyperlipidemic effect, analgesic effect, liver and kidney protection, bacteriostasis, anti-rheumatic effect, diarrhea improvement, and blood stasis improvement. Traditionally, LA has been widely applied to treat cold coagulation and stagnation of 'Qi', chest and abdomen distension and pain, dyspnea, bladder deficiency, frequent enuresis, bladder cold, colic pain, menstrual cold and abdominal pain. Currently, there is a lack of research on the traditional application of LA in fields such as menstrual irregularities. Modern pharmacological research has basically excluded the traditional application of LA, and in-depth research on the physiological activities of LA extracts has been confirmed. The research on the anti-inflammatory effect and hepatoprotective effect of LA is relatively comprehensive;

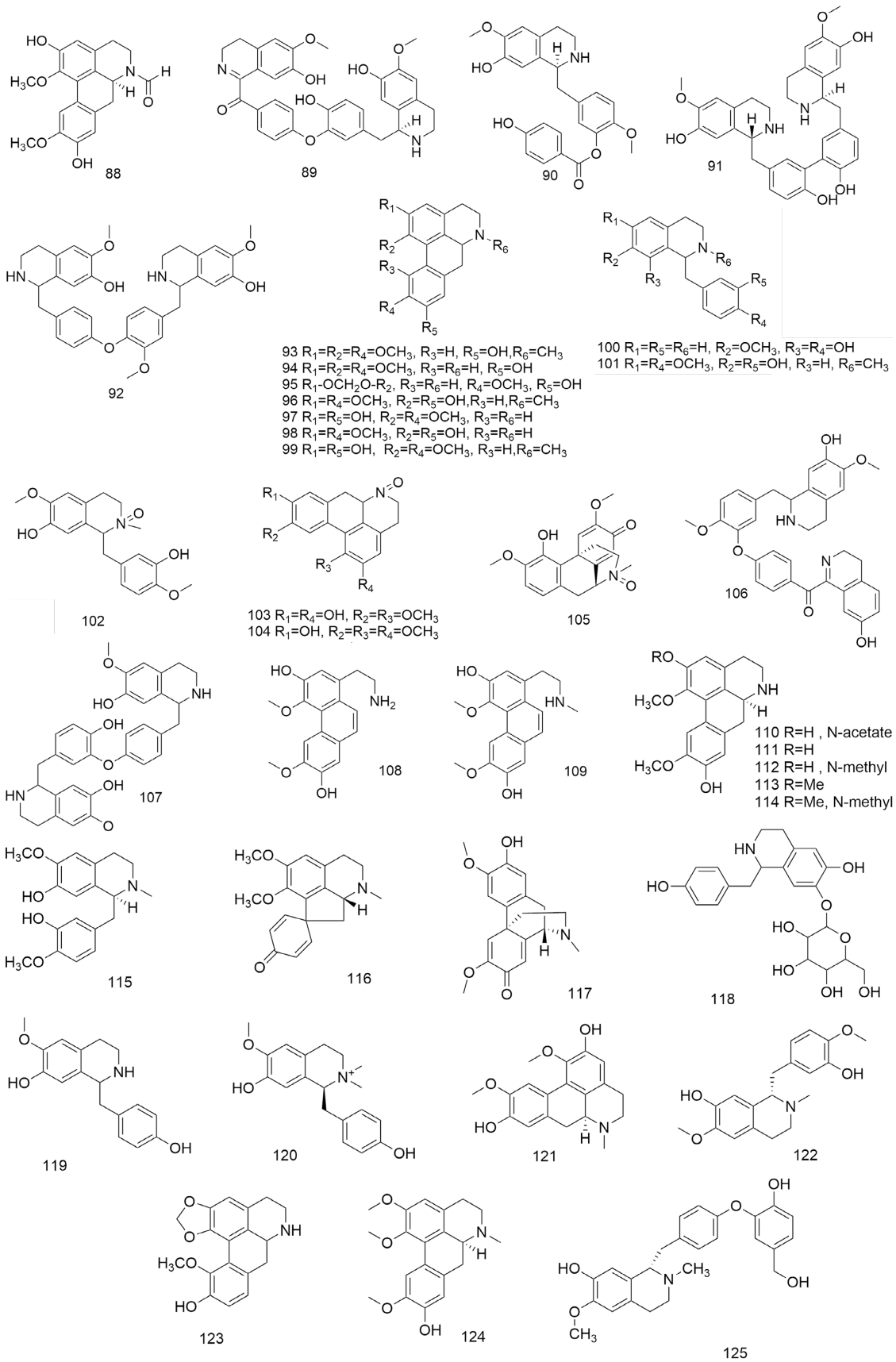

Fig. 4 Structures of alkaloids (88-125) isolated from *Lindera aggregata*.

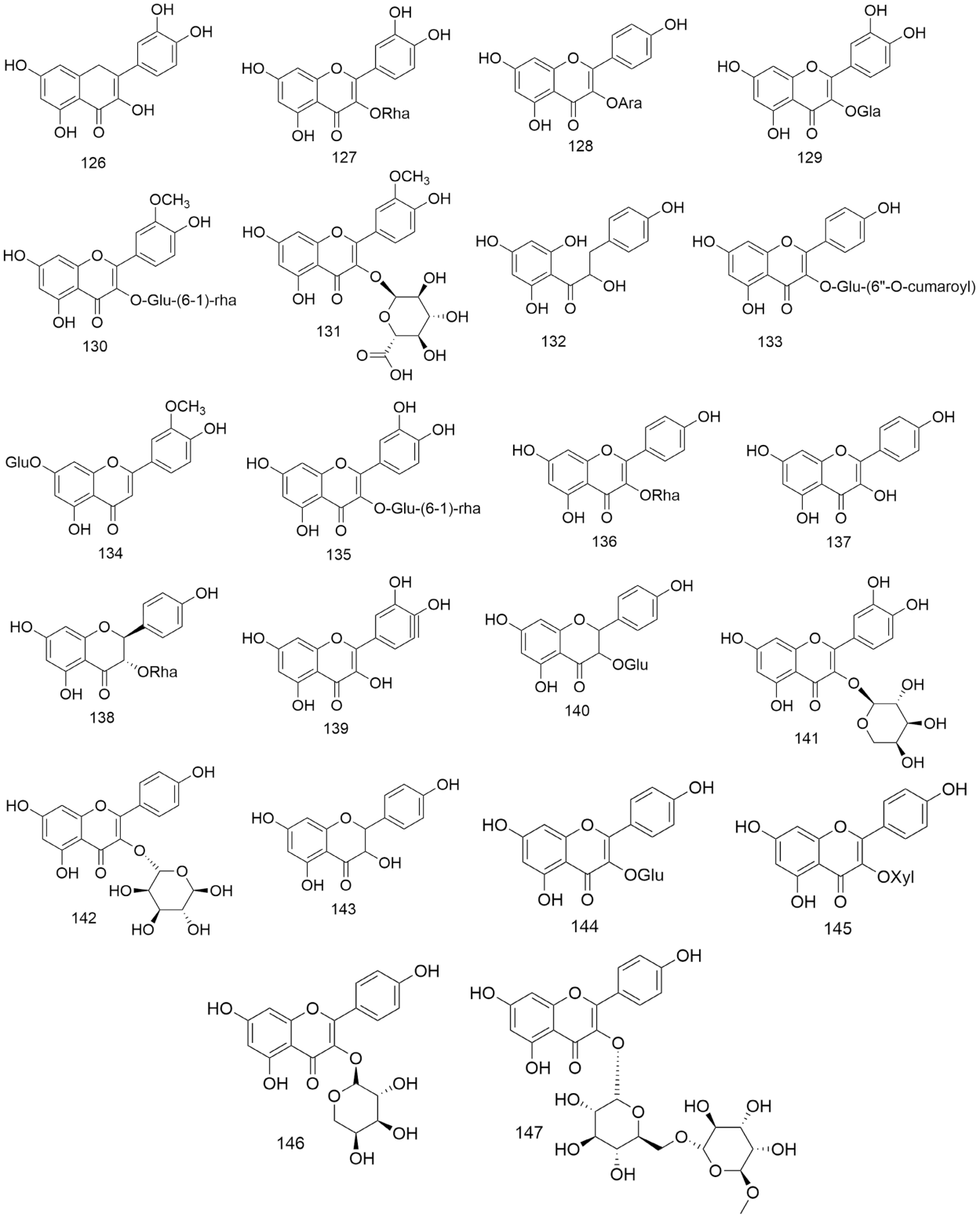

Fig. 5 Structures of flavonoids (126–147) isolated from *Lindera aggregata*.

however, in-depth research on the analgesic effect of LA is lacking. Therefore, the field of pharmacological activity of the analgesic effect of LA should be explored further in future studies. The analgesic effect alone, as a traditional application of LA, has been mentioned to some extent in modern pharmacological research. We therefore need to strengthen the research on the traditional application of LA to provide a basis for its clinical use. The main biological activities of LA and corresponding mechanisms are shown in Fig. 8. These effects are summarized in Table 3 and discussed in greater detail in the following sections.

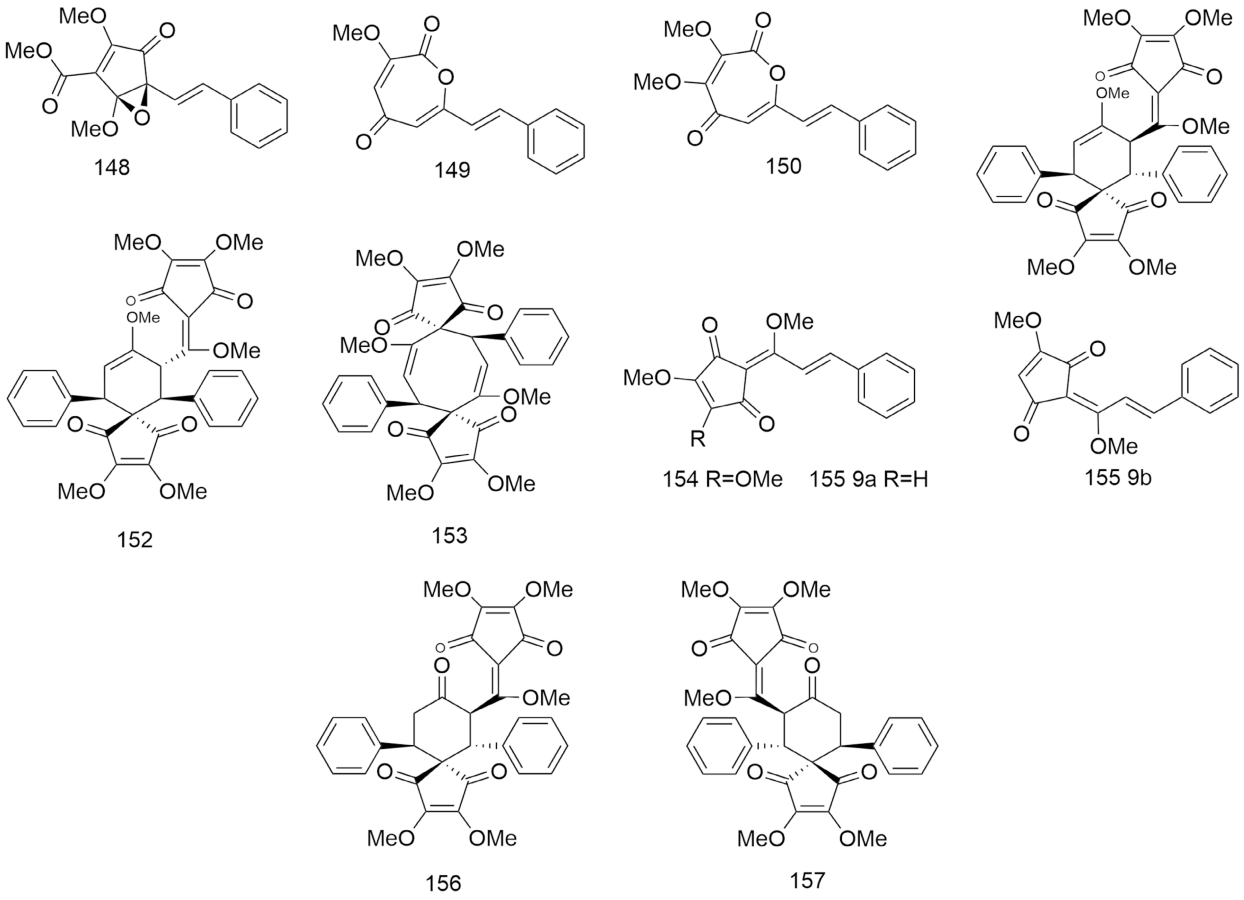

Fig. 6 Structures of cyclopentanedione derivatives and enantiomers of ketone derivatives (148–157) isolated from *Lindera aggregata*.

Anti-inflammatory activity

LA extracts show anti-inflammatory activity in many diseases, including colitis, arthritis, pelvic infection, hepatitis and so on. In a mice model with symptoms of ulcerative colitis, the ethanol extract of LA not only decreased IL-6 production and secretion but also inhibited the signal transduction of the IL-6/STAT3 signaling pathway. It also alleviated disease manifestations, reduced intestinal permeability, and improved histopathological alterations in a mouse model of colitis[49]. For a rat model of ulcerative colitis (UC) induced by TNBS (2, 4, 6-trinitrobenzene sulfonic acid), LREE (the ethanolic extract of LA) exerted anti-UC effects and the mechanism might be related to suppression of proinflammatory cytokines, namely IL-6 and TNF-α[50]. Alkaloids, particularly norisoboldine obtained from the ethanolic extract of LA, exhibit remarkable anti-inflammatory activity. In mice showing DSS (dextran sulfate sodium)-induced colitis with CH223191 and HK2 plasmids, norisoboldine from LA promoted the differentiation of Tregs and alleviated colitis development through the regulation of the AhR/glycolysis axis and the NAD+/SIRT1/SUV39H1/H3K9me3 signaling pathway, indicating that norisoboldine attenuated ulcerative colitis (UC) as well as induced Treg cell generation[51]. However, to date, the mechanisms by which LA extracts induce their effects remain unclear. None of the above-mentioned studies examined LA's effectiveness in animal models other than mice. Therefore, future studies should attempt to use other animal models to determine the mechanism and apply it to clinical practice.

LA tuberous roots contain abundant alkaloids, particularly norisoboldine. According to some studies, norisoboldine has a relevant role in combating arthritis. By using the delayed-type hypersensitivity model, the author suggested that norisoboldine could be a potential therapeutic agent for rheumatoid arthritis (RA), and it functions by affording protection against joint destruction and by regulating abnormal immune responses[52]. The mechanism underlying the anti-RA effect of NOR (norisoboldine, sourced from the ethanolic extract of LA) in the above study has been gradually revealed. A rat model study showed that the prevention of IL-6 release from fibroblast-like synoviocytes (FLSs) could function as a critical pathway for NOR to exhibit anti-RA effect, and NOR's action was relative to the inhibition of the PKC/MAPKs/p65/CREB pathways[53]. In osteoclast differentiation models developed with mouse bone marrow-derived macrophages (BMMs) and RAW 264.7 cells, it was demonstrated that the prevention of osteoclast differentiation and function at an early stage is a crucial anti-bone destruction mechanism of NOR, which could be ascribed to the attenuation of TRAF6 ubiquitination, TRAF6-TAK1 complex accumulation, and the MAPKs/NF-kB/c-Fos/NFATc1 pathway activation[54]. In the *in vivo* studies, NOR reduced the proportion of OCs (osteoclasts) and alleviated bone erosion in the joints of rats with collagen-induced arthritis, along with CYP1A1 upregulation and VEGF mRNA expression downregulation in rat synovium. Thus, NOR attenuated bone erosion and OC differentiation by activating AhR and suppressing both NF-κB and HIF pathways[55]. Furthermore,

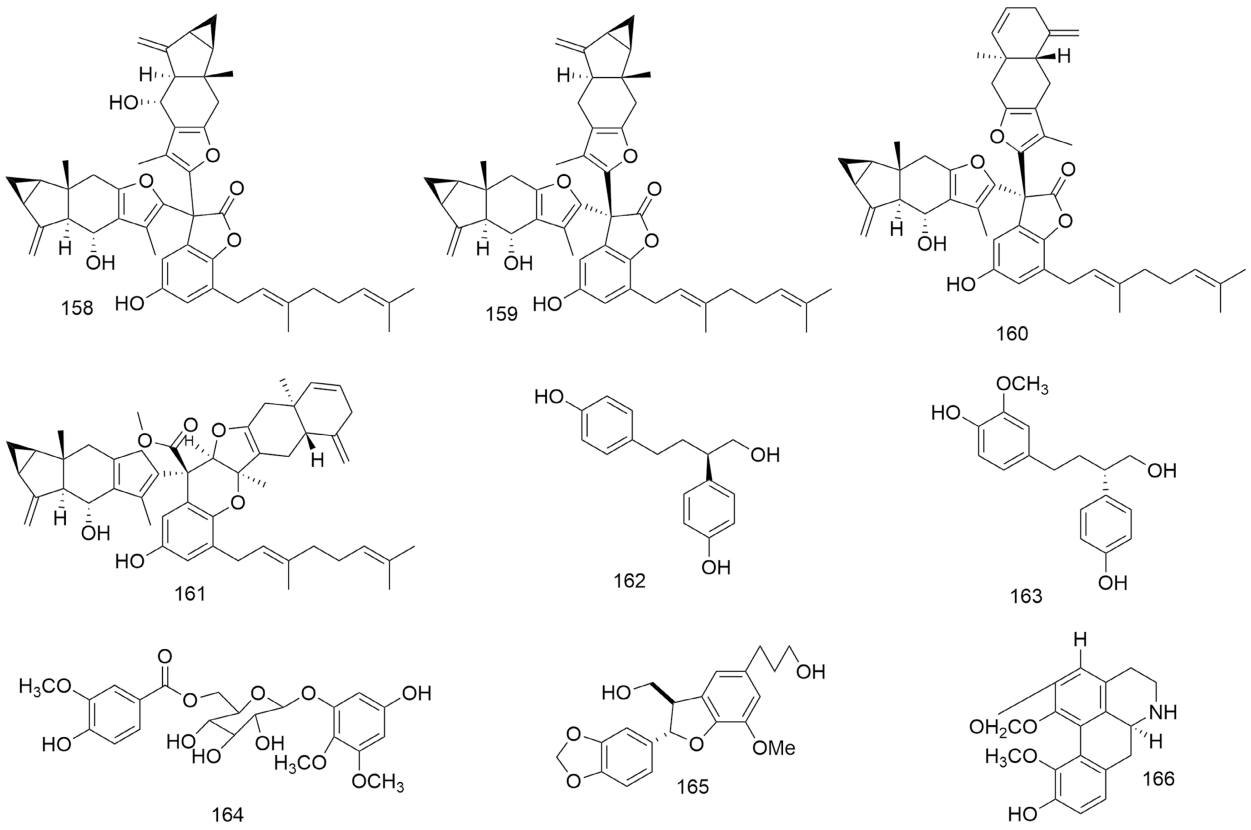

Fig. 7 Structures of disesquiterpenoid–geranylbenzofuranone conjugates, benzenoids and benzenoid glycosides and other compounds isolated from *Lindera aggregata*.

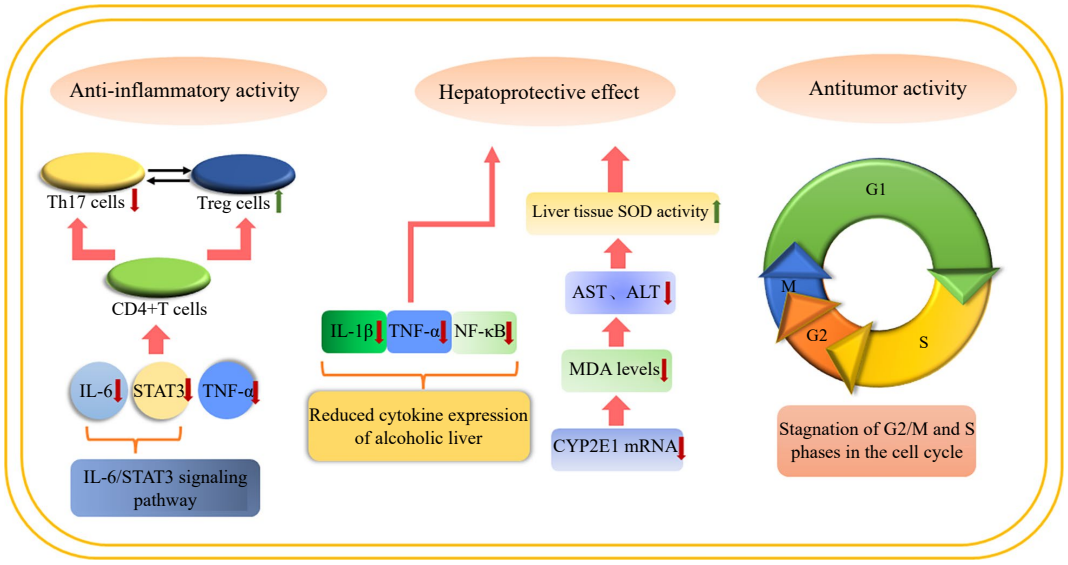

Fig. 8 The main biological activities and corresponding mechanisms of *Lindera aggregata*.

together with the determination of the mechanism of the anti-arthritis effect of NOR, the following study also proposed that NOR's possible effect mainly occurs in the intestine, and NOR has an anti-inflammatory effect on the regulation of intestinal cells. Norisoboldine showed dismal bioavailability in normal rats, and it exerted anti-arthritis effects by regulating Th17 and Treg cell balance in intestinal lymph nodes as well as by controlling lymphocyte (particularly Treg cells) trafficking from the gut to the joint[56]. Nevertheless, the function of the correlation between NOR and intestine has not been examined in depth.

The authors also found that LA component exerted a remarkable curative effect on rats with adjuvant-induced arthritis and had a significant antagonistic effect on wind, cold, and dampness in model rats. It could obviously decrease the inflammatory exudate prostaglandin (PGE2) content in the model animal

Table 3. Pharmacological activities of *Lindera aggregata*.

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Result	Dose range	Time period of application	References
Anti-inflammatory activity	Ethanol extract	C57BL/6 mice	Colonic tissue	Regulated the IL-6 signaling pathway to modulate the balance of Th17 and Treg cells, thus attenuated DSS-induced colitis in mice	1–1.7 g/kg	21 d	Lai et al.[49]
	Ethanol extract	SD rats	Feces and serum	Exerted anti-UC effects on the rat model induced by TNBS and that the mechanism might be associated with the inhibition of inflammatory cytokines, such as IL-6 and TNF-α	0.5, 1, 2 g /kg	9 d	Lai et al.[50]
	\	C57BL/6 mice	Colonic tissue	Promoted Treg differentiation and attenuates colitis via targeting glycolysis and subsequent NAD+/SIRT1/SUV39H1/H3K9me3 signaling pathway	40 mg/kg	10 d	Qi et al.[51]
	Ethanol extract	ICR mice	Paw	Exhibited a potential therapeutic effect on CIA in mice as the main active constituent of LA responsible for the benefits for RA remedy	10, 20, 40 mg/kg	20 d	Luo et al.[52]
	\	SD rats	Cell	Been able to prevent IL-1b-induced release of IL-6 from rat FLS, key producers of IL-6 in synovial membranes of joints	3, 10, 30, 60 mM	14 d	Wei et al.[53]
	\	ICR mice	Cell	Suppressed osteoclast differentiation through Preventing the accumulation of TRAF6-TAK1 complexes and activation of MAPKs/NF-kB/c-Fos/NFATc1 Pathways	3, 10, 30 mM	5 d	Wei et al.[54]
	\	Wistar rats	Paw	Attenuated osteoclast differentiation and Inflammatory bone Erosion in an aryl hydrocarbon receptor-Dependent Manner	15 mg/kg	14 d	Wei et al.[55]
	\	Wistar rats	Paw	Ameliorated collagen-induced arthritis through regulating the balance between Th17 and regulatory T cells in gut-associated lymphoid tissues	15, 30 mg/kg	14 d	Tong et al.[56]
	Ethanol extract	SD rats	Paw	Had obvious therapeutic effect on adjuvant arthritis in rats	200, 100, 50 mg/kg	11 d	Liu et al.[57]
	\	Sprague – Dawley rats	Synovial tissue	Reduced the number of blood vessels and the expression of growth factors in the synovium of AA rats, inhibited VEGF-induced in vitro angiogenesis in HUVECs	\	10 d	Lu et al.[58]
Hepatoprotective effect	WYSTW (water extract)	SD rats	Serum and liver tissue	Suppressed NF-κB, TNF- α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	WYCTW (ethanol extract)	SD rats	Serum and liver tissue	Significantly reduced serum ALT content and serum AST content, suppressed NF-κB, TNF-α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	WYCTC1 (alcohol extract petroleum ether extract)	SD rats	Serum and liver tissue	Significantly reduced serum ALT content and serum AST content, suppressed NF-κB, TNF-α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	WYCTC2 (ethyl acetate extract of LA alcohol extract)	SD rats	Serum and liver tissue	Significantly reduced serum ALT content and serum AST content, suppressed NF-κB, TNF-α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	WYCTC3 (alcohol extract n-butanol extract)	SD rats	Serum and liver tissue	Significantly reduced serum ALT content and serum AST content, suppressed NF-κB, TNF-α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	WYCTC4 (alcohol extract water extract)	SD rats	Serum and liver tissue	Significantly reduced serum ALT content and serum AST content, suppressed NF-κB, TNF-α expression, reducing IL-1β	2 g/kg	10 d	Wang et al.[59]
	Water extract	SD rats	Liver tissue and blood	Had preventive effect on alcoholic liver injury by inhibiting serum ACT and AST levels, and this beneficial effect might be associated with anti-inflammation and anti-oxidation	1 ml/100 g	10 d	Wang et al.[62]
	Ethanol extract	SD rats	Liver tissue and blood	Had preventive effect on alcoholic liver injury by inhibiting serum ACT and AST levels, and this beneficial effect may be associated with anti-inflammation and anti-oxidation	1 ml/100 g	10/d	Wang et al.[62]

(to be continued)

Table 3. (continued)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Result	Dose range	Time period of application	References
	WYSTW	SD rats	Serum and small intestine tissue	Had the effect of protecting liver	4 g/kg	33 d	Ji et al.[63]
	WYCTW	SD rats	Serum and small intestine tissue	Had the effect of protecting liver	4 g/kg	33 d	Ji et al.[63]
	WYCTC1 (alcohol extract petroleum ether extract)	SD rats	Serum and small intestine tissue	Had the effect of protecting liver	4 g/kg	33 d	Ji et al.[63]
	WYCTC2 (ethyl acetate extract of LA alcohol extract)	SD rats	Serum and small intestine tissue	Had the effect of protecting liver	4 g/kg	33 d	Ji et al.[63]
	WYCTC3 (alcohol extract n-butanol extract)	SD rats	Serum and small intestine tissue	Had the effect of protecting liver	4 g/kg	33 d	Ji et al.[63]
	Ethanol extract	RAW 264.7 cells	Cell	Inhibitory activities on nitric oxide production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells, with IC50 values of 37.8 and 38.7 μM, respectively	5, 10, 20, 40, 50 μM/ml	26 h	Yang et al.[36]
	WYSTW	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	WYCTW	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	WYCTC1	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	WYCTC2	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	WYCTC3	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	WYCTC4	SD rats	Serum and liver tissue	Increased serum SOD activity, decreased the expression of CYP2E1 mRNA	2 g/kg	10 d	Tang et al.[60]
	Ethanol extract	SD rats	Serum and liver tissue	Better reduced the content of serum MDA, increased the activity of SOD in serum and liver tissue, and reduced the expression of CYP2E1 mRNA in rats with acute alcoholic liver injury	1 ml/100 g	10 d	Chen et al.[61]
	Ethanol extract	ICR mice	Serum and liver tissue	Reduced the serum transaminase activity and the production of lipid peroxidation intermediate MDA in CCl4 liver injured mice, and significantly enhanced the TAOC and SOD activities	50, 100, 200 mg/kg	7 d	Gu et al.[64]
	Ethanol extract	Human umbilical vein endothelial cells (HUVEcs)	Cell	Improved the ability of endogenous antioxidation	62.5, 125, 250, 500 μM	5 h	Han et al.[44]
	\	SD rats	Serum and liver tissue	Increased the activity of SOD and GSH Px in serum of model rats and reduced the content of MDA, improved the antioxidant capacity against the liver injury induced by CCl4 in rats	5, 15, 45 mg/kg	6 weeks	Chen et al.[65]
Anti-tumor activity	Ethanol extract	Human colon carcinoma cell line HCT-116	Cell	Cytotoxic activities against human colon carcinoma cell line (HCT-116), with IC50 values of 51.4 and 27.1 μM, respectively	2.5, 5, 10, 20, 40, 50, 80, 100 μM/ml	24~25 h	Yang et al.[66]
	Ethanol extract	Human colon carcinoma cell line HCT-116	Cell	The inhibition of cell proliferation in HCT116 occurred via induction of apoptosis and arrested of the G2/M and S cell cycle phases	\	\	Yang et al.[66]
	Volatile oil extract	A549, Eca-109and so on	Cell	Leaf essential oil exhibited significant cytotoxicity against all the cells tested with a potential selectivity for cancerous cells	12.5~400 μg/mL	28 h	Yan et al.[68]
	Volatile oil extract	HepG2	Cell	Inhibited HepG2 cell proliferation and induced HepG2 cell apoptosis	50, 100, 150, 200 μg/mL	8 h	Yan et al.[67]

(to be continued)

Table 3. (continued)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Result	Dose range	Time period of application	References
	Volatile oil extract	A549	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	Bel7402	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	Eca-109	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	HeLa	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	HT29	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	MDA-MB-231	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	PC-3	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	SGC-7901	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	SW1990	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	Volatile oil extract	U-2 OS	Cell	Inhibited cell proliferation	6.25, 12.5, 25, 50, 100, 200, 400 μg/ml	4 h	Yan et al.[70]
	\	SGC-7901	Cell	Induced the apoptosis of SGC-7901 by regulating the expression of p53, Bax, Bcl-2 and other key proteins	0, 160, 200, 240 μmol/L	24 h	Liang et al.[69]
	\	BALB/c nude mice	Tumor tissues	Regulated the BCL-2/caspase-3/PARP pathway and suppressed tumor growth in a human glioblastoma multiforme xenograft mouse model	1, 2.5, 5 mg/kg,	14 d	Hwang et al.[71]
	\	Human A549 lung cancer cells	Cell	Inhibited the invasion and migration of the A549 cancer cells and exhibited a dose-response association.	1, 5, 10, 20 μM	24 h	Chuang et al.[72]
	\	The human OC cell lines SKOV-3 and OVCAR-3	Cell	Decreased phophorylation of serine 727 and tyrosine 705 of STAT3 and expression of survivin, a STAT3-regulated gene	0, 5, 10, 20, 50 μM	48 h	Rajina et al.[73]
Anti-hyperlipidemic effect	Water extract	SD rats	Serum and liver tissue	Had lipid-lowering effect on hyperlipidemia model of rats	1, 3, 9 g/kg	6 weeks	Chen et al.[75]
	Water extract	SD rats	Serum and renal tissue	Significantly promoted the reduction of TG, TC and LDL-C in rats fed with high-fat diet	0.33, 0.66, 2.00 g/kg·bw	45 d	Chen et al.[76]
	Water extract	ICR mice	Serum and liver tissue	Had the effect of lowering blood lipid, improved the steatosis of liver cells, and had a good therapeutic effect on fatty liver	50, 100, 200 mg/kg	4 weeks	Cao et al.[77]
	Water extract	ICR mice	Serum	AqLA-L treatment regulated the disorders of the serum lipid and liver function, reduced hepatic GLU contents both in normal and HCL mice	0.3, 0.6, 1.2 g/kg	10 d	Wang et al.[78]

(to be continued)

Table 3. (continued)

Pharmacological activity	Tested substance	Model	Tested living system/ organ/cell	Result	Dose range	Time period of application	References
	\	SD rats	Serum and liver tissue	Reduced serum lipid level, improved liver cell lipid accumulation, and increased AMPK α Protein phosphorylation level, activating AMPK α to promote lipid metabolism	1.6, 0.8 g/kg	8 weeks	Sun et al.[79]
	Water extract	rats of SPF	Serum and liver tissue	Had significant improving effect on changes in pathology of the liver tissues in rat models with hyperlipidemia. Its mechanism is probably realized by blocking TLR- 4/NF- κB signaling pathway, and reducing protein expression of TNF-α and IL-2	1.6, 0.8 g/kg	8 weeks	Han et al.[80]
Antibacterial activity	Polyphenol water extract	Staphylococcus aureus	Diameter of bacteriostatic ring	Significantly inhibited the growth of Staphylococcus aureus	2.5 mg/mL	24 h	Shen et al.[81]
	\	H.pylori	Bcterial growth	Ihibited he growth of H.pylori	2, 4, 8, 16, 32, 64, 128 μg/mL	\	Tan et al.[74]
Analgesic effect	Water extract	SD rats	Serum	Inhibited the serum MTL level of IBS-D rats and increased serum Sec level	0.94, 1.88, 3.76 g/kg	14 d	Xiao et al.[83]
	Ethanol extract	Zebrafish model	Total motion distance	Had analgesic effect	100 μg/mL	1 h	Peng et al.[38]
Renal protection	Ethanol extract	SD rats	Renal tissue	Mitigated adenine-induced CKD by modulating the metabolic profile and TGF-β/Smad signaling pathway	150 mg/kg	14 d	Cai et al.[85]
	Water extract	SD rats	Renal tissue	Mitigated adenine-induced CKD by modulating the metabolic profile and TGF-β/Smad signaling pathway	150 mg/kg	14 d	Cai et al.[85]
Inhibition is emptying effect	Aqueous extract	SD rats	Plasma	Suppressed gastric emptying rate, increased the content of cAMP, reduced the content of cGMP, increased the ratio of cAMP / cGMP	10 mL/kg	20 min	Nie et al.[86]
	Volatile oil extract	SD rats	Plasma	Suppressed gastric emptying rate, increased the content of cAMP, reduced the content of cGMP, increased the ratio of cAMP / cGMP	10 mL/kg	20 min	Nie et al.[86]
	Ethanol extract	SD rats	Plasma	Reduce the content of cGMP	10 mL/kg	20 min	Nie et al.[86]
	Ether extract	SD rats	Plasma	\	10 mL/kg	20 min	Nie et al.[86]
	Ethanol-extraction ether extract	SD rats	Plasma	Suppressed gastric emptying rate, increased the ratio of cAMP/cGMP	10 mL/kg	20 min	Nie et al.[86]
Intestinal microbial regulation	\	SD rats	Blood and faeces	Improved the species diversity of intestinal flora in rats, increased the stability of bacterial community structure, and regulated intestinal microorganisms in rats with alcoholic liver injury	3, 2, 1 g/kg	20 d	Xu et al.[87]
Antidepressant effect	Water extract	C57/BL6 mice	Blood	Reduced the serum level of corticosterone and expression of caspase-3, while increased expression of BDNF *in vivo* and increased cell viability in corticosterone treated PC12 cells, which was accompanied by decreased caspase-3 expression and the ratio of Bax/Bcl-2 mRNA expression as well as increased BDNF expression *in vitro*.	30, 100, 300 mg/kg	2 weeks	Choi et al.[88]

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and thus showed good application prospect as an anti-rheumatic agent[57]. However, it remains unclear which specific compounds in the LA extract show anti-rheumatic effect. Norisoboldine could inhibit synovial angiogenesis in rats; this could be considered a new mechanism that underlies its anti-rheumatic effect. NOR exerts its anti-angiogenesis effects probably by controlling the Notch1 pathway-related endothelial tip cell phenotype with the Notch1 transcription complex as the potential action target[58]. Although studies have proved the *in vitro* mechanism of NOR adjuvant-induced synovial angiogenesis in rats with arthritis (AA), the mechanism of anti-rheumatic effect of NOR in other animal models deserve further exploration.

Hepatoprotective effect

Based on *in vivo* and *in vitro* models, LA root extracts, namely water extract, ethanol extract, petroleum ether extract, alcohol extract, ethyl acetate extract of alcohol extract, and n-butanol extract, have different effects on acute alcoholic liver injury. Ethanol extracts and alcohol extract petroleum ether extracts could significantly reduce serum ALT (Alanine aminotransferase) content and serum AST (Aspartate aminotransferase) content. All these extracts can suppress NF-κB and TNF-α expression and reduce IL-1 β[59]. However, this study was unable to obtain a readily isolated single component of LA as an experimental drug, which brought LA to the exploration of the liver protective component. LA extract had protective antioxidant activity in acute alcoholic liver injury rats and can protect against the liver injury induced by acute ethanol administration and the mechanisms may be associated with antioxidative stress and inhibition of the expression of CYP2E1 mRNA in rat liver[60]. LA water extract and alcohol extract can reduce MDA (malonaldehyde) content in serum, increase SOD (superoxide dismutase) activity in serum and liver tissue, and reduce CYP2E1 mRNA expression in rats with acute alcoholic liver injury[61]. However, these studies did not perform the chemical analyses of the aqueous and ethanol extracts of LA. Besides, the mechanism by which LA extracts protect the liver is unknown. It was found that LA ethanol extract improved the histopathological state and decreased serum AST, ALT, TC (total cholesterol), TG (triglyceride), and MDA levels. Treatment with the ethanolic extract reduced the levels of inflammatory mediators (TNF-α, IL-1β, and NF-κB) and MDA in liver tissues and reduced CYP2E1 mRNA overexpression[62]. These studies demonstrated that the inhibit CYP2E1 mRNA expression is related to the treatment of acute alcoholic liver injury. However, a limitation of this study is that it did not isolate and identify the active components in each LA extract. Hence, additional studies are needed to isolate and identify these active components in LA extracts, which may contribute to develop novel treatment strategies against ALD (alcoholic liver disease). The mechanism of the anti-alcoholic liver injury of rats by different extracts of LA was related to the inhibition of endotoxin TNF-α pathway, which may be achieved by improving the intestinal mucosal injury induced by alcohol and alleviating the intestinal endotoxemia. Based on the above research, Ji et al. speculated that the furan sesquiterpenoid component may be the active component of the LA for protecting the liver[63]. Another study by Yang et al. reported that LA exhibits inhibitory activity against lipopolysaccharide-induced nitric oxide production in macrophage RAW 264.7 cells of mice, with IC_{50} values of 37.8 and 38.7 μM, respectively[36]. LA extracts afforded protection against ALD, and the responsible mechanism may be associated with the anti-inflammatory and antioxidative effects. Presently, the relationship between anti-inflammatory, antioxidant, and hepatoprotective mechanisms remains to be clarified.

In addition to the extracts from the roots of the main medicinal parts, the research on the extracts from the leaves (non-medicinal parts) was being further expanded. Current research has shown that flavonoids and quercetin-3-O-α-L-rhamnopyranoside are the main components isolated from LA leaf extracts. Flavonoids, as the main extracts of leaves, are largely involved in antioxidative effects in rats with acute alcoholic liver injury. In rats with acute liver injury induced by carbon tetrachloride, flavonoids at the concentrations of 50~200 mg/kg significantly minimized the AST and ALT activities and MDA content and enhanced the activities of SOD (superoxide dismutase) and total antioxidation capacity in serum[64]. Moreover, quercetin-3-O-α-L-rhamnopyranoside (QI) is a kind of flavonoid, which was separated from the leaves of LA and had antioxidant activity. In an oxidative stress model by using H_2O_2, QI exerted a protective effects on cells against H_2O_2-induced damage and enhanced the function of SOD and the compound glutathione (GSH) in the culture medium. Moreover, QI reduced oxidative stress by promoting Nrf2 [the nuclear transfer of nuclear factor erythroid 2-related factor 2] and heme oxygenase-1 through autophagy activation and by inhibiting the competition of Bach1 from Nrf2. These findings supported the application of QI as a health supplement to minimize oxidative stress or for further development of this compound for use as an antioxidant drug[44]. Although some studies have revealed that flavonoids and quercetin-3-O-α-L-rhamnopyranoside from LA leave can protect the liver through antioxidant action, these beneficial effects and the underlying mechanisms are yet to be comprehensively investigated. In addition, linderane was found to have hepatoprotective effects. Linderane shows antioxidative activities in liver injury rat model. It could also dose-dependently decrease the activity of serum AST and ALT in model rats, increase serum SOD and GSH-Px activity, decrease serum MDA content, and significantly reduce the score of pathological changes of liver tissues in model rats. These results indicated that LA improves the antioxidant capacity against the liver injury induced by CCl_4 in rats[65]. However, in these investigations, only flavonoids and other compounds mentioned above have antioxidant activity, and it is unknown how these specific compounds affect cellular metabolic processes on a molecular level. Thus, the information on the antioxidant activity is limited. The above-mentioned studies demonstrated that in a rat model of alcoholic liver injury, oxidative stress can reduce the score of pathological changes in liver tissue, indicating a certain relationship between antioxidant and liver protective effects. However, the mechanism of antioxidant effect on liver protection remains unclear.

Antitumor activity

Cancer is one of the commonly occurring diseases globally and has a high mortality rate. Systematic *in vivo* and *in vitro* studies have shown that the ethanolic extract and volatile oil extract of LA exert antitumor effects. A 24-h treatment of HCT-116 cells (a human colon carcinoma cell line) with the LA ethanolic extract showed cytotoxic activity with IC_{50} values of

51.4 and 27.1 μM[36]. The inhibition of HCT-116 cell proliferation by sesquiterpenes occurred through apoptosis induction and cell cycle arrest in the G2/M and S phases[66]. These results indicated that sesquiterpenes from LA could be applied as potential antiproliferative agents in the treatment of colorectal cancer.

Volatile oil of the root of LA also showed inhibitory effects on cells. The volatile oil of LA roots could effectively inhibit hepatocellular carcinoma HepG2 cell proliferation and showed certain cancer cell selectivity. It simultaneously induced HepG2 cell apoptosis[67]. However, the specific mechanism of its inhibition of cell proliferation and tumor cell apoptosis induction remains unelucidated. A previous study reported that the root oil exhibits a particularly significant inhibitory effect on the proliferation of SGC-7901 cells [human gastric cancer cell line] and Eca-109 cells [human esophageal cancer cell line] (IC_{50} = 24.8 μg/mL); germacrone was obtained as a cytotoxic constituent of the essential oil of the LA root[68]. Although germacrone has been successfully isolated, its antitumor effect and molecular mechanism *in vivo* need to be further explored. In an *in vitro* experiment, the screened root LA active ingredient germacrone was used for preliminarily verifying the core targets and pathways of SGC-7901 cells. The results showed that germacrone remarkably suppressed gastric cancer cell proliferation and induced SGC-7901 cell apoptosis by controlling the expression of p53, Bax, Bcl-2 and other key proteins[69]. In addition to the root volatile oil, the leaf volatile oil had antitumor activity. The researcher conducted cytotoxicity test on human carcinoma cell lines (HepG2, Eca-109, MDA-MB-231, HT29, SGC7901, SW1990, PC-3, and U2-OS) and HL-7702 (a normal cell line) by using the MTT assay. The results revealed that the leaf essential oil exerted remarkable cytotoxicity against all the tested cells, with a particular potential selectivity for cancer cells[70]. However, it remains known whether the presence of a single compound or a synergistic effect between various components and/or the presence of other active compounds is probably responsible for the essential oil's cytotoxicity. However, none of these studies evaluated the effectiveness of LA using animal models.

Experimental studies in cell and animal models as well as several human clinical trials have shown that isolinderalactone, isolated from the root extract of LA, have anti-tumor activity. One study proved that isolinderalactone suppressed the expression of BCL-2 [B-cell lymphoma 2]; it also suppressed the expression of survivin and XIAP [X-linked inhibitor of apoptosis protein], which are apoptosis inhibitors, and enhanced cleaved caspase-3 level. Therefore, isolinderalactone promotes U-87 GBM cell apoptosis *in vitro* and *in vivo* and prevents tumor growth; thus, it is suggested as a potential candidate for designing anti-glioblastoma drugs[71]. However, it remains unclear how isolinderalactone regulates the expression of survivin, BCL-2, and XIAP. Isolinderalactone can also attenuate the invasion and migration of A549 cancer cells; the potential mechanisms involves MMP-2 and β-catenin protein expression inhibition resulting from the upregulation of NM23-H1 expression[72]. However, further investigation into the relevant mechanisms of metastasis is required. Isolinderalactone inhibits xenograft growth in a mouse xenograft model at 2.5 or 5.0 mg/kg doses without toxicity[73]. The dose of isolinderalactone investigated in *in vitro* studies is, however, relatively high, and it would be cumbersome to administer this dose under physiological conditions. Thus, future studies should prioritize the reduction of the effective dose of isolinderalactone by using various strategies, including the alteration of its chemical structure, to enable its use in clinical applications.

Antihyperlipidemic effect

Hyperlipidemia, a chronic disease due to abnormal lipid metabolism, is closely associated with cardiovascular disease occurrence[74]. The water extract of LA leaves has antihyperlipidemic effect. In rat model of hyperlipidemia, water extract of LA can decrease serum TG, TC and LDL-C (low-density lipoprotein cholesterol) levels, increase HDL-C (high-density lipoprotein cholesterol) level, and decrease TG and TC level in rat liver homogenate[75]. Water extracts significantly antagonized and decreased the level of serum LDL-C, TG, and TC in rats fed with a high-fat diet (HFD), and significantly enhanced the levels of HDL-C/LDL-C and HDL-C/TC of rats fed with a HFD[76]. Previous studies have also shown that flavonoids are the main effective components of the water extract of LA leaves that have antihyperlipidemia properties. In mice models with hyperlipidemia fatty liver, 100 and 200 mg/kg of FL-flavonoids decreased serum TC, TG and LDL-C levels, which dose-dependently reduced the lipid droplet formation in HepG2 cells[77]. The above study did not explain the mechanism of LA water extract on hyperlipidemia; however, the following study will put forward some explanations on the mechanism. Through in-depth research, the mechanism of lowering hyperlipidemia effect of LA leaves has been gradually discovered. The researcher demonstrated that the probable mechanisms for cholesterol-lowering effects of AqLA-L might be the upregulation of ABCA1 (ATP-binding cassette transporter A1) and CYP7A1 (cholesterol 7-alpha-hydroxylase) as well as the downregulation of HMGCR (3-hydroxy-3-methylglutaryl CoA reductase)[78]. Another study proved that the extract of LA leaves can reduce serum lipid levels, improve lipid accumulation in hepatocytes, increase AMPKα phosphorylation and activate AMPKα, thus promoting lipid metabolism[79]. Furthermore, the extract of LA can obviously improve the pathological changes of liver tissue in hyperlipidemia model rats, and its mechanism may be achieved by blocking the TLR-4/NF-κB signaling pathway and decreasing IL-2 and TNF-α protein expression[80]. However, it is unclear whether LA plays its role through other mechanisms, which needs further investigation.

Antibacterial activity

LA extracts can exert antibacterial activity. Studies have found that polyphenols and isolinderalactone from LA have antibacterial activity. The inhibition zone diameter, the minimum inhibitory concentration, and the minimum bactericidal concentration of polyphenols from the leaves of LA on *S. aureus* (*Staphylococcus aureus*) were (13.10 ± 0.29) mm, 2.50 and 5.00 mg/mL, respectively[81]. This meant that the polyphenols obtained from leaves of LA have obvious antibacterial effect on *S. aureus*. Another study found that isolinderalactone had significant inhibitory effect on *H. pylori* (*Helicobacter pylori*) and the effect was specific, which can be used to antagonize *H. pylori*[82]. In addition, thus far, the mechanism of the antibacterial effect of LA extracts remains unelucidated, and none of the above-mentioned studies have assessed the antibacterial effectiveness of LA by using animal models. Therefore, additional studies should be conducted to elucidate the active component of these extracts and the detailed mechanism underlying this antibacterial effect.

Analgesic effect

Pain relief is one of the traditional effects of LA. Because of its analgesic effect, LA is often used to treat epigastric pain. In diarrheal irritable bowel syndrome model rats, researcher found that LA water extract significantly decreased serum SP (P substance) and MTL (Motilin) levels and increased sec levels ($p < 0.01$). This implies that LA extract may improve the abdominal pain and diarrhea symptoms of IBS-D rats by reducing the serum SP and MTL levels[83]. However, this evidence is limited, and more evidence obtained from randomized controlled trials is needed to determine additional mechanisms that could induce the analgesic effects. The concentration-based analgesic and toxic effects of LA have been shown in zebrafish experiments, and the overall ranking followed the order of JRAL (Jointed tuberous roots of LA) > TRAL (Taproots of LA) > LAL (Leaves of LA). The finding could provide relevant data for applying traditional nonmedicinal parts of LA in food and pharmaceutical industries[38]. The above limited articles prove that the mechanism of LA analgesia is still unclear. The research on the application of traditional analgesic effects to chest and abdominal pain, menstrual pain, and other aspects should be further explored.

Renal protective activity

LA has the function of protecting the kidney and can be used for treating enuresis and other symptoms caused by kidney yang deficiency. Kidney yang is a warm and promoting part of the function of the kidney, which can promote human health[84]. The author found that the water extract and ethanol extract of LA can alleviate adenine-induced CKD by altering the metabolic profile and the TGF-β/Smad signaling pathway[85]. However, some results did not display a dose-effective relationship, while some studies lacked positive controls.

Other activities

LA can also protect the stomach, regulate the balance of intestinal flora, and resist depression in animal experiments. Among them, protecting the stomach and intestines is the main clinical prescription, but there are few experiments on these effects in modern pharmacological research. In rats by using cold stimulation method for three days, the extract of LA could significantly inhibit the gastric emptying rate ($p < 0.05$ or $p < 0.01$), increase cAMP content ($p < 0.01$), reduce the content of cGMP ($p < 0.01$), and increase cAMP/cGMP ($p < 0.01$). These effects suggested that LA could significantly inhibit gastric empty and significantly increased cAMP/cGMP[86]. However, the mechanism through which gastric emptying is inhibited remains unclear. In rats with acute alcoholic liver injury, the number of OTUs in the group was significantly more than that in the normal group, suggesting that the medicine had a certain regulatory effect on the normal intestinal microecology[87]. We can intensively investigate the relationship between the regulatory role of intestinal microorganisms and alcoholic liver injury. In addition, the combination of LA and other drugs increased the viability of corticosterone-treated PC12 cells, together with decreased caspase-3 expression and Bax/Bcl-2 mRNA expression ratio as well as increased BDNF expression *in vitro*. These indicate that SOCG (So-ochimtang-gamibang) could serve as a potential antidepressant agent to control depressive behaviors and corticosterone-induced neuronal damage due to chronic stress[88]. Additional studies are needed to gain insights into the mechanisms driving the possible interactions and synergistic effects of LA in combination with other ingredients from polyherbal preparations.

In summary, many traditional uses of LA are not validated by modern pharmacological studies. For example, LA has been shown traditionally to beneficial for treating colitis, arthritis, pelvic infection, and hepatitis and to induce the analgesic effect, these beneficial effects and the mechanisms underlying them remain to be assessed. Therefore, further investigations are required regarding these traditional uses of LA.

Pharmacokinetic studies

LA has the effects of promoting 'Qi' and relieving pain. Studies have found that the alkaloids had obvious analgesic and anti-inflammatory effects, can significantly reduce the instances of body twisting in mice, and significantly reduce the granuloma, ear swelling rate and foot swelling degree in rats[89]. Norsoboldine is an isoquinoline alkaloid reported from the LA, with significant biological activity, and is considered as the characteristic ingredient of anti-inflammatory and analgesic in the LA[90]. By HPLC, the order of absorption of total alkaloids in each intestinal segment is colon > ileum > jejunum > duodenum, and the absorption of total alkaloids in each intestinal segment is better. The apparent absorption coefficient (Papp) and absorption rate constant (ka) of different mass concentrations did not differ significantly ($p > 0.05$). However, the ka and Papp values of perfusates with different pH values were significantly different ($p < 0.05$)[91]. Using SD rats as model animals, the plasma concentrations of norisoportine and its glucuronide were determined by UPLC/MS, and the pharmacokinetic parameters were estimated. The absolute bioavailability of norisoboldine and its glucuronide were 2.77% and 88.6%, respectively, which represents the rapid biotransformation and low bioavailability of norisoboldine *in vivo*[92]. An UPLC/MS method was used to determine the plasma concentrations of norisoboldine and norisoboldine-9-O-α-glucuronide in rat plasma. After oral administration of three doses of total alkaloid, the main pharmacokinetic parameters of norisoboldine and norisoboldine-9-O-α-glucuronide were as follow: C_{max} was (0.10 ± 0.06), (0.10 ± 0.05), (0.15 ± 0.11) μg·mL^{-1} and (9.23 ± 3.33), (11.88 ± 3.87), (12.42 ± 2.52) μg·mL^{-1}, respectively; T_{max} was (10.83 ± 9.70), (7.50 ± 2.74), (9.17 ± 5.85) min and (40.83 ± 10.21), (50.83 ± 35.41), (52.50 ± 8.22)min, respectively ; $AUC_{0-\infty}$ was (5.38 ± 1.24), (8.06 ± 5.63), (8.22 ± 2.77) mg·min·mL^{-1} and (3,071.99 ± 1,036.37), (6,469.75 ± 3,068.94), (6,469.75 ± 3068.94), (6,947.36 ± 1,036.37) mg·min·mL^{-1}, respectively. The data showed that norisoboldine can be quickly absorbed and biotransformed into norisoboldine-9-O-α-glucuronide, a major metabolite of the parent drug *in vivo*[93]. Impaired activity and expression of P-gp in AIA rats are critically involved in the absorption enhancement of NOR[94]. Although these three studies showed differences in drug dose forms, doses, animal species, and gender and all these factors may cause various changes in the pharmacokinetic parameters of norsoboldine, the results of these studies showed that norisoboldine was easily absorbed and rapidly eliminated following oral administration. Moreover, it was found that the bioavailability of norsoboldine *in vivo* is low. Additional studies are needed to determine the mechanisms of actions as well as pharmacokinetics of the other bioactive compounds present in LA, such as isolinderalactone, linderane, and lindenenol.

Quality control

To perform the quality control of LA-isolated drugs, the Chinese Pharmacopoeia suggests morphological analysis, microscopy studies, and TLC [thin layer chromatography] - based identification together with determination using the hot dipping method. According to the guidelines of Chinese Pharmacopoeia, moisture should not exceed 11.0% ('Chinese Pharmacopoeia moisture determination drying method'), while total ash should not exceed 4.0% ('Chinese Pharmacopoeia ash determination method')[95] .

At present, there are many methods to measure the effective components of LA, the most used of which is HPLC. The author determined the content of norisoboldine by HPLC[96]. Moreover, other researchers determined the content of the effective chemical components of the LA by HPLC[97]. HPLC is the main method used to determine the effective chemical components of LA. However, HPLC has some disadvantages, such as water bath temperature, condensed water temperature, and the impact of pretreatment such as extraction and filtration on the experimental results, which can be time-consuming and labor-intensive. In addition, with the development of modern technology, there are also some other methods to determine the effective components of LA. By ultraviolet spectrophotometry, Zhang et al. determined the content of total alkaloids in LA[98]. In addition, someone established a quantitative model of near infrared spectrum to determine the linderane and norisoboldine in LA[99]. Although researchers continue to develop new measurement methods, HPLC is still the main method used to measure the content of active ingredients in LA.

Quantitative marker could be inadequate to determine the quality of the LA extract by using only one crude. In LA extracts, the active ingredient content—which includes alkaloids, sesquiterpenoids, and volatile oils—differs in quality with the methods of processing and the extraction procedures used as well as the habitat and growth conditions of source plants. Kaibao Herbology (《开宝本草 》) (Song dynasty, A.D. 973-974) says: 'The remaining taproot can't be used'. To date, the Chinese Pharmacopoeia stipulates that the old, non-spindle taproot cannot be used for medicine. However, in recent years, some researchers have shown that whether the main component or the secondary component, the taproot of LA is not inferior to the root of LA, and the content of some components is even higher than the root of LA[6]. By the hot dip method and chromatographic column, it was found that the water and alcohol extracts in the spindle root of LA were the highest, and the old root of LA was the lowest. Moreover, the contents of linderalactone, linderane and isolinderalactone in the spindle root of LA were 1.10, 1.51 and 3.10 mg/g, respectively, and 0.90, 1.34 and 3.36 mg/g in the straight root of aconite; 0.55, 0.78 and 1.40 mg/g in the old root of LA[100]. In one study, the content determination results showed that the content of norisoboldine, aconitine ether lactone and bordine in the root tuber sample was higher than that in the root tuber sample, and the content of isoaconitine lactone was lower than that in the root tuber sample[101]. Therefore, whether taproot should be included in the category of medicine is a direction for further research of LA.

According to the TCM guidelines, Dao-di herbs are the best-quality medicinal herbs grown in a specific area with a long traditional use history and excellent medicinal efficacy[102]. According to 'Illustrated Canon of Herbology' (《本草图经》) (A.D. 1061) written by Su Song, the best-quality medicinal LA is 'Tiantai Wuyao' (Dao-di herbs) and occurs in Tiantai in Zhejiang Province. Tests using a RP-HPLC method to determine Linderane in LA from 6 different habitats revealed that the content of linderane is higher in Zhejiangtiantai, Jiangxi, among which the content in Zhejiangtiantai is the highest (3.72 $mg{\cdot}g^{-1}$). In addition, it was found that the sesquiterpenoid content in LA significantly differed between samples collected from different habitats[103]. Tests using a RP-HPLC method to determine Linderane in LA from the region of Gannan proved that content of linderane in the root of collected sample was 0.529% and the linear range of linderane was between 0.08–2.00 μg, the regression equation was $y = 20.851\ x + 9.421$ ($R^2 = 0.9996$)[104]. In Hunan Province, it was found that Changsha LA roots had the highest norisoboldine content of 10.85 $mg{\cdot}g^{-1}$, Liuyang LA roots had the highest Linderalactone content of 3.642 $mg{\cdot}g^{-1}$, Changsha LA roots had the highest isolinderactone content of 2.826 $mg{\cdot}g^{-1}$ by comparing 3 kinds of chemical components in LA roots, stems, leaves of different areas in Hunanfferent areas in Hunan[105]. Determining a total of 17 batches LA roots produced in different areas and time, it indicated that norisoboldine of LA roots produced in Hunan is significantly higher than that of LA roots produced in Zhejiang and Jiangxi[106]. Through the above research, we can know that there is different of effective chemical components contents in LA from different origins, and those in Tiantai Wuyao as a genuine medicinal material are slightly higher than others. However, the mechanism responsible for the high quality of Dao-di herbs remains unclear.

In addition, the quality of LA is closely related to harvest time, growth environment, growth year and other factors. Through gradient elution using Agilent HC-C_{18} column and acetonitrile (A) and 0.4% phosphoric acid solution (B) as mobile phases, author found that rutin, hyperoside, isoquercitrin, and quercitrin have good linear relationships in the range of 0.0967–0.7733, 0.0967–1.933, 0.1083–2.1667 and 0.0933–37.3333 μg, respectively[107]. It meant that the contents of rutin, hyperoside, isoquercitrin and quercetin in the leaves of LA from different places in Hunan are different, which may be related to the growth environment and harvest time. In addition, the growth year and harvest time also affect the content of active ingredients to a certain extent. Re searcher determined the content of bordine in the root tubers of Tiantai Wuyao in different years and places. The results: the content of bordine is the highest in Sanzhou Township, which is 6 years old, up to 0.17%; the order of the content of bordine in the 5-year-old root tuber of Tiantai Wuyao is Sanzhou Township (0.16%) > Tianxin Township (0.14%) > Yongxi Township (0.10%) > Tongbai Township (0.06%), indicating that the content of bordine in root tubers is related to the development age and growth of plants and soil conditions[108]. There is no mature research report on the factors affecting the quality of LA.

In recent years, the extraction technology of flavonoids has been continuously developing. According to the study of chemical components, total flavonoids are the main components isolated from the leaves of LA. The total flavones of the leaves of LA have antioxidant effects, which can effectively eliminate oxygen free radicals in the body and suppress lipid peroxidation[109]. By microwave-assisted extraction (MAE) technique, researchers found that the flavonoid content in LA leaves is the highest, followed by that in branches, fibrous

roots, stems, and taproot root tubers[110]. By reflux extraction conditions, the flavonoid content in LA leaves is 2.1%, and the leaves may mainly contain flavonoids[111]. By polyamide adsorption-aluminum ion color method, the total flavonoids showed a good linear relationship in 0.002–0.10 mg·ml^{-1} range (r = 0.9995)[112]. With rutin as the standard sample, the total flavonoids in the sample are in the range of 0.002-0.020 mg·mL^{-1}, and the linear relationship is good. The regression equation is A = 30.076 C + 0.0065, R^2 = 0.9996, the average recovery rate of adding sample = 101.0%, RSD = 1.27% (n = 6)[113]. These results could serve as a reference for the quality evaluation of AE leaves. Furthermore, the extraction process of total flavonoids is also being further optimized. Current research shows that a higher extraction rate of total flavonoids can be obtained by selecting the method of alcohol extraction before water extraction[114]. The field of total flavonoids process improvement is worth further exploration.

Safety

Based on the available animal trials, LA appears to induce little or no toxicity. Body weight measurement and microscopic examination of the organs (spleen, kidney, and liver) showed no toxic effects of LA powder and its polysaccharides at the maximum dose of 10.0 g·kg^{-1} on mice[115]. Through various experiments, the results of acute toxicity test of LA in rats and mice were greater than 10.0 g·kg^{-1}. The results of mouse sperm abnormality test, mouse micronucleus test, and Ames test were also negative[116]. It was reported that the doses of male and female were greater than 20 g·kg^{-1}, through maximal tolerance dose (MTD) test of oral acute toxicity in rat[117]. Furthermore, one study used the MTT method to determine the cytotoxicity of extracts of LA, such as CE-LS, PE-LS, BE-LS, EE-LS, and WE-LS on four types of human cancer cells and one type of human normal cells and found that the extract of LA has strong cytotoxicity to the tested human cancer cell lines[118]. By thoroughly studying the irreversible inhibitory effect of LDR on cytochrome P4502C9 (CYP2C9), the researchers found that CYP2C9 inactivation by LDR was NADPH-dependent and irreversible[119]. There are no reports of adverse reactions caused by using LA. However, additional investigations with a specific focus on the toxicity of AE are required.

Shennong Herbal Classic (《神农本草经疏》, A.D. 1625) charted: "The LA is pungent, warm, and disperses 'Qi'". Those who suffer from deficiency of 'Qi' should avoid it. Compendium of Materia Medica (《本草征要》, A.D. 1673): "Do not use for those with deficiency of 'Qi' and blood". Medication and Dispensing (《要药分剂》, A.D. 1773): 'All diseases of yin deficiency and internal heat should be avoided'. Yin deficiency can be the deficiency of essence, blood and body fluid[120]. In short, ancient classics reveal the taboo of using LA, which is not suitable for people with deficiency of 'Qi' and blood and internal heat. Regarding the contraindication of the use of LA, there is no clear research to prove that LA will have toxicity after interacting with other drugs. Moreover, the usage and dosage of LA are different in different prescriptions. For the conventional dosage of LA, a dose of 6 to 10 g is stipulated (Chinese Pharmacopoeia).

Conclusions and future perspectives

The tuberous roots of LA, a plant belonging to the *Lindera* genus in the *Lauraceae* family, are widely used in TCM formulations. This article summarizes the existing studies on LA in the fields of botany, traditional applications, and phytochemical and pharmacological characteristics and puts forward some views and opinions on it. In classical TCM and the Chinese Pharmacopoeia, LA is usually used in the form of a drug to promote 'Qi' and warm the kidney. Pharmacological research showed that LA has several biological activities, including anti-inflammatory activity, hepatoprotective effect, anti-tumor activity, anti-hyperlipidemia, analgesic effect, liver, and kidney protection, bacteriostasis, anti-rheumatism, diarrhea improvement, blood stasis improvement and so on. However, these pharmacological investigations cannot fully support LA's traditional use. Thus far, over 166 compounds have been derived from LA, among which alkaloids and sesquiterpenoids are the main bioactive constituents.

Currently, our understanding of pharmacological and phytochemical properties of LA is not comprehensive. First, in terms of studying the chemical composition and properties of LA, it mainly contains sesquiterpenoids, alkaloids and flavonoids; however, there is less information on the analysis and role of other compounds, namely disesquiterpenoid-geranylbenzofuranone conjugates, benzenoids, and benzenoid glycosides. Further research is needed for these compounds that have recently been isolated from LA, with an emphasis on bioactivity-led, structurally modified, absorption, distribution, and metabolism in the body. Meanwhile, we have extracted some suggestions for the application of the monomer compounds extracted from LA. Because most studies have been conducted at the cellular level, additional *in vivo* studies are needed in different animal models as well as in clinical situations to verify the anti-tumor effect of LA. Second, the main medicinal part of LA is tuberous root, while some modern research suggested that taproot may also be used as a medicinal part. There are disputes about whether taproot can be used as a valuable medicinal material. Therefore, it would be an interesting initiative to further extend the research to the taproot to ensure complete utilization of its medicinal values. Thirdly, in terms of the toxicity and use of LA, we should explore the dosage of LA and its compatibility with traditional Chinese medicine. There are currently no studies demonstrating the toxicity of LA in animal models, its long-term toxicity requires further assessment. The potential biotoxicity and adverse effects of LA extracts and their active components require further evaluation through *in vitro*, *in vivo*, and clinical studies. The doses of LA studied in previous investigations were different, wherein the maximum oral dose for mice is 20 g·kg^{-1}. It is impossible to determine whether LA is toxic from an accurate cutoff dose; hence, in toxicological experiments, the test dose should be pharmacologically related and tested at multiple doses. Moreover, LA is often used in combination with various TCMs such as the immature fruit of *Citrus* × *aurantium* and *Aucklandia costus* for treating diseases. Further investigations are required to determine the underlying mechanisms of the possible interactions and synergistic effects of LA with other medicinal plants. It is possible to expand the development space of LA through the combined use of LA and other traditional Chinese medicines. Finally, the concept that LA supplements 'Qi' requires validation through modern pharmacological investigations for the specific underlying mechanism. In addition, the traditional role of LA basically revolves around the function of regulating 'Qi'. Obviously, the current pharmacological research has not been carried out in the traditional medicine of LA.

To summarize, future studies should assess the ADME pathways (absorption, distribution, metabolism, and excretion) for new compounds to elucidate the mechanisms underlying LA's biological activities. Advanced *in vivo* pharmacological studies are required to determine the validity of traditional applications of LA. Additional studies should investigate the clinical safety and efficacy of the plant extracts and LA-derived bioactive compounds to treat enuresis and abdominal pain and for other traditional applications of LA.

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Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. The Editorial Coomittee of Flora of China. 2015. *Flora of China*. Beijing: Science Press
2. Chen SQ, Zuo T. 2005. Medicinal plant resources lindera genus in henan: Studies of its pharmacology, chemical components and application. *Journal of Henan University of Chinese Medicine* 03:25−27(in Chinese)
3. Chen F, Cao JL, Yang YC, Wang EH, Chang H, et al. 2022. Herbal Textual Research on Linderae Radix in Famous Classical Formulas. *Chinese Journal of Experimental Traditional Medical Formulae* 29(17):75−87(in Chinese)
4. Wen Z, Chen H. 2009. Textual research on the materia medica of *Lindera aggregata*. *Jiangxi Journal of Traditional Chinese Medicine* 40(3):57−59(in Chinese)
5. Shao J, Yan JQ, Ma CL. 2018. Key techniques of high yield cultivation and biological control of *Lindera aggregata*. *Shaanxi Journal of Agricultural Sciences* 64(1):100−1(in Chinese)
6. Yuan DC, Yuan L, Yuan PP, Lu YM, Nan Y. 2021. Textual research on the materia medica of *Lindera aggregata*. *Shanxi Journal of Traditional Chinese Medicine* 37(7):55−58(in Chinese)
7. Liu XL, Zhao HH, Qin ZP, Sun NN. 2020. An analysis of Qi and modern research. *Clinical Journal of Chinese Medicine* 12(14):23−25(in Chinese)
8. Wang WQ. 2010. *Research on mechanism of syndrome of Qi-stagnancy with blood stasis based on the movement of qi*. Thesis. Fujian University of Traditional Chinese Medicine, Fuzhou, China. (in Chinese)
9. Ouyang LQ, Jinag SC, Chen Z, Wang SM, He Y, et al. 2022. Effect of volatile oil from Linderae Radix on hemorheology and NO-sGC-cGMP signaling pathway in rats with qi stagnation and blood stasis syndrome. *Chinese Traditional and Herbal Drugs* 53(15):4730−37(in Chinese)
10. Huan N, Yu JS, Liu YP. 2017. Review of the science of Chinese pharmacology of Wuyao and clinical application. *Chinese Medicine Modern Distance Education of China* 15(9):148−50(in Chinese)
11. Li ZG. 2012. Clinical application of Tiantai Wuyao San. *Clinical Journal of Chinese Medicine* 4(3):96−97(in Chinese)
12. Zhou YQ, Zhu JJ. 2022. Oral administration of Simo decoction affects symptom score and living quality of functional dyspepsia patients. *Inner Mongolia Journal of Traditional Chinese Medicine* 41(8):4−5(in Chinese)
13. Jiao SD. 2013. Liver Warm Decoction, an experienced prescription of Jiao Shude. *Chinese Medicine Modern Distance Education of China* 11(12):20(in Chinese)
14. Du HQ, Ji CY. 1998. Appropriate compatibility of *Lindera aggregata* makes a big progress in clinical efficacy. *Zhejiang Journal of Traditional Chinese Medicine* 00(6):279(in Chinese)
15. Yin DH, Song L, Xie YQ, Zhu Y, Wu Z. 2021. Alpiniae Oxyphyllae Fructus and Linderae Radix combination protect diabetic nephropathy mice podocyte cell via regulating cell autophagy. *Lishizhen Medicine and Materia Medica Research* 32(9):2088−90(in Chinese)
16. Liu JY, Fang HZ. 2012. Comparative analysis of volatile constituents in herbal pair Aucklandiae Radix-Linderae Radix and its single herb by GC-MS. *Journal of Qiqihar University of Medicine* 33(9):1123−25(in Chinese)
17. Tian N, Wu HB, Liu MH, Du WY, Zhang TY, et al. 2018. Oil in herbal pair Tangerine Peel - Linder Aggregata and its single herb by GC - MS. *Heilongjiang Medicine and Pharmacy* 41(1):41−42+27(in Chinese)
18. Wang HB, Feng GB, Li SX, Fang HZ. 2018. GC/MS analysis of herb pair chuanxiong rhizoma - linderae radix on the components of volatile oil. *Heilongjiang Medicine and Pharmacy* 41(1):82−84(in Chinese)
19. Zhang GY, Ma LQ, Miao S, Zhang CH, Jin PP, et al. 2021. Analysis of chemical constituents of the volatile oil from compatibility *Perilla frutescens* (L.) Britt with *Lindera aggregata* (Sims) Kosterm by GCMS. *Journal of Guangzhou City Polytechnic* 15(4):83−87(in Chinese)
20. Qin B, Li SX. 2022. Comparative analysis of the volatile oil components of Rhizoma Zingiberensis, Radix Aconiti and its single herbs. *Heilongjiang Medicine and Pharmacy* 45(5):11−12(in Chinese)
21. Wang JW, Ruan B. 2006. Phytochemistry and pharmacology of *Lindera aggregate*: A review. *Zhejiang Journal of Traditional Chinese Medicine* 11:675−77(in Chinese)
22. Zhu FW, Wang BH, Shen XX, Wang ZA, Sun YM, et al. 2016. Polymorphism and genetic diversity analysis of amplified fragments in various *Lindera aggregata* germplasms. *Zhejiang Journal of Traditional Chinese Medicine* 51(5):387−88(in Chinese)
23. Liu C. 2018. Processing technology of *Lindera aggregata*: A review. *Diet Health Care* 5(23):66−67(in Chinese)
24. Ouyang R, Liao JP, Pi XH, Deng GM. 2010. Optimization of technological process of vinegar-prepared Radix Linderae by orthogonal design. *China Pharmacist* 13(5):663−64(in Chinese)
25. Kuo PC, Wu YH, Hung HY, Lam SH, Ma GH, et al. 2020. Anti-inflammatory principles from Lindera aggregata. *Bioorganic & Medicinal Chemistry Letters* 30(13):4
26. Qiang Y, Yang ZD, Yang JL, Gao K. 2011. Sesquiterpenoids from the Root Tubers of Lindera aggregata. *Planta Medica* 77(14):1610−16
27. Cheng XL, Ma SC, Wei F, Wang GL, Xiao XY, et al. 2007. A new sesquiterpene isolated from *Lindera aggregata* (Sims) Kosterm. *Chemical & Pharmaceutical Bulletin* 55(9):1390−92
28. Gan LS, Zheng YL, Mo JX, Liu X, Li XH, et al. 2009. Sesquiterpene Lactones from the root tubers of *Lindera aggregata*. *Journal of Natural Products* 72(8):1497−501
29. Liu X, Fu J, Shen RS, Wu XJ, Yang J, et al. 2021. Linderanoids A-O, dimeric sesquiterpenoids from the roots of *Lindera aggregata* (Sims) Kosterm. *Phytochemistry* 191:112924
30. Liu X, Fu J, Yang J, Huang AC, Li RF, et al. 2021. Linderaggrenolides A−N, oxygen-conjugated sesquiterpenoid dimers from the roots of *Lindera aggregata*. *ACS Omega* 68:5898−909

31. Liu X, Yang J, Fu J, Yao XJ, Wang JR, et al. 2019. Aggreganoids A–F, carbon-bridged sesquiterpenoid dimers and trimers from *Lindera aggregata*. *Organic Letters* 21(14):5753–56
32. Liu Q, Ahn JH, Kim SB, Lee C, Hwang BY, et al. 2013. Sesquiterpene lactones from the roots of *Lindera strychnifolia*. *Phytochemistry* 87:112–18
33. Zhang ZF, Sun QS, Wang ZT, Chou GX. 2001. Studies on constituents of the leaves of *Lindera aggregata* (Sims) Kosterm. *China Journal of Chinese Materia Medica* 26(11):43–45(in Chinese)
34. Sun CR, Yu SL, Li SM, Yuan LX, Wang FR, et al. 2022. Chemical constituents from the leaves of *Lindera aggregata*. *Chinese Traditional Patent Medicine* 44(2):464–69(in Chinese)
35. Wen SS, Wang Y, Xu JP, Liu Q, Zhang L, et al. 2022. Two new sesquiterpenoid lactone derivatives from *Lindera aggregata*. *Natural Product Research* 36(21):5407–15
36. Yang JJ, Chen Y, Guo ML, Chou GX. 2020. Chemical constituents from the roots of *Lindera aggregata* and their biological activities. *Journal of Natural Medicines* 74(2):441–47
37. Gan LS, Yao W, Mo JX, Zhou CX. 2009. Alkaloids from Lindera aggregata. *Natural Product Communications* 4(1):43–46
38. Peng X, Luo YY, Wang J, Ji T, Yuan LX, et al. 2020. Integrated analysis of the transcriptome, metabolome and analgesic effect provide insight into potential applications of different parts of *Lindera aggregata*. *Food Research International* 138:109799
39. Zhang ZF, Sun QS, Zhao YY, Wang ZT. 2001. Studies on Flavonoids from Leaves of *Lindera aggregata* (Sims) Kosterm. *Chinese Journal of Medicinal Chemistry* 11(5):274–76(in Chinese)
40. Zhang ZF, Sun QS, Chou GX, Wang ZT. 2003. Studies on the flavonoids from leaves of *Lindera aggregata* (Sims) Kosterm. (2). *Journal of Shenyang Pharmaceutical University* 20(5):342–44(in Chinese)
41. Xiao M, Cao N, Fan JJ, Shen Y, Xu Q. 2011. Studies on Flavonoids from the Leaves of *Lindera aggregata*. *Journal of Chinese Medicinal Materials* 34(1):62–64(in Chinese)
42. Luo L, Zhang L, Tian JK, Yang SL. 2009. Chemical constituents from leaves of *Lindera aggregate*. *Chinese Traditional and Herbal Drugs* 40(6):856–58(in Chinese)
43. Chen FL, Yu CQ. 2011. Pharmacology of *Lindera aggregata*: A review. *Strait Pharmaceutical Journal* 23(12):44–46(in Chinese)
44. Han HT, Xu B, Amin A, Li HL, Yu XY, et al. 2019. Quercetin-3-O-α-L-rhamnopyranoside derived from the leaves of *Lindera aggregata* (Sims) Kosterm. evokes the autophagy-induced nuclear factor erythroid 2-related factor 2 antioxidant pathway in human umbilical vein endothelial cells. *International Journal of Molecular Medicine* 43(1):461–74
45. Chen L, Liu B, Deng JJ, Zhang JS, Li W, et al. 2018. *Lindera* cyclopentenedione intermediates from the roots of Lindera aggregata. *RSC Advances* 8(32):17898–904
46. Liu X, Yang J, Yao XJ, Yang X, Fu J, et al. 2019. Linderalides A–D, disesquiterpenoid-geranylbenzofuranone conjugates from *Lindera aggregata*. *Journal of Organic Chemistry* 84(12):8242–47
47. Ma GH, Lin CW, Hung HY, Wang SY, Shieh PC, et al. 2015. New Benzenoids from the Roots of Lindera aggregata. *Natural Product Communications* 10(12):2131–33
48. Zhu YZ, Liu MC, Hu DY, Jin LH, Xue W, et al. 2012. Chemical Constituents of *Lindera aggregata*. *Chinese Journal of Experimental Traditional Medical Formulae* 18(16):123–26(in Chinese)
49. Lai HM, Yang ZB, Lou ZH, Li F, Xie F, et al. 2021. Root extract of *Lindera aggregata* (Sims) Kosterm. modulates the Th17/Treg balance to attenuate DSS-induced colitis in mice by IL-6/STAT3 signaling pathway. *Frontiers in Pharmacology* 12:615506
50. Lai HM, Huang MC, Lou ZH, Xie F, Pan W, et al. 2021. The effect of Tiantai Radix Linderae on a rat model of ulcerative colitis induced by TNBS. *Chinese Journal of Comparative Medicine* 31(2):37–44(in Chinese)
51. Lv Q, Wang K, Qiao SM, Yang L, Xin Y, et al. 2018. Norisoboldine, a natural AhR agonist, promotes Treg differentiation and attenuates colitis via targeting glycolysis and subsequent NAD^+/SIRT1/SUV39H1/H3K9me3 signaling pathway. *Cell Death & Disease* 9:258
52. Luo Y, Liu M, Xia Y, Dai Y, Chou G, et al. 2010. Therapeutic effect of norisoboldine, an alkaloid isolated from Radix Linderae, on collagen-induced arthritis in mice. *Phytomedicine* 17(10):726–31
53. Wei ZF, Wang FY, Song J, Lu Q, Zhao P, et al. 2012. Norisoboldine inhibits the production of interleukin-6 in fibroblast-like synoviocytes from adjuvant arthritis rats through PKC/MAPK/NF-κB-p65/CREB pathways. *Journal of Cellular Biochemistry* 113(8):2785–95
54. Wei ZF, Tong B, Xia YF, Lu Q, Chou GX, et al. 2013. Norisoboldine suppresses osteoclast differentiation through preventing the accumulation of TRAF6-TAK1 complexes and activation of MAPKs/NF-κB/c-Fos/NFATc1 Pathways. *PLoS One* 83:e59171
55. Wei ZF, Lv Q, Xia Y, Yue MF, Shi C, et al. 2015. Norisoboldine, an anti-arthritis alkaloid isolated from *Radix Linderae*, attenuates osteoclast differentiation and inflammatory bone erosion in an aryl hydrocarbon receptor-dependent manner. *International Journal of Biological Sciences* 11(9):1113–26
56. Tong B, Dou YN, Wang T, Yu JT, Wu X, et al. 2015. Norisoboldine ameliorates collagen-induced arthritis through regulating the balance between Th17 and regulatory T cells in gut-associated lymphoid tissues. *Toxicology and Applied Pharmacology* 282(1):90–99
57. Chou GX, Li QL, Wang ZT, Xu LS, Xu GJ, et al. 1999. Compositions and ant-irheumatism effect of LEF fraction from the root of *Lindera aggregata* (Sims) Kosterm. *Journal of Plant Resources and Environment* 8(4):2–7(in Chinese)
58. Lu Q, Lu S, Gao XH, Luo YB, Tong B, et al. 2012. Norisoboldine, an alkaloid compound isolated from Radix Linderae, inhibits synovial angiogenesis in adjuvant-induced arthritis rats by moderating Notch1 pathway-related endothelial tip cell phenotype. *Experimental Biology and Medicine* 237(8):919–32
59. Wang JW, Hu PY, Chen XY. 2014. Effect of *Lindera Aggregata* (Sims) kosterm on inflammation-related factors in rats with acute alcoholic liver injury. *Chinese Journal of Disaster Medicine* 2(7):373–76(in Chinese)
60. Tang XG, Wang JW, Hu PY, Tan MM, Hong RT. 2014. Anti-oxidant activity of different extracts on lindera aggregata (Sims) Kosterm in acute alcoholic liver injury rats. *Chinese Archives of Traditional Chinese Medicine* 32(12):2934–36(in Chinese)
61. Chen ZL, Wang JW, Tan MM, Hu PY. 2015. Comparative study on antioxidant effects of water extract and alcohol extract of Radix Linderae on acute alcoholic liver injury model rats. *Zhejiang Journal of Traditional Chinese Medicine* 50(6):414–15(in Chinese)
62. Wang JW, Chen XY, Hu PY, Tan MM, Tang XG, et al. 2016. Effects of Linderae radix extracts on a rat model of alcoholic liver injury. *Experimental and Therapeutic Medicine* 11(6):2185–92
63. Ji MP, Lou ZH, Tan MM, Ding HZ, Hu ZX, et al. 2018. Extracts from *Lindera aggregata* (Sims) Kosterm for intervention of alcoholic liver disease in rats. *Zhejiang Medicine* 40(6):551–553+572(in Chinese)
64. Gu LY, Luo Q, Xiao M, Wu XX, He GQ, et al. 2008. Anti-oxidative and hepatoprotective activities of the total flavonoids from the leaf of *Lindera aggregata* (Sims) Kosterm. Against mice liver injury induced by carbon tetrachloride. *Traditional Chinese Drug Research and Clinical Pharmacology* 19(6):447–50(in Chinese)
65. Chen FL, Huang RP, Chen QH, Xu XE. 2016. Hepatoprotective effects of the linderane on liver injury model of rats. *Chinese Journal of Modern Applied Pharmacy* 33(12):1512–15(in Chinese)
66. Yang HJ, Kwon EB, Li W. 2022. Linderolide U, a new sesquiterpene from *Lindera aggregata* root. *Natural Product Research* 36(7):1914–18
67. Yan RW, Hua JH. 2014. Effect of *Lindera Strychnifolia* root essential oil on proliferation and apoptosis of HepG2 cells. *Journal of Nanchang University (Natural Science)* 38(5):483–87(in Chinese)

68. Yan RW, Hua JH. 2014. *In vitro* antitumor activity of *Lindera strychnifolia* root essential oil and its active constituent. *Journal of Wuhan University (Natural Science Edition)* 60(4):345−48(in Chinese)
69. Liang X, Zhang JH, Bai HT, Li YL, Sun SH, et al. 2022. Mechanism of Linderae Radix against gastric cancer based on network pharmacology and in vitro experimental validation. *China Journal of Chinese Materia Medica* 47(18):5008−21(in Chinese)
70. Yan RW, Yang Y, Zou GL. 2014. Cytotoxic and apoptotic effects of *Lindera strychnifolia* leaf essential oil. *Journal of Essential Oil Research* 26(4):308−14
71. Hwang JY, Park JH, Kim MJ, Kim WJ, Ha KT, et al. 2019. Isolinderalactone regulates the BCL-2/caspase-3/PARP pathway and suppresses tumor growth in a human glioblastoma multiforme xenograft mouse model. *Cancer Letters* 443:25−33
72. Chuang CH, Wang LY, Wong YM, Lin ES. 2018. Anti-metastatic effects of isolinderalactone via the inhibition of MMP-2 and up regulation of NM23-H1 expression in human lung cancer A549 cells. *Oncology Letters* 15(4):4690−96
73. Rajina S, Kim WJ, Shim JH, Chun KS, Joo SH, et al. 2020. Isolinderalactone induces cell death via mitochondrial superoxide- and STAT3-mediated pathways in human ovarian cancer cells. *International Journal of Molecular Sciences* 21(20):14
74. Tan C, Xu JY, Wang X, Guan AX, Liao LJ, et al. 2022. Screening of the anti-H.pylori and its antibacterial spectrum of isolinderalactone. *Journal of Youjiang Medical University for Nationalities* 44(2):155−157+179(in Chinese)
75. Chen FL, Yu CQ, Chen QH, Huang RP. 2013. Hypolipidemic effects of the extract from *Linderae* on hyperlipemia model of rats. *Strait Pharmaceutical Journal* 25(3):15−17(in Chinese)
76. Chen JG, Luo HX, Liu DY, Hu ZH, Liu Z, et al. 2020. The effect of leaves of *Lindera aggregata* on the regulation of blood lipids and histomorphology in hyperlipidemia rats. *Journal of Toxicology* 34(4):305−10(in Chinese)
77. Cao N, Guo WJ, Tang JY, Fan JJ, He GQ, et al. 2011. Effects of the total flavonoids from folium linderae on lipid metabolism in mice with hyperlipidemia fatty liver. *Traditional Chinese Drug Research and Clinical Pharmacology* 22(2):149−53(in Chinese)
78. Wang J, Wang FR, Yuan LX, Wu Y, Peng X, et al. 2020. Aqueous extracts of *Lindera aggregate* (Sims) Kosterm leaves regulate serum/hepatic lipid and liver function in normal and hypercholesterolemic mice. *Journal of Pharmacological Sciences* 143(1):45−51
79. Sun Y, Huang JJ, Ye K, Mao PJ, Wang ZA, et al. 2020. Effect of *Lindera aggregata* extract on lipid-lowering and hepatic LKB1-AMPK pathway in hyperlipidemic rat model. *Chinese Journal of Modern Applied Pharmacy* 37(7):821−25(in Chinese)
80. Han YD, Ye K, Huang JJ, Mao PJ, Wang ZA, et al. 2020. Effect of extract of *Linderae aggregate* leaf on pathology of the liver tissuesandTLR-4/NF-κBsignalingpathwayinratswithhyperlipidemia. *Journal of New Chinese Medicine* 52(15):15−18(in Chinese)
81. Shen W, Zhang YW. 2022. Optimization of extraction technology of polyphenols from leaves of Lindera aggregata and its antibacterial effect against *Staphylococcus aureus*. *Journal of Food Safety and Quality* 13(4):1256−63(in Chinese)
82. Tian SQ, Li YL, Pei HL, Tian Y, Zuo ZP, et al. 2022. The pathogenesis and drug therapy of hyperlipidemia. *Chemistry of Life* 42(12):2237−47(in Chinese)
83. Xiao XQ, Shu YY, Deng GM, Ge JW, Yang LP, et al. 2017. Effect of water extract of *Lindera aggregata* on Ghrelin, MTL, SP and Sec levels in rats with diarrhea-predominant irritable bowel syndrome. *Journal of Hunan University of Chinese Medicine* 37(5):477−80(in Chinese)
84. Lv Y. 2016. *Theoretical and Literature Research on Heart Yang and Kidney Yang*. Master Thesis. Beijing University of Chinese Medicine, China. (in Chinese)
85. Cai HD, Wang J, Luo YY, Wang FR, He GQ, et al. 2021. Lindera aggregata intervents adenine-induced chronic kidney disease by mediating metabolism and TGF-β/Smad signaling pathway. *Biomedicine & Pharmacotherapy* 134:111098
86. Nie ZW, Guo JS, Chen J, Zhang M, Liu HY. 2011. Effect of extraction of *Linderae radix* on cAMP cGMP GAS MTL level in rat stomach cold models. *Chinese Journal of Experimental Traditional Medical Formulae* 17(20):162−65(in Chinese)
87. Xu CD, Tan MM, Wang JW. 2020. Intestinal microecological regulating effect of *Lindera aggregata* in acute alcoholic liver injured rats. *Zhejiang Journal of Traditional Chinese Medicine* 55(9):685−86(in Chinese)
88. Choi JE, Park DM, Chun EH, Choi JJ, Seo JH, et al. 2017. Control of stress-induced depressive disorders by So-ochim-tang-gamibang, a Korean herbal medicine. *Journal of Ethnopharmacology* 196:141−50
89. Wang QH, Hu M, Wang GF. 2015. Analgesic and anti-inflammatory effect of alkaloids from *Linderae radix*. *Chinese Archives of Traditional Chinese Medicine* 33(4):910−12(in Chinese)
90. Chen FY, Liu Y, Xie D, Luo YM. 2022. Research progress on chemical constituents and their bioactivities of Lindera aggregata. *China Journal of Chinese Materia Medica* 00:1−10(in Chinese)
91. Tan R, Chou GX, Feng NP, Zhao JH, Wang Z. 2011. In situ intestinal absorption of total alkaloids from Linderae Radix in rats. *Chinese Traditional Patent Medicine* 33(5):787−90(in Chinese)
92. Chen JZ, Chou GX, Wang CH, Wang ZT. 2012. Pharmacokinetics and bioavailability of norisoboldine and its metabolite in rats. *Chinese Journal of Modern Applied Pharmacy* 29(6):473−77(in Chinese)
93. Chen JZ, Wang CH, Chou GX, Wang ZT. 2012. Pharmacokinetics of the total alkaloid from linderae radix in rats. *Chinese Journal of New Drugs* 21(18):2145−2148+2155(in Chinese)
94. Duan C, Guo JM, Dai Y, Xia YF. 2017. The absorption enhancement of norisoboldine in the duodenum of adjuvant-induced arthritis rats involves the impairment of P-glycoprotein. *Biopharmaceutics & Drug Disposition* 38(1):75−83
95. Pharmacopoeia Commission. 2020. *Chinese Pharmacopoeia*. Beijing: China Medical Science and Technology Press. 79 pp.
96. Xiao JP, Li Y, Chou GX, Chen JZ. 2013. Determination of Norisoboldine in Radix Linderae by UPLC. *Journal of Fujian University of TCM* 23(1):34−36(in Chinese)
97. Zuo ML. 2013. Content determination of isolinderalactone in Radix linderae. *China Journal of Modern Medicine* 23(33):58−60(in Chinese)
98. Zhang J, Liu BJ, Li C, Wu WY, Du B. 2014. Total alkaloids content determination of *Lindera aggregata* using ultraviolet spectroscopy. *Jiangsu Agricultural Sciences* 42(3):266−67(in Chinese)
99. Du WF, Wu Y, Yue XK, Ling J, Gu C, et al. 2017. Rapid determination of linderane and norisoboldine in Radix *Linderae* by near-infrared spectrometry. *Chinese Journal of New Drugs* 26(6):709−15(in Chinese)
100. Huang KY, Shu JN, Ouyang R, Zhou XB. 2010. Quality comparison of different forms linderae radix. *Chinese Journal of Modern Drug Application* 4(19):1−3(in Chinese)
101. Li SM, Sun CL, Zhou G, Ge JX, Zhang YJ, et al. 2021. Characteristic spectra and multi-component content determination of different root forms of *Lindera Aggregate*. *Chinese Journal of Modern Applied Pharmacy* 38(20):2548−53(in Chinese)
102. Liao BS, Song JY, Xie CX, Han JP, Chen SL. 2014. Study on traceability system of genuine medicinal materials. *China Journal of Chinese Materia Medica* 39(20):3881−88(in Chinese)
103. Chen RF, Cao GZ, Wu MC, Liu M. 2011. The determination of Radix linderae ether lactone's content from Radix linderae of six different areas. *Chinese Archives of Traditional Chinese Medicine* 29(5):1123−24(in Chinese)
104. Liu BJ, Zhang J, Cheng QL, Wen HL, Li C, et al. 2012. Determination of *Linderane* in roots, stems and leaves of *Lindera aggregate*

from the region of Gannan by HPLC. *Hubei Agricultural Sciences* 51(21):4870−72(in Chinese)
105. Chen WM, Li S, Tang Y, Ouyang R. 2017. Comparative study on the main chemical constituents of *Lindera* roots, stems, leaves in different regions of Hu'nan. *Guiding Journal of Traditional Chinese Medicine and Pharmacology* 23(22):32−36(in Chinese)
106. She ZH, Wen XK, Wu YL. 2013. HPLC determination of effective components in Radix *Linderae* produced in different areas and tim. *Central South Pharmacy* 11(7):541−44(in Chinese)
107. Yi L, Wang RY, Gao YF, Lin LM, Ouyang R. 2021. Study on the content determination and pattern recognition of four flavonoids in Wuyaoye (*Linderae Folium*) from different habitats in hunan. *Guiding Journal of Traditional Chinese Medicine and Pharmacology* 27(8):31−35(in Chinese)
108. Wang YB, Tong XQ, Liu BT, Yu JH, Qian H. 2010. Study on the content of Boldine from different ages of Tiantai *Linderae* Radix earthnut. *Modern Chinese Medicine* 12(9):28−30(in Chinese)
109. Xing MY, Tian CM, Xia DZ. 2017. Review on chemical constituents and pharmacological effects of *Lindera aggregata* Kosterm. *Natural Product Research and Development* 29(12):2147−51(in Chinese)
110. Wang XW, Jin ZX, Li JH. 2008. Flavonoids extracted from *Lindera aggregata* using microwave-assisted technology. *Jiangsu Agricultural Sciences* 36(5):220−23(in Chinese)
111. Gu XM, Xu HD. 2008. Preliminary analysis of flavonoids isolated from *Lindera aggregata* leaves. *Journal of Taizhou University* 30(3):36−38(in Chinese)
112. Gu XM, Xu HD. 2009. Total flavonoids content determination of *Lindera aggregata* leaves using polyamide adsorption-aluminum ion color developing technology. *Lishizhen Medicine and Materia Medica Research* 20(1):196−97(in Chinese)
113. Xu HD, Chen Z, Gu XM. 2010. Determination of total flavonoids in *Lindera aggregate* leaves. *Applied Chemical Industry* 39(9):1405−07(in Chinese)
114. Sun Y, Ye K, Mao PJ, Wang ZA. 2020. Content determination and extraction process optimization of total flavonoids in *Lindera aggregata* leaves. *Zhejiang Journal of Traditional Chinese Medicine* 55(10):774−75(in Chinese)
115. Lai WQ, Zhu RF, Chen JG, Mei S, Fu Y, et al. 2003. Study on the toxicity of *Lindera aggregata* (Sims) kosterm. *Occupation and Health* 19(12):78−80(in Chinese)
116. Tao S, Jiang YX. 2008. Study on toxicology of leaf of *Lindera aggreqata*. *Chinese Journal of Hospital Pharmacy* 28(18):1548−51(in Chinese)
117. He GQ. 2009. *Research and Development of Tiantai Wuyao Health Food*. Master Thesis. Jiangnan University, China. (in Chinese)
118. Yan RW, Peng XM, Zou GL. 2011. Anticancer and Antioxidant Activity of Lindera st rychni folia Extracts. *Journal of Wuhan University (Nature Science Edition)* 57(3):265−68(in Chinese)
119. Wang H, Wang K, Mao X, Zhang QQ, Yao T, et al. 2015. Mechanism-based inactivation of CYP2C9 by linderane. *Xenobiotica* 45(12):1037−46
120. Tan K, Shi QW, Zhan LB, Zhang HM, Wu CY. 2021. Connotation of Yin Deficiency in ancient Chinese medical literature. *Journal of Basic Chinese Medicine* 27(6):888−90(in Chinese)