Chemical Constituents From the Fruits of *Ligustrum lucidum W.T.Aiton* and Their Role on the Medicinal Treatment

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Abstract

Fruits of *Ligustrum lucidum W.T. Aiton* (*FLL*) is a well-known traditional Chinese medicine, which has the functions of protecting liver, anticancer, antosteoporosis, and antioxidant, etc. Various chemical constituents including triterpenes, secoiridoids, phenylethanoid glycosides, and flavonoids have been isolated and identified from *FLL*. In this article, the advances in research on the chemical constituents and their pharmacological effects were summarized by reviewing the recent literatures. In addition, the relationship between the chemical constituents and pharmacological activity of *FLL* was also discussed.

Keywords

fruits of *Ligustrum lucidum W.T. Aiton*, chemical constituents, pharmacological effect, glycosides, flavonoids

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Fruits of *Ligustrum lucidum W.T. Aiton* (*FLL*) is known as *Nvzhenzi* in traditional Chinese medicine and is the dried mature fruit of *Ligustrum lucidum W.T. Aiton*. *FLL* belongs to the Oleaceae family,¹ which is widely distributed in eastern Asia and India.² *FLL* has been used as a common herbal medicine in clinical practice in China for nearly 2000 years, which is usually used for supplying kidney, nourishing Yin and strengthening the liver, and clearing vision.¹ Modern researches show that water or ethanol extracts of *FLL* are useful for regulating the immune system, protecting the liver, lowering serum glucose, and exerting antioxidant, anti-inflammatory, anticancer, and antiaging functions in humans.³,⁴ In the clinical practice of traditional Chinese medicine, *FLL* is a component of many kidney-tonifying Chinese herbal formulae for the treatment of osteoporosis. In our previous studies, the antiaging effect of *FLL* was also investigated using rat model.⁵,⁶ In recent decades, great progress about *FLL* has been achieved by scholars in the world. Various chemical constituents have been isolated and identified from *FLL*, including triterpenes, secoiridoids, phenylethanoid glycosides, and flavonoids. Additionally, some chemical constituents isolated from *FLL* have been applied for the pharmacological effects on protecting liver, anticancer, antosteoporosis, and antioxidant, etc.

In this review, we summarize the updated researches on the chemical constituents of *FLL*. In addition, we also discuss several pharmacological effects of these constituents.

Chemical Constituents From *FLL*

**Triterpenes**

At present, more than 20 triterpenes have been extracted and identified from *FLL*. Oleanolic acid is the highest content among the triterpenes.

As shown in Figure 1, Li et al isolated 9 new triterpenoids from *FLL*, including tormentic acid (1), 19α-hydroxyursolic acid (2), 2α-hydroxyoleanolic acid (3), 2α-hydroxyursolic acid (4), 3β-O-trans-p-coumaroylmaslinic acid (5), 3β-O-cis-p-coumaroylmaslinic acid (6), 19α-hydroxy-3-acetylursolic acid (7), oleanolic acid (8)/ursolic acid (9), acetyoleanolic acid (10) and acetyursolic acid (11).⁸ In addition, a pair of cis and trans isomers named 3β-O-cis-p-coumaroylmaslinic acid and 3β-O-trans-p-coumaroylmaslinic acid was also detected in the 80% methanol extract of the processed *FLL*.

Two triterpenes, tormentic acid (1) and 2α-hydroxyursolic acid (4) shown in Figure 1, were successfully identified by ultra-performance liquid chromatography coupled with an

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Twenty compounds were isolated and purified from *FLL* by using silica gel, Sephadex LH-20, ODS column chromatographic methods. Their structures were identified on the basis of spectroscopic data and physicochemical properties. Among them, 15 triterpenes were successfully identified as 2α-hydroxyoleanolic acid (3), oleanolic acid (8), and acetyloleanolic acid (10) (Figure 1), lupeol (12), betulin (13), dammarene-diol-II (14), fouqueriol (15), 3β-acetyl-20,25-epoxydammarane-24α-ol (16), dammar-24-ene-3β-acetyl-20S-ol (17), 20S, 24R-dammarane-25-ene-24-hydroperoxy-3β,20-diol (18), 25-epoxydammarane-3β, 24S-diol (19), oliganthas A (20), dammarenediol II 3-O-palmitate (21), octillol II 3-O-palmitate (22), and (E)-25-hydroperoxydammar-25-ene-3β, 20-diol (23) (Figure 2).

**Secoiridoids**

Among all obtained chemical constituents from *FLL*, secoiridoids are often used as the characteristic compound for the identification of the *FLL* genus; moreover, they are considered as the main active ingredients in the pharmacological effects. Recently, the chemical ingredients of secoiridoids have been the focus of the study of *FLL*.

He et al reported that 10 secoiridoid glucosides were isolated through bioassay-guided analysis from the ethanol extraction of *FLL*. Their structures were elucidated by spectroscopic methods and depicted in Figure 4. The results showed that lucidumoside C (32) and lucidumoside D (33) were newly discovered, and the other 8 compounds were identified as oleoside dimethyl ester (34), ligustroside (35), oleuropein (36), nuezhenide (37), isonuezhenide (38), neonuezhenide (39), lucidumoside A (40), and lucidumoside B (41). Besides, 6 secoiridoid glucosides exhibited in Figure 4 also were obtained by Ma et al., including lucidumoside C (32), oleoside dimethyl ester (34), ligustroside (35), oleuropein (36), neonuezhenide (39), and lucidumoside A (40).

As displayed in Figure 5, 4 new secoiridoid glucosides, such as *p*-hydroxyphenethyl 7-β-α-glucosideelenolic acid ester (42), 6'-elenolynicotiflorine (43), 6"'-acetylnicotiflorine (44), and apigenin-7-O-rutinoside (27). The structures of the isolated flavonoids are presented in Figure 3.

**Flavonoids**

Li et al isolated 7 flavonoids that belonged to quercetin-3-O-rutinoside (24), luteolin-7-O-rutinoside (25), luteolin-7-O-glucoside (26), apigenin-7-O-rutinoside (27), apigenin-7-O-glucoside (28), luteolin (29), and apigenin (30). In addition, quercetin (31) was also isolated from *FLL* by Xu and Zhang et al. Three flavonoids were elucidated by UPLC/ESI-QTOF-MS, including luteolin (29), apigenin (30), and apigenin-7-O-rutinoside (27). The structures of the isolated flavonoids are presented in Figure 3.
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oleoside 7-ethyl 11-methyl ester (45), together with 6 known glucosides, including nuezhenide (37) isonuezhenide (38), neo-nuezhenide (39) (Figure 4), nuezhenoside Gl-3 (46), nicotiflorine (47), and oleoside 11-methyl ester (48), were isolated from FLL in 2010. Their structures were elucidated by spectroscopic methods.

In 2015, Gao et al reported that 1 new antioxidant secoiridoid glucoside dimer derivative, 4′,5′-(2′-hydroxy ligustrosidic acid) dimer (49) (Figure 5), together with 1 known compound, nuezhenide (37) (Figure 4), was identified from FLL by analyzing the spectroscopic data of 1-dimensional nuclear magnetic

Figure 2. Structures of triterpenoids isolated from the fruits of Ligustrum lucidum W.T.Aiton.

Figure 3. Structures of flavonoids isolated from the fruits of Ligustrum lucidum W.T.Aiton.
Zhang et al isolated 5 new secoiridoids from the FLL, namely, nuzhenal C (50), 6′-O-trans-cinnamoyl iso-8-epikingisidic acid (51), ligulucidumosides A (52), B (53), and C (54) (Figure 6). And the compound 52, the 1- OCH₃ substituent secoiridoid, was obtained first from plant kingdom presented in Figure 7.18

Recently, Qiu et al reported 3 new secoiridoid glucosides isolated from FLL. The structure was elucidated as nuezhenelenolidiscide (55), isojaslanceoside B (56), and 6′-O-trans-cinnamoyl-secologanoside (57) (Figure 7) by the comprehensive spectroscopic analysis. Among them, the compound 55 featured a rare rearrangement product of secoiridoid, which underwent the cleavage of chemical bond between C-1 and O-2, and the reformation of a new iridoid ring between C-8 and O-2.19

He et al extracted and separated 3 secoiridoid glycosides from FLL by using the combined methods of ultrahigh-pressure extraction and high-speed counter-current chromatography, including isonuezhenide (38 in Figure 4), nuezhenoside Gl-3 (46 in Figure 5), and nuezhenide (37 in Figure 4).20

As presented in Figure 8, Aoki et al isolated 6 new secoiridoid constituents from the FLL, namely, isoligustrosidic acid (58), 6′-O-trans-cinnamoyl 8-epikingisidic acid (59), 6′-O-cis-cinnamoyl 8-epikingisidic acid (60), oleopolynuzhenide A (61), and nuezhenal A (62) and B (63).21

Pang et al isolated 9 secoiridoid glycosides (36, 59, 64-70) together with 2 secoiridoids (71 and 72) and evaluated the anti-influenza A virus activities of 36, 59, and 64-72. The structures of the isolated constituents were established by using the NMR spectra and MS data as well as the necessary chemical evidence, in which the compounds 64, 65, 66 (ligulucisides A-C), 71 (liguluciridoids A), and 72 (liguluciridoids B) were identified as new secoiridoid analogs (Figure 9).22

In addition, oleoside 11-methyl ester (48), secologanoside (73), 10-hydroxyoleuropein (74), and elenolic acid (75) were also identified in the 80% methanol extract of the processed FLL by applying UHPLC-ESI-Q-TOF-MS.8 The structures of the isolated secoiridoids are presented in Figure 9.

### Phenylethanoid Glycosides

Phenylethanoid glycosides are an important class of compounds in FLL. Li et al detected 1 phenylethanoid and 7 phenylethanoid glycosides in the 80% methanol extract of FLL using a UHPLC-ESI-Q-TOF-MS method. They are hydroxytyrosol (76), hydroxytyrosol glucoside (77), salidroside (78), osmanthuside H (79), β-hydroxyverbascoside (80), echinacoside (81), verbascoside (82), and isoverbascoside (83) displayed in Figure 10.8 Furthermore, verbascoside (82) was isolated from FLL by high-speed counter-current chromatography coupled with ultrahigh-pressure extraction.20 Salidroside (78) was regarded as a key active

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**Figure 4.** Structures of secoiridoid glucosides isolated from the fruits of *Ligustrum lucidum* W.T.Aiton.
competent of the pharmacological effect in FLL.\textsuperscript{12} The structures of the isolated chemical constituents are presented in Figure 10. \(\beta\)-d-glucopyranoside, 2-(4-hydroxyphenethyl) 6-acetate (84) was isolated for the first time from nature reported by Liu et al.\textsuperscript{23}

**Other Chemical Constituents**

Modern chemical studies showed that there were other chemical constituents isolated from FLL. For example, Liu et al isolated (3-ethylidene-2-oxotetrahydropyran-4-yl)-acetic acid methyl ester (85) (Figure 11) from FLL.\textsuperscript{23} Besides, 2 iridoids, forsythide (86)\textsuperscript{9} and loganic acid (87),\textsuperscript{8} were isolated from FLL.

It was found that FLL also contained polysaccharides that were mainly composed of sucrose, rhamnose, arabinose, glucose, and fucose.\textsuperscript{24} In addition, \(\beta\)-sitosterol-3-O-\(\beta\)-d-glucoside (88) and d-mannitol (89) were obtained from this plant.\textsuperscript{12} Some chemical components such as palmitic acid (90), phyeosin (91), (132 \(S\))-hydroxyphacophytin A (92), (132 \(R\))-hydroxy-phacophytin A (93), \(\beta\)-sitosterol (94), and stigmasterol (95) (Figure 11) were also isolated and purified from the...
extracts of the petroleum ether and ethyl acetate part of FLL.\textsuperscript{25,26}

**Pharmacological Effects of the Isolated Chemical Constituents**

Modern pharmacological studies indicate clearly that the extracted chemical constituents from FLL show their respective pharmacological activities, such as immunomodulatory, hypolipemic, antiinflammatory, hepatoprotective, antitumor, and antiaging effects.

**Pharmacological Effects of Secoiridoids**

The secoiridoids isolated from FLL have been reported to show antioxidation, antiosteoporosis, hypolipidemic, and antiviral activities, and they may be the major bioactive components of FLL.

*Antioxidation activity.* Gao et al isolated nuezhenide (37) and 4',5'-(2'-hydroxy ligustrosidic acid) dimer (49) from the aqueous extract of FLL and evaluated its antioxidant activity by using 1,1-diphenyl-2-picrylhydrazyl radical scavenging assay.
The results showed that the half-maximal inhibitory concentration (IC₅₀) values for compounds 37 and 49 were found to be 391.13 and 7.83 µg/mL, respectively, which were much higher than that for ascorbic acid (IC₅₀ = 2.45 µg/mL) as a positive control. Furthermore, nuezhenoside Gl-3 (46) also was proved to have strong antioxidation activity.

He et al reported that 5 compounds, oleoside dimethyl ester (34), oleuropein (36), neonuezhenide (39), lucidumoside B (41),...
and lucidumoside C (32), exhibited significant antioxidation effect against hemolysis of red blood cells (RBC) induced by free radicals. The compounds 32-41 in Figure 4 were tested for their antioxidation effects on free radical-induced hemolysis of RBC. The results demonstrated that oleuropein (36), neoneuzhenide (39), and lucidumoside C (32) showed strong antioxidant effect (IC_{50} = 9.3-37.5 µM), which were significantly better than that of trolox. While oleoside dimethyl ester (34) and lucidumoside B (41) exhibited far weaker antioxidation activity than trolox. The IC_{50} values of ligustroside (35), nuezhene (37), isonuezhenide (38), lucidumoside A (40), and lucidumoside D (33) exceeded 200 mM. The experimental results suggested that the hemolysis inhibitory effect of these compounds may be related to the number of their phenolic hydroxyl groups.\(^{14}\)

**Antosteoporosis activity.** In addition, Qiu et al found that nuezhelenoliciside (55) and 6′-O-trans-cinnamoyl- secoiridoglycoside (57) exhibited potential effects on pre-osteoblastic MC3T3-E1 cells, which could be utilized as a potential antosteoporosis drug.\(^{19}\)

**Hypolipidemic activity.** Furthermore, the triglyceride (TG) accumulation inhibitory effects of secoiridoids were evaluated. Compared with normal HepG2 cells group, intracellular TG accumulation significantly increased after free fatty acid incubation for 48 hours, which could be downregulated by 0.1 µM orlistat, a lipase inhibitor. The results demonstrated that secoiridoids (50-54) significantly inhibited the TG accumulation at 10 µM.\(^{18}\)

**Antiviral activity.** Secoiridoid glycosides were reported to exhibit significant antiviral activity against the respiratory syncytial virus (RSV) and parainfluenza type 3 virus (Para 3).\(^{15}\) Results suggested that none of the glucosides had any significant activity against herpes simplex type 1 virus (HSV-1) and Flu A. Compared with the positive control group, oleuropein (36), however, showed significant antiviral activities against RSV and Para 3 with IC_{50} values of 23.4 and 11.7 µg/mL, respectively. Lucidumoside C (32), oleoside dimethyl ester (34), and ligustroside (35) displayed potent or moderate antiviral activities against Para 3 with IC_{50} values of 15.6-20.8 µg/mL.\(^{15}\)

Pang et al isolated 9 secoiridoid glycosides (64-70, 36, 59) together with 2 secoiridoids (71 and 72) depicted in Figure 10, and the compounds 64, 66, 36, and 71 displayed the inhibitory activities against influenza type A (Flu A) virus with the IC_{50} values of 16.5, 12.5, 13.1, and 18.5 µM, respectively, which were better than the positive control Ribavirin (IC_{50} 22.6 µM).\(^{22}\)

**Pharmacological Effects of Polysaccharides**

Polysaccharides from *FLL* can promote the B- and T-lymphocyte proliferation and increase natural killer cell activity and the phagocytosis of macrophage, inhibiting the growth of tumor cells in vivo by enhancing the immunology.\(^{28,29}\) Moreover, the polysaccharides can hinder the adhesion of melanoma B16BL6 cells in vitro and dampen the system of B16BL6 cells, thus exerting its antitumor effect.\(^{20}\) Furthermore, the polysaccharides possessed a protective effect on the liver damaged by chemical agent carbon tetrachloride (CCl4). Compared with the results of the bifendate control group, the
protective effect on liver damage by treatment with FLL was better at 200 mg/kg/day.31

Pharmacological Effects of Oleanolic Acid and Ursolic Acid

In recent years, there were many studies on pharmacological activities of oleanolic acid (OA) (8) and ursolic acid (UA) (9). A variety of pharmacological effects were reported, such as antioseoporosis, hepatoprotective action, etc.

Antioseoporosis action. Lots of studies were with respect to the antioseoporosis effects of OA and UA. Up to now, the study on the mechanism of antioseoporosis has not attracted enough attention.32 In order to prove the osteogenic effects of the water extract of FLL on MC3T3-E1 cells, Li et al used cell counting kit-8, real-time fluorescence quantitative polymerase chain reaction, enzyme-linked immunosorbent assay, and western blot assays. The experimental results demonstrated that UA was proved to have osteogenic effects. FLL can promote the protein levels of extracellular signal-regulated kinase (ERK), phosphorylated (p)-ERK, p-c-Jun N-terminal kinase (JNK), p38, pp38, protein kinase B (AKT), and p-AKT and inhibit the protein levels of JNK. The water extract of FLL can enhance cell proliferation and differentiation, messenger ribonucleic acid (mRNA), and protein expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) on MC3T3-E1 cells. The effects of cell proliferation and leakage of OPG were related to mitogen-activated protein kinase (MAPK) and AKT signaling pathways in different ways.

In addition, Xu et al examined the action of ethanol extract of FLL on osteoclast differentiation and bone resorption. The results showed that it can inhibit osteoclastogenesis in RAW264.7 cells via RANKL signaling pathways and its active compounds may be OA and UA.33

Furthermore, Cao et al designed to determine whether OA or OA + UA mimicked the effects of FLL on bone and calcium homeostasis using ovariectomized (OVX) rats. Serum was obtained for measurement of 1, 25-dihydroxylcholecalciferol (1, 25(OH)2D3) and bones were collected for micro-CT analysis. In addition, calcium balance and calcium kinetic were also measured. The experimental results confirmed that both OA and OA + UA can increase the bone properties, the concentration of serum 1, 25(OH)2D3, and the calcium use in OVX rats suggesting their potential effect on antioseoporosis.34

Hepatoprotective action. Yim et al evaluated the antioxidation activities of OA and other various fractions of FLL by examining the effect on hepatotoxicity induced by CCl4 in mice. The results demonstrated that the hepatoprotective action may be mainly mediated by enhancing the regeneration capacity of hepatic glutathione, especially under the condition of oxidative stress induced by CCl4. OA was considered as the principal active compound in the hepatoprotective action of FLL.35

Pharmacological Effects of Total Glycosides

The chemical compounds of total glycosides have been proved to have the effects of liver preservation and antidiabetic.

Lv et al have verified that the FLL extract can increase glucose tolerance and decrease insulin tolerance. These antidiabetic effects of the FLL extract can be related to its regulation of lipid metabolism since the total glycosides extracted from FLL can decrease the serum and hepatic lipids, reduce lipid peroxidation, and regulate lipid metabolism.36

Yang et al evaluated the preventive effect of total glycosides from FLL against nonalcoholic fatty liver in mice. The results showed that simvastatin or total glycoside administration also individually reversed the alterations of the liver index and lipid levels compared with the model group (P < 0.05 to P < 0.01). The total glycosides significantly decreased the activities of alanine aminotransferase and aspartate aminotransferase, as well as the contents of TG and cholesterol in the serum. Total glycosides can significantly reduce the levels of the liver X receptor-α (LXR-α) protein and sterol regulatory element-binding protein-1c (SREBP-1c) and downregulated the expression of LXR-α, SREBP-1c, and interleukin-6 mRNA in the liver.37

Other Pharmacological Effects of FLL

Many studies do not specify which chemical components play an important role in pharmacological effects. Generally, various pharmacological effects of water extracts and ethanol extracts of FLL have been reported.

Ethanol extract of FLL shows the notable function in treating osteoporosis. Many research groups evaluated the protective actions of the ethanol extract of FLL on the bone. Their results suggested that the ethanol extract of FLL enhanced renal 25-dihydroxyvitamin D3-1α-hydroxylase (1-OHase) mRNA expressions, improving significantly the bone mechanical properties.38-40 These effects are related to the treatment of osteoporosis. Zhang et al and Li et al tested the pharmacological effect of FLL extract on promoting the osteogenesis of mesenchymal stem cells. They found that the ethanol extract of FLL can improve the bone properties in rats, which was possibly related to its direct action on osteoblastic cells by enhancing the mineralization process and upregulating the expression of several osteoblast differentiation regulators.41,42 Additionally, the ethanol extract of FLL can greatly decrease the level of lipid peroxides and increase the levels of catalase, glutathione peroxidase, and superoxide dismutase in liver and lung, thus exhibiting the antioxidation action.43

Many studies were designed to elucidate the pharmacological action of the water extract of FLL. A variety of pharmacological effects have been reported, such as antioseoporosis,44,45 antiviral activity,46 antioxidation activity, hypoglycemic activity,47 anti-inflammatory activity,48 apoptosis-inducing activity,49 and anti-inflammatory activity.50 It was reported in the literature that the water extract of FLL played a beneficial role in the treatment of lumbar disc herniation.51 In addition, the FLL...
extract can increase Na\(^+\), K\(^+\), and Ca\(^{2+}\)-ATPase activity, improve the activity of the total nitric oxide synthase in the different tissues of rats, and regulate the activity of antioxidant enzymes in rat heart, thus extending the exercise time to avoid fatigue.\(^\text{52-55}\)

**Effects of Signaling Pathways**

The **FLL** can play a pharmacological role through a variety of signaling pathway changes, such as NOX4-reactive oxygen species-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), RANKL signaling pathway.

Wang et al evaluated the antioxidant effect of aqueous extracts of **FLL** in OVX rats.\(^\text{56}\) The results showed that treatment of the OVX rats with **FLL** aqueous extract improved redox homeostasis by increasing the levels of total antioxidant capacity and NO as well as decreasing the levels of malondialdehyde (MDA) and 8-hydroxy-desoxyguanosine in serum, tibias, and uteri. Furthermore, the aqueous extracts of **FLL** can also downregulate the expression of nicotinamide adenine dinucleotide phosphate oxidase 4 (NF-κB-p65), phosphorylation of NF-κB-p65, and phosphorylation of IkBz in the uteri and tibias.\(^\text{56}\) Estradiol valerate (EV) was administered in a positive control group. **FLL** seemed to be more potent in reducing the MDA level in OVX rats than EV. Interestingly, the improvement of **FLL** on bone microstructures was more evident in **FLL** group rats than in EV group rats. In summary, the **FLL** aqueous extract comprehensively exhibited an antioxidant effect in the tibias and uteri in the OVX rats.

Ji et al examined the effect of **FLL** extracts on glioma cell growth.\(^\text{57}\) Western blot analysis exhibited that treatment with **FLL** extracts caused downregulation of the phosphatidylinositol-3 kinase/Akt pathway, thereby overexpression of Akt prevented the cell death induced by the **FLL** extracts. These results suggested that the **FLL** extracts resulted in glioma cell death through regulation of the Akt/mammalian target of rapamycin/survivin pathway in vitro and inhibited glioma tumor growth in vivo.\(^\text{57}\) In addition, the researches by Xu et al indicated that **FLL** can inhibit osteoclastogenesis in RAW264.7 cells via RANKL signaling pathways.\(^\text{58}\) The **FLL** water extract also displayed osteogenic effects on MC3T3-E1 cells. Besides, the effect of the **FLL** water extract can be related to MAPK and AKT signaling pathways.\(^\text{58}\)

**Conclusion**

**FLL** has been used in traditional Chinese medicine for over 2000 years. In recent years, **FLL** has received special attention to its chemical constituents and pharmacological effects. Several chemical constituents, including triterpenes, secoiridoids, phenylethanoid glycosides, and flavonoids have been isolated and identified by various modern analysis methods, showing good pharmacological activity. The link between its chemical constituent and pharmacological effect has been explored. The **FLL** extracts have been reported to show liver protection, antiosteoporosis, antiviral, and antioxidation activities. Especially, antiosteoporosis activity has more thoroughly researched. Further research is needed to regulate the signaling pathways to exert pharmacological effects. Thus, with the development of science and technology, more chemical constituents will be isolated from **FLL**, and their pharmacological activities will become better understood.

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