



REVIEW

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Phytochemical and pharmacological studies on *Solanum lyratum*: a review

Yue Zhao[†], Wen-Ke Gao[†], Xiang-Dong Wang[†], Li-Hua Zhang, Hai-Yang Yu and Hong-Hua Wu^{*} 

Abstract

Solanum lyratum is one of the temperate plants, broadly distributed in Korea, China, Japan, India, and South-East Asia and well-documented in those oriental ethnic medicine systems for curing cancers, jaundice, edema, gonorrhea, cholecystitis, phlogosis, rheumatoid arthritis, etc. This review systematically summarized the research progress on *S. lyratum* respecting the botany, traditional uses, phytochemistry, pharmacology, and toxicology to increase people's in-depth understanding of this plant, by data retrieval in a series of online or off-line electronic databases as far as we can reach. Steroidal saponins and alkaloids, terpenoids, nitrogenous compounds, and flavonoid compounds are the main chemical constituents in *S. lyratum*. Among them, steroidal alkaloids and saponins are the major active ingredients ever found in *S. lyratum*, exerting activities of anti-cancer, anti-inflammation, anti-microbial, anti-allergy, and anti-oxidation in vivo or in vitro. As a result, *S. lyratum* has been frequently prescribed for the abovementioned therapeutic purposes, and there are substantial traditional and modern shreds of evidence of its use.

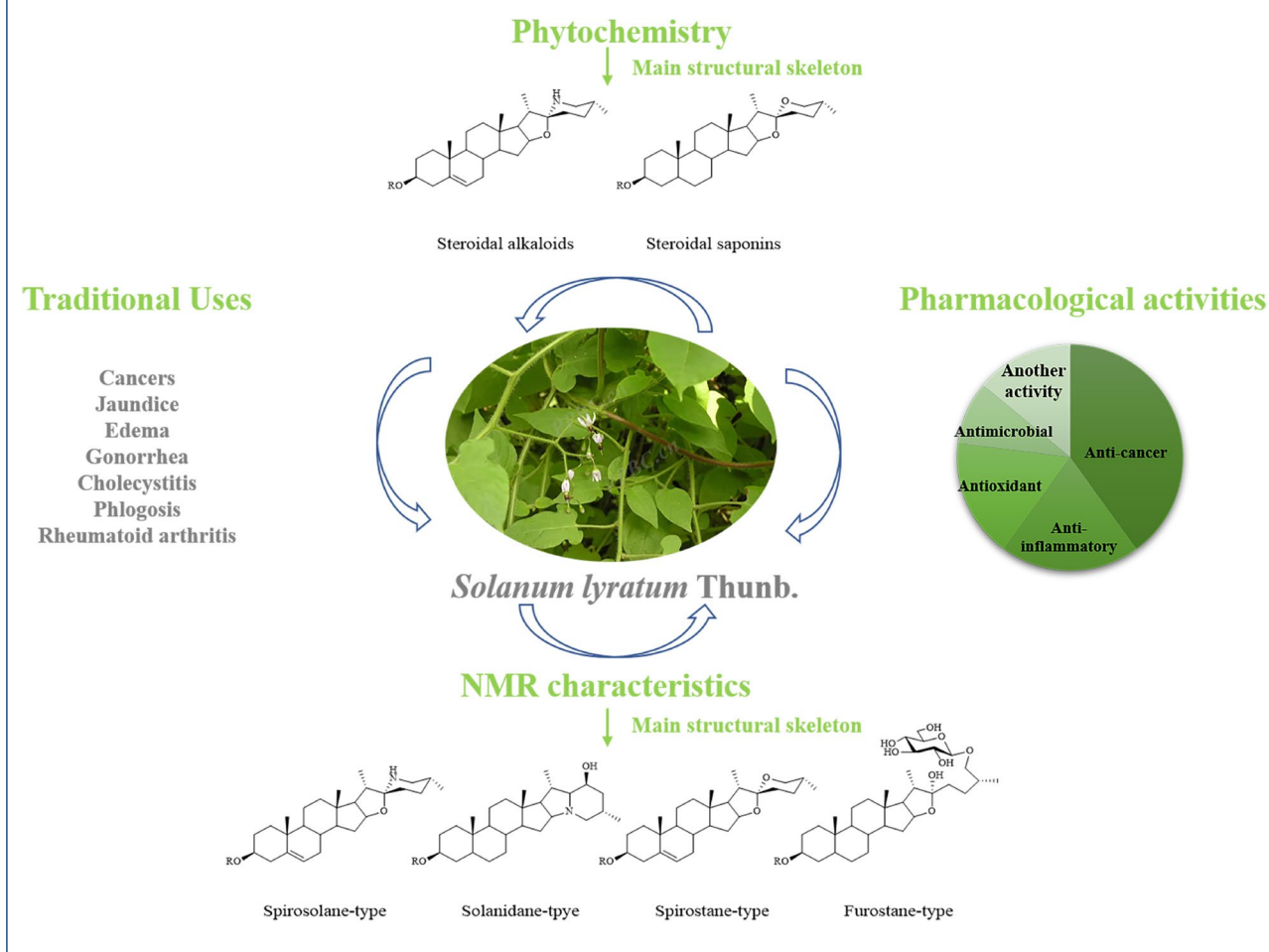
Keywords: *Solanum lyratum* Thunb., Steroidal saponins, Steroidal alkaloids, Anti-cancer, Toxicity

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Graphical Abstract



1 Introduction

Solanum lyratum Thunb. is a herbaceous vine of the family Solanaceae, with white villous hairs on violin-shaped leaves and stems, distributed throughout China, Japan, Korea, etc. [1]. *S. lyratum* prefers a warm and humid environment and is distributed widely in valley grass, roadside and field. *S. lyratum* is commonly known as "Bai-Mao-Teng" in traditional Chinese medicine and "Back-Mo-Deung" in traditional Korean medicine [2]. In traditional Chinese medicine (TCM), *S. lyratum* has the functions of clearing heat and removing toxicity ("Qingre Jiedu" in Chinese), dispelling wind and eliminating dampness ("Qufeng Lishi" in Chinese). Therefore, *S. lyratum* has been traditionally prescribed mainly for healing jaundice, edema, gonorrhea, cholecystitis, phlogosis, and rheumatoid arthritis [3]. Modern phytochemistry and pharmacological studies revealed that *S. lyratum* consists of a variety of active ingredients, including steroidal saponins, steroidal alkaloids,

terpenoids, lignans, and flavonoids [4]. And steroidal saponins and steroidal alkaloids have been used in the modern clinic to treat various cancers, especially lung cancer, cervical cancer, and liver cancer [3].

In the last ten years, dozens of reviews on the research progress of *Solanum* plants have been published, occasionally referring few phytochemistry and pharmacological reports on *S. lyratum* [5–8] (Fig. 1). However, there is no specialized and systematic research review on the *S. lyratum* species, especially on its phytochemistry and pharmacological aspects. Thus, this review intends to provide an updated and comprehensive summary on the botanical characterization, phytochemistry, and pharmacological and toxicity studies of *S. lyratum* to fill a gap in the research review of this plant and provides for a better exploration and application of *S. lyratum*. The literature for this manuscript was obtained from reports published from 1981 to Mar 2022.

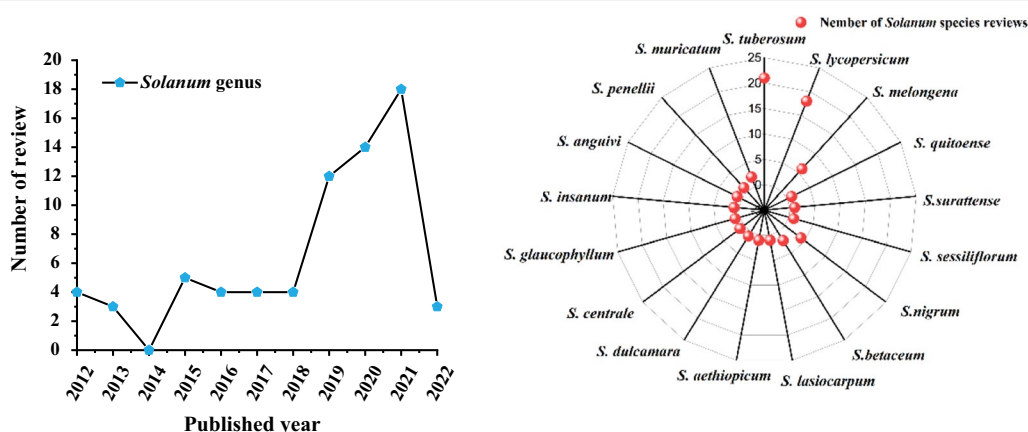


Fig. 1 Reviews of *Solanum* species published in last ten years



Fig. 2 Plant morphology of *S. lyratum*, (a) leaves, (b) flowers (c) fruits (d) the whole plant [data originated from the Plant Photo Bank of China (<http://ppbc.iplant.cn/>), accessed 10 April 2022]

2 Botany

S. lyratum is a herbaceous vine of the family Solanaceae, well-known native in China, India, Japan, Korea, North Vietnam, and the Indochina Peninsula [1]. This plant grows in a warm and humid environment, prefers light and fertile organic soil, and is distributed on hillsides, grass, ditch, and roadside at altitudes of 100–850 m. *S. lyratum* is 0.5–1 m long, and its stems and twigs are densely covered with white villous hairs

[2]. The botanical characteristics of *S. lyratum* were recorded in many classics of TCM, including "Tang Xinxu Bencao" in the Tang Dynasty [9], "Zhenglei Bencao" in the Song Dynasty [10], and "Compendium of Materia Medica" in Ming Dynasty [11].

S. lyratum is commonly known as "Bai-Mao-Teng" in TCM. It should be noted that there are several adulterants of *S. lyratum*, including *Aristolochia mollissima*, *Paederia scandens* (Lour.) Merr. and *Solanum*

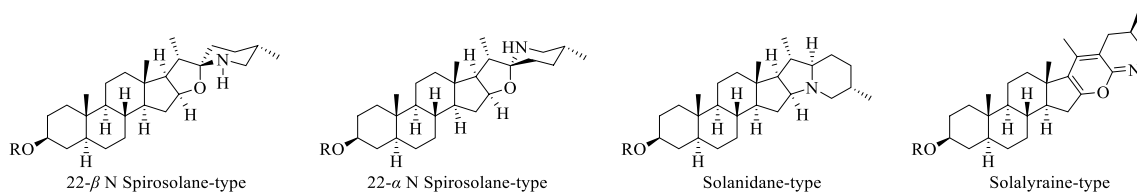


Fig. 3 Three types of steroidal alkaloid aglycones reported in *S. lyratum*

dulcamara L., all of which are so called as "Bai-Mao-Teng" that it may easily cause an event of medication confusion [12]. For example, a misuse of *A. mollissima* instead of *S. lyratum*, has ever led to a renal failure event in patients of Hong Kong [13]. Those adulterants closely resemble *S. lyratum* in botanical morphology, it is very important to seek advice from a professional or pharmacist before use. The plant morphological characteristics of *S. lyratum* are as follows: Root is slender and cylindrical. Leaves are mostly violin-shaped, with 3.5–5.5 cm long and 2.5–4.8 cm wide, and the base is 3–5 cm deep-lobed. Lateral lobes are smaller near the base. Middle lobes are usually larger oval and tend to apex acuminate. Both sides of the leaves were covered with white shiny villous hairs, and the levels own mid-vein and lateral veins. Flowers are sparsely terminal inflorescence or extra-axillary inflorescence, and the pedicel is approximately 2–2.5 cm long. Corollas are blue-purple or white and corollas are about 1.1 cm in diameter. Fruits are spherical and about 8 cm in diameter, which become reddish-black when it matures. Seeds are nearly disc-shaped and about 1.5 mm in diameter. The flowering period of *S. lyratum* is between May and June, while the fruiting period is between August and October. Significantly, the suitable harvest time has been recommended to be between October and December (Fig. 2) [14, 17].

3 Traditional uses

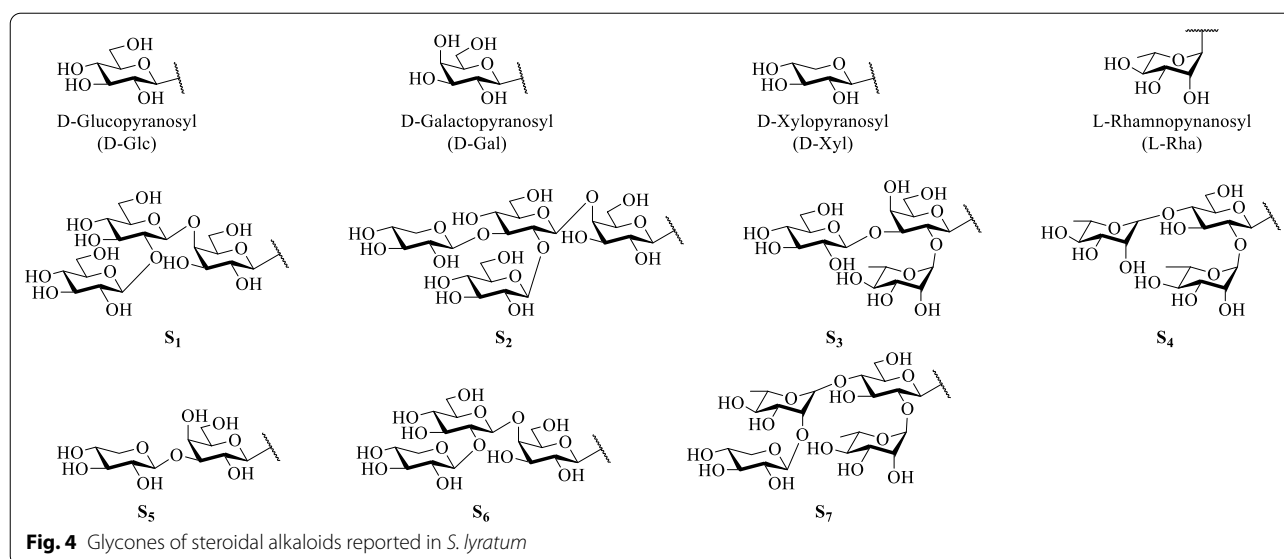
In TCM, *S. lyratum* has been considered as one of the "Top-grade" herbs in "*Shennong Bencao Jing*" (100 BC–200 AD, Han Dynasties) [18]. For centuries, it has been used for the treatments of cold and fever, malaria, jaundice, nephritis, edema, cholecystitis, rheumatoid arthritis, vaginitis, uterine erosion, and several types of cancer including lung cancer, cervical cancer, and gastric cancer [19, 21]. External applications of *S. lyratum* [22] have been recorded to treat carbuncle, furuncle and swollen poison, etc. In the "*Compendium of Materia Medica*", *S. lyratum* is documented [11] to have the effects of clearing heat, detoxification, and expelling rheumatism, for the treatment of rubella, erysipelas, malaria, cancer, etc. The traditional uses of *S. lyratum* in Korea, Japan, and the Indochina Peninsula focused mainly on the treatments of several types of cancers, warts, herpes, pyretic syndrome, diarrhea, etc., as summarized in Table 1.

4 Phytochemistry

So far, hundreds of phytochemicals have been isolated and identified from *S. lyratum*, including steroidal alkaloids (1–41), steroids and steroidal saponins (42–101), terpenoids (102–153), nitrogenous compounds (154–178), phenylpropanoids (179–227), flavonoids (228–258) and other compounds (259–270). Among them,

Table 1 Traditional uses of *S. lyratum*

Plant part used	Place	Traditional uses	Refs.
Herba, fruit	People's Republic of China	Clearing heat and removing toxicity, dispelling wind, malaria, jaundice, nephritis, edema, cholecystitis, rheumatoid arthritis, vaginitis, uterine erosion, carbuncle, cancer, diarrhea, wind-fire toothache, vaginitis	[17, 19–21]
Herba	Europe	Cancers, tumors, herpes and warts	[23, 24]
Herba	Korea	Febrifuge, diarrhea, eye disease, cancer, antitumor, anti-inflammatory, immunomodulatory, anti-anaphylactic, antioxidant agent, pyretic syndrome, diarrhea	[19, 21, 25–27]
Herba	Japan	Cancer, herpes, clearing heat and detoxifying, dispelling wind and resolving phlegm, eliminating dampness and removing jaundice, diarrhea, eye disease, pyretic syndrome	[19, 21, 27, 28]
Herba, Leaf	Taiwan, People's Republic of China	Leukemia, liver cancer, lung cancer, esophagus cancer, tumors, and warts	[29, 30]
Herba	Indochina Peninsula	Cancer, tumor, rheumatoid arthritis, leucorrhea, cold fever, damp-heat jaundice, herpes, and nephritis dropsy, pyretic syndrome, diarrhea	[21, 31]



steroidal alkaloids, steroidal saponins and terpenoids are so often recognized as the main active constituents of *S. lyratum* [32, 33].

4.1 Steroidal alkaloids

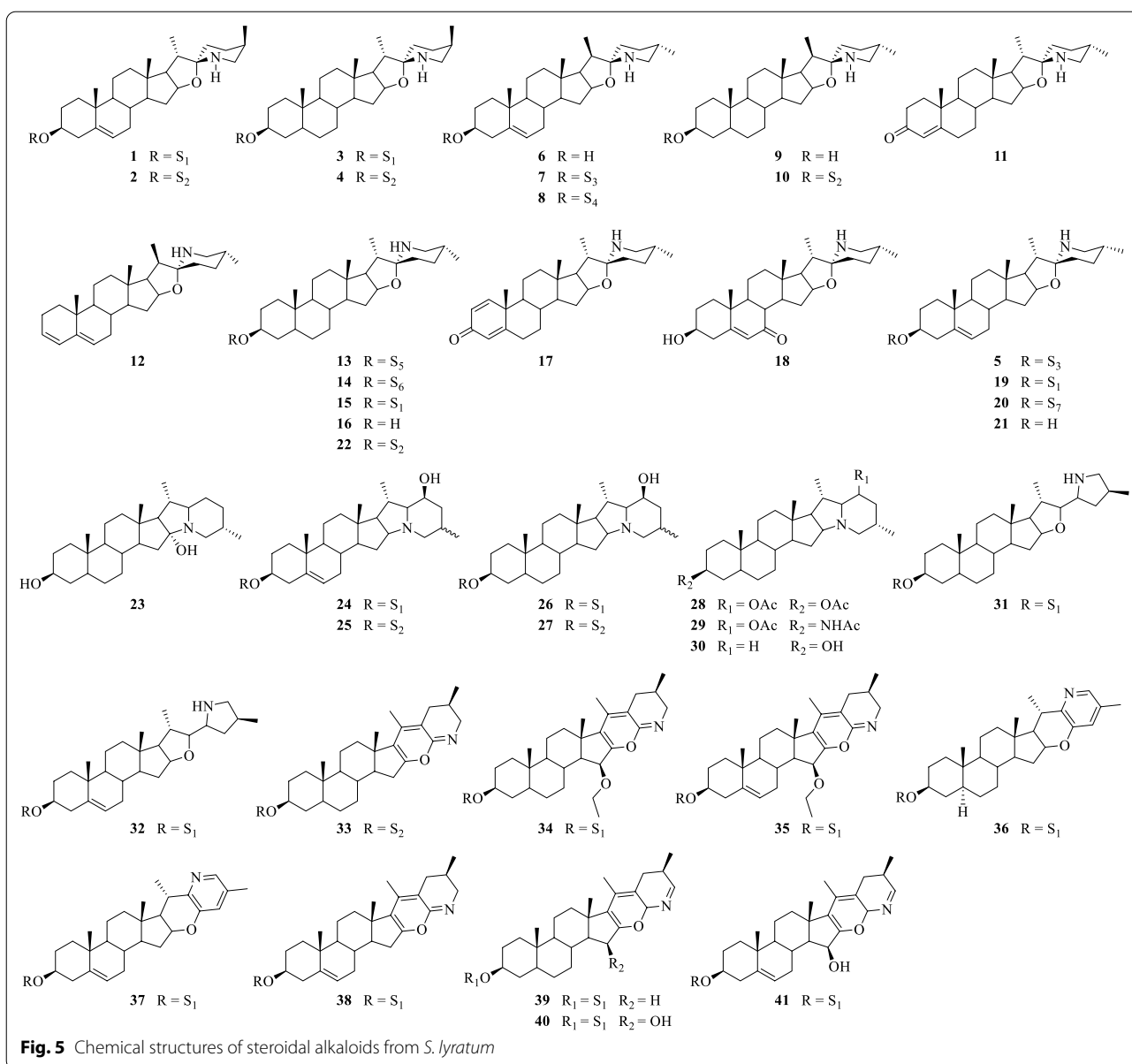
Steroidal alkaloids in *S. lyratum* include mostly solanidane (27 carbon atoms), spirosolane (27 carbon atoms) and solayraine (27 carbon atoms) (Fig. 3) types of nitrogenous sapogenins. The glycone moieties are most likely to be substituted at C-3 position of the nitrogenous sapogenin aglycone. D-glucose (D-Glc), D-galactose (D-Gal), D-xylose (D-Xyl), and L-rhamnose (L-Rha) are the common components of the glycones, in which one to four monosaccharides linked linearly or with one or more branched chains, as shown in Fig. 4.

Steroidal alkaloid is one of the characteristic ingredients of *Solanum* plants [34]. Until now, a total of forty-one steroidal alkaloids (1–41) have been identified from *S. lyratum* (Table 2). It is noteworthy that there were two epimers for the most abundant spirosolane-type steroidal alkaloids in *Solanum* plants, one is 22- β N type (1–4, 6–11) [33, 35–39] and the other is 22- α N type (5, 13–22) [24, 35–40] in clue of the existence of an oxa-azaspirodecane system. In addition, solanidane-type steroidal alkaloids (23–30) [35, 36, 41, 42], with a unique octahydroindolizine complex cholestane skeleton, have also been found to be existed in this plant. Further, other unusual spirosolane-type glycoalkaloids with a deformed E and F rings (piperidine, pyridine or other derived F rings) have been also occasionally discovered from *S. lyratum*, exemplified by compounds 31–41 [39, 43], as shown in Fig. 5.

4.2 NMR characteristics of steroidal alkaloids

Representative NMR data of the common steroidal alkaloids and saponins from *S. lyratum* were summarized in Tables 3, 4, 5 and 6. ^{13}C NMR spectra of the spirosolane-type, spirostanol-type, and furostanol-type steroidal alkaloids or saponins, with intrinsic twenty-seven steroid skeleton, normally exhibit characteristic carbon signals for C-22 around δ_{C} 98.0 [35], 109.0 [22], and 112.0 [40] ppm, respectively. In addition, in the high field of the ^1H NMR spectra of steroidal alkaloids and saponins, the resonance signals of methylene and methine protons are generally around δ_{H} 1.1–3.0, while the four methyl groups show proton resonances at δ_{H} 0.6–1.4, among which there are two singlets for the methyl groups at C-18 and C-19 [44], and two doublets for those methyls at C-21 and C-27 [45].

In the ^{13}C NMR spectra, spirosolane-type of steroidal alkaloids, characterizing a A/B/C/D ring system of C_{27} steroid scaffold (Table 3 and Fig. 6), show twenty-seven carbon signals generally containing four methyl carbon signals around at δ_{C} 16.0 (C-18), 19.0 (C-19), 15.0 (C-21), and 19.0 (C-27). Steroidal alkaloid can be simply recognized to be a steroidal saponin with a replacement of the oxygen atom in F ring by a nitrogen atom, resulting in the high-field shifting of the carbon chemical shifts of C-22 and C-26, from δ_{C} 109.0 and 67.0 to 98.0 and 47.5, respectively [30, 39, 40, 46]. In the ^{13}C NMR spectra of the solanidane-type steroidal alkaloids, there were four methyl carbon signals around at δ_{C} 16.0 (C-18), 12.0 (C-19), 19.0 (C-21), and 22.0 (C-27) [30, 38, 39, 46] besides those characteristic carbon signals around at δ_{C} 69.0 (C-16), 78.0 (C-22) and 58.0 (C-26) [35, 41]. And, chemical shifts of the glycosyl anomeric carbon are at



δ_C 100.0–108.0, especially when the glycosidation taking place at OH-3 of the steroidal alkaloids [47–49].

4.3 Steroids and steroidal saponins

4.3.1 Steroids

Cholesterol, containing a perhydrocyclopentenophenanthrene moiety (rings A, B, C and D) with a acyclic side-chain, has been considered as the precursor of furostanol and spirostanol (Fig. 7). At present, thirty steroids have been isolated from *S. lyratum* (42–71) (Table 4) [35, 36, 39, 47, 48, 50, 52].

4.3.2 Steroidal saponins

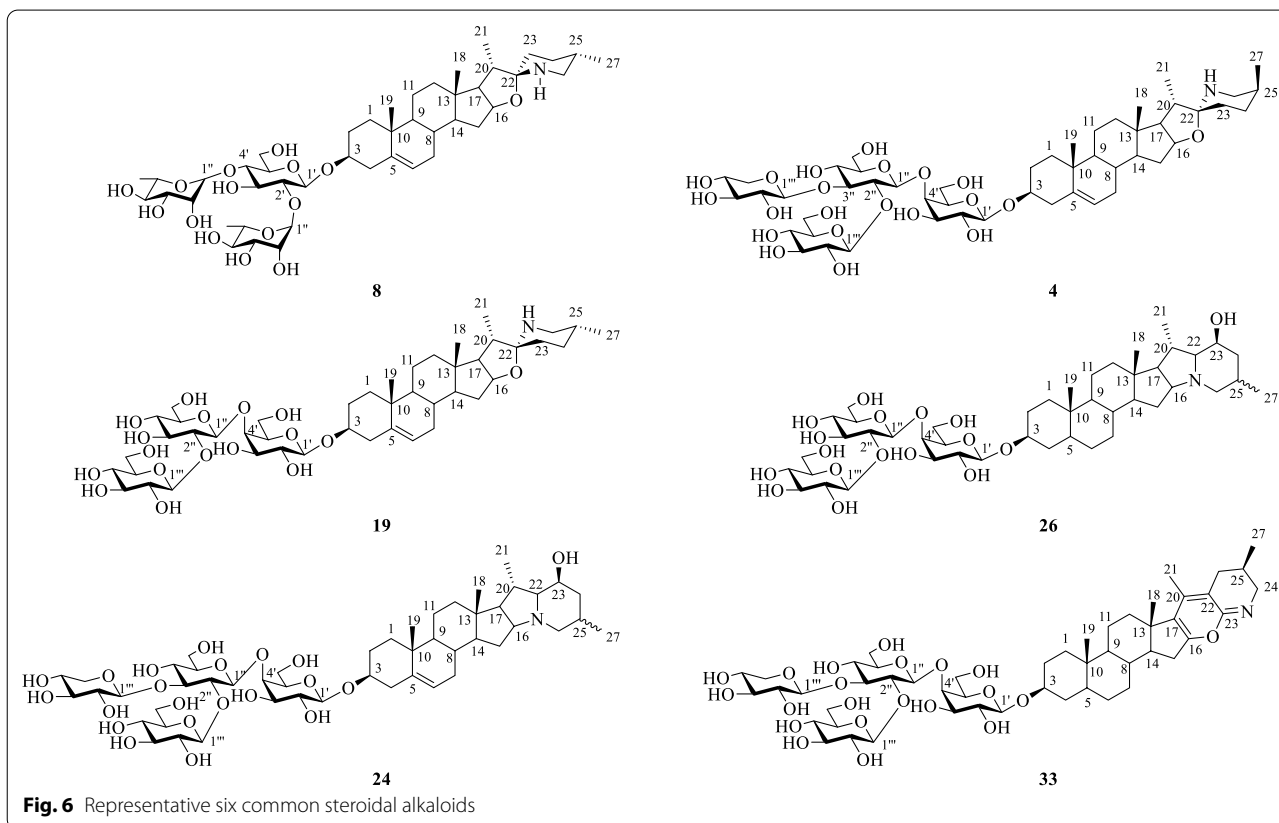
Steroidal saponins reported in *S. lyratum* are well-known characterized by possessing the steroid-derived aglycones normally consisting of a hydrophobic C_{27} -skeleton of cholesterol with an oxygen fused into the F ring, exemplified by the spirostanol (27 carbon atoms), furostanol (27 carbon atoms) and cholesterol (27 carbon atoms) as the most common scaffolds. Nevertheless, C_{21} -steroidal saponins have also been reported to be existed in *S. lyratum* (Fig. 8). As is known, the remaining hydrophilic glycone unit of a steroidal saponin has been frequently reported to be substituted at the C-3 position of the sapogenin.

Table 2 Steroidal alkaloids isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
1	(3 β ,22 α ,25R)-Spirosol-5-en-3-ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₃ NO ₁₇	899.4878	[33]
2	(3 β ,22 α ,25R)-Spirosol-5-en-3-ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[O- β -D-xylopyranosyl-(1 $\rightarrow$ 3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₈₁ NO ₂₁	1031.5301	[33]
3	(3 β ,5 α ,22 α ,25R)-Spirosol-3-ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₅ NO ₁₇	901.5035	[33]
4	(3 β ,5 α ,22 α ,25R)-Spirosol-3-ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[O- β -D-xylopyranosyl-(1 $\rightarrow$ 3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₈₃ NO ₂₁	1033.5458	[33]
5	Solasonine	C ₄₅ H ₇₅ NO ₁₆	885.5086	[35]
6	Tomatidenol	C ₂₇ H ₄₃ NO ₂	413.3294	[36]
7	Solamarine	C ₄₅ H ₇₃ NO ₁₆	883.4929	[35]
8	Solamargine	C ₄₅ H ₇₃ NO ₁₅	867.4980	[35, 37]
9	Soladulcidine	C ₂₇ H ₄₅ NO ₂	415.3450	[35, 37]
10	Soladulcidine-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[O- β -D-xylopyranosyl-(1 $\rightarrow$ 3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₈₃ NO ₂₁	1033.5458	[34, 38]
11	4-Tomatiden-3-one	C ₂₇ H ₄₁ NO ₂	411.3137	[36]
12	Solasodiene	C ₂₇ H ₄₁ NO	395.3188	[35]
13	Solalyratine A	C ₃₈ H ₆₂ NO ₁₁	709.4401	[24]
14	Solalyratine B	C ₄₄ H ₇₃ NO ₁₆	871.4929	[24]
15	Solalyratine B'	C ₄₅ H ₇₅ NO ₁₇	901.5035	[39]
16	Soladulcidine	C ₂₇ H ₄₅ NO ₂	415.3450	[40]
17	1,4-Solasodadien-3-one	C ₂₇ H ₃₉ NO ₂	409.2981	[36]
18	7-Oxosolasodine	C ₂₇ H ₄₁ NO ₃	427.3086	[36]
19	Solalyraine A'	C ₄₅ H ₇₃ NO ₁₇	899.4878	[39]
20	(3 β ,22 β ,25S)-Spirosol-5-ene-3-O- β -D-xylopyranosyl-(1 $\rightarrow$ 2)-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)-[O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranoside	C ₅₀ H ₈₁ NO ₁₉	999.5403	[35]
21	Solasodine	C ₂₇ H ₄₃ NO ₂	413.3294	[36]
22	Solalyratine C	C ₅₀ H ₈₃ NO ₂₁	1033.5458	[35]
23	5 α -Solanidane-3 β ,16 α -diol	C ₂₇ H ₄₅ NO ₂	415.3450	[36]
24	(25S or R)-Solanid-5-ene-3 β ,23 β -diol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₃ NO ₁₇	899.4878	[41]
25	(25S or R)-Solanid-5-ene-3 β ,23 β -diol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[xylopyranosyl-(1,3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₈₁ NO ₂₁	1031.5301	[35]
26	(25S or R)-Solanidane-3 β ,23 β -diol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₅ NO ₁₇	901.5035	[41]
27	(25S or R)-Solanidane-3 β ,23 β -diol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[xylopyranosyl-(1 $\rightarrow$ 3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₈₃ NO ₂₁	1033.5458	[35, 41]
28	Dihydroleptinidin diacetate	C ₃₁ H ₄₉ NO ₄	499.3662	[41]
29	Solanogantamine diacetate	C ₃₁ H ₅₀ N ₂ O ₃	498.3821	[41]
30	Dihydroleptinidine	C ₂₇ H ₄₅ NO	399.3501	[42]
31	Solalyraine A	C ₄₅ H ₇₅ NO ₁₇	901.5035	[43]
32	Solalyraine B	C ₄₅ H ₇₃ NO ₁₇	899.4878	[43]
33	(3 β ,5 α ,25S)-16,23-Epoxy-23,24-iminocholest-16,20,23(N)-triene-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-[β -D-xylopyranosyl-(1 $\rightarrow$ 3)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₀ H ₇₇ NO ₂₁	1027.4988	[39]
34	15 β -Hydroxyl-(3 β ,25R)-16,23-epoxyl-23,24-iminocholestane-5,16,20,23(N)-tetraen-3 β -ol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₇ H ₇₄ NO ₁₈	940.4931	[39]
35	15 β -Ethoxyl-(3 β ,5 α ,25R)-16,23-epoxyl-23,24-iminocholest-16,20,23(N)-trien-3 β -ol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₇ H ₇₂ NO ₁₈	938.4790	[39]
36	16,23-Epoxy-22,26-iminocholestane-22(N),23,25(26)-trien-3 β -ol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₆₉ NO ₁₇	895.4565	[39]
37	Solalyraine C	C ₄₅ H ₆₇ NO ₁₇	893.4409	[43]
38	Solalyraine D	C ₄₅ H ₆₇ NO ₁₇	893.4409	[43]

Table 2 (continued)

No	Compounds	Chemical formula	Molecular Wt	Refs.
39	Solalyraïne E	C ₄₅ H ₆₉ NO ₁₇	895.4565	[43]
40	Solalyraïne F	C ₄₅ H ₆₉ NO ₁₈	911.4515	[43]
41	Solalyraïne G	C ₄₅ H ₆₇ NO ₁₈	909.4358	[43]

**Fig. 6** Representative six common steroidal alkaloids

D-Glc, D-Gal, D-Xyl, L-Rha, and L-arabinose (L-Ara) are the common members of the glycones, in which one to five monosaccharides linked linearly or with one or more branched chains, as shown in Fig. 9.

Till now, a total of thirty steroidal saponins (72–101) have been identified from *S. lyratum* (Table 5 and Fig. 10). Most of the isolated steroidal saponins of *S. lyratum* belong to the spirostane-type (72–87) [4, 22, 46, 47, 49], C₂₁-steroidal subclass (89–93) [40, 46, 51] and furostanol-type (94–101) [22, 23, 40, 46]. Notably, when F-ring of a spirostanol is ring-opened, a new saponin skeleton of a furostanol is then afforded. As far as we know, the furostanol and its derivatives are the only reported ring-opened steroidal saponins ever isolated from *S. lyratum* up to now (94–101) [22, 23, 40, 46].

4.4 NMR characteristics of steroidal saponins

In short, in the ¹³C NMR spectra, spirostanol and furostanol-types of steroidal saponins, characterizing a A/B/C/D ring system of C₂₇-steroidal scaffold, show twenty-seven carbon signals generally containing four methyl carbon signals at δ_C 16.0 (C-18), 19.0 (C-19), 14.0 (C-21), and 17.0 (C-27) or two olefinic carbon signals at δ_C 140.0 (C-5) and 120.0 (C-6) [47, 49] (Table 6 and Fig. 11). The carbon chemical shift of CH₃-19 will down-field shifted from δ_C 12.0 to δ_C 19.0 [47, 49], when the two methylenes at C-5,6 being dehydrogenated (-H₂) to form a double bond [53]. The carbon resonances of C-16, 17, 22 (spiroketal carbon) and C-26 in a spirostanol-type steroidal saponin, were at about δ_C 81.0, 62.0, 109.0 and 67.0, respectively [47, 49], while those in a furostanol-type steroidal saponin were at about δ_C 81.0, 64.0, 112.0

Table 3 Representative ^{13}C NMR data of six common steroid alkaloids

Position	Compound 8 ^a (spirosolane-type)	Compound 4 ^b (spirosolane-type)	Compound 19 ^b (spirosolane-type)	Compound 26 ^c (solanidane-type)	Compound 24 ^c (solanidane-type)	Compound 33 ^b (solalyraïne-type)
1	37.6	38.2	38.5	37.1	37.3	29.7
2	30.3	30.4	30.7	31.5	31.5	30.4
3	78.1	79.3	79.9	71.2	71.6	79.3
4	39.0	35.3	39.6	38.2	42.3	30.4
5	148.0	46.0	142.1	45.0	141.0	46.1
6	121.9	29.8	122.3	28.7	121.3	32.9
7	32.7	33.2	33.1	32.3	32.1	35.3
8	31.8	36.5	32.8	35.4	31.7	38.0
9	50.4	55.6	51.5	54.5	50.2	55.7
10	37.2	36.8	38.0	35.6	36.6	36.9
11	21.3	22.1	21.9	21.0	20.8	22.2
12	40.2	40.6	40.4	39.6	39.4	37.1
13	40.7	42.4	42.2	41.4	41.4	48.1
14	56.8	57.5	57.7	57.4	57.7	57.2
15	32.5	33.0	33.0	31.5	31.5	35.2
16	78.9	84.7	84.8	69.6	69.6	138.7
17	63.6	63.2	63.0	62.2	62.2	149.8
18	16.7	16.7	16.5	16.8	16.6	17.1
19	19.5	12.7	19.8	12.4	19.4	12.6
20	41.7	42.8	42.8	30.6	30.6	141.4
21	15.8	14.7	14.9	18.9	18.9	12.3
22	98.5	100.2	100.2	78.9	78.9	162.6
23	34.8	33.4	33.2	67.0	67.0	141.7
24	31.2	28.9	28.9	37.1	37.1	63.2
25	31.7	29.5	29.5	26.9	26.9	31.6
26	48.2	46.7	46.7	58.7	58.7	38.2
27	19.9	18.6	18.6	22.4	22.4	16.6
Gal-(1 → 3)-skeleton						
1'		102.7	102.8	102.3	102.3	102.7
2'		73.2	73.2	73.1	73.1	73.2
3'		75.3	75.2	75.4	75.4	75.3
4'		80.2	80.5	80.8	80.8	80.2
5'		75.9	76.3	76.5	76.5	75.9
6'		61.1	60.9	60.4	60.4	61.1
Glc-(1 → 3)-skeleton						
1'	100.3					
2'	78.0					
3'	77.8					
4'	78.6					
5'	77.0					
6'	61.3					
Rha'-(1 → 4)-Gal						
1''	102.1					
2''	72.6					
3''	72.9					
4''	74.2					
5''	69.6					
6''	18.8					

Table 3 (continued)

Position	Compound 8 ^a (spirosolane-type)	Compound 4 ^b (spirosolane-type)	Compound 19 ^b (spirosolane-type)	Compound 26 ^c (solanidane-type)	Compound 24 ^c (solanidane-type)	Compound 33 ^b (solalyraïne-type)
Rha''-(1 → 2)-Gal						
1''	102.9					
2''	72.6					
3''	72.8					
4''	74.0					
5''	70.5					
6''	18.6					
Glc'-(1 → 4)-Gal						
1''		104.3	104.9	105.0	105.0	104.3
2''		81.0	85.0	85.8	85.8	81.1
3''		87.9	77.6	78.0	78.0	87.9
4''		71.0	70.7	71.7	71.7	71.0
5''		78.3	78.2	77.4	77.4	78.3
6''		62.7	62.0	61.4	61.4	62.0
Glc''-(1 → 2)-Glc'						
1'''		104.7	106.2	106.7	106.7	104.7
2'''		75.6	75.6	74.9	74.9	75.6
3'''		78.5	78.7	78.2	78.2	78.5
4'''		71.6	71.8	70.2	70.2	71.6
5'''		78.0	77.9	77.4	77.4	78.0
6'''		63.2	63.2	63.1	63.1	63.1
Xyl-(1 → 3)-Glc'						
1'''		105.0			104.8	105.0
2'''		75.2			75.5	75.3
3'''		77.5			78.5	77.5
4'''		70.4			70.4	70.5
5'''		67.2			67.2	67.2

^a In C₅D₅N; ^b In CD₃OD; ^c In CDCl₃

and 75.0, respectively [22, 48]. It is worth noting that the proton chemical shift (δ_H) difference ($\Delta_{ab} = \delta_a - \delta_b$) of the two geminal protons (Ha and Hb) of CH₂-26 has been recognized for ascertaining 25*R* or 25*S* orientation of the CH₃-27 [$\Delta_{ab} \leq 0.48$ for 25*R*, $\Delta_{ab} \geq 0.57$ for 25*S*] in the spirostanol and furostanol-types of steroidal saponins [45, 54, 55]. Similarly, the abovementioned empirical law for configuration assignment of C-25 applies equally well to spirosolane-type of steroidal alkaloids (Table 3).

4.5 Terpenoids

So far, fifty-one terpenoids, including sesquiterpenoids, monoterpenoids and triterpenoids (Table 7 and Fig. 12), have been isolated from *S. lyratum*. Among them, sesquiterpenoids are the most common terpenoids in *S. lyratum*, including eudesmane-type sesquiterpenoids (102–119) [52, 56–64] and the related derivatives (120–128) [39, 47, 58, 60, 62], monocyclic sesquiterpenoids (129–139) [25, 47, 56, 58, 62],

vetispirane-type sesquiterpenoids (140–147) [1, 56, 62, 64], and guaiane-type sesquiterpenoids (148) [47]. In addition to the abovementioned constituents, two monoterpenoids (149–150) and three pentacyclic triterpenoids (151–153) have also been found in *S. lyratum*.

4.6 Nitrogenous compounds

Nitrogenous compounds found in *S. lyratum* include arylamides (154–167) [36, 47, 65–68], aliphatic amides (168–169) [47], and other nitrogenous compounds (170–178) (Table 8 and Fig. 13) [47, 65].

4.7 Phenylpropanoids

4.7.1 Lignans

Till now, a total of twenty-eight lignans (179–205) have been isolated from *S. lyratum* (Table 9, Fig. 14), including simple lignans (184, 188) [32, 47, 68], lignanolides

Table 4 Steroids isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
42	Tigogenin	C ₂₇ H ₄₄ O ₃	416.3290	[47]
43	Diosgenin	C ₂₇ H ₄₂ O ₃	414.3134	[47]
44	(25 <i>R</i>)-Spirost-4-ene-3,12-dione	C ₂₇ H ₃₈ O ₄	426.2770	[47]
45	(25 <i>R</i>)-Spirostane-4,6-dien-3-one	C ₂₇ H ₃₈ O ₃	410.2821	[47]
46	(25 <i>R</i>)-Spirost-4-en-3-one	C ₂₇ H ₄₀ O ₃	412.1977	[47]
47	7-Ketodiosgenin	C ₂₇ H ₄₀ O ₄	428.2927	[47]
48	Agigenin	C ₂₇ H ₄₄ O ₅	448.3189	[47]
49	Hecogenin	C ₂₇ H ₄₂ O ₄	430.3083	[47]
50	Δ ⁵⁽⁶⁾ -22-Isospirostene-2,3-diol	C ₂₇ H ₄₂ O ₄	430.3038	[47]
51	Gitogenin	C ₂₇ H ₄₄ O ₄	432.3240	[47]
52	20-Hydroxydiosgenone	C ₂₇ H ₄₀ O ₄	428.2927	[47]
53	(25 <i>R</i>)-25-Hydroxyspirost-4-en-3-one	C ₂₇ H ₄₂ O ₄	430.3083	[47]
54	Tigogenone	C ₂₇ H ₄₂ O ₃	414.3134	[50]
55	Δ ^{3,5} -deoxytigogenin-(25 <i>R</i>)-spirost-3,5-diene	C ₂₇ H ₄₀ O ₂	396.3208	[48]
56	Diosgenin	C ₂₇ H ₄₂ O ₂	398.3185	[35]
57	Yamogenin	C ₂₇ H ₄₂ O ₂	398.3185	[35]
58	Periplogenin	C ₂₃ H ₃₄ O ₅	390.2406	[47]
59	16-Dehydropregnenolone	C ₂₁ H ₃₀ O ₂	314.2246	[51]
60	3-Hydroxy-5-pregn-16-en-20-one	C ₂₁ H ₃₂ O ₂	316.2402	[51]
61	3β,6α,16β-Trihydroxy-5α-pregnane-(20 <i>S</i>)-carboxylic acid (22,16)-lactone	C ₂₂ H ₃₂ O ₃	344.2351	[47]
62	24-Methylcholest-5-en-3,16-diol	C ₂₈ H ₄₈ O ₂	416.3654	[47]
63	Cholesterol	C ₂₇ H ₄₆ O	386.3549	[40]
64	5α-Stigmanstane-3,6-dione	C ₂₉ H ₄₈ O ₂	428.3654	[40]
65	4-Methylcholest-7-en-3β-ol	C ₂₈ H ₄₈ O	400.3705	[50]
66	24α-Methylcholestane-7,22-diene-3β,5α,6β-triol	C ₂₈ H ₄₆ O ₃	430.3447	[36]
67	5α-Stigmanstane-3-hydroxy-6-dione	C ₂₉ H ₅₀ O ₂	430.3811	[40]
68	β-Sitosterol	C ₃₀ H ₅₂ O	428.7330	[44]
69	Daucosterol	C ₃₅ H ₆₀ O ₆	576.4390	[44]
70	Ergosterol endoperoxide	C ₂₈ H ₄₄ O ₃	428.3290	[52]
71	9,11-Dehydroergosterol endoperoxide	C ₂₈ H ₄₂ O ₃	426.3134	[52]

(185) [47], cyclolignans (179–183) [32, 47], monoepoxy-lignans (187), bisepoxy-lignans (189–193) [32, 47, 66], and norlignans (203–205) [20, 32, 47]. Lignans with one or more isovaleroyloxyl substitution, as exemplified by compounds 195–204 [20], has been frequently uncovered from *S. lyratum* in recent years. Notably, neolignans including compounds 186–187 [47], and 195–202, exhibited neuroprotective effects against human neuroblastoma SH-SY5Y cell injury induced by H₂O₂ [20].

4.7.2 Coumarins, simple phenylpropanoids and their derivatives

So far, seven coumarins (206–212) and eight simple phenylpropanoids (213–220) and their derivatives (221–227) have been isolated from *S. lyratum* as shown in Table 10 and Fig. 15.

4.8 Flavonoids

Thirty-one flavonoids (228–258) have been reported from *S. lyratum* (Table 11, Fig. 16), including flavonols (228, 230, 232–236, 246–249, 251, 256–258) [47, 54, 68, 70–72], flavanones (229, 245) [47, 72], isoflavones (237–244, 250) [47, 54, 69, 71], chalcones (231) [47], and isoflavan-4-ols (252–255) [73], usually in the form of flavonoid glycoside with C-3 or C-7 substitution of the monosaccharides (D-Glc, D-Gal, D-Xyl, L-Rha, and L-Ara) and disaccharides [Rha (1 → 6) Glc, Xyl (1 → 2) Glc, Api (1 → 2) Glc and Xyl (1 → 6) Glc].

4.9 Other compounds

In addition to the abovementioned constituents, other compounds including anthraquinones and fatty acids have also been isolated from *S. lyratum* (Table 12, Fig. 17).

Table 5 Steroidal saponins isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
72	Diosgenin-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-[O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galcopyranoside	C ₅₁ H ₈₄ O ₂₃	1064.5403	[22]
73	Diosgenin-3-O- β -D-xylopyranosyl-(1 $\rightarrow$ 3)-[O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-glucopyranoside	C ₅₀ H ₈₂ O ₂₂	1034.5298	[22]
74	Diosgenin-3-O- β -D-glucopyranosiduronic acid methyl ester	C ₃₄ H ₅₂ O ₉	604.3611	[47]
75	Diosgenin-3-O- α -L-rhamnosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosiduronic acid	C ₃₉ H ₆₀ O ₁₃	736.4034	[47]
76	Diosgenin-3-O- α -L-rhamnosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosiduronic acid methyl ester	C ₄₀ H ₆₂ O ₁₃	750.1490	[47]
77	Diosgenin-3-O- β -D-glucopyranosiduronic acid	C ₃₃ H ₅₀ O ₉	590.3455	[47]
78	Diosgenin-3-O- β -D-xylopyranosyl-(1 $\rightarrow$ 3)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-[O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranoside	C ₅₀ H ₈₀ O ₂₁	1016.5192	[47]
79	Diosgenin-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₃₉ H ₆₂ O ₁₃	738.4190	[47, 49]
80	Diosgenin-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-[O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranoside	C ₄₅ H ₇₂ O ₁₇	884.4770	[4]
81	(25 <i>R</i>)-Spirost-5-en-3 β -ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-[O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-galactopyranoside	C ₄₅ H ₇₂ O ₁₇	884.4770	[22]
82	Funkioside D	C ₄₅ H ₇₂ O ₁₈	900.4719	[22]
83	Aspidistrin	C ₅₁ H ₈₄ O ₂₂	1048.5454	[22]
84	(25 <i>R</i>)-Spirost-5-en-3 β -ol-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-[O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-O- β -D-glucopyranosiduronic acid methyl ester	C ₄₆ H ₇₂ O ₁₈	912.4719	[4]
85	Gitogenin-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₃₉ H ₆₄ O ₁₃	740.4347	[47]
86	(3 β ,25 <i>S</i>)-Spirost-5-ene-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₄ O ₁₈	902.4875	[46]
87	(3 β ,25 <i>S</i>)-Spirost-5-ene-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₄₅ H ₇₂ O ₁₈	900.4719	[47]
88	Lyratoside D	C ₃₃ H ₅₂ O ₉	592.3611	[40]
89	16-Dehydropregnenolone-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosiduronic acid	C ₃₃ H ₄₈ O ₁₂	636.3146	[51]
90	Lyratoside E	C ₃₉ H ₆₀ O ₁₆	784.3881	[40]
91	Lyratoside F	C ₃₉ H ₆₀ O ₁₇	800.3831	[40]
92	5 α -Pregn-16-en-3 β -ol-20-one-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₃₉ H ₆₂ O ₁₇	802.3987	[46]
93	Pallydifloside B	C ₄₅ H ₇₂ O ₁₉	916.4668	[40]
94	26-O- β -D-Glucopyranosyl-(22 <i>S</i> ,25 <i>S</i>)-3 β ,26-dihydroxy-22-methoxyfurost-5-ene-3-O- α -L-rhamnose-(1 $\rightarrow$ 2)-3-O- β -D-glucuronopyranoside	C ₄₆ H ₇₄ O ₁₉	930.4824	[23]
95	26-O- β -D-Glucopyranosyl-(22 <i>S</i> ,25 <i>S</i>)-3 β ,26-dihydroxy-22-methoxyfurost-5-ene-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 3)-[O- α -L-rhamnose-(1 $\rightarrow$ 2)]-3-O- β -D-glucuronopyranoside	C ₅₁ H ₈₂ O ₂₄	1078.5196	[23]
96	26-O- β -D-Glucopyranosyl-(22,25 <i>R</i>)-3 β ,26-dihydroxy-22-methoxyfurost-5-ene-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosiduronic acid methyl ester	C ₄₇ H ₇₆ O ₁₉	944.5247	[40]
97	Lyratoside C	C ₅₂ H ₈₆ O ₂₄	1094.5509	[40]
98	26-O- β -D-Glucopyranosylfurostane-3,22,26-triol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₁ H ₈₆ O ₂₄	1082.5509	[46]
99	26-O- β -D-Glucopyranosyl-22-methoxyfurost-3,26-diol-3-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)-O- β -D-glucopyranosyl-(1 $\rightarrow$ 4)-O- β -D-galactopyranoside	C ₅₂ H ₈₈ O ₂₄	1096.5666	[46]
100	26-O- β -D-Glucopyranosyl-(25 <i>R</i>)-5,20(22)-dienefurostane-3 β ,26-diol	C ₃₃ H ₅₂ O ₈	576.3662	[22]
101	26-O- β -D-Glucopyranosyl-(25 <i>R</i>)-5 α -furost-20(22)-ene-3 β ,26-diol	C ₃₃ H ₅₄ O ₈	578.3819	[22]

5 Pharmacology

Water decoction of the whole herb of *S. lyratum* was commonly used to treat various diseases, and the fresh whole herb was mashed to remedy herpes and warts for external use. Modern pharmacological evaluations revealed that extracts, fractions or compounds isolated from *S. lyratum* possessed various therapeutic potentials.

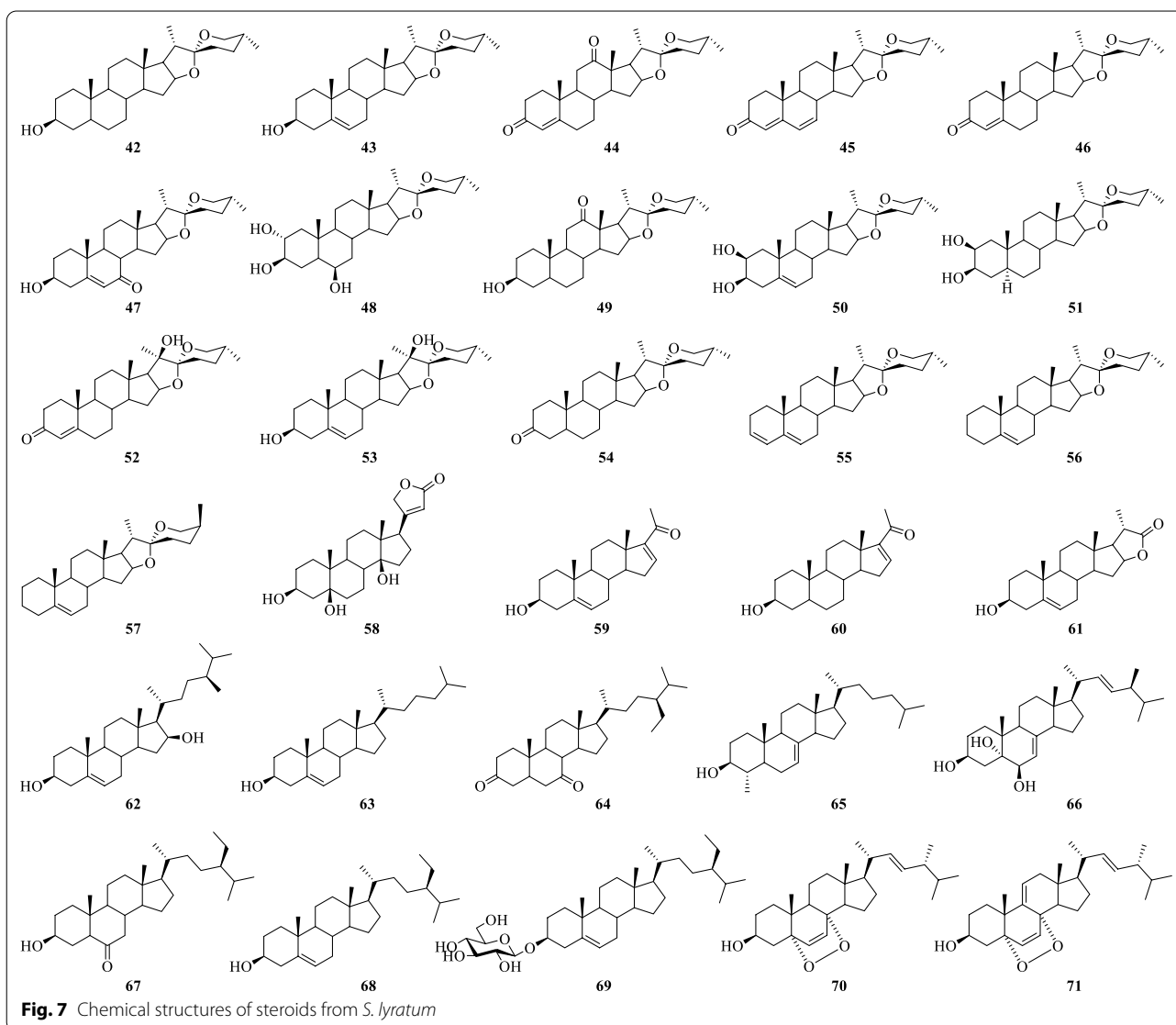
Recently, the plant has been most extensively studied for its anti-cancer pharmacological properties. Meanwhile, other pharmacological effects such as anti-inflammatory, anti-oxidant, anti-microbial, anti-allergy, and hepatoprotective activities of *S. lyratum* have also been assessed, as summarized in Table 13.

Table 6 Representative ^{13}C NMR data of six common steroidal saponins (in $\text{C}_5\text{H}_5\text{N}-d_5$)

Position	Compound 73 (spirostanol-type)	Compound 79 (spirostanol-type)	Compound 60 (C_{21} -steroid-type)	Compound 91 (C_{21} -steroid-type)	Compound 97 (furostanol-type)	Compound 99 (furostanol-type)
1	37.2	37.6	32.5	37.3	37.4	37.2
2	29.9	30.4	32.2	30.2	30.2	30.8
3	78.5	78.4	70.6	78.0	77.2	77.4
4	34.8	39.4	37.3	39.3	39.2	34.8
5	44.7	141.2	45.5	141.4	141.0	44.7
6	28.9	121.6	29.1	121.3	121.6	28.9
7	32.4	32.4	32.3	31.7	32.1	32.4
8	35.3	31.9	34.0	30.3	31.6	35.2
9	54.4	50.5	56.6	50.7	50.2	54.4
10	35.8	37.2	36.0	37.1	37.0	35.8
11	21.3	21.3	21.4	20.9	21.0	21.2
12	40.1	40.1	39.3	35.1	39.7	40.0
13	40.8	40.6	46.6	46.3	40.5	41.1
14	56.4	56.8	55.4	56.4	56.5	56.3
15	32.1	32.3	35.4	32.3	32.2	32.1
16	81.1	81.2	144.7	144.6	81.3	81.3
17	63.0	63.2	155.5	155.2	64.2	64.3
18	16.5	16.4	16.3	15.9	19.3	16.5
19	12.3	19.5	12.4	19.2	19.3	12.3
20	42.0	42.1	196.3	196.2	40.7	40.5
21	14.9	15.0	30.5	27.1	16.3	16.3
22	109.2	109.3			112.6	112.6
23	31.8	32.0			30.8	30.0
24	29.2	29.4			28.4	28.2
25	30.6	30.7			34.2	34.2
26	66.9	67.0			75.2	75.2
27	17.2	17.3			17.2	17.1
22-OCH ₃					47.2	47.2
Gal-(1 → 3)-skeleton						
1'	102.5	103.0		100.3	102.7	102.4
2'	73.1	73.5		73.2	73.3	73.3
3'	75.5	75.4		75.6	75.6	75.6
4'	79.8	79.8		81.0	81.0	81.0
5'	75.3	75.9		75.1	75.2	75.2
6'	60.6	61.0		60.4	60.4	60.5
Glc'-(1 → 4)-Gal						
1''	104.9	107.0		105.2	105.0	105.0
2''	81.2	75.2		86.1	86.1	86.1
3''	87.0	78.4		78.5	78.5	78.4
4''	70.4	72.4		71.8	71.8	71.8
5''	77.6	78.7		78.2	78.2	78.9
6''	63.0	63.1		63.2	63.2	63.2
Glc''-(1 → 2)-Glc'						
1'''	104.7			106.9	106.9	106.9
2'''	76.1			76.6	76.7	76.7
3'''	77.5			77.6	77.6	77.6
4'''	71.1			70.3	70.3	70.3
5'''	77.8			78.9	78.9	78.9
6'''	62.5			61.6	61.6	61.6

Table 6 (continued)

Position	Compound 73 (spirostanol-type)	Compound 79 (spirostanol-type)	Compound 60 (C ₂₁ -steroid-type)	Compound 91 (C ₂₁ -steroid-type)	Compound 97 (furostanol-type)	Compound 99 (furostanol-type)
Xyl-(1 → 3)-Glc'						
1'''	104.9					
2'''	75.0					
3'''	78.5					
4'''	70.7					
5'''	67.2					
26-Glc						
1'''					105.2	105.2
2'''					75.2	75.2
3'''					78.6	78.6
4'''					71.7	71.7
5'''					78.5	78.5
6'''					62.9	62.9



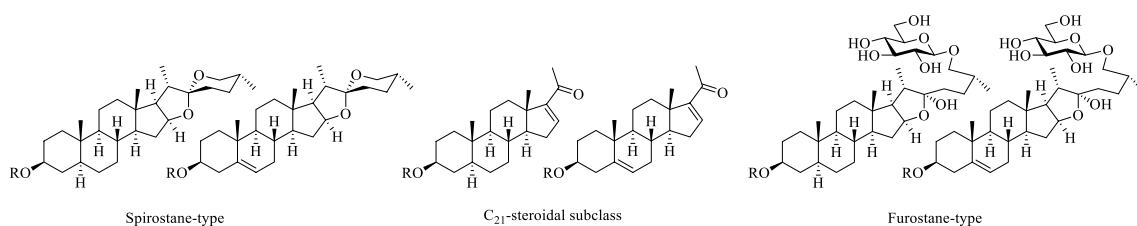


Fig. 8 Sapogenin scaffolds of saponins reported in *S. lyratum*

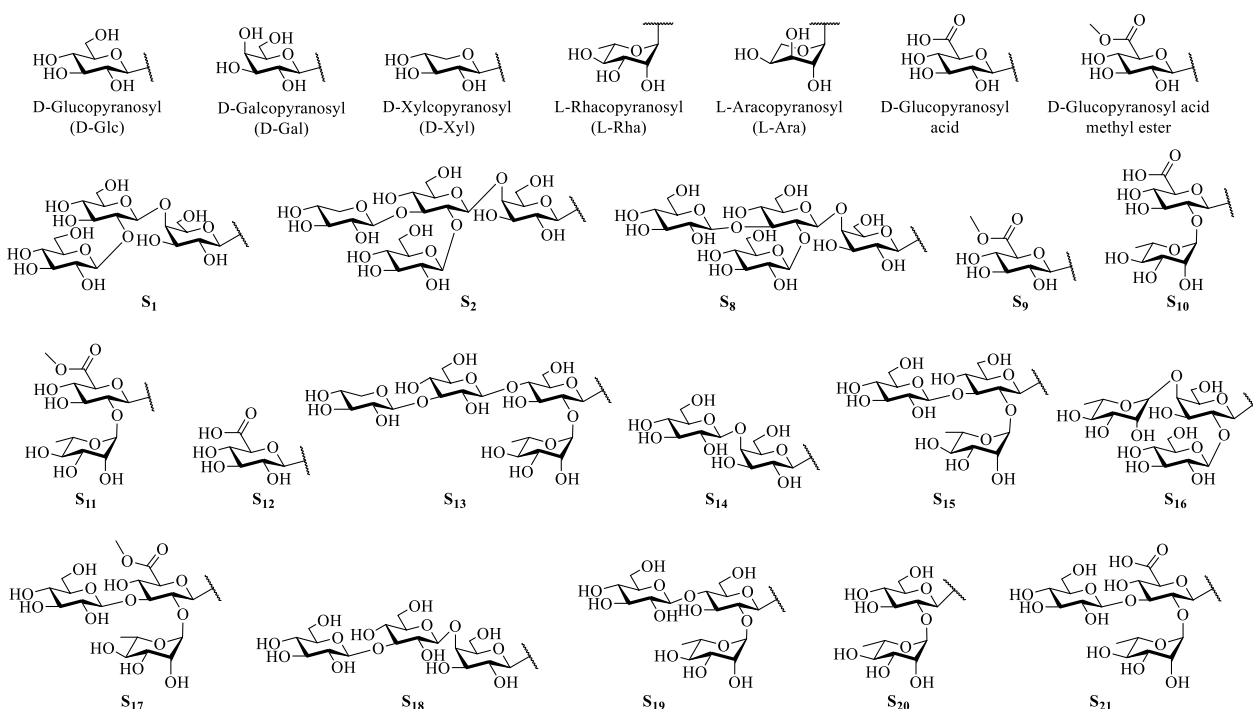


Fig. 9 Glycones of saponins reported in *S. lyratum*

5.1 Anti-cancer

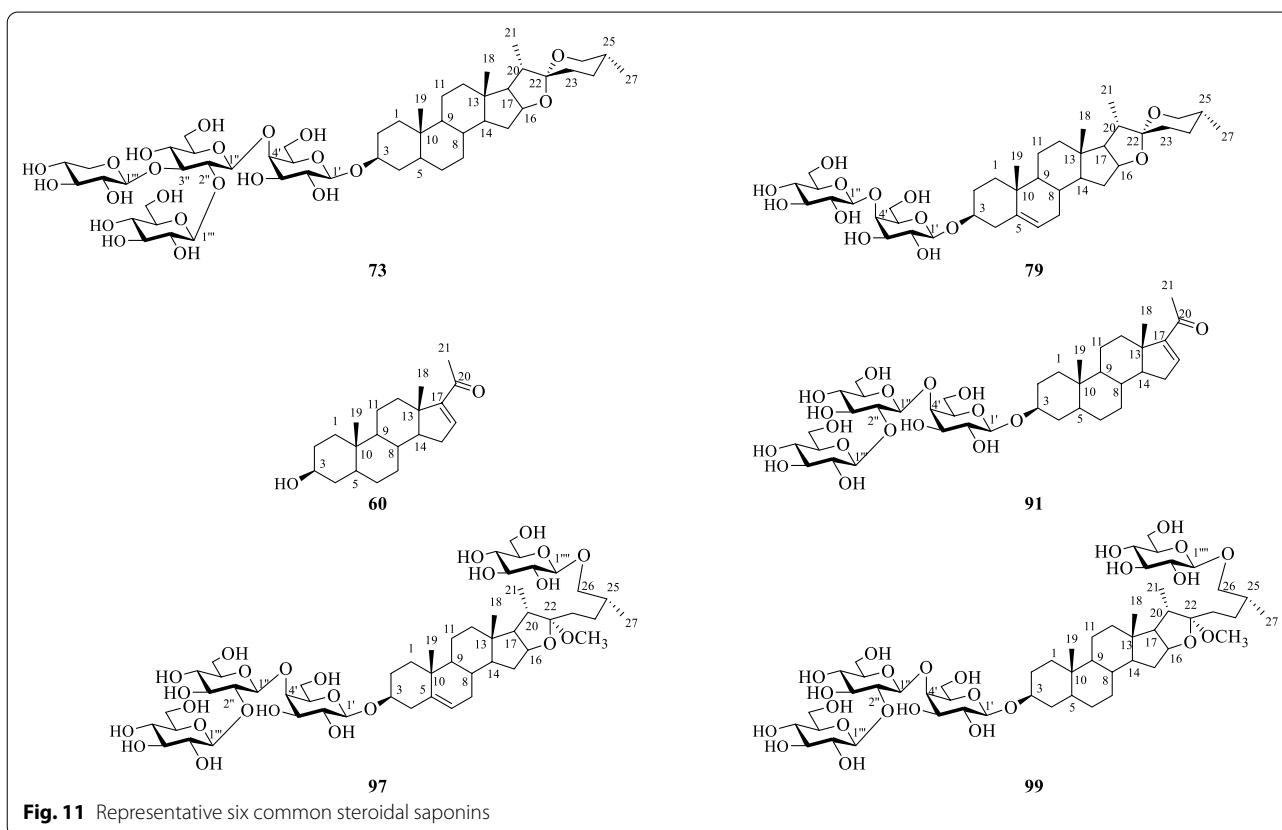
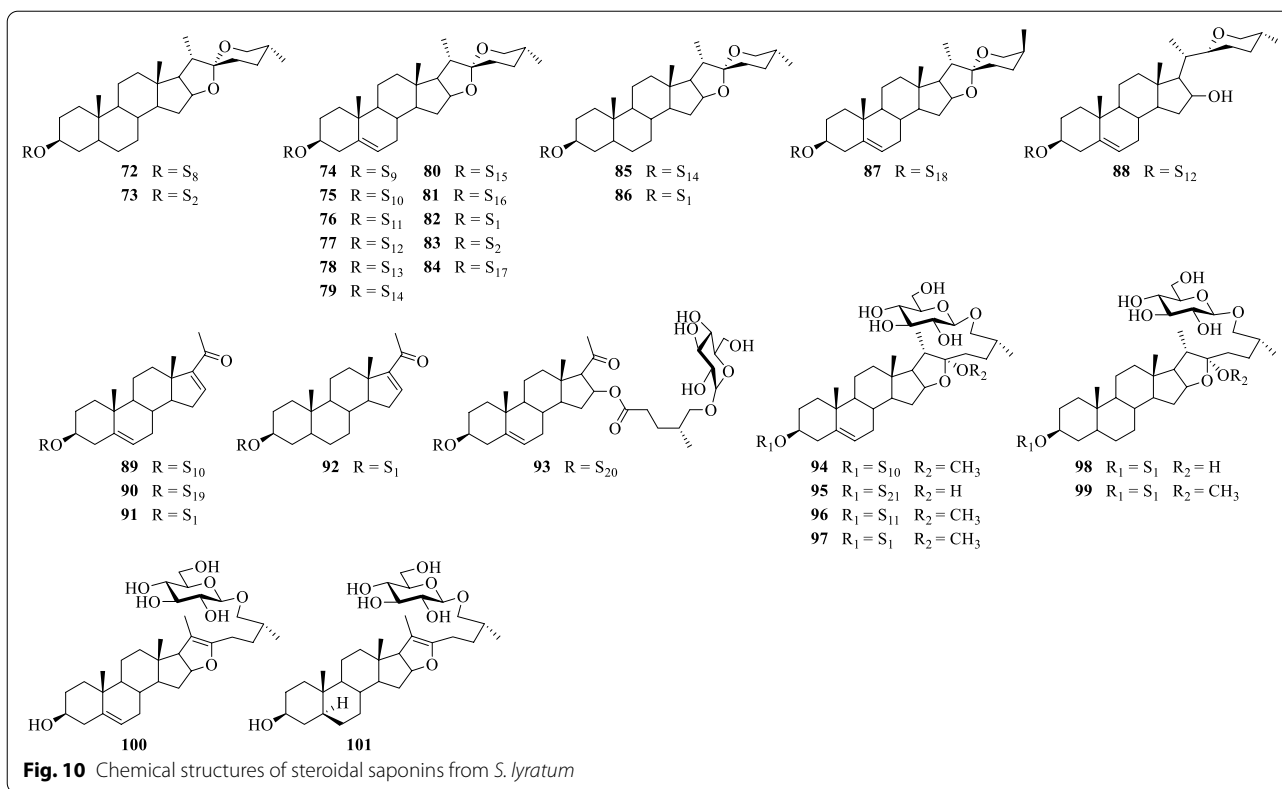
5.1.1 Extracts and fractions

The heat-clearing and detoxicating property of *S. lyratum* is favorable in the treatment of cancer [17, 19, 21]. It has been reported that *S. lyratum* treats various cancers by inhibiting the tumor growth [74, 75], enhancing immunity [76, 78] and inducing apoptosis via activating both extrinsic and intrinsic apoptotic pathways [27, 34, 79].

In S₁₈₀ tumor-bearing mice, both ethanol and aqueous extracts of *S. lyratum* could improve immune function and exhibited anti-cancer potential with certain tumor inhibitory effect by improving the activities of natural killer (NK) and cluster of differentiation 4 (CD4) cells, and elevating the contents of serum Interleukin-2 (IL-2) and tumor necrosis factor- α (TNF- α) [77, 78, 80]. Total alkaloids from *S. lyratum* (SLTA, 24 mL/kg) could inhibit the tumor growth in mice with Lewis lung cancer, and

when combined with cisplatin, a synergistic effect had been shown to down-regulate the mRNA expression of Notch1, Notch3 and Jagged1 in Notch signaling pathway [81]. In addition, the hexane fraction of the methanol extract (50 mg/kg) of *S. lyratum* showed similar inhibitory activity on tumor growth in mice with Lewis lung carcinoma tumor, potentially acting through up-regulating Fas, caspase-8, caspase-3, and p53, and down-regulating FasL and B-cell lymphoma-2 (Bcl-2) in the mitochondrial pathway [27, 79].

Further studies revealed that the 70% ethanol extract of *S. lyratum* (SLE) could suppress tumor angiogenesis in vitro by repressing migration, invasion, and tube formation of tumor-derived vascular endothelial cells (Td-ECs). The mechanism of the anti-angiogenic effect of SLE may be related to the inhibitory activity of vascular endothelial growth factor (VEGF) via reducing



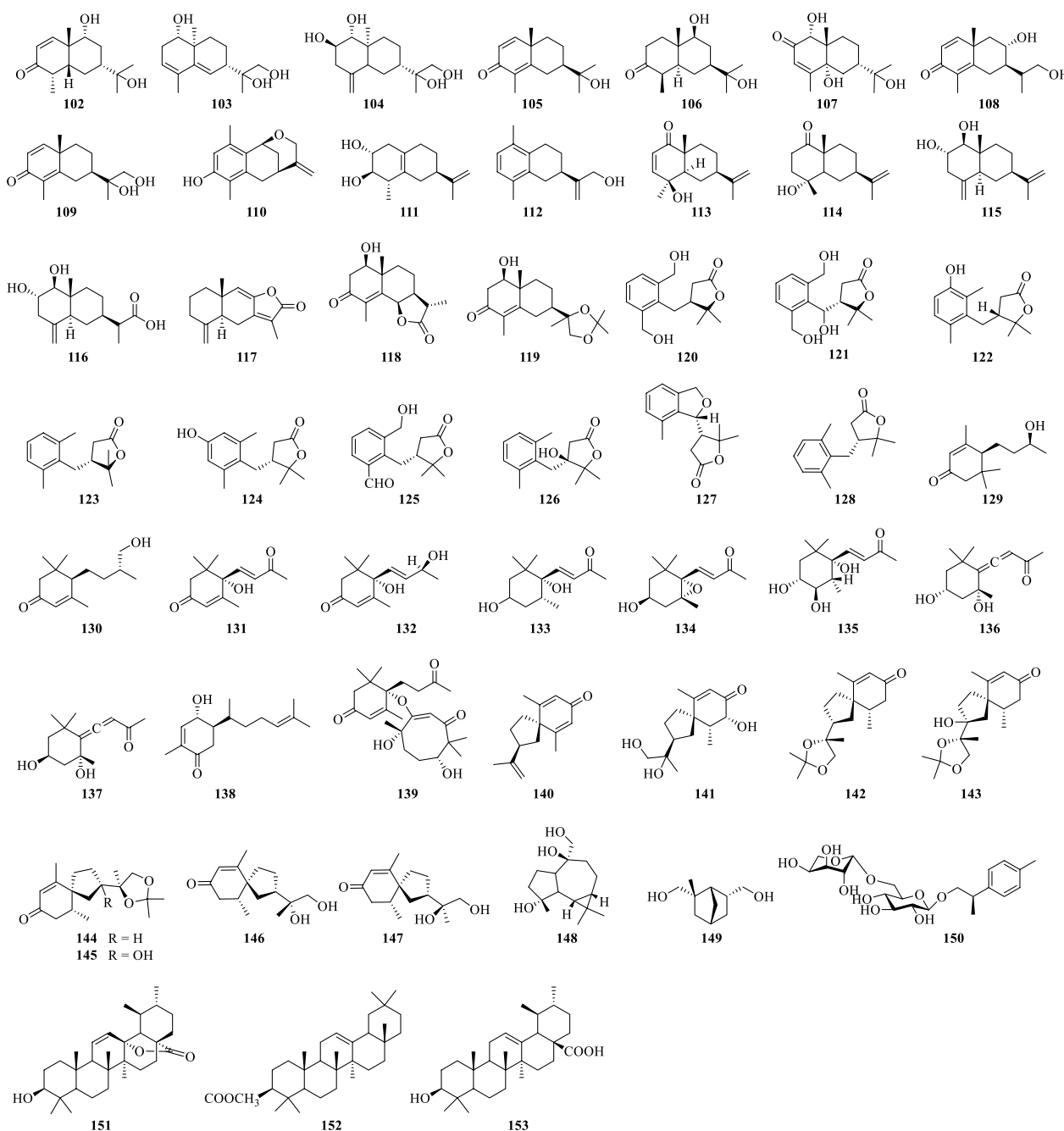


Fig. 12 Chemical structures of terpenoids from *S. lyratum*

the number of lipid rafts in the cell membrane [43] and interfering with the lipid rafts by agglutinating cell membrane cholesterol [75]. These changes led to the inhibition of VEGFR2 phosphorylation and activation of its downstream signaling molecules, thereby inhibiting tumor angiogenesis [43]. In addition, SLTA could induce apoptosis of lung carcinoma A549 cells by inhibiting the nuclear factor-kappa B (NF- κ B) signaling pathway [82],

while glycoalkaloids of *S. lyratum* (SLGS) significantly inhibited the activity of A549-derived exosomes with $IC_{50} = 99.59 \mu\text{g/mL}$ [43].

5.1.2 Compounds

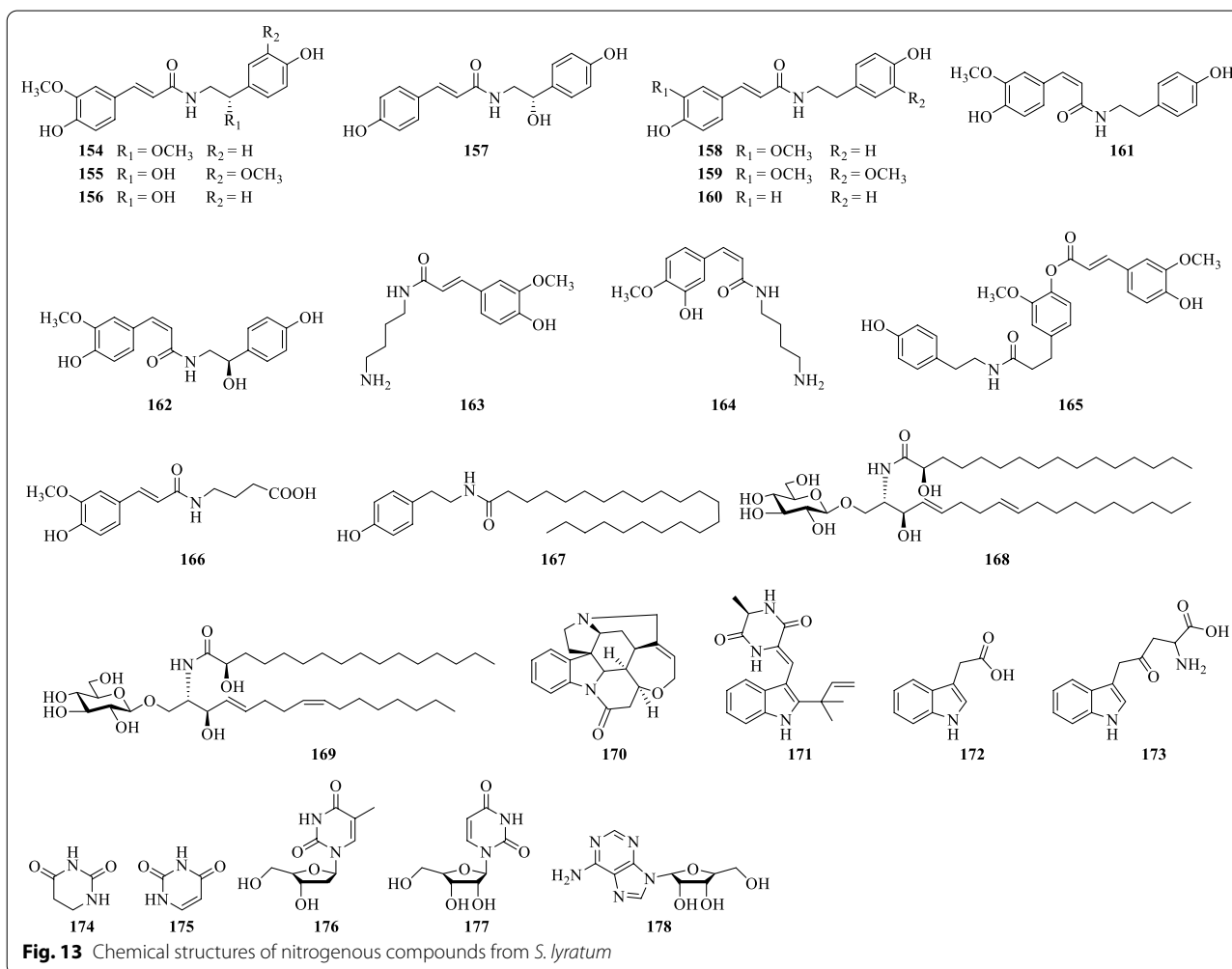
The cytotoxic tests involved in most in vitro studies of *S. lyratum* have shown that the compounds isolated

Table 7 Terpenoids isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
102	Lyratol A	C ₁₅ H ₂₄ O ₃	252.1725	[56]
103	Lyratol B	C ₁₅ H ₂₄ O ₃	252.1725	[57]
104	Lyratol C	C ₁₅ H ₂₆ O ₄	270.1831	[58]
105	Dehydrocarlssone	C ₁₅ H ₂₂ O ₂	234.162	[52]
106	Lyratol G	C ₁₅ H ₂₆ O ₃	254.1882	[59]
107	Solajiangxin A	C ₁₅ H ₂₄ O ₄	268.1675	[60]
108	Solajiangxin G	C ₁₅ H ₂₂ O ₃	250.1529	[61]
109	Solajiangxin F	C ₁₅ H ₂₂ O ₃	250.1529	[61]
110	Solanoid A	C ₁₅ H ₁₈ O ₂	230.1307	[62]
111	Rishitin	C ₁₄ H ₂₂ O ₂	222.162	[63]
112	Solanoid B	C ₁₅ H ₂₀ O	216.1514	[62]
113	Solanoid D	C ₁₅ H ₂₂ O ₂	234.162	[62]
114	(4 <i>R</i> ,5 <i>R</i> ,7 <i>R</i> ,10 <i>R</i>)-4-Hydroxyleudesmane-2,11-dien-1-one	C ₁₅ H ₂₂ O ₂	234.162	[62]
115	Nardoeudesmol A	C ₁₅ H ₂₄ O ₂	236.1776	[62]
116	Solajiangxin D	C ₁₅ H ₂₄ O ₄	268.1675	[60]
117	Atrectylsnolde I	C ₁₅ H ₁₈ O ₂	230.1307	[52]
118	1β-Hydroxy-1,2-dihydro-α-santonin	C ₁₅ H ₂₀ O ₄	264.1362	[59]
119	Solajiangxin H	C ₁₈ H ₂₈ O ₄	308.1988	[64]
120	Septemlobin G	C ₁₅ H ₂₀ O ₄	264.1362	[47]
121	Septemlobin H	C ₁₅ H ₂₀ O ₅	280.1311	[47]
122	Lycifuranone A	C ₁₅ H ₂₀ O ₃	248.1412	[62]
123	(+)-(R)-5,5-Dimethyl-4-(2,6-dimethylbenzyl)-solafuranone	C ₁₅ H ₂₀ O ₂	232.1463	[47]
124	Lyratol D	C ₁₅ H ₂₀ O ₃	248.1412	[58]
125	Solajiangxin B	C ₁₅ H ₁₈ O ₄	262.1205	[60]
126	Solanoid C	C ₁₅ H ₂₀ O ₃	248.1412	[62]
127	Solajiangxin C	C ₁₅ H ₁₈ O ₃	246.1256	[60]
128	Solafuranone	C ₁₅ H ₂₀ O ₂	232.1463	[39]
129	Blumenol C	C ₁₃ H ₂₂ O ₂	210.162	[47]
130	Blumenol	C ₁₄ H ₂₄ O ₂	224.1776	[47]
131	Dehydrovomifoliol	C ₁₃ H ₁₈ O ₃	222.1256	[58]
132	Blumenol A	C ₁₃ H ₂₀ O ₃	224.2412	[58]
133	Boscialin	C ₁₃ H ₂₂ O ₃	226.1529	[56]
134	3β-Hydroxyl-5 <i>α</i> ,6 <i>α</i> -epoxy-7-megastigmen-9-one	C ₁₃ H ₂₀ O ₃	224.1412	[56]
135	Lyratol E	C ₁₃ H ₂₂ O ₄	242.1518	[56]
136	(4 <i>R</i>)-4-(3-Oxo-1-butene-1-ylidene)-3 <i>α</i> ,5,5-trimethylcyclohexane-1 <i>α</i> ,3 <i>β</i> -diol	C ₁₃ H ₂₀ O ₃	224.1412	[56]
137	Lyratol F	C ₁₃ H ₂₀ O ₃	224.1412	[56]
138	1 <i>α</i> -Hydroxybisabol-2,10-dien-4-one	C ₁₅ H ₂₄ O ₂	236.1776	[62]
139	Solalyratin B	C ₂₄ H ₃₄ O ₆	418.2355	[25]
140	Anhydro-β-rotunol	C ₁₅ H ₂₀ O	216.1514	[62]
141	2-(1',2'-Dihydroxyl-1'-methylethyl)-6,10-dimethyl-9-hydroxyspirodec-6-en-8-one	C ₁₅ H ₂₄ O ₄	268.1675	[56]
142	Solajiangxin E	C ₁₈ H ₂₈ O ₃	292.2038	[1]
143	2-Hydroxysolajiangxin E	C ₁₈ H ₂₈ O ₄	308.1988	[1]
144	Solajiangxin I	C ₁₈ H ₂₈ O ₃	292.2038	[64]
145	7-Hydroxysolajiangxin I	C ₁₈ H ₂₈ O ₄	308.1988	[64]
146	(1' <i>S</i> ,2 <i>R</i> ,5 <i>S</i> ,10 <i>R</i>)-2-(1',2'-Dihydroxy-1'-methylethyl)-6,10-dimethylspiro[4,5]dec-6-en-8-one	C ₁₅ H ₂₄ O ₃	252.1725	[56]
147	(1' <i>R</i> ,2 <i>R</i> ,5 <i>S</i> ,10 <i>R</i>)-2-(1',2'-Dihydroxy-1'-methylethyl)-6,10-dimethylspiro[4,5]dec-6-en-8-one	C ₁₅ H ₂₄ O ₃	252.1725	[56]
148	Pipelol A	C ₁₅ H ₂₆ O ₃	254.1882	[47]
149	Paeoveitol C	C ₁₀ H ₁₈ O ₂	170.1307	[47]
150	2-Phenylethyl-(6- <i>O</i> - <i>α</i> -L-arabinofuranosyl)- <i>O</i> -β-D-glucopyranoside	C ₂₁ H ₃₂ O ₁₀	444.1995	[47]

Table 7 (continued)

No	Compounds	Chemical formula	Molecular Wt	Refs.
151	3-Hydroxyl-II-ursen-28,13-olide	C ₃₀ H ₄₆ O ₃	454.3447	[47]
152	β-Amyrin acetate	C ₃₂ H ₅₂ O ₂	468.3967	[47]
153	Ursolic acid	C ₃₀ H ₄₈ O ₃	456.3603	[47]

**Fig. 13** Chemical structures of nitrogenous compounds from *S. lyratum*

from *S. lyratum* possess a good cytotoxic potential for several cancer cells.

In the process of cytotoxic investigation by MTT assay and flow cytometry, the characteristic compounds **5**, **8**, **21** from the methanolic extract of *S. lyratum* showed significant cytotoxicities against hup-7 and HepG2 cell lines with IC₅₀ values of 9.6 ± 0.5 and 10.8 ± 0.1 μM, 11.7 ± 0.3 and 19.4 ± 0.4 μM, and 10.3 ± 1.5 and 91.8 ± 9.4 μM, respectively. The mechanism was attributed to cell cycle arrest at S-phase [83]. while sesquiterpenoids **104**, **106**, **108**, **109**, **116**, **118**,

124, **126**, **127**, **132**, **135**, **142**, and **143** were evaluated for their cytotoxicity activities with IC₅₀ 1.9–8.6 μg/mL against HONE-1 cells [1, 57, 58, 60, 61]. Among them, compounds **126**–**127** showed potent cytotoxicity activity with IC₅₀ 2.1 and 1.9 μg/mL, slightly weaker than the positive controls etoposide and cisplatin (IC₅₀ 1.6 and 1.7 μg/mL) [1, 57, 58, 60, 61]. Notably, the IC₅₀ differences of the positive controls (etoposide and cisplatin) may have been caused by the operation of the author, so the experimental cytotoxicity results need to be further verified.

Table 8 Nitrogenous compounds isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
154	3-(4-Hydroxy-3-methoxyphenyl)- <i>N</i> -[2-(4-hydroxyphenyl)-2-methoxyethyl] acrylamide	C ₁₉ H ₂₁ NO ₅	343.142	[65]
155	<i>N</i> - <i>trans</i> -Feruloyl-3-methoxyoctopamine	C ₁₉ H ₂₁ NO ₆	359.1369	[36]
156	<i>N</i> - <i>trans</i> -Feruloyloctopamine	C ₁₈ H ₁₉ NO ₅	329.1263	[65]
157	(<i>E</i>)- <i>N</i> -(2-Hydroxy-2-(4-hydroxyphenyl)-ethyl)-3-(4-hydroxyphenyl) acrylamide	C ₁₇ H ₁₇ NO ₄	299.1158	[66]
158	<i>N</i> - <i>trans</i> -Feruloyltyramine	C ₁₈ H ₁₉ NO ₄	313.353	[65]
159	<i>N</i> - <i>trans</i> -Feruloyl-3- <i>O</i> -methyl-dopamine	C ₁₉ H ₂₁ NO ₅	343.142	[47, 65]
160	<i>N</i> - <i>trans</i> -Coumaroyltyramine	C ₁₇ H ₁₇ NO ₃	283.1208	[47, 67]
161	<i>N</i> - <i>cis</i> -Feruloyltyramine	C ₁₈ H ₁₉ NO ₄	313.353	[47]
162	<i>N</i> - <i>cis</i> -Femloyloctopamine	C ₁₈ H ₁₉ NO ₅	329.1263	[36]
163	(<i>E</i>)- <i>N</i> -(4-Aminobutyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide	C ₁₄ H ₂₀ N ₂ O ₃	264.1474	[68]
164	(<i>Z</i>)- <i>N</i> -(4-Aminobutyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide	C ₁₄ H ₂₀ N ₂ O ₃	264.1474	[68]
165	Hibiscuwanin B	C ₂₈ H ₂₉ NO ₇	491.1944	[47]
166	<i>N</i> - <i>trans</i> -Femloylbutyric acid	C ₁₄ H ₁₇ NO ₅	279.1107	[36]
167	<i>N</i> -Docosanoyltyramine	C ₃₀ H ₅₃ NO ₂	459.4076	[47]
168	Soyacerebroside I	C ₄₀ H ₇₅ NO ₉	713.5442	[47]
169	Soyacerebroside II	C ₄₀ H ₇₅ NO ₉	713.5442	[47]
170	Strychnine	C ₂₁ H ₂₂ N ₂ O ₂	334.1681	[65]
171	Neoechinulin A	C ₁₉ H ₂₁ N ₂ O ₃	323.1634	[47]
172	β -Hydroxyindole acetic acid	C ₁₀ H ₉ NO ₂	175.0633	[47]
173	(<i>R</i>)-2-Amino-5-(1 <i>H</i> -indol-3-yl)-4-oxopentanoic acid	C ₁₃ H ₁₄ N ₂ O ₃	246.1004	[47]
174	Dihydrouracil	C ₄ H ₆ N ₂ O ₂	114.0429	[47]
175	Uracil	C ₄ H ₄ N ₂ O ₂	112.0273	[47]
176	Thymidine	C ₁₀ H ₁₄ N ₂ O ₅	242.0903	[47]
177	Uridine	C ₉ H ₁₂ N ₂ O ₆	244.0695	[47]
178	Adenosine	C ₁₀ H ₁₃ N ₅ O ₄	267.0968	[47]

Further, the cytotoxic potentials of nine steroids saponins and alkaloids (**36**, **72**, **73**, **81–83**, **86**) against ASGC7901 and BEL-7402 cancer cell lines were tested, and compounds **72**, **73**, and **83** showed attractive anti-proliferative activities with respective IC₅₀ values of 6.39–9.11 μ M, 3.19–8.86 μ M and 0.39–1.16 μ M, as compared with IC₅₀ values of 0.17–5.34 μ M and 8.15–23.06 μ M of positive control adriamycin and 5-fluorouracil, respectively [22]. Another, a glycoalkaloid (**10**) exhibited significant cytotoxicity against mouse colon cancer CT-26 cells with IC₅₀ 3.5 μ M, as compared to IC₅₀ values of 1.8 μ M of positive control etoposide, in clue of the inhibition on the expressions of survivin and NF- κ B/p65 and the induction of the AIF nuclear translocation [74]. Besides those characteristic constituents of *S. lyratum*, four other compounds **267–270** have been evaluated their cytotoxicities against hepatocellular carcinoma cell lines, and **267** and **269** showed significant inhibitory activities against HepG2 cell lines with IC₅₀ values of 46.07 μ M and 45.39 μ M, respectively [26].

5.2 Anti-inflammatory

5.2.1 Extracts and fractions

Inflammation is closely related to cancer disease [84]. The detoxication and detumescence effect of *S. lyratum* can be used as a supplement to modern anti-inflammatory agents.

Total alkaloid fraction from the 70% ethanol extract of *S. lyratum* significantly relieved the inflammatory effect of the lipopolysaccharide-stimulated RAW264.7 macrophages for 48 h. Further evaluation revealed that this total alkaloid fraction could inhibit the release of Cyclooxygenase-2 (COX-2), and Prostaglandin E2 (PGE2) from lipopolysaccharide-stimulated RAW264.7 macrophages [85].

5.2.2 Compounds

In vitro, diosgenin-3-*O*- α -L-rhamnosyl-(1 $\rightarrow$ 2)-*O*- β -D-glucopyranosiduronic acid (**75**) could inhibit the lipopolysaccharide-induced expression of intercellular cell adhesion molecule-1 (ICAM-1) protein at 16 μ g/mL, and exhibited anti-inflammatory activities [86]. In addition, in the anti-inflammatory experiments with

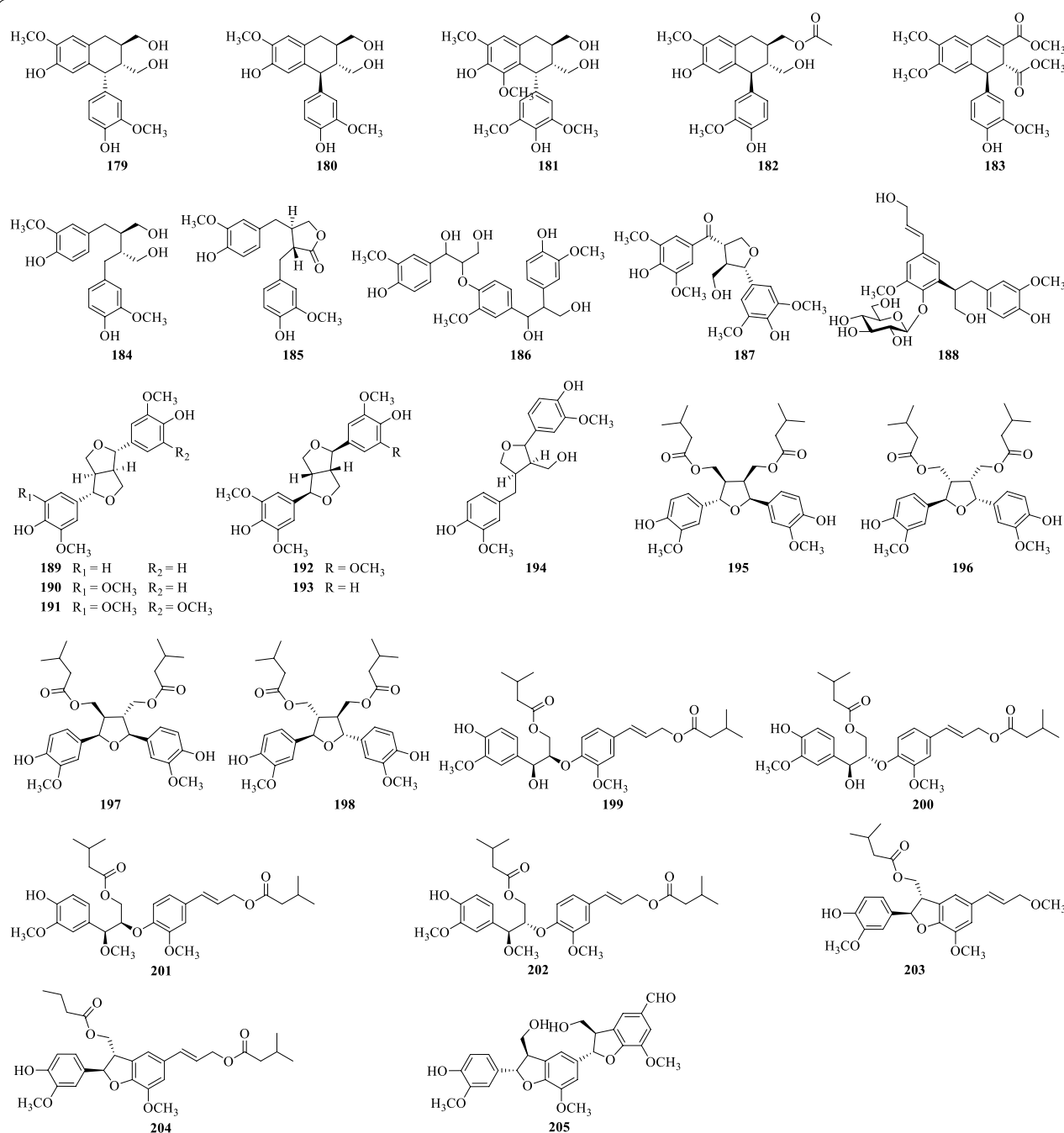


Fig. 14 Chemical structures of lignans from *S. lyratum*

polymorphonuclear leukocytes of rats (rat PMNs) with ginkgolide B as the positive control, compounds **139**, **207–210** showed significant β -glucuronidase inhibitory activities with IC_{50} values range of 6.3–9.1 μM [25], while four 4-hydroxyisoflavans **252–255** afforded anti-inflammatory activities with inhibitory ratios release of β -glucuronidase in the range of 30.3–38.6% at 10 μM [73].

5.3 Antioxidant activity

5.3.1 Extracts

Modern pharmacological studies have revealed that cancer or other diseases are primarily associated with the production and accumulation of excessive free radicals [87], which are commonly produced by the continuous contact between our body and the outside world. Thus,

Table 9 Lignans isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
179	(+)-Isolariciresinol	C ₂₂ H ₂₂ O ₈	414.1315	[47]
180	ent-Isolariciresinol	C ₂₂ H ₂₂ O ₈	414.1315	[32, 47]
181	(+)-Lyoniresinol	C ₂₂ H ₂₈ O ₈	420.1784	[47]
182	Isolariciresinol-9-acetate	C ₂₂ H ₂₆ O ₇	402.1679	[66]
183	Aviculin	C ₂₂ H ₂₂ O ₈	414.1315	[32, 47]
184	(-)-Secoisolariciresinol	C ₂₀ H ₂₆ O ₆	362.1729	[32, 47]
185	(+)-Matairesinol	C ₂₀ H ₂₂ O ₆	358.1416	[47]
186	Leptolepisol D	C ₂₇ H ₃₂ O ₁₀	516.1995	[32, 47]
187	Ciwujiatone	C ₂₂ H ₂₆ O ₉	434.1577	[32, 47]
188	3-Methoxy-4-hydroxy-5-[(8'S)-3'-methoxy-4'-hydroxyphenylpropyl alcohol]-E-cinnamic alcohol-4-O-β-D-glucopyranoside	C ₂₆ H ₃₄ O ₁₁	522.2101	[68]
189	(+)-Pinioresinol	C ₂₀ H ₂₂ O ₆	358.1416	[32, 47]
190	(+)-Medioresinol	C ₂₁ H ₂₄ O ₇	388.1522	[47]
191	(+)-Syringaresinol	C ₂₂ H ₂₆ O ₈	418.1628	[32]
192	(-)-Syringaresinol	C ₂₂ H ₂₆ O ₈	418.1628	[47]
193	(-)-Epipinioresinol	C ₂₁ H ₂₄ O ₇	388.1522	[32, 47]
194	(+)-Lariciresinol	C ₂₀ H ₂₄ O ₆	360.1573	[47]
195	(7S,8R,7'R,8'R)-Solanumin A	C ₃₀ H ₄₀ O ₉	544.2672	[20]
196	(7R,8S,7'S,8'S)-Solanumin A	C ₃₀ H ₄₀ O ₉	544.2672	[20]
197	Solanumin B	C ₃₀ H ₄₀ O ₉	544.2672	[20]
198	Solanumin C	C ₃₀ H ₄₀ O ₉	544.2672	[20]
199	Solanumin D	C ₃₀ H ₄₀ O ₉	544.2672	[20]
200	Solanumin E	C ₃₀ H ₄₀ O ₉	544.2672	[20]
201	Solanumin F	C ₃₁ H ₄₂ O ₉	558.2829	[20]
202	Solanumin G	C ₃₁ H ₄₂ O ₉	558.2829	[20]
203	Solanumin H	C ₂₆ H ₃₂ O ₇	456.2148	[20]
204	Solanumin I	C ₃₀ H ₃₈ O ₈	526.2567	[20]
205	Cinnacassin D	C ₂₈ H ₂₈ O ₉	508.1733	[47]

antioxidants can effectively relieve the harmful effects of free radicals. It has been confirmed that *S. lyratum* extracts and compounds possess significant antioxidant activities.

50% Ethanol extract of *S. lyratum* (10 µg/mL) could protect against oxidized low-density lipoprotein (Ox-LDL)-induced injury in cultured human umbilical vein endothelial cells (HUVECs) by direct antioxidative action [88]. In the DPPH radical-scavenging tests in vitro using the spectrophotometric method with vitamin C as the positive control, the ethanol and ethyl acetate extracts from *S. lyratum* showed antioxidative potential with IC₅₀ of 0.230 mg/mL and 1.010 mg/mL, respectively [89].

5.3.2 Compounds

Five flavones **236**, **248**, **249**, **251**, and **258** from the ethanol extracts of *S. lyratum* possessed the capability of scavenging DPPH free radicals with IC₅₀ values of

2.56–21.33 µg/mL [70]. It seems that the glycosidation of the flavone C-3 and C-5 is essential for the scavenging of DPPH free radicals.

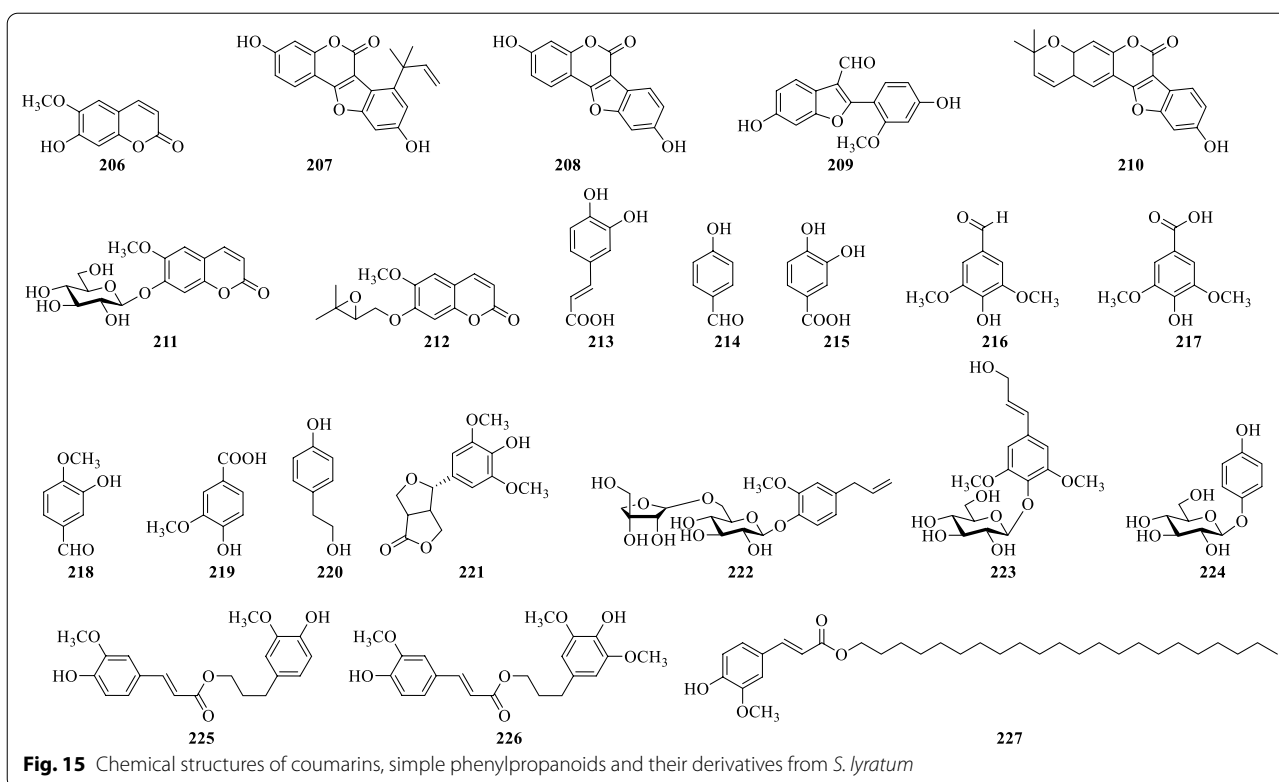
5.4 Antimicrobial

5.4.1 Extracts and fractions

There were reports verified the antibacterial potential of *S. lyratum* extracts. For example, the water-soluble polysaccharide of *S. lyratum* exerted a significant antibacterial activity against *Staphylococcus aureus*, *Salmonella*, *Pasteurella*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa*. The inhibition zone diameters were > 13 mm at a concentration of 120 mg/mL [90].

5.4.2 Compounds

Several gram-positive bacteria (*S. aureus* and *Enterococcus faecalis*) were used to assess the antimicrobial activity of a new compound **266** from *S. lyratum*, with minimum inhibitory concentration (MIC) values of



2.0 μM (1.08 $\mu\text{g/mL}$) and 10.0 μM (5.44 $\mu\text{g/mL}$), respectively [21].

5.5 Other activities

The extracts of *S. lyratum* showed a therapeutic potential on the tetrachloride-induced liver damage in rats, by decreasing significantly the activity of transaminase in rat serum [91, 92]. Further, there was an in vivo report revealed that the aqueous extract of *S. lyratum* possessed strong antiallergy activity [93] by inhibiting dose-dependently the histamine release from the rat peritoneal mast cells and decreasing the mRNA expression of L-histamine decarboxylase [94]. Lastly, the ethanol extract of *S. lyratum* possesses molluscicidal activities with IC_{50} values of 30–50 mg/mL [95].

Notably, several Chinese patent prescriptions with *S. lyratum* as the major component herb, showed significant anticancer efficacies in reported clinic trials. For example, 'Baiyingtang' (composed of *S. lyratum*, *Herba Patriniae*, *Houttuynia cordata*, *Lilium brownii* var., *Asparagus cochinchinensis* (Lour.) Merr.) retention enema could reduce plasma transforming growth factor- β 1 (TGF- β 1), interleukin-6 (IL-6) levels and increase plasma IL-4 levels in patients with pelvic tumors receiving radiotherapy [96]. 'Baiying decoction' (composed of *S. lyratum*, *Ophiocordyceps sinensis*, *Houttuynia cordata*, *Lilium brownii*

var., *Asparagus cochinchinensis* (Lour.) Merr.) treatment could ameliorate the marrow suppression and the quality of life in patients with advance non-small cell lung cancer, with high safety [97].

6 Toxicology

Up to now, the toxicity studies of the isolated compounds and extracts of *S. lyratum* may have been overlooked by researchers, while few studies have found the toxic potential of *Solanum* glycoalkaloid [125]. The toxic properties of Glycoalkaloids including solamargine (8) have been reviewed by Sinani AI S.S.S. et al. are due to (1) their ability to disrupt cell-membrane function by complexation with membrane 3β -hydroxysterols to form aggregates and damage the membrane integrity [126], (2) their anti-acetylcholinesterase activity on the central nervous system [126, 127], and (3) changes caused by them in active transport of ions through membranes, resulting in disorders in general body metabolism [126]. Additionally, in the acute toxicity experiment with rats, neither mortality nor clinical alterations were shown, except for the mild transient diarrhea with 70% ethanol extract of *S. lyratum* at 5000 mg/kg [31]. In future, more pharmacological evidences should be sought on the possible adverse effects and the toxicities of *S. lyratum* extracts and their bioactive constituents when

Table 10 Coumarins, simple phenylpropanoids and their derivatives isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
206	Scopoletin	C ₁₀ H ₈ O ₄	192.0423	[47]
207	Solalyratin A	C ₂₀ H ₁₆ O ₅	336.0998	[25]
208	Coumestrol	C ₁₅ H ₈ O ₅	268.0372	[25]
209	Puerariafuran	C ₁₆ H ₁₂ O ₅	284.0685	[25]
210	9-Hydroxy-2,2-dimethylpyrano[5,6:2,3]-coumestan	C ₂₀ H ₁₆ O ₅	336.0998	[25]
211	Magnolioside	C ₁₆ H ₁₈ O ₉	354.0951	[69]
212	7-(2,3-Epoxy-3-methyl-3-butyloxy)-6-methoxycoumarin	C ₁₅ H ₁₆ O ₅	276.0998	[47]
213	Caffeic acid	C ₉ H ₈ O ₄	180.0423	[47]
214	<i>p</i> -Hydroxybenzaldehyde	C ₇ H ₆ O ₂	122.0368	[47]
215	Protocatechuic acid	C ₇ H ₆ O ₄	154.0266	[47]
216	Syringaldehyde	C ₉ H ₁₀ O ₄	182.0579	[47]
217	Syringate	C ₉ H ₁₀ O ₅	198.0528	[47]
218	Isovanillin	C ₈ H ₈ O ₃	152.0473	[47]
219	Vanillic acid	C ₈ H ₈ O ₄	168.0423	[36]
220	<i>p</i> -Hydroxyphenethyl alcohol	C ₈ H ₁₀ O ₂	138.0681	[36]
221	Zhebeiresinol	C ₁₄ H ₁₆ O ₆	280.0947	[32, 47]
222	Eugenyl- <i>O</i> -β- <i>D</i> -apiofuranosyl-(1*→6)- <i>O</i> -β- <i>D</i> -glucopyranoside	C ₂₀ H ₂₈ O ₁₁	444.1632	[47]
223	Syringin	C ₁₇ H ₂₄ O ₉	372.1420	[32]
224	Arbutin	C ₁₂ H ₁₆ O ₇	272.0896	[70]
225	Dihydroconiferyl ferulate	C ₂₀ H ₂₂ O ₆	358.1416	[36]
226	Dihydrosinapyl ferulate	C ₂₁ H ₂₄ O ₇	388.1522	[36]
227	Docosyl ferulate	C ₃₂ H ₅₄ O ₄	502.4022	[47]

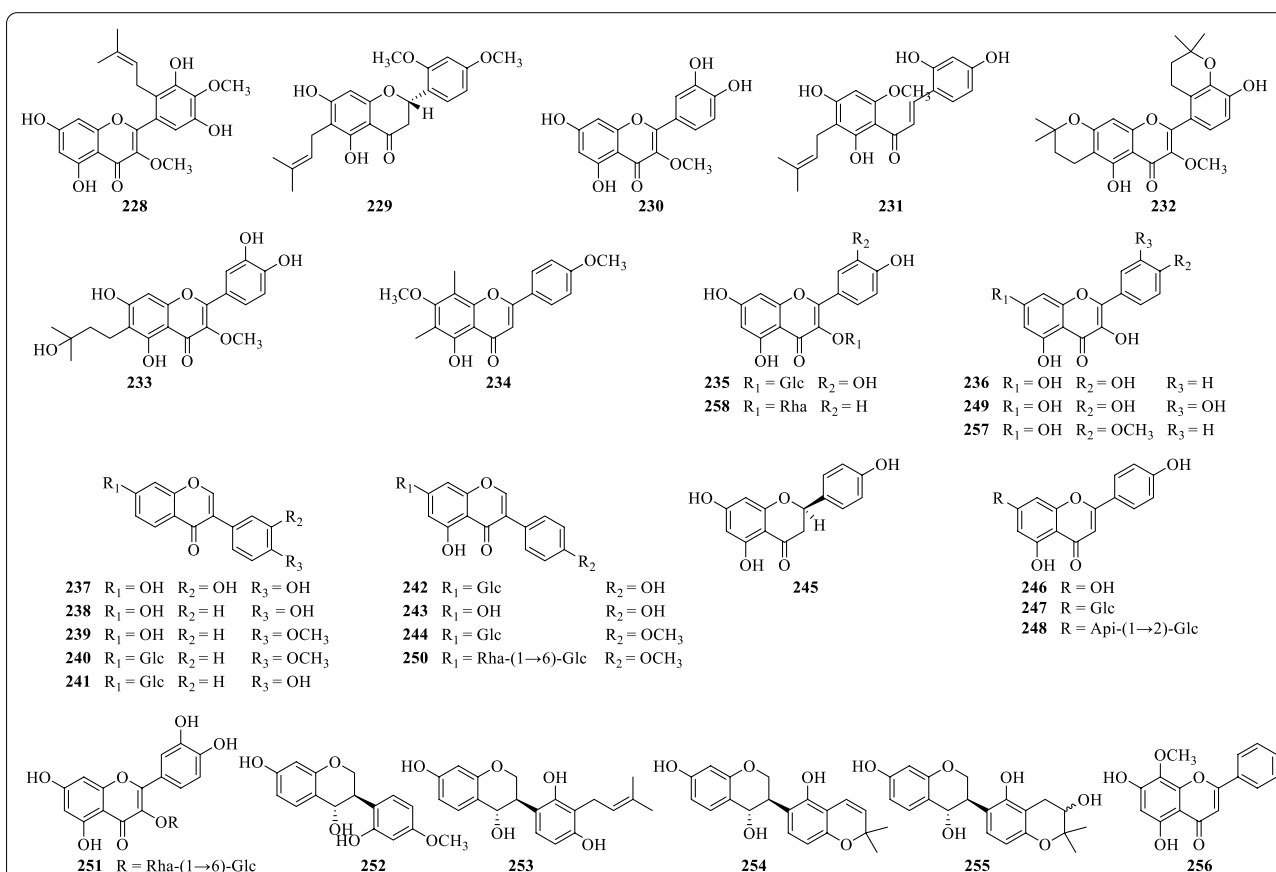
**Fig. 16** Chemical structures of flavonoids from *S. lyratum*

Table 11 Flavonoids isolated from *S. lyratum*

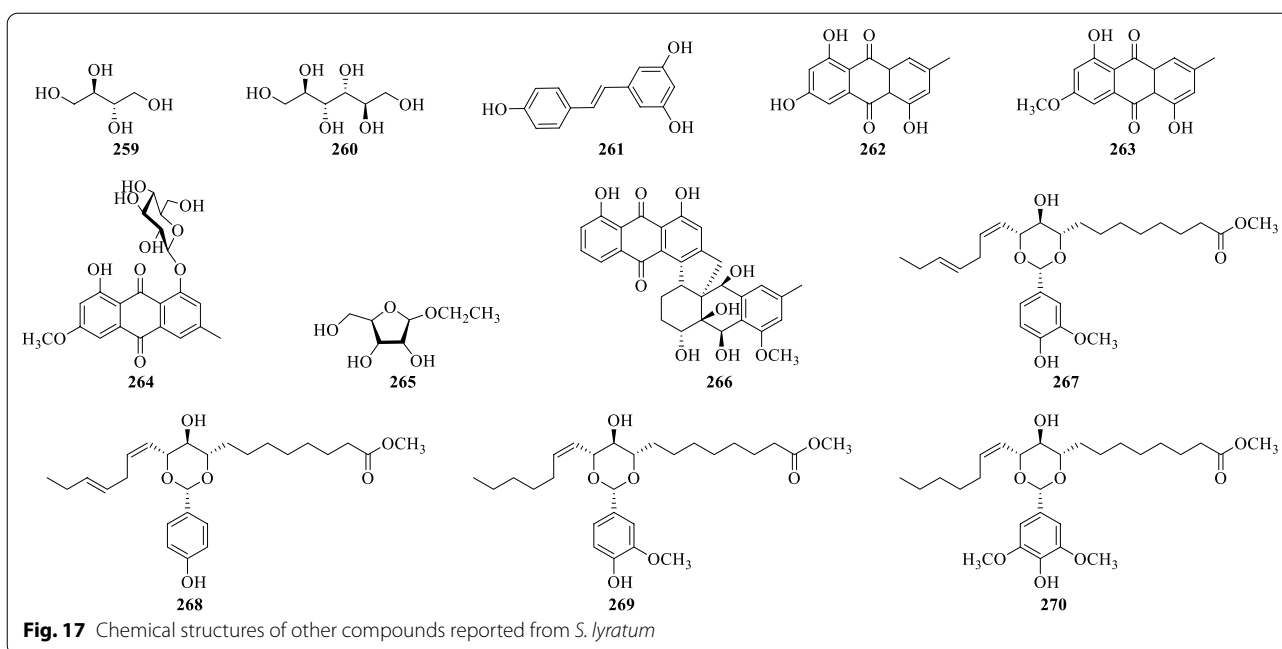
No	Compounds	Chemical formula	Molecular Wt	Refs.
228	5,7,3',5'-Tetrahydroxy-3,4'-dimethoxy-6'-prenylflavonoide	C ₂₂ H ₂₂ O ₈	414.1315	[47]
229	5,7-Dihydroxy-6-isopentenyl-2',4'-dimethoxydihydroflavone	C ₂₂ H ₂₄ O ₆	384.1573	[47]
230	3-Methoxyquercetin	C ₁₆ H ₁₂ O ₇	316.0583	[47]
231	7,9,2',4'-Tetrahydroxyl-8-isopentenyl-5-methoxychalcone	C ₂₁ H ₂₂ O ₆	370.1416	[47]
232	6,7-Bis-2',3'-(2,2-dimethyldihydropyrano)-5,4'-dihydroxy-3-methoxyflavone	C ₂₆ H ₂₈ O ₇	452.1835	[47]
233	Wightianin	C ₂₁ H ₂₂ O ₈	402.1315	[47]
234	5-Hydroxy-4',7-dimethoxy-6,8-dimethylflavone	C ₁₉ H ₁₈ O ₅	326.1154	[47]
235	Quercetin-3'-O-β-D-glucoside	C ₂₁ H ₂₀ O ₁₂	464.0955	[47]
236	Kaempferol	C ₁₅ H ₁₀ O ₆	286.0477	[47]
237	3'-Hydroxydaidzein	C ₁₅ H ₁₀ O ₅	270.0528	[47]
238	Daidzein	C ₁₅ H ₁₀ O ₄	254.0579	[47]
239	Formononetin	C ₁₆ H ₁₂ O ₄	268.0736	[71]
240	Ononin	C ₂₂ H ₂₂ O ₉	430.1264	[69]
241	Daidzin	C ₂₁ H ₂₀ O ₉	416.1107	[69]
242	Genistin	C ₂₁ H ₂₀ O ₁₀	432.1056	[69]
243	Genistein	C ₁₅ H ₁₀ O ₅	270.0528	[71]
244	5-Hydroxylononin	C ₂₂ H ₂₀ O ₁₀	446.1213	[69]
245	Naringenin	C ₁₅ H ₁₂ O ₅	272.0685	[72]
246	Apigenin	C ₁₅ H ₁₀ O ₅	270.0528	[71]
247	Apigenin-7-O-β-D-glycoside	C ₂₁ H ₂₀ O ₁₀	432.1056	[68]
248	Apigenin-7-O-β-D-apiofuranosyl(1 → 2)-O-β-D-glucopyranoside	C ₂₆ H ₂₈ O ₁₄	564.1479	[68]
249	Quercetin	C ₁₅ H ₁₀ O ₇	302.0427	[72]
250	Acacetin-7-O-rutinoside	C ₂₈ H ₃₂ O ₁₅	592.5174	[50]
251	Rutin	C ₂₇ H ₃₀ O ₁₆	610.1534	[67]
252	4,7,2'-Trihydroxy-4'-methoxyisoflavan	C ₁₆ H ₁₆ O ₅	288.0998	[73]
253	Lyratin A	C ₂₀ H ₂₂ O ₅	342.1467	[73]
254	Lyratin B	C ₂₀ H ₂₀ O ₅	340.1311	[73]
255	Lyratin C	C ₂₀ H ₂₂ O ₆	358.1416	[73]
256	Kaempferide	C ₁₆ H ₁₂ O ₆	300.0634	[70]
257	Wogonin	C ₁₆ H ₁₂ O ₅	284.0685	[47]
258	Afzelin	C ₂₁ H ₂₀ O ₁₀	432.1056	[70]

used in treatments of acute, subchronic, or chronic diseases. Further, more clinical trials must be conducted to evaluate the safety and clinical efficacy of *S. lyratum* in humans.

7 Conclusion

This review summarized the latest advancements of *S. lyratum* in botany, traditional uses, phytochemistry, pharmacology, and toxicology. Phytochemical and pharmacological studies have validated many modern usages of this plant. A total of 270 chemical constituents have been isolated from *S. lyratum*, including steroidal alkaloids, steroidal saponins, terpenoids, nitrogenous compounds, phenylpropanoids, flavonoids,

etc. It has been popular in traditional practices due to its potential efficacy on cancer and inflammation, and showed important biological properties in scientific investigations. In the phytochemical analysis of *S. lyratum* extracts, aqueous and ethanol extracts were commonly acquired from *S. lyratum*, whose main components included total alkaloids and total saponins. In modern pharmacological studies, compounds and extracts from *S. lyratum* were evaluated in vivo and in vitro, and their anticancer and cytotoxic, anti-inflammatory, antioxidant, antimicrobial, anti-allergy, and hepatoprotective activities have been demonstrated. However, many aspects of *S. lyratum* have not been studied yet and some relative studies on *S.*

**Table 12** Other compounds isolated from *S. lyratum*

No	Compounds	Chemical formula	Molecular Wt	Refs.
259	Erythritol	C ₄ H ₁₀ O ₄	122.0579	[47]
260	Mannitol	C ₆ H ₁₄ O ₆	182.0790	[47]
261	3,4,5-Trihydroxystilbene	C ₁₄ H ₁₂ O ₃	228.0786	[72]
262	1,3,5-Trihydroxy-7-methylantraquinone	C ₁₅ H ₁₂ O ₅	272.0685	[50]
263	1,5-Dihydroxy-3-methoxy-7-methylantraquinone	C ₁₆ H ₁₄ O ₅	286.0841	[50]
264	Physcion-8-O-β-D-glucopyranoside	C ₂₂ H ₂₄ O ₁₀	446.1213	[50]
265	Ethyl-α-D-arabinofuranoside	C ₇ H ₁₄ O ₅	178.0841	[69]
266	Solanrubiellin A	C ₃₁ H ₂₈ O ₉	544.1733	[21]
267	Solacetal A	C ₂₇ H ₄₀ O ₇	476.2774	[26]
268	Solacetal B	C ₂₆ H ₃₈ O ₆	446.2628	[26]
269	Solacetal C	C ₂₇ H ₄₂ O ₇	478.2931	[26]
270	Solacetal D	C ₂₈ H ₄₄ O ₈	508.3036	[26]

lyratum should be further explored in the following aspects in the future.

Firstly, the pharmacological activities are mostly proven from the aqueous and ethanol extracts from *S. lyratum*, while insufficient pharmacological studies have been conducted on pure compounds. In addition, some activities are lacking comparisons to standards or positive and negative controls. Other studies especially on anticancer and anti-inflammatory activities have shown that the IC₅₀ values of the test extracts/compounds of *S. lyratum* are above 200 µg/mL, which can be considered that such extracts/compounds are actually poorly active.

Secondly, pharmacological studies were mostly performed in cell models and animals while investigations in humans have been seldomly performed. Hence, the future investigation should be focused on the bioactivity of *S. lyratum* in various clinical studies with humans. In addition, the DPPH radical scavenging test and antimicrobial activities also should be guaranteed in vivo, instead of solely relying on method models in vitro.

Thirdly, global quality control standards of *S. lyratum* are needed urgently and should be improved. Simultaneous qualitative and quantitative measures are recommended to be used for those major active constituents of *S. lyratum*.

Table 13 Pharmacological activities of *S. lyratum*

Bioactivities	Object	In vitro /in vivo	Mechanism	Extracts/Compounds	Refs.
Anti-lung cancer	mice with Lewis lung cancer	In vivo	Down-regulating the expression of Notch signaling pathway, improving the NK cell activity, increasing the number of CD ₄ cells, increasing sub-G ₁ peaks, and activating caspase-8, -9, and -3 protein, IC ₅₀ = 170 µg/mL	Total alkaloids, methanol and ethanol extracts	[19, 82, 98]
	Balb/C mouse with A549 lung cancer	In vivo/in vitro	Up-regulating the expression of bid mRNA, caspase-9, and inhibiting the tumor angiogenesis in Balb/C mice	50%, 80% ethanol extracts	[99]
	A549 cells and tumor-derived vascular endothelial cells	In vitro	Interfering with cell membrane lipid rafts, inhibiting tumor angiogenesis, inhibiting the activity of A549-derived exosomes, increasing immunity, suppressing Td-ECs migration, invasion, and tube formation, inhibiting pathways proteins, IC ₅₀ = 99.59–100 µg/mL	Compounds 1–4, 19, 31, 32, 37–41	[33, 43]
	A549 cells	In vitro	Increasing expression of IκBα and fas protein, decreasing expression of NF-κB/p65, Survivin, fasL and p-IκBα proteins, arresting the cell cycle at the G ₂ phase, down-regulating the protein levels of PI3K, protein kinase B (Akt), Ras, micro-tubule-associated protein2 (MAP2), and VEGF, activating caspase-8 and caspase-3 proteins, IC ₅₀ = 6.54–13.49 µg/mL	Total alkaloids, ethanol and aqueous extracts, Compounds 42, 44, 55, 231	[47, 82, 86, 100–102]
Anti-hepatoma	SPC-A-1 cells	In vitro	Inhibiting cell proliferation, promoted cell apoptosis, decreasing the expression of Bcl-xl, increasing the expression of fas, caspase-3, and bid, IC ₅₀ = 5–12.5 mg/mL	Ethanol and aqueous extracts	[103, 104]
	Hep3B cells	In vitro	Inducing apoptosis and inhibit proliferation, 140 IC ₅₀ = 47.81 µM, 269 IC ₅₀ = 46.07 µM, 271 IC ₅₀ = 45.39 µM	Compounds 138, 267, 269	[20, 26, 62]
	BEL-7402 cells	In vitro	Inducing apoptosis, activity similar to adriamycin and greater than 5-fluorouracil, IC ₅₀ = 0.39–23.0 µM	Compounds 36, 72, 73, 81–83, 86	[22]
	Huh-7 cells	In vitro	Inducing apoptosis, activating p38 and Caspase-3 protein, IC ₅₀ = 15 mg/mL	Total alkaloids	[105]
	SMMC-7721 cells	In vitro	Up-regulating Fas, caspase-8, caspase-3, and p53, down-regulating FasL, survivin and Bcl-2 in the mitochondrial pathway, IC ₅₀ = 5 mg/L	75% ethanol extracts	[79]

Table 13 (continued)

Bioactivities	Object	In vitro /in vivo	Mechanism	Extracts/Compounds	Refs.
Anti-sarcoma	HepG2 cells	In vitro	Arresting the cell cycle at S-phase, inducing apoptosis, solamargine IC ₅₀ = 10.8 ± 0.1 μM, solasodine IC ₅₀ = 19.4 ± 0.4 μM, and solasonine IC ₅₀ = 91.8 ± 9.4 μM	Compounds 5, 8, 21	[83]
	S180 tumor-bearing mice	In vivo	Arresting the cell cycle at G ₀ /G ₁ phase, improving immune response, promoting splenocytes proliferation, NK cell and Cytotoxic T lymphocyte (CTL) activity, interleukin-2 and interferon-γ production from splenocytes, and increasing the thymus and spleen indices to a certain extent	EtOAc fractions, total saponins, ethanol extracts	[77, 80, 106]
Anti-cervical cancer	HeLa cells	In vitro	Up-regulating the expression of caspase-3 mRNA, down-regulating the expression of survivin mRNA, activation of caspase-3, IC ₅₀ = 14.53 μg/mL	75% Ethanol and aqueous extracts, total saponins, compounds 44, 55, 59, 74, 75, 177, 229, 231, 237	[42, 47, 107–109]
Anti-ovarian cancer	A2780 cells	In vitro	Inducing cell cycle arrest, enhanced reactive oxygen species (ROS) accumulation, activating the p53 signaling pathway, increasing the percentage of Cluster of Differentiation 86 (CD86 +) cells, decreasing the percentage of Cluster of Differentiation 26 (CD26 +) cells, and down-regulating expression of Bcl-2 mRNA	Ethanol and aqueous extracts	[110]
	HO8910 cells	In vitro	Inducing apoptosis, inhibiting proliferation in a dose-dependent, IC ₅₀ = 5 μg/mL	75% Ethanol extracts	[111]
	SKOV3 cells	In vitro	Arresting the cell cycle at the G ₁ /S phase, up-regulating the expression of caspase-3, caspase-9 mRNA anti-tumor effect, and increasing the lactate dehydrogenase (LDH) release, IC ₅₀ = 4.51–7.78 μg/mL	90% Ethanol extracts	[112]
Anti-breast cancer	CHO cells	In vitro	Arresting the cell cycle at G ₂ phase, and inhibiting proliferation of CHO cells, IC ₅₀ = 0.5–1 g/mL	Aqueous extracts	[113]
	MCF-7 cell	In vitro	Up-regulating the expression of Bax mRNA and down-regulating the expression of survivin mRNA, IC ₅₀ = 160 μg/mL	Total saponins	[114]

Table 13 (continued)

Bioactivities	Object	In vitro /in vivo	Mechanism	Extracts/Compounds	Refs.
Anti-oral cancer	HSC-3, SAS, and CAL-27 cell	In vitro	Arresting the cell cycle at G0/G1 phase, suppressing the anti-apoptotic proteins Bcl-2 and Bcl-xl, increasing the pro-apoptotic proteins Bax and Bad, promoting the production of ROS and Ca^{2+} , decreasing the mitochondrial membrane potential, stimulating NO production, and activating caspase-8, -9, and -3 proteins activities, $IC_{50} = 40 \mu\text{g/mL}$	Chloroform extracts	[115]
Anti-stomach cancer	BGC823 cells	In vitro	Blocking the cell cycle in the G ₁ /M phase, inducing apoptosis and inhibiting proliferation, $IC_{50} = 25 \mu\text{g/mL}$	Compounds 44, 55, 231	[47]
	SGC-7901 cells	In vitro	Down-regulating expression of Bcl-xl mRNA and proteins, up-regulating expression of bid mRNA and proteins, caspase-9 and bid genes, strengthening the activity of Caspase-3; blocking the cell cycle in the G ₂ /M phase, $IC_{50} = 12.45\text{--}47.65 \text{ g/L}$	Aqueous extracts, total saponin, compounds 8, 86	[3, 116, 117]
Anti-colon cancer	HT-29 cells	In vitro	Down-regulating expression of survivin gene, up-regulating the expression of Caspase-3, 8, 9 mRNA and proteins; down-regulating the expression of Notch I mRNA, influencing the Notch signaling pathway to inhibit colorectal cancer cell proliferation and inducing apoptosis	Aqueous extracts	[118]
	CT-26 cells	In vitro	Increasing caspase-independent apoptosis associated with increased nuclear translocation of AIF, $IC_{50} = 3.5 \mu\text{M}$	Compounds 10, 105	[74]
	HT-29 cells	In vitro	Inducing apoptosis and inhibiting proliferation, $ED_{50} = 1.9\text{--}3.7 \mu\text{g/mL}$	Compounds 107, 116, 125, 127, 134, 136, 142, 143	[1, 60, 119]
Anti-leukemia	Leukemia mice	In vivo	Inhibiting the precursors of T cells and B cells, promoting the precursors of macrophages, increasing macrophage and NK cell activities, promoting the activity of macrophage phagocytosis in the peripheral blood mononuclear cells (PBMC) and peritoneal cells	Ethanol extracts	[78]
	HL-60 cells	In vitro	Up-regulating the expression of Bax mRNA, down-regulating expression of Bcl-2 mRNA, increasing Bax/ Bcl-2 protein ratio, $IC_{50} = 3.5 \text{ mg/mL}$	Aqueous extracts	[120]
	P-388 cells	In vitro	Inhibiting proliferation and inducing apoptosis, $ED_{50} = 2.7\text{--}3.1 \mu\text{g/mL}$	Compounds 134, 136	[119]

Table 13 (continued)

Bioactivities	Object	In vitro /in vivo	Mechanism	Extracts/Compounds	Refs.
Anti-prostate cancer	DU-145 cells and xenograft athymic nude mice	In vitro/in vivo	Blocking the expression of cell cycle proteins (Cyclin D1, Cyclin E1, CDK2, CDK4, CDK6, and P21) and inducing apoptosis via ROS and activation of the P38 pathway, IC ₅₀ = 32.18 μM	Steroidal glycoalkaloid	[121]
Anti-bone cancer	U-2 OS cells	In vitro	Arresting the cell cycle at the G ₁ phase, promoting the production of ROS and NO, decreasing the levels of mitochondrial membrane potential and promoting the activations of caspase-8, 9, 3; promoting the Bax level and release of cytochrome C, IC ₅₀ = 25 μg/mL	50% Ethanol extracts	[122]
Anti-neuroblastoma	SH-SY5Y cells	In vitro	Increasing the expression of Bcl-2 protein, and inhibiting the expression of Bax protein in tert-Butyl hydroperoxide (tBHP)-induced SH-SY5Y cells, inhibiting tBHP-induced ROS production, IC ₅₀ = 25–50 μM	Total alkaloids, compounds 194–203	[20, 123]
Anti-inflammatory	SD rats	In vivo	Decreasing the content of PGE2 and cyclooxygenase-2 (COX-2) in serum	Aqueous and ethanol extracts, total saponins	[85, 86, 124]
	polymorphonuclear leukocytes of rats	In vivo	Inhibiting the release of β-glucuronidase, IC ₅₀ = 10 μM	Compounds 252–255	[73]
Anti-microbial	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Salmonella</i> , <i>Candida albicans</i> , <i>Pseudomonas aeruginosa</i>	In vitro	Inhibiting the growth of <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>salmonella</i> , and <i>Candida albicans</i> , MIC = 100 mg/mL; <i>pseudomonas aeruginosa</i> , MIC = 50 mg/mL	Crude extracts, polysaccharides	[90]
	<i>Gram-positive bacteria</i>	In vitro	Inhibiting the <i>S. aureus</i> and <i>E. faecalis</i> , MIC = 2–10 μM	Compound 266	[21]
Anti-allergy	Normal mice	In vivo	Inhibiting the histamine release, adding the level of cAMP, inhibiting overexpression of L-histamine decarboxylase mRNA	Aqueous extracts	[2]
	Mast cells	In vitro	Reducing the expression level of the mRNA of histidine decarboxylase (HDC), affecting IgE-mediated anaphylactic reaction and substance P-induced HDC mRNA over-expression	Aqueous extracts	[93]
	Normal mice	In vivo	Inhibiting the allergy to peritoneal mast cell histamine, delaying the kinetics of Low-Density Lipoprotein (LDL) oxidation, increasing the activity of peroxidase (POD) and superoxide dismutase (SOD), reducing the activity of malonaldehyde (MDA)	Aqueous extracts	[88]

Table 13 (continued)

Bioactivities	Object	In vitro / in vivo	Mechanism	Extracts/Compounds	Refs.
Antioxidant activity	SH-SY5Y cells	In vitro	Preserving mitochondrial membrane potential and reducing oxidative stress, $LC_{50} = 4.64 \mu\text{M}$, $457.12 \mu\text{M}$, respectively; inhibiting tBHP-induced ROS production, oxidative stress, $IC_{50} = 20 \text{ mg/L}$	Compounds 9,10 Total alkaloids	[87, 123]
	DPPH	In vitro	Scavenging activity of the stable DPPH free radical, $IC_{50} = 5.98\text{--}23.16 \text{ mg/L}$	Ethyl acetate extracts, compounds 236 , 248 , 249 , 251 , 258	[70]
	DPPH	In vitro	Scavenging free radical, ethanol extract $IC_{50} = 0.23 \text{ mg/mL}$, ethyl acetate extract $IC_{50} = 1.01 \text{ mg/mL}$, 251 $IC_{50} = 3.30 \text{ mg/mL}$, 253 $IC_{50} = 6.73 \text{ mg/mL}$	Ethanol and ethyl acetate extract of <i>S. lyratum</i> fruits, compounds 249 , 251	[89]
Hepatoprotective activity	CCl4 induce mice	In vivo	Decreasing alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) contents, reducing CCl ₄ -induced liver injury, anti-lipid peroxidation effect, decreasing transaminase activities in serum	Ethanol extracts	[91, 92]
Molluscicidal activity	Snails	In vitro	Having a molluscicidal effect, $IC_{50} = 30\text{--}50 \text{ mg/mL}$	Ethanol extracts, compound 21	[95]

Finally, in toxicological studies of *S. lyratum*, no unequivocal proof of the toxicological activities in human exists. Further, relationship studies between systematic toxicity and safety evaluation are still needed to assure safety for clinical application in the future. Pharmacological effects of *S. lyratum* have been demonstrated by ethanol and aqueous extracts of high doses, the effectiveness of high doses extracts in treating diseases provides the possibility of finding active compounds. Therefore, it is important to study the therapeutic window (the range between the doses that produce the desired therapeutic effect and doses that produce toxicity) and the long-term in vivo toxicity for further research on *S. lyratum*.

In summary, *S. lyratum* can be considered as an important and valuable resources for human's health. Further research is needed in terms of quality control, toxicity and pharmacological mechanism to provide a theoretical basis for exploitation of the medicinal functions of *S. lyratum*.

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Author contributions

The manuscript was prepared by Y. Zhao, Y. Zhao, W.-K. Gao, and X.-D. Wang completed the writing of this review. The research work was supported by the projects of H.-H. Wu. All the authors reviewed the final version of the manuscript and approve it for publication. To the best of our knowledge and belief, this manuscript has not been published in whole or in part nor is it being considered for publication elsewhere. All authors have seen the manuscript and approved to submit to your journal. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no conflict of interest.

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