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REVIEW ARTICLE

Lycopodium japonicum: A comprehensive review on its phytochemicals and biological activities

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Serratane triterpenoids;
Bioactivity

Abstract *Lycopodium japonicum* Thunb (Lycopodiaceae) is a common and abundant plant widely distributed in China, Japan and countries of Southern Asia and used in traditional Chinese medicine for the treatment of sprains, strains and myasthenia. This review focuses on the phytochemicals and biological actions, with the objective of stimulating further studies on the plant. 132 chemical compounds have been identified and isolated from this plant, and the most important are alkaloids and serratane triterpenoids. The isolated compounds of *L. japonicum* were shown to possess acetylcholinesterase inhibitory, cytotoxic, anti-inflammatory, anti-HIV-1 and α-glucosidase inhibitory activities. Further studies should be carried out on this plant in order to disclose many more active principles and mechanisms of active components.

Contents

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1. Introduction

Lycopodium alkaloids are compounds isolated from plants of Lycopodiaceae and Huperziaceae, with diverse structures including many unusual skeletons of interest from biogenetic and biological points of view, and challenging targets for total synthesis (Hartrampf et al., 2017; Pinto et al., 2017; Saborit et al., 2016; Wang et al., 2017). Alkaloids are known to possess important bioactivities including acetylcholinesterase inhibitory activity (Benamar et al, 2016, 2017; Les et al, 2017). Since huperzine A, a potent, reversible and selective acetylcholinesterase inhibitor and a promising drug for the treatment of symptoms of Alzheimer's disease was discovered from *Huperzia serrata* (Thunb. Ex Murray) Trev. (Huperziaceae), numerous efforts on the isolation of new potent alkaloids from *H. serrata* and related plants have been carried out by many research groups, which led to the isolation of a series of plant constituents, especially *Lycopodium* alkaloids with diverse structures (Hirasawa et al., 2018; Li et al., 2017; Nakayama et al., 2019; Tang et al., 2016). *Lycopodium japonicum* Thunb (Lycopodiaceae) is a common and abundant plant widely distributed in China, Japan and countries of Southern Asia and used in traditional Chinese medicine for the treatment of sprains, strains and myasthenia (Zhang & Zhang, 2004). In the last decade, there has been a dramatic progress in the chemical constituents and these compounds show potent bioactivities, such as acetylcholinesterase inhibitory, cytotoxic and anti-inflammatory activities. However, so far, no comprehensive review has been published. In the present review, we summarize systematically the research advances on the chemical constituents and their biological activities of *L. japonicum* reported in the literature, with the aim of providing a basis for further research of natural product drug discovery.

2. Chemical constituents

To date, 132 compounds have been isolated and identified from the club moss of *L. japonicum*, including 83 alkaloids (**1**–**83**), 36 triterpenoids (**87**–**122**), two diterpenoids (**85**, **86**), one sesquiterpenoid (**84**), two sterols (**123**, **124**), four flavans (**125**–**128**), two diaryl propanes (**129**, **130**), one anthraquinone (**1 3 1**) and one phthalate (**1 3 2**). As it can be seen, alkaloids and serratane-type triterpenoids are the dominant chemical constituents in the plant *L. japonicum*. Their structures, names, and references are summarized in Tables 1–4 and Figs. 1–7.

2.1. Alkaloids

Alkaloids are naturally occurring compounds containing basic nitrogen atoms. Alkaloids **1**–**83** have been isolated from *L. japonicum*. Alkaloids **1**–**48** were Lycopodine alkaloids. This class is characterized by four connected six-membered rings, with positions C-4, C-5, C-6, C-8, C-11 and C-12 usually being oxidized to hydroxyl and carbonyl groups or esterified by acetic acid, and the C=C bond may existed at C-2(3), C-4 (5), and C-11(12). Flabelline (**36**) is an alkaloid with the lycopodine skeleton carrying a second nitrogen atom (Niu et al., 2015). In addition, the nitrogen could be oxygenated as *N*-oxide, such as in **40**–**47** (He et al., 2014; Niu et al., 2015; Sun et al., 2008; Yang et al., 2016; Zhu et al., 2019). Lycoposerramine G nitrate (**48**) was an artifact (He et al., 2014), which was produced during the isolation as verified by the TLC (Al_2O_3). Alkaloids **49**–**57** were lycodine alkaloids, which has four rings in general, with two nitrogen atom in pyridine or pyridone rings. Hydroxypropyllycodine (**51**) and *N*-methylhydroxypropyllycodine (**52**) are possessing a 19-carbon skeleton (Niu et al., 2015; Wu et al., 2015). Huperzinine (**57**), like huperzine A is the product of N-C-9 bond cleavage and elimination of C-9, giving a $C_{15}N_2$ skeleton with three rings (Wu et al., 2015). Alkaloids **58**–**82** belong to fawcettimine class, which could be regarded as the products of C-4(13) to C-4(12) bond migration from lycopodine group precursors, with C-13 usually being oxidized to hydroxyl group or forming C=C bond with C-14. Phlegmariurine B (**61**) was formed by further cleaving the C-12(13) bond (Zhu et al., 2019), whereas lycojapodine A (**62**) had a six-membered lactone ring between C-5 and C-13 with a novel 6/6/6/7 tetracyclic ring system, formed by the cleavage of C-4(5) bond, and bonded between C-4 and C-12 (He et al., 2009). Alkaloids **63**–**75** all possess the cleavage of N-C-13 bond. In obscurinine (**64**) and isoobscurinine (**65**), an extra ring is formed by a nitrogen atom bridging between C-3 and C-13 (Li et al., 2012; Zhu et al.,

Table 1 Lycopodine alkaloids from *L. japonicum*.

No.	Name	Ref.
1	lycopodine	He et al. (2009)
2	lycodoline	Sun et al. (2008)
3	clavolonine	Li et al. (2012)
4	8*β*-acetoxy-12*β*-hydroxylycopodine	Li et al. (2012)
5	8*β*-hydroxylycodoline	Wang et al. (2013a)
6	12*β*-hydroxyacetylfawcettiine = acetyllycofawcine	Li et al. (2012)
7	acetylfawcettiine	Li et al. (2012)
8	lycofawcine	Wang et al. (2013a)
9	fawcettine	Zhu et al. (2019)
10	*α*-lofoline	Li et al. (2012)
11	deacetylfawcettiine	Wang et al. (2013a)
12	11*α*-O-acetyllycopodine	Liu and Wang (2012)
13	lycoposerramine M	Li et al. (2012)
14	8*β*-acetoxy-11*α*-hydroxylycopodine	Li et al. (2012)
15	8*β*-hydroxy-11*α*-acetoxylycopodine	Wang et al. (2013a)
16	11*α*-hydroxyacetylfawcettine	Wang et al. (2013a)
17	lycoclavine	He et al. (2014)
18	lycoposerramine L	Liu and Wang (2012)
19	6*α*-hydroxylycopodine	He et al. (2014)
20	6-*epi*-8*β*-acetoxylycoclavine	He et al. (2014)
21	serratezomine C	He et al. (2014)
22	6*α*,8*β*-dihydroxylycopodine	Wang et al. (2013a)
23	4*α*,8*β*-dihydroxylycopodine	Wang et al. (2013a)
24	4*α*,8*β*,12*β*-trihydroxylycopodine	Wang et al. (2013a)
25	lycoposerramine G	Wang et al. (2013a)
26	12-epilycodoline	Ge et al. (2016)
27	11*β*-hydroxy-12-epilycodoline	Shi & He, 2012
28	4*α*-hydroxyanhydrolycodoline	He et al. (2014)
29	4*α*,6*α*-dihydroxyanhydrolycodoline	He et al. (2014)
30	8*β*-hydroxylycoposerramine K	Wang et al. (2013a)
31	anhydrolycodoline	Wang et al. (2013a)
32	lycoposerramine K	He et al. (2014)
33	gnidioidine	Niu et al. (2015)
34	lucidioline	Sun et al. (2008)
35	diacetyllycofoline	Zhu et al. (2019)
36	flabelline	Niu et al. (2015)
37	12-deoxyhuperzine O	He et al. (2014)
38	8*β*-hydroxyhuperzine E	Wang et al. (2013a)
39	huperzine E	He et al. (2014)
40	fawcettine *N*-oxide	Zhu et al. (2019)
41	lycoposerramine F = miyoshianine A	Sun et al. (2008)
42	miyoshianine C	Sun et al. (2008)
43	acetylfawcettine *N*-oxide	Zhu et al. (2019)
44	12*β*-hydroxy-acetylfawcettiine *N*-oxide	Yang et al. (2016)
45	Lycoposerramine M *N*-oxide	Niu et al. (2015)
46	diphaladine A	He et al. (2014)
47	12-epilycodoline *N*-oxide	He et al. (2014)
48	lycoposerramine G nitrate	He et al. (2014)

2019). whereras 6-hydroxyl-6,7-dehydro-8-deoxy-13-dehydro serratinine (**66**), 8-deoxy-13-dehydroserratinine (**67**) and 15-*epi*-6-hydroxy-6,7-dehydro-8-deoxy-13-dehydroserratinine (**68**) formed an additional pyrole ring between N and C-4 (Wang et al., 2013b; Zhu et al., 2019). Alkaloids **69**–**74** could be the products of *N*-methylation followed by C–C bond formation between the *N*-methyl and C-4 (He et al., 2009; Niu et al., 2015; Wang et al., 2012a; 2013a, 2013b; Yang et al., 2018). In palhinines A (**75**) and D (**76**), C-16 were fused to a new ring through a C-16(4) linkage (Wang et al., 2013b; 2016). Lycojaponicumin D (**77**) possesses an unprecedented 5/7/6/6 tetracyclic skeleton formed by an unusual C-3(13) linkage (Wang et al., 2012a). Lycojaponicumins A-C (**78**–**80**) represent a unique heterocyclic skeleton formed by the new linkage C-4(9) (Wang et al., 2012b). Notably, lycojaponicumins A and B are the first examples of natural products possessing a 5/5/5/5/6 pentacyclic ring system with a 1-aza-7-oxabicyclo[2.2.1]heptane moiety. Isopalhinine A (**81**) with C-4(16) and N-C-5 linkage, possesses a sterically congested architecture built with a tricyclo[4.3.1.03,7]decane (isotwistane) moiety and a 1-azabicyclo[4.3.1]decane moiety (Yang et al., 2018). Lycopladine H (**82**) is an unprecedented

Table 2 Lycodine alkaloids from *L. japonicum*.

No.	Name	Ref.
49	lycodine	Wang et al. (2013a)
50	*N*-methyllycodine	Wu et al. (2015)
51	hydroxypropyllycodine	Niu et al. (2015)
52	*N*-methylhydroxypropyllycodine	Wu et al. (2015)
53	α-obscurine	Sun et al. (2008)
54	des-*N*-methyl-α-obscurine	Li et al. (2012)
55	*des*-*N*-methyl-*β*-obscurine	Niu et al. (2015)
56	*β*-obscurine	Wu et al. (2015)
57	huperzinine	Wu et al. (2015)

Table 3 Fawcettimine and phlegmarine alkaloids from *L. japonicum*.

No.	Name	Ref.
Fawcettimine		
58	fawcettimine	He et al. (2009)
59	lycopoclavamine A	Li et al. (2012)
60	fawcettidine	Niu et al. (2015)
61	phlegmariurine B	Zhu et al. (2019)
62	lycojapodine A	He et al. (2009)
63	(15R)-14,15-dihydroepilobscurinol	Wang et al. (2013b)
64	obscurinine	Li et al. (2012)
65	isoobscurinine	Zhu et al. (2019)
66	6-hydroxyl-6,7-dehydro-8-deoxy-13-dehydroserratinine	Wang et al. (2013b)
67	8-deoxy-13-dehydroserratinine	Wang et al. (2013b)
68	15-*epi*-6-hydroxy-6,7-dehydro-8-deoxy-13-dehydroserratinine	Zhu et al. (2019)
69	lycoflexine	He et al. (2009)
70	17α-methyllycoflexine	Yang et al. (2018)
71	6-hydroxyl-6,7-dehydrolycoflexine	Wang et al. (2013b)
72	14,15-dehydrolycoflexine	Wang et al. (2013b)
73	lycojaponicumin E = palcernine A	Wang et al. (2012a), Yang et al. (2018)
74	lycoflexine *N*-oxide	Niu et al. (2015)
75	palhinine A	Wang et al. (2013b)
76	palhinine D	Wang et al. (2013a), Wang et al. (2016)
77	lycojaponicumin D	Wang et al. (2012a)
78	lycojaponicumin A	Wang et al. (2012b)
79	lycojaponicumin B	Wang et al. (2012b)
80	lycojaponicumin C	Wang et al. (2012b)
81	isopalhinine A	Yang et al. (2018)
82	lycopladine H	Yang et al. (2018)
Phlegmarine		
83	lycocernuine	Yang et al. (2018)

C_{16}N-type Lycopodium alkaloid possessing a novel fused-tetracyclic ring system consisting of an azocane ring (C-9 (14), C-5, and N-1) fused to a [2,2,2]-bicyclooctane ring and a 3-piperidone ring (Yang et al., 2018). Lycocernuine (**83**) is likely that it is formed by a 4 + 2 cycloaddition reaction with a derivative of phlegmarine that has undergone opening of ring D *via* cleavage of the C7(12) bond (Yang et al., 2018).

2.2. Terpenoids

2.2.1. Sesquiterpenoid

Japonicumin D (**84**), a unique and new C13 dinorsesquiterpene was isolated from *L. japonicum* (Li et al., 2006).

2.2.2. Diterpenoids

The abietane-type diterpene, 8α,9α-epoxy-7-oxoroyleanon (**85**) and the labdane-type diterpene, (-)-13,13-ethylenedioxy-15,16-dinorlabd-7-en-6*β*-ol (**86**) were isolated from *L. japonicum* (Li et al., 2015; Wu et al., 2006).

2.2.3. Triterpenoids

Thirty-six triterpenoids, **87**–**122,** were isolated from *L. japonicum*. Triterpenoids, **87**–**113,** belong to serratane-type, in which positions C-3 and C-21 were usually being oxidized to hydroxyl groups, ketone or further esterified by acetic and formic acids and the C═C bond may existed at C-14(15). Sometimes, C-12, 20, and 24 also could be oxidized to hydroxyl groups, and C-24 could be oxidized further to carboxylic acid or esterified by *p*-hydroxycinnamic acid. Besides, C═C bond at C-14 (15) may be hydrated to hydroxyl group and C-16 may be oxidized to ketone. Lycojaponicuminol F (**104**) bearing the isopropylidene acetal has not been reported in nature, and this functionality was suggested to arise from the acetone used for the extract separation by chromatography on silica gel (Zhang et al., 2014). In fact, lycoclaninol (**103**) is the precursor of **104** which was also isolated from this plant (Yan et al., 2005a). Lycopodiin A (**113**) was a 16(15 → 14) abeoserratan-15-al (Yan et al., 2005a). Triterpenoids **114**–**121** belong to onocerin type. Compounds **116**–**121** were noronocerins, and **121** was the first example of onoceranoid triterpene bearing a seven-member ring isolated from Lycopodiaceae plants (Zhang et al., 2014). Betulin (**122**) was a lupane triterpeoid.

2.3. Sterols

Daucosterol (**123**) and (24*S*)-24-methyl cholesterol (**124**) were isolated from *L. japonicum* (Li et al., 2015; Shi & He, 2012).

2.4. Flavones

A Flavones lycopodone (**125**) along with tricin (**126**), tricetin 3′,4′,5′-OMe (**127**) and 5,7,4′-trihydroxy-3′-methoxyflavone (**128**) were isolated (Yan et al., 2005b).

2.5. Diaryl propanes

Tomentosanan B (**129**) and (-)-1-(4′-hydroxy-3′-methoxyphenyl)-2-(4′′-hydroxy-3′′-methoxyphenyl)propan-3-ol (**130**) were isolated from *L. japonicum* (Li et al., 2015).

2.6. Others

Physcion (**131**), an anthraquinone and di-(2-ethylhexyl) phthalate (**132**) were isolated from *L. japonicum* (Cai et al., 1991; Li et al., 2015). Compound **132** is much likely a contaminator released from plastic containers (Bianco et al., 2014; Venditti, 2018).

Table 4 Triterpenoids from *L. japonicum*.

No.	Name	Ref.
Serratene		
87	serrat-14-en-3*β*-yl-acetate	Wang et al. (2014)
88	serrat-14-ene-3*β*,21*β*-diol	Shi et al. (2012)
89	21*β*-hydroxyserrat-14-en-3*β*-yl-acetate	Wang et al. (2014)
90	serratenediol	Shi et al. (2012)
91	3*β*-hydroxyserrat-14-en-21*β*-yl-formate	Wang et al. (2014)
92	21*β*-hydroxyserrat-14-en-3*β*-yl-formate	Wang et al. (2014)
93	diepiserratenediol	Ge et al. (2016)
94	serrate-14-en-3,21-dione	Wang et al. (2014)
95	3-epilycoclavanol	Yan et al. (2005a)
96	lycernuic acid A	Zhang et al. (2014)
97	lycojaponicuminol D	Zhang et al. (2014)
98	lycojaponicuminol E	Zhang et al. (2014)
99	phlegmaric acid	Zhang et al. (2014)
100	lycoclavanol	Yan et al. (2005a)
101	lycojaponicuminol A	Zhang et al. (2014)
102	japonicumin A	Li et al. (2006)
103	lycoclaninol	Yan et al. (2005a)
104	lycojaponicuminol F	Zhang et al. (2014)
105	16-oxo-3α-hydroxyserrat-14-en-21*β*-ol	Li et al. (2015)
106	3β, 21α-dihydroxyserrat-14-en-16-one	Yang et al. (2014)
107	lycernuic ketone C	Sun et al. (2017)
108	16-oxo-3α-hydroxyserrat-14-en-21α-ol	Shi et al. (2012)
109	3α,21α-dihydroxy-16-oxoserrat-14-en-24-yl *p*-coumarate	Sun et al. (2017)
110	japonicumin B	Li et al. (2006)
111	tohogenol	Sun et al. (2017)
112	japonicumin C	Li et al. (2006)
113	lycopodiin A	Yan et al. (2005a)
Onocerin		
114	α-onocerin	Shi et al. (2012)
115	α-onoceradienedione	Wang et al. (2014)
116	26-nor-8-oxo-α-onocerin	Zhang et al. (2014)
117	lycojaponicuminol B	Zhang et al. (2014)
118	(3*β*,8*β*,14α,21α)-26,27-dinoronocerane-3,8,14,21-tetrol	Yan et al. (2005a)
119	(3*β*,8*β*,14α,21*β*)-26,27-dinoronocerane-3,8,14,21-tetrol	Yan et al. (2005a)
120	(3α,8*β*,14α,21*β*)-26,27-dinoronococerane-3,8,14,21-tetrol	Zhang et al. (2014)
121	lycojaponicuminol C	Zhang et al. (2014)
Lupane		
122	betulin	Li et al. (2015)

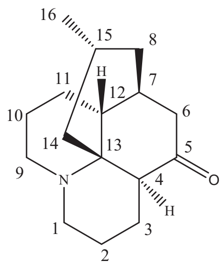
3. Biological activities

3.1. Acetylcholinesterase inhibitory activity

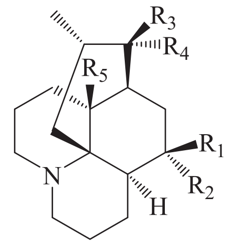
Lycojapodine A (**62**) inhibited acetycholinesterase with an IC_{50} value of 90.3 μM (He et al., 2009), which was comparable to that of huperzine A, a potent, reversible and selective acetylcholinesterase inhibitor, and approved as the drug for treatment of Alzheimer's disease in China, and marketed in USA as a dietary supplement (Ma & Gang, 2004). Lycoclavanol (**100**) and α-onocerin (**114**) showed acetylcholinesterase inhibition activity (20.0% and 39.0%, resp.) at 0.6 mg/mL concentration, with galanthamine as the standard (63.6%) (Yan et al., 2005a).

3.2. Cytotoxic activity

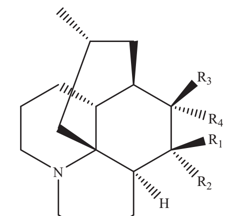
3-Epilycoclavanol (**95**) and lycopodiin A (**113**) showed moderate activity against human tumor A549 or K562 cells with IC_{50} of 10–100 μg/ml (Yan et al., 2005a). **95,** lycernuic acid A (**96**), lycojaponicuminol F (**104**), 26-nor-8-oxo-α-onocerin (**116**), and lycojaponicuminol B (**117**) exhibited moderate activities against A549, hepatocellular carcinoma HepG2 and breast cancer MCF-7 with IC_{50} values of 2.28–11.81 μg/mL (Zhang et al., 2014). Lycopodone (**125**) and tricin (**126**) indicated moderate activity against human tumor K562 cells with IC_{50} of 10–100, and 11.68 μg/ml (Yan et al., 2005b).



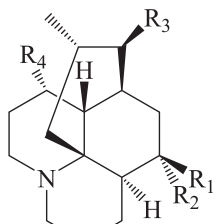
Lycopodine



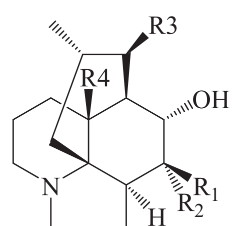
1 R_1+R_2= O, R_3~ R_5= H
2 R_1+R_2= O, R_3= R_4= H, R_5= OH
3 R_1+R_2= O, R_3= OH, R_4= R_5= H
4 R_1+R_2= O, R_3= OAc, R_4= H, R_5= OH
5 R_1+R_2= O, R_3= R_5= OH, R_4= H
6 R_1= R_3= OAc, R_2= R_4= H, R_5= OH
7 R_1= R_3= OAc, R_2= R_4= R_5= H
8 R_1= OAc, R_2= R_4= H, R_3= R_5= OH
9 R_1= OAc, R_2= R_4= R_5= H, R_3= OH
10 R_1= OAc, R_2= R_3= R_5= H, R_4= OH
11 R_1= R_3= OH, R_2= R_4= R_5= H



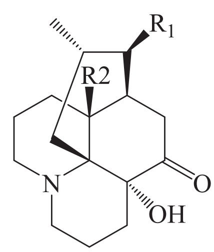
17 R_1= OAc, R_2= R_3= H, R_4= OH
18 R_1+R_2= O, R_3= OH, R_4= H
19 R_1+R_2= O, R_3= H, R_4= OH



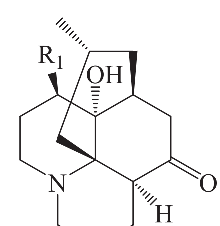
12 R_1+R_2= O, R_3= H, R_4= OAc
13 R_1+R_2= O, R_3= H, R_4= OH
14 R_1+R_2= O, R_3= OAc, R_4= OH
15 R_1+R_2= O, R_3= OH, R_4= OAc
16 R_1= R_3= OAc, R_2= H, R_4= OH



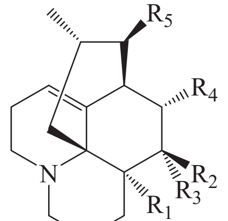
20 R_1= R_3= OAc, R_2= R_4= H
21 R_1+R_2= O, R_3= H, R_4= OH
22 R_1+R_2= O, R_3= OH, R_4= H



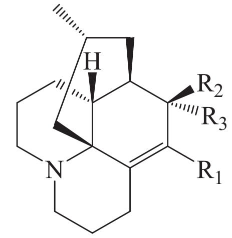
23 R_1= OH, R_2= H
24 R_1= R_2= OH
25 R_1= H, R_2= OH



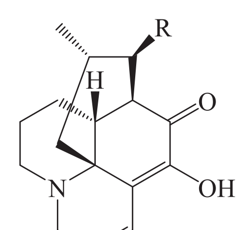
26 R_1= H
27 R_1= OH



28 R_1= OH, R_2+R_3= O, R_4= R_5= H
29 R_1= R_4= OH, R_2+R_3= O, R_5= H
30 R_1= H, R_2+R_3= O, R_4= R_5= OH
31 R_1= R_4= R_5= H, R_2+R_3= O
32 R_1= R_5= H, R_2+R_3= O, R_4= OH
33 R_1= R_4= H, R_2+R_3= O, R_5= OH
34 R_1= R_5= H, R_2= R_4= OH, R_3= H
35 R_1= R_3= R_4= H, R_2= R_5= OAc

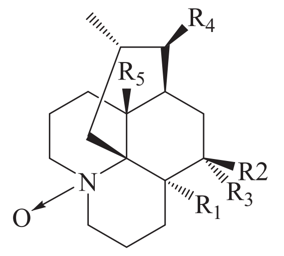


36 R_1= NHAc, R_2= R_3= H
37 R_1= OH, R_2+ R_3= O

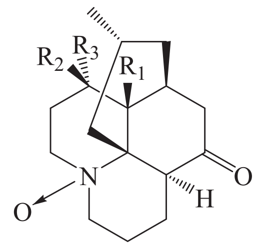


38 R= OH
39 R= H

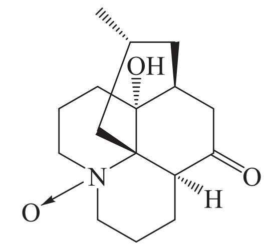
Fig. 1 Lycopodine alkaloids from *L. japonicum*.



40 R_1= R_3= R_5= H, R_2= OAc, R_4= OH
41 R_1= R_5= OH, R_2+R_3= O, R_4= H
42 R_1= H, R_2+R_3= O, R_4= R_5= OH
43 R_1= R_3= R_5= H, R_2= R_4= OAc
44 R_1= R_3= H, R_2= R_4= OAc, R_5= OH



45 R_1= R_2= H, R_3= OH
46 R_1= R_2= OH, R_3= H



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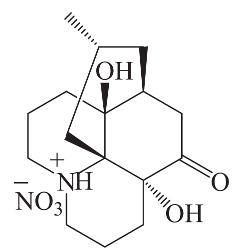
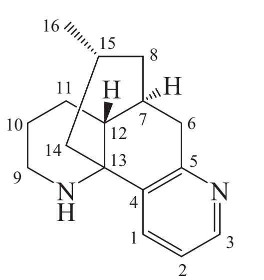
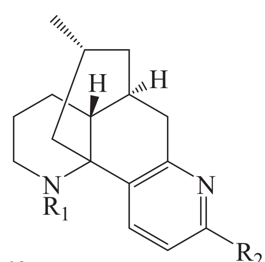


48

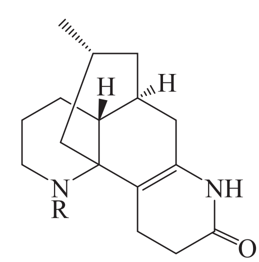
Fig. 1 (*continued*)



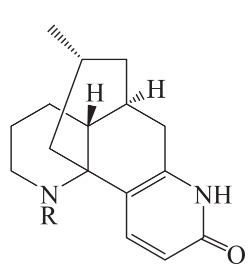
Lycodine



49 R_1= R_2= H
50 R_1= Me, R_2= H
51 R_1= H, R_2= $CH_2CH(OH)CH_3$
52 R_1= Me, R_2= $CH_2CH(OH)CH_3$



53 R= Me
54 R= H



55 R= H
56 R= Me

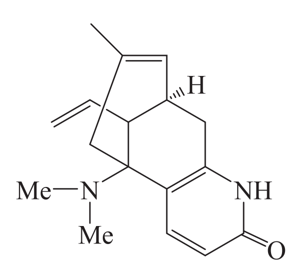


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Fig. 2 Lycodine alkaloids from *L. japonicum*.

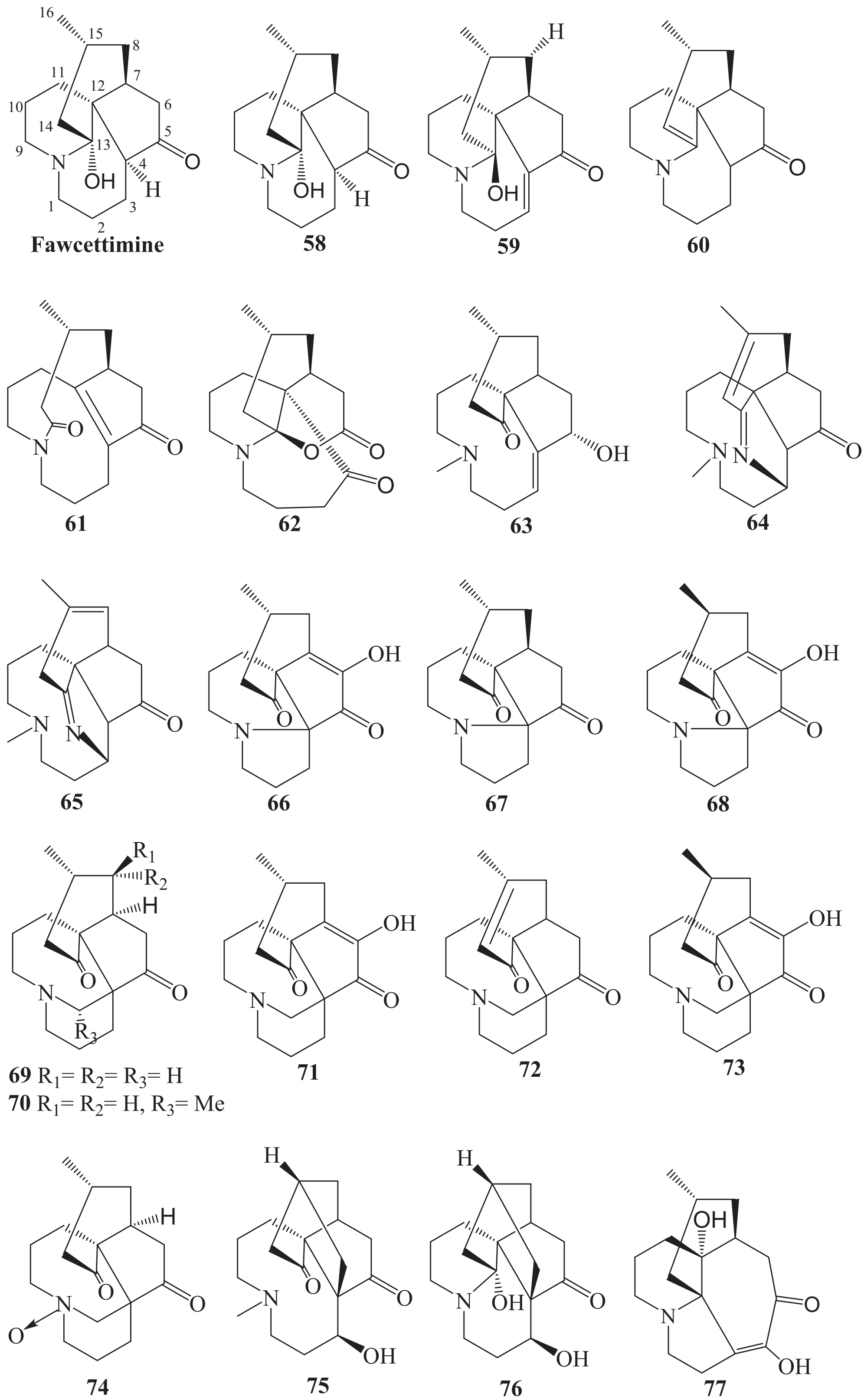


Fig. 3 Fawcettimine and phlegmarine alkaloids from *L. japonicum*.

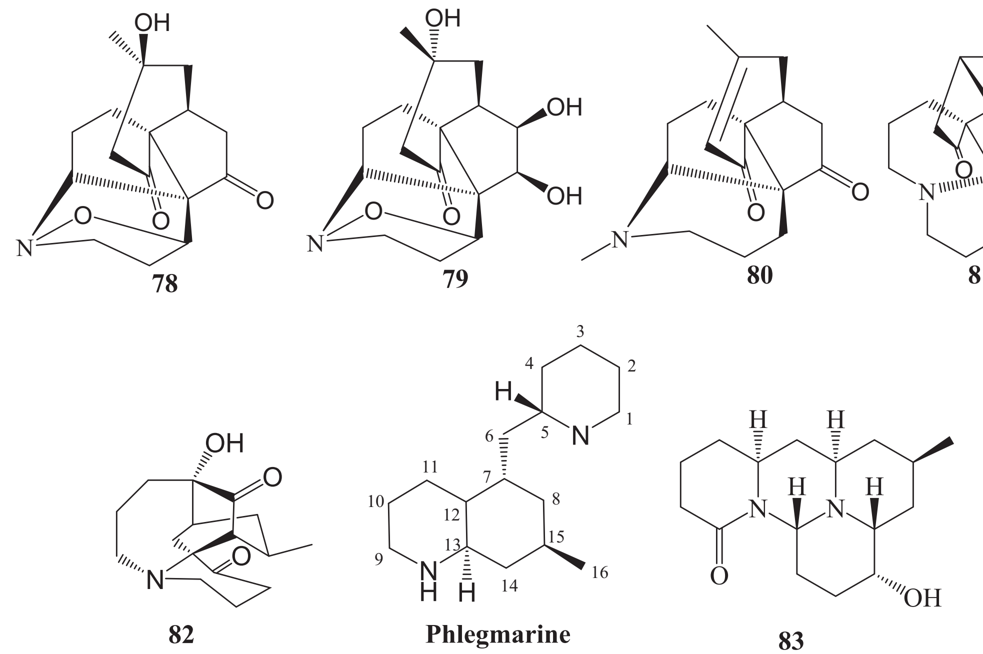


Fig. 3 (*continued*)

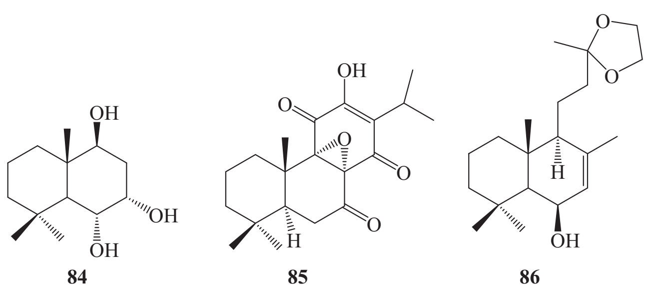


Fig. 4 Sesquiterpenoid and diterpenoids from *L. japonicum*.

3.3. Anti-inflammatory activity

Biological testing *in vitro* showed that ten alkaloids lycopodine (**1**), 8*β*-hydroxylycodoline (**5**), acetyllycofawcine (**6**), α-lofoline (**10**), deacetylfawcettiine (**11**), 11*β*-hydroxy-12-epilycodoline (**27**), lycojaponicumin D (**77**), and lycojaponicumins A-C (**78–80**) inhibited lipopolysaccharide (LPS)-induced pro-inflammatory factors in BV2 macrophages with IC_{50} of 4.23–64.97 μM (curcumin was used as the positive control, IC_{50} 3.12 μM) (Wang et al., 2012a, 2012b; 2013a). Miyoshianine C (**42**) and lycoflexine *N*-oxide (**74**) exhibit the potent inhibition of NO release from LPS-induced RAW264.7 cells, with IC_{50} of 31.82 and 40.69 μM resp. (Niu et al., 2015).

3.4. Anti-HIV-1 activity

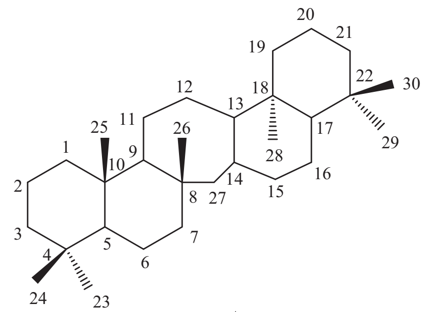
Lycojapodine A (**62**) was tested using the MTT method, showing an EC_{50} value of 85 μg/mL against HIV-1 (He et al., 2009).

3.5. α-Glucosidase inhibitory activity

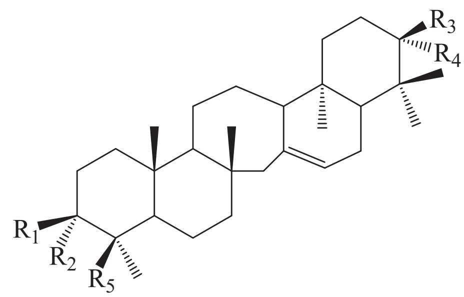
Lycodine (**49**) showed weak α-glucosidase inhibitory activity, with inhibition of 30.56% at 100 μM (Yang et al., 2018), with acarbose as the positive control.

4. Conclusion

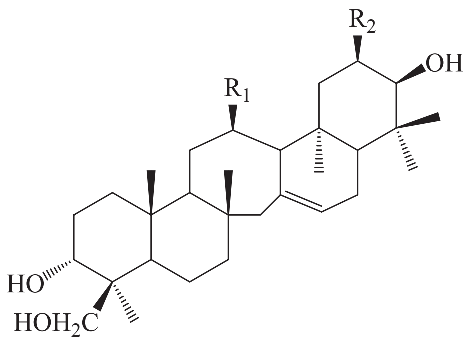
The chemical studies on *L. japonicum* have revealed that the typical constituents of this plant are mainly alkaloids and serratane-type triterpenoids. Other types of compounds such as onocerin type triterpenids, diterpenoids, flavones, and diaryl propanes are also important components. The biological research on the plant constituents showed that some components exhibit bioactivities, especially acetylcholinesterase inhibitory, cytotoxic and anti-inflammatory activities, which supported the use of *L. japonicum* in traditional medicines or revealed the new activities on modern pharmacological levels. Biological testing on anti-inflammatory activity could help fellow researchers to find more active compounds or active core framework and mechanisms of active components.



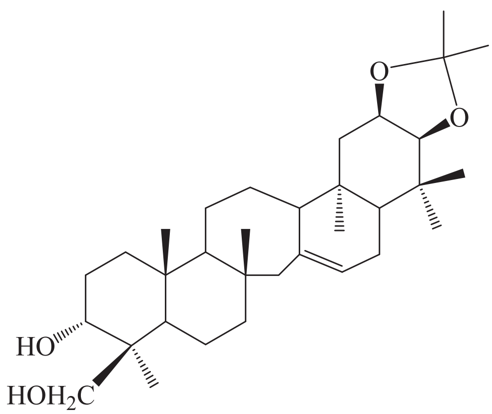
serratane



87 R_1= OAc, R_2~ R_4= H, R_5= CH_3
88 R_1= R_3= OH, R_2= R_4= H, R_5= CH_3
89 R_1= OAc, R_3= OH, R_2= R_4= H, R_5= CH_3
90 R_1= R_4= OH, R_2= R_3= H, R_5= CH_3
91 R_1= OH, R_2= R_4= H, R_3= OCHO, R_5= CH_3
92 R_1= OCHO, R_2= R_4= H, R_3= OH, R_5= CH_3
93 R_1= R_4= H, R_2= R_3= OH, R_5= CH_3
94 R_1+R_2= R_3+ R_4= O, R_5= CH_3
95 R_1= R_3= OH, R_2= R_4= H, R_5= CH_2OH
96 R_1= R_3= OH, R_2= R_4= H, R_5= COOH
97 R_1= R_4= OH, R_2= R_3= H, R_5= CH_2OA
98 R_1= R_3= H, R_2= R_4= OH, R_5= CH_2OA
99 R_1= R_4= OH, R_2= R_3= H, R_5= COOH
100 R_1= R_4= H, R_2= R_3= H, R_5= CH_2OH
101 R_1+R_2= O, R_3= OH, R_4= H, R_5= CH_2OH



102 R_1= OH, R_2= H
103 R_1= H, R_2= OH



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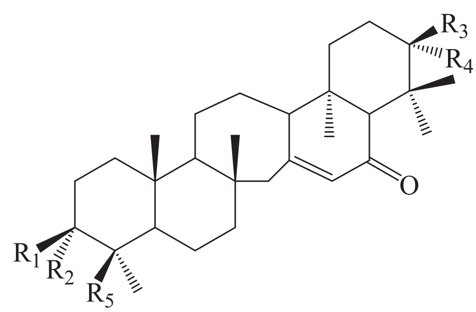
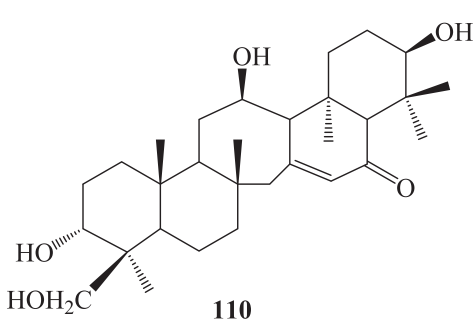


105 R_1= R_4= H, R_2= R_3= OH, R_5= CH_3
106 R_1= R_4= OH, R_2= R_3= H, R_5= CH_3
107 R_1= R_4= H, R_2= R_3= OH, R_5= CH_2OH
108 R_1= R_3= H, R_2= R_4= OH, R_5= CH_3
109 R_1= R_3= H, R_2= R_4= OH, R_5= CH_2OA



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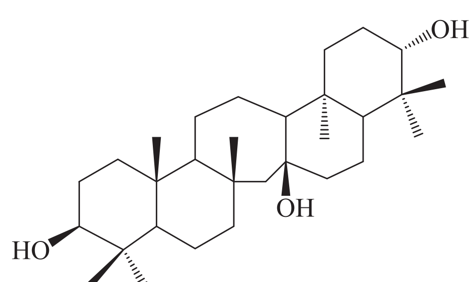
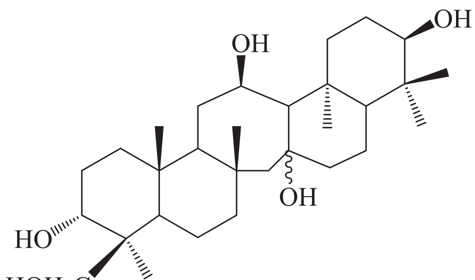


111

Fig. 5 Triterpenoids from *L. japonicum*.



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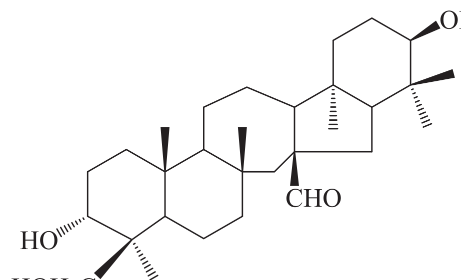
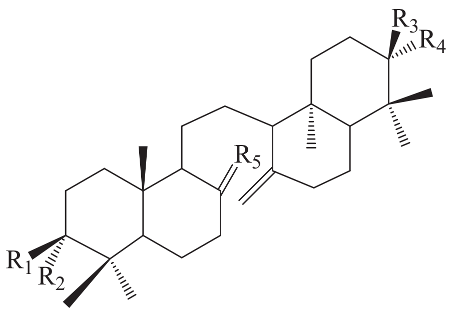
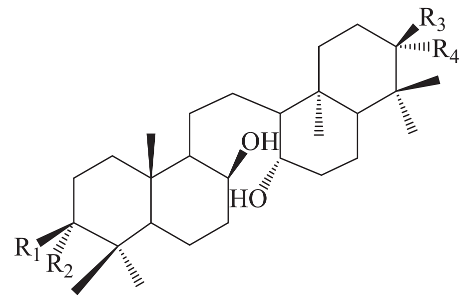


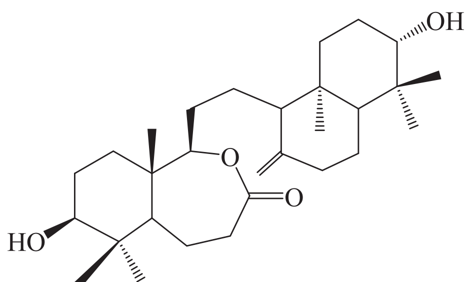
113



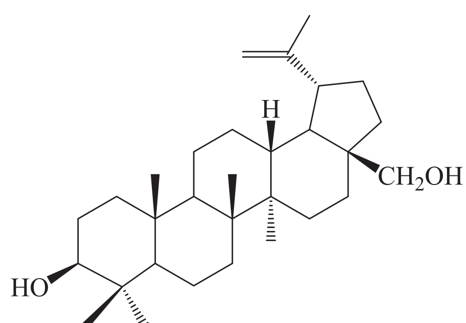
114 R_1= R_4= OH,R_2= R_3= H, R_5= CH_2
115 R_1+ R_2= R_3+ R_4= O, R_5= CH_2
116 R_1= R_4= OH,R_2= R_3= H, R_5= O
117 R_1= R_3= OH, R_2= R_4= H, R_5= O



118 R_1= R_4= OH, R_2= R_3= H
119 R_1= R_3= OH, R_2= R_4= H
120 R_1= R_4= H, R_2= R_3= OH



121



122

A:

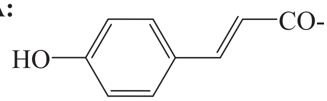
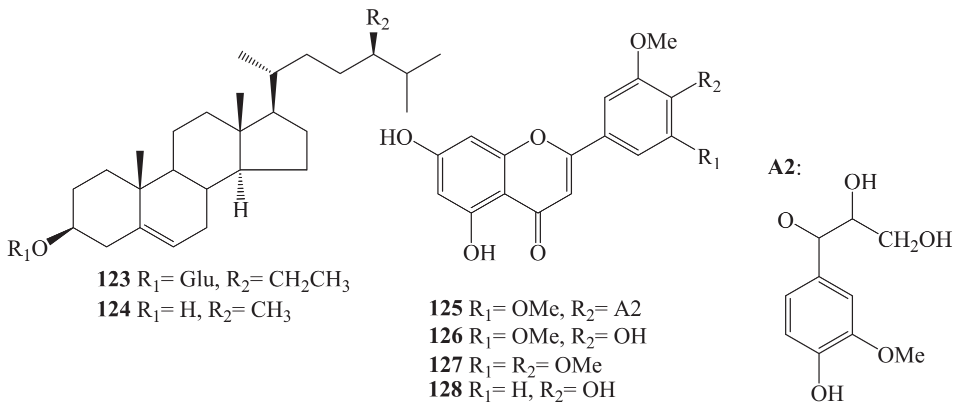
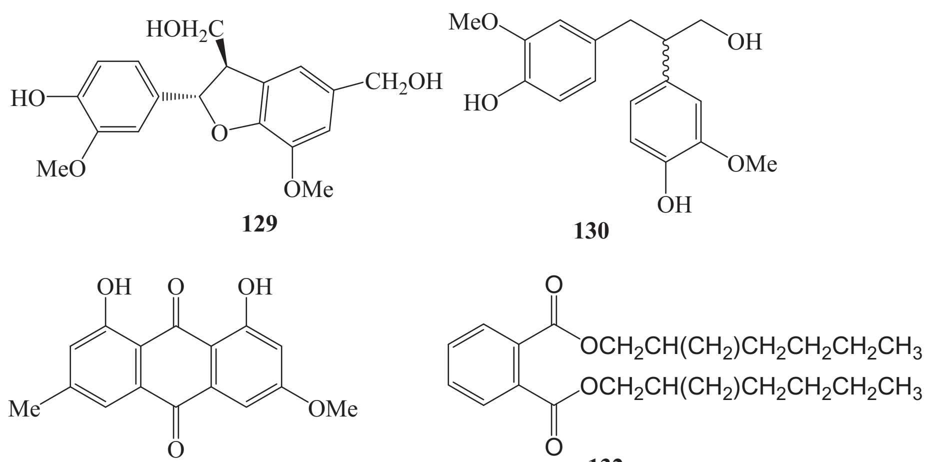


Fig. 5 (*continued*)



123 R_1= Glu, R_2= CH_2CH_3
124 R_1= H, R_2= CH_3
125 R_1= OMe, R_2= A2
126 R_1= OMe, R_2= OH
127 R_1= R_2= OMe
128 R_1= H, R_2= OH

Fig. 6 Sterols and flavones from *L. japonicum*.



129 **130** **131** **132**

Fig. 7 Diaryl propanes and other compounds from *L. japonicum*.

Declarations of interest

None.

Acknowledgement

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