·Reviews·

Photochemistry and pharmacology of 9, 19-cyclolanostane glycosides isolated from genus *Cimicifuga*

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[ABSTRACT] The constituents of *Cimicifuga* plants have been extensively investigated, and the principal metabolites are 9, 19-cyclolanostane triterpenoid glycosides, which often exhibit extensive pharmacological activities. 9, 19-Cyclolanostane triterpenoid glycosides are distributed widely in genus *Cimicifuga* rather than in other members of the Ranunculaceae family. So far, more than 140 cycloartane triterpene glycosides have been isolated from *Cimicifuga spp.*. The aim of this review was to summarize all 9, 19-cyclolanostane triterpenoid glycosides based on the available relevant scientific literatures from 2000 to 2014. Biological studies of cycloartane triterpene glycosides from *Cimicifuga spp.* are also discussed.

[KEY WORDS] *Cimicifuga spp.*; 9, 19-Cyclolanostane glycosides; Chemical structure; Biological effects

Introduction

The genus *Cimicifuga* is one of the smallest genera of the Ranunculaceae family and has been shown to possess a broad range of biological activities [1], such as anti-inflammatory, anti-headache, anti-viral, cooling, detoxification, anti-diabetic, and anti-pyretic effects [2], since the first medicinal description in an ancient Chinese medical book "Shengnong Bencao Jing" [3-5]. Up to now, three main classes of compounds have been isolated from *Cimicifuga spp.*: 9, 19-cyclolanostane glycosides, chromones, and cinnamic acid derivatives, of which the triterpene glycosides are considered to be the main active compounds, are used as marker compounds to standardize the *Cimicifuga* extracts, which is thought to be responsible for the pharmacological activity of the plant, which is relieving unpleasant symptoms associated with menopause [6]. Especially in Europe and the United States, 9, 19-cyclolanostane glycosides isolated from black cohosh (*Cimicifuga racemosa*) are well-known dietary supplements for women's health in alleviating menstrual pain and for menopausal disorders [7]. Furthermore, the anti-cancer properties of Genus Cimicifuga have received a lot of attentions in recent years, and the main active constituents are still thought to be triterpenoids, showing inhibitory effects on human breast cancer [8-9], liver cancer [10-11], and prostate cancer [12] cell lines, due to their anti-osteoporosis and anti-complement activities [13-14]. It is worth noting that triterpenoids may be useful candidates for the development of new drugs for cardiovascular disorders, due to their anti-oxidant and anti-inflammatory activities [4]. The publication number of the 9, 19-cyclolanostane glycosides isolated from *Cimicifuga spp.* in PubMed in the recent years [15] has been increasing rapidly, and the research topic has gradually become a new hotspot. Therefore, a review of the structures of 9, 19-cyclolanostane glycosides and their biological activities is necessary for further research and development of these compounds.

Above 140 different triterpene glycosides from *Cimicifuga* species have been described from 2000−2014 and new constituents are still being isolated. The aims of this review were

to propose a classification of 9, 19-cycloartane triterpene derivatives isolated from the roots of Cimicifuga spp. based on further modification of the carbon skeletons by minor rearrangement, homologation, cleavage, and degradation and to summarize new phytochemical reports of naturally derived compounds of this type during the period 2000−2014, as well as biological activity for each compound, if reported.

Compound types

9, 19-Cyclolanostane glycosides have a very characteristic system of proton signals in the high field region around 0.3−0.5 ppm. In general, C-15, C-16, and C-17 have high degree of oxidation, and C-16 usually forms hemiacetal structure. Furthermore, the glycoside substituents are usually located on C-3. There is no significant difference in the structures of A, B, C and D rings, but with different side chain, which can be divided into 8 subtypes as shown below, and all compounds that have been identified are listed in Table 1 and their structures are provided in Figs. 1−4.

Table 1 Name and references of all compounds identified

No.	Compound	Ref.	No.	Compound	Ref.
1	Cimigenol-12-one	[24]	**2**	12*β*-Hydroxy-15-deoxycimigenol	[24]
3	12*β*-Hydroxy-7(8)-en-cimigenol	[26]	**4**	11*β*-Hydroxy-7(8)-en-cimigenol	[26]
5	24-*Epi*-cimigenol-3-one	[2]	**6**	Cimigenol-7(8)-en-3-one	[26]
7	12*β*-Hydrocimigenol-3-one	[24]	**8**	11*β*-Hydroxy-15-deoxycimigenol-7(8)-en-3-one	[26]
9	Cimicifoetisides A	[23]	**10**	2'-*O*-Acetyl-24-epi-cimigenol-3-*O*-*α*-L-arabinopyranoside	[24]
11	Cimicifoetisides B	[23]	**12**	2'-*O*-Acetylcimigenol-3-*O*-*β*-D-xylopyranoside	[24]
13	Cimigenol-3-*O*-[2′-*O*-(E)-2-butenoyl]-*α*-L-arabinopyranoside	[26]	**14**	25-*O*-Acetylcimigenol-3-*O*-[3'-*O*-acetyl]-*α*-L-arabinopyranoside	[26]
15	25-*O*-Acetylcimigenol-3-*O*-[4′-*O*-acetyl]-*α*-L-arabinopyranoside	[26]	**16**	Cimifoetiside B	[27]
17	Cimifoetiside IV	[19]	**18**	Cimifoetiside V	[19]
19	Cimiracemosides C	[15]	**20**	Cimiracemosides A	[15]
21	3-*O*-*α*-L-Arabinopyranosyl-cimigenol-15-*O*-*β*-D-glucopyranoside	[17]	**22**	25-*O*-Acetyl-12*β*-hydroxycimigenol 3-*O*-*α*-L-arabinopyranoside	[18]
23	Bugbanosides F	[16]	**24**	12*β*, 21-Dihydroxycimigenol 3-*O*-*α*-L-arabinopyranoside	[18]
25	Cimiracemosides D	[15]	**26**	(23*R*, 24*R*)-16*β*, 23; 16*α*, 24-Diepoxy-cycloartane-3*β*, 15*α*, 25-triol 3-*O*-*β*-D-xylopyranoside	[21]
27	Cimiracemosides B	[15]	**28**	(23*R*, 24*S*)-16*β*, 23; 16*α*, 24-Diepoxycycloartane-3*β*, 12*β*, 25-triol 3-*O*-*β*-D-xylopyranoside	[21]
29	(23*R*, 24*R*)-16*β*, 23; 16*α*, 24-Diepoxy-cycloart-7-en-3*β*, 12*β*, 15*α*, 25-tetraol 3-*O*-*β*-D-xylopyranoside	[21]	**30**	Cimiracemoside	[20]
31	(23*R*, 24*R*)-16*β*, 23; 16*α*, 24-Diepoxy-12*β*-acetoxy-cycloart-7-en-3*β*, 15*α*, 25-triol 3-*O*-*β*-D-xylopyranoside	[21]	**32**	(23*R*, 24*S*)-16*β*, 23; 16*α*, 24-Diepoxy-cycloart-7-en-3*β*, 11*β*, 25-triol 3-*O*-*β*-D-xylopyranoside	[21]
33	Cimifoetiside II	[22]	**34**	7, 8-Didehydrocimigenol-3-*O*-*β*-D-galactopyranoside	[25]
35	25-*O*-Acetyl-7, 8-didehydrocimigenol-3-*O*-*β*-D-alactopyranoside	[25]	**36**	Cimifoetiside I	[22]
37	12*β*-Hydroxy-25-anhydrocimigenol	[24]	**38**	25-Anhydrocimigenol-3-*O*-*α*-L-arabinopyranoside	[24]
39	Cimiracemosides J	[28]	**40**	Cimiracemosides K	[28]
41	Cimifoetiside Ⅲ	[29]	**42**	9, 10-Seco-1(10), 7(8), 9(11)-triencimigenol	[26]
43	Bugbanosides D	[16]	**44**	Bugbanosides E	[16]
45	Cimidahuside 1	[30]	**46**	Cimidahuside 2	[30]
47	(3*β*, 12*β*, 15*α*, 24*R*)-12, 2'-Diacetoxy-24, 25-epoxy-15-hydroxy-16, 23-dione-3-*O*-*α*-L-arabinopyranoside	[31]	**48**	Isocimipodocarpaside	[32]
49	Cimifetidanoside C	[33]	**50**	Cimifetidanoside D	[33]
51	Heracleifolinoside A	[34]	**52**	Heracleifolinoside B	[34]
53	Heracleifolinoside C	[34]	**54**	Bugbanosides C	[16]
55	Cimifetidanols A	[33]	**56**	Cimifetidanols B	[33]
57	(10*α*, 24*R*)-10, 24, 25-Trihydroxy-9, 10-seco-9, 19-cyclolanost-7, 9(11)-diene-16, 23-dione	[33]	**58**	Foetidinosides B	[35]
59	Cimifetidanoside A	[33]	**60**	Cimifetidanoside B	[33]

Continued

No.	Compound	Ref.	No.	Compound	Ref.
61	24-Hydroxy-12*β*-acetoxy-25, 26, 27-trinorcycloartan-16, 23-dione 3*β*-*O*-*α*-L-arabinopyranoside	[17]	62	Cimifetidanoside E	[33]
63	23, 24-Diacetoxy-3, 15, 25-trihydroxy-cycloart-7-en-16-one 3-*O*-xylopyranoside	[36]	64	23-Acetoxy-3, 15, 24, 25-dihydroxy-cycloart-7-en-16-one 3-*O*-xylopyranoside	[36]
65	23-*O*-Acetylshengmanol 3-*O*-*α*-L-arabinopyranoside	[18]	66	15, 23-*O*-diacetyl-7(8)-en-shengmanol-3-*O*-*α*-L- arabinopyranoside	[26]
67	Cimiracemoside L	[28]	68	Cimiracemoside M	[28]
69	2', 23-*O*-Diacetylshengmanol-3-*O*-*α*-L- arabinopyranoside	[24]	70	2', 24-Di-*O*-acetyl-25- anhydrohydroshengma-nol-3-*O*-*α*-L-arabinopyranoside	[24]
71	24-*O*-Acetylisodahurinol	[26]	72	24-*O*-acetyl-7(8)-en-isodahurinol	[26]
73	2', 24-*O*-Diacetylisodahurinol-3-*O*-*α*-L- arabinopyranoside	[24]	74	25-Methoxy-24-*O*-acetylisohurinol	[38]
75	24-*O*-Acetylisodahurinol-3-*O*-*α*-L-arabinopyranoside	[24]	76	Heracleifolinosides D	[34]
77	Heracleifolinosides E	[34]	78	Heracleifolinosides F	[34]
79	Cimiracemosides E	[15]	80	7, 8-Didehydro-24S-*O*-acetylhydroshengmanol-3-*O*-*β*-D-galactopyranoside	[25]
81	24-*O*-hydroxy-7, 8-didehydrohydroshengmanol 3-*O*-*β*-D-galactopyranoside	[1]	82	24-*Epi*-24-*O*-hydroxy-7, 8-didehydrohydroshengmanol 3-*O*-*β*-D-galactopyranoside	[1]
83	Cimifoetisides VI	[39]	84	Cimifoetisides VII	[39]
85	26-Methoxy-acteol-12(18)-en	[38]	86	2′-*O*-Acetyl-27-deoxyactein	[41]
87	2′-*O*-acetylactein	[41]	88	Cimiracemoside N	[28]
89	7*β*-Hydroxy-23-epi-acteol-3-*O*-*α*-L-arabinopyranoside	[38]	90	Cimiracemoside I	[28]
91	7, 8-Didehydro-27-deoxyactein	[40]	92	Cimiracemoside O	[28]
93	Cimiracemoside P	[28]	94	7*β*-Hydroxy-23-*epi*-acteol-3-*O*-*β*-D-xylosepyranoside	[38]
95	Yunnanterpene G	[38]	96	Yunnanterpene B	[42]
97	Yunnanterpene C	[42]	98	Yunnanterpene A	[42]
99	Yunnanterpene F	[42]	100	Yunnanterpene E	[42]
101	Yunnanterpene D	[42]	102	Cimifetidanoside H aglycone	[33]
103	Cimifetidanoside H	[33]	104	20*S*, 22*R*, 23*S*, 24*R*-16*β*, 23, 22, 25-Diepoxy-cycloartane-3*β*, 23, 24-triol 3-*O*-*β*-D-glucopyranosyl-(1-2)-*β*-D-glucopyranosyl-(1-2)-*β*-D-xylopyranoside	[43]
105	20*S*, 22*R*, 23*S*, 24*R*-16*β*, 23, 22, 25-Diepoxy-cycloartane-3*β*, 23, 24-triol 3-*O*-(6-*O*-trans- isoferuloyl-*β*-D-glucopyranosyl)-(1-2)-*β*-D-glucopyranosyl-(1-2)-*β*-D-xylopyranoside	[43]	106	(22*R*, 23*R*, 24*R*)-12*β*-acetyloxy-16*β*, 23 : 22, 25-diepoxy-23, 24-dihydroxy-9, 19-cyclolanostan-3*β*-yl *α*-L-arabinopyranoside	[18]
107	Cimiracemosides G	[15]	108	Cimiracemosides H	[15]
109	Cimiracemosides F	[15]	110	Cimilactone C	[42]
111	12*β*-Acetoxy-3*β*-hydroxy-24, 25, 26, 27-tetranorcycloartan-23, 16*β*-olide 3-*O*-*β*-D-xylopyranoside	[44]	112	12*β*-Acetoxy-3*β*-hydroxy-24, 25, 26, 27-tetranor-cycloart-7-en-23, 16*β*-olide 3-*O*-*β*-D-xylopyranoside	[44]
113	3*β*, 11*β*-Dihydroxy-24, 25, 26, 27-tetranor-cycloart-7-en-23, 16*β*-olide 3-*O*-*β*-D-xylopyranoside	[36]	114	20(S), 22(R), 23(R), 24(S)-12*β*-acetoxy-16*β* : 23, 23a : 24-diepoxy-3*β*, 22*β*, 25-trihydroxy-9, 19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[45]
115	Cimifetidanoside G	[38]	116	Cimidahuside C	[46]
117	Cimidahuside D	[46]	118	15, 16-Seco-shengmanol C	[38]
119	24-Acetoxy-15, 16-seco-cycloart-7-en 3-*O*-xyloside	[47]	120	24-Hydroxy-15, 16-seco-cycloart-7-en 3-*O*-xyloside	[47]
121	24-Acetoxy-15, 16-seco-23*R*, 24*R*-cycloartane 3-*O*-xylopyranoside	[48]	122	24-Hydroxy-15, 16-seco-23*R*, 24*R*-cycloartane 3-*O*-xylopyranoside	[48]
123	24-Hydroxy-15, 16-seco-23*R*, 24*S*-cycloartane 3-*O*-xylopyranoside	[48]	124	15, 16-Seco-cimiterpenes A	[42]
125	15, 16-Seco-cimiterpenes B	[42]	126	Neocimicigenosides A	[49]
127	Neocimicigenosides B	[49]	128	Foetidinosides A	[35]
129	Foetidinosides B	[35]	130	Foetidinosides C	[35]

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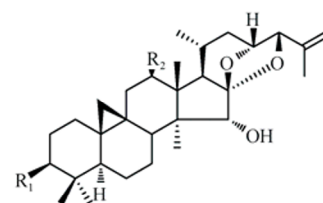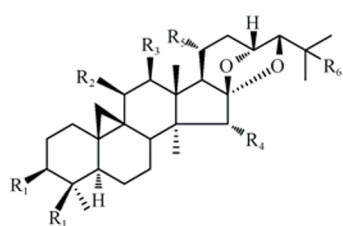| No.	Compound	Ref.	No.	Compound	Ref.
131	Foetidinosides D	[35]	**132**	Foetidinosides E	[35]
133	Foetinoside	[2]	**134**	3β,16α-Dihydroxy-12-acetoxy-16, 22-cyclo-23-ketone-24R, 25-epoxy-cycloartane-7-ene 3-O-β-D-galactopyranoside	[1]
135	Foetidinol-3-O-β-D-xylopyranosyl-(1″→3′)-β-D-xylopyranoside	[37]	**136**	16α, 24α-Dihydroxy-12β-acetoxy-25, 26, 27-trinor-16, 24-cyclocycloartan-23-one 3-O-α-L-arabinopyranoside	[17]
137	28-Hydroxy-foetidinol-3-O-β-D-xylopyranoside	[37]	**138**	3β, 15α, 16α, 24α-Tetrahydroxy-25, 26, 27-trinor-16, 24-cyclo-cycloartane-23-one 3-O-β-D-xylopyranoside	[36]
139	3β, 15α, 16α, 24α-tetrahydroxy-25, 26, 27-trinor-16, 24-cyclo-cycloartane-7-en-23-one 3-O-β-D- xylopyranoside	[36]	**140**	15α-Hydroxy-16-dehydroxy-16(24)-en-foetidinol-3-O-β-D-xylopyranoside	[37]
141	12β-acetoxy-3β, 15α, 16α, 24α-tetrahydroxy-25, 26, 27-trinor-16, 24-cyclo-cycloart-7-en-23-one 3-O-β-D-xylopyranoside	[36]	**142**	Cimicifugadine	[50]

Cimignol type

Cimignol type has an unprecedented 16-*O*-23*R*, 24*S*-*O*-16 cyclization unit attached to the side chain and represents a significant structural variation in this compound class. In the ^{13}C NMR, C-16 reflects on the δ_C 112.0. In the ^{1}H NMR, cyclopropane methylene appears at δ_H 0.27 and 0.58. In the ^{13}C NMR, the signal of C-15, C-16 and C-17 appear in δ_C 77−81，δ_C 111−113，δ_C 59−61, respectively. Since 2000, all of the stereochemistry of the known compound has been found to be 23R and 24S, and totally 42 new Cimignol analogues (**1−42**) have been obtained and identified from Cimicifuga species, with their structures being shown in Fig. 1 and their names in Table 1. Occasionally, C-9 and C-19 are fused in some derivatives, such as compound 9, 10-seco-1(10), 7(8), 9(11)-triencimigenol (**42**) [26], and the typical spectral data show that two protons of H-19 appear between δ_H 3.15 and 3.21, together with C-19 in δ_C 43 and 44.

Both cimicifoetisides A (**9**) and cimicifoetisides B (**11**) [23] exhibit potent cytotoxicity against rat ehrlichascites carcinoma and human breast cancer MDA-MB-A231 cells with IC$_{50}$ values of 0.52−6.74 μ mol·L^{-1} for cimicifoetisides A (**9**), and 0.19−10.21 μ mol·L^{-1} for cimicifoetisides B (**11**), respectively, suggesting their potential as anti-cancer agents. In other researches, 2′-*O*-acetylcimigenol- 3-*O*- β-D-xylopyranoside (**12**) [24] and 25-anhydrocimigenol- 3-*O*- α-L-arabinopyranoside (**38**) [24], Cimigenol-3-*O*-[2′-*O*- (E)-2- butenoyl]- α-L-arabinopyranoside (**13**), 25-*O*-acetylcimigenol- 3-*O*-[3′-O-acetyl]- α-L-arabin opyranoside (**14**), and 25-*O*- acetylcimigenol-3-*O*-[4′-*O*-acetyl]- α-L- arabinopyranoside (**15**) [26] exhibit broad-spectrum and moderate cytotoxicities with IC$_{50}$ values ranging from 6.20−22.74 μ mol·L^{-1} and 4.2−14.5 μmol·L^{-1}. 12 β -hydroxy- 15-deoxycimigenol (**2**) [24] exhibits moderate cytotoxicity against SMMC-7721 cell lines, with IC$_{50}$ values being s 17.65−35.14 μ mol·L^{-1}. Cimifoetiside B (**16**) [27] effectively inhibits the proliferation of murine splenocytes induced by concanavalin A, with IC$_{50}$ values being 12.7 nmol·L^{-1}. The main structural characteristics of these compounds are that: (1) the configurations of C-23 and C-24 are R and S, respectively; and (2) carbonyl and

acetoxy groups are at C-3 or C-25 instead of a hydroxyl group. It has been reported that cimigenol-type aglycone actrin-3-one has potent and moderate activities against human HepG-2 and HT 29 cell lines, respectively. Based on the analyses of these data, it may be proposed that, for cimigenol-type aglycones, hydrophobic groups, such as carbonyl and acetoxy instead of a hydroxyl group at C-3 or C-25, are essential for cytotoxicity.

16-ketone type

16-Ketone type is easy to be recognized because of the characteristic structure of 16-ketone. The ^{13}C NMR data reflects on the δ_C 220.0 of C-16 and δ_C 205.0 of C-23. Basically, C-15 is around δ_C 80.7, and C-20 is around δ_C 27.5. Furthermore, this type is usually divided into two sub-classes, namely cimicidanol and cimicidol, according to the structures of C-24 and C-25. Cimicidanol subtype possesses C-24, 25-epoxy due to hydroxyl dehydration between C-24 and C-25 to form double bond with C-23 around δ_C 205, while cimicidol owns C-24, 25-dihydroxy with C-23, usually appearing in δ_C 213.0. In addition, C-24, C-25, and C-26 of cimicidanol are around δ_C 65.5, 60.4, and 18.1, compared with these data of cimicidol that are around δ_C 84.0, 72.0, and 25.5. In ^{1}H NMR spectrum, cyclopropane methylene signals exhibit at δ_H 0.61 and 1.1 ppm. Since 2000, 8 new cimicidanol subtype glycosides (**43−50**) have been isolated from cimicifuga genus, together with 10 new cimicidol subtype glycosides (**51−60**), among which 9 new compounds possess 9, 10-seco structure. Furthermore, one trinocimicidol compound 24-hydroxy-12 β -acetoxy-25, 26, 27-trinorcycloartan-16, 23-dione-3 β -*O*- α -L-arabinopyranoside (**61**) [17] and one C-24, 25-ene cimifetidanoside E (**62**) [33] compound have been isolated from Cimicifuga species. Liu *et al*. have reported that heracleifolinoside B (**52**) [34] is effectively resistant to hypoxia and reoxygenation-induced human umbilical vein endothelial cell injury, with cell viabilities being 61.95% ± 2.04%, 77.04% ± 4.44%, and 83.65% ± 3.29% at concentrations of 1, 10, and 100 μmol·L^{-1}, respectively, indicating that they exhibit good anti-hypoxic effects in a dose-dependent manner. Compared with 16,

	R1	R2	R3	R4	R5	R6	△7,8
1	OH	H	=O	OH	CH₃	OH	−
2	OH	H	OH	H	CH₃	OH	−
3	OH	H	OH	OH	CH₃	OH	+
4	OH	OH	H	OH	CH₃	OH	+
5	=O	H	H	OH	CH₃	OH	−
6	=O	H	H	OH	CH₃	OH	+
7	=O	H	OH	H	CH₃	OH	+
8	=O	OH	H	H	CH₃	OH	+
9	*O*-2'-*O*-acetyl-α-L-Ara 24*S*	H	H	OH	CH₃	OH	−
10	*O*-2'-*O*-acetyl-α-L-Ara 24*R*	H	H	OH	CH₃	OH	−
11	*O*-2'-*O*-acetyl-α-L-Ara	H	H	OH	CH₃	OAc	−
12	*O*-2'-*O*-acetyl-β-D-Xylose	H	H	OH	CH₃	OH	−
13	*O*-2'-*O*-(E)-2-butenoyl-α-L-Ara	H	H	OH	CH₃	OH	−
14	*O*-3'-*O*-acetyl-α-L-Ara	H	H	OH	CH₃	OAc	−
15	*O*-4'-*O*-acetyl-α-L-Ara	H	H	OH	CH₃	OAc	−
16	*O*-β-D-glc-(1"-2')-β-D-Xyl	H	H	OH	CH₃	OH	−
17	*O*-β-D-glc-(1"-2')-β-D-Xyl	H	H	OH	CH₃	OAc	−
18	*O*-β-D-glc-(1'''-2")-β-D-Glu-(1"-2')-β-D-Xyl	H	H	OH	CH₃	OAc	−

	R1	R2
37	OH	OH
38	*O*-Ara	H
39	*O*-Ara	OAc
40	*O*-Xyl	OAc
41	*O*-Gal	H

	R₁	R₂	R₃	R₄	R₅	R₆	△7,8
19	*O*-Ara	H	H	OH	CH₃	OH	−
20	*O*-Ara	H	H	OH	CH₂OH	OH	−
21	*O*-Ara	H	H	OGlc	CH₃	OH	−
22	*O*-Ara	H	OH	OH	CH₃	OH	−
23	*O*-Ara	H	OH	OH	CH₃	OH	+
24	*O*-Ara	H	OH	OH	CH₂OH	OH	−
25	*O*-Ara	H	OAc	OH	CH₃	OH	−
26	*O*-Xyl	H	H	OH	CH₃	OH	−
27	*O*-Xyl	H	H	OH	CH₂OH	OH	−
28	*O*-Xyl	H	OH	H	CH₃	OH	−
29	*O*-Xyl	H	OH	OH	CH₃	OH	+
30	*O*-Xyl	H	OAc	OH	CH₃	OH	−
31	*O*-Xyl	H	OAc	OH	CH₃	OH	+
32	*O*-Xyl	OH	H	H	CH₃	OH	+
33	*O*-Gal	H	H	OH	CH₃	OH	−
34	*O*-Gal	H	H	OH	CH₃	OH	+
35	*O*-Gal	H	H	OH	CH₃	OAc	+
36	*O*-Gal	H	OH	OH	CH₃	OH	−

42
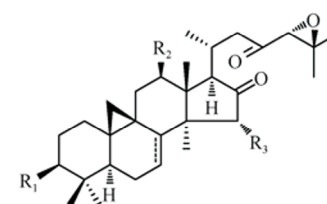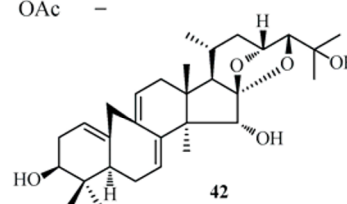
	R₁	R₂	R₃	△7,8
43	*O*-Ara	OAc	OH	+
44	*O*-Ara	OAc	H	+
45	*O*-Xyl	H	H	+
46	*O*-Xyl	H	OH	+
47	*O*-2'-acetoxy-Ara	OAc	OH	−

Fig. 1   Structures of compound 1−47

	R	△ 1, 10
48	H	+
49	β-OH	–
50	α-OH	–

	R_1	R_2	R_3	R_4
51	OH	H	OH	*O*-Glc-Xyl
52	*O*-Xyl	H	H	*O*-Glc
53	*O*-Xyl	H	OH	*O*-Glc
54	*O*-Ara	OAc	OH	OH

	R_1	R_2	R_3	△ 1, 10	
55	OH	--	OH	+	24*R*
56	OH	--	OH	+	24*S*
57	OH	α-OH	OH	–	24*S*
58	*O*-Xyl	--	OGlc	+	24*S*
59	*O*-Xyl	β-OH	OH	–	24*S*
60	*O*-Xyl	α-OH	OH	–	24*S*

	R	
63	OAc	24*S*
64	OH	24*R*

	R_1	R_2	△ 7, 8	
65	*O*-Ara	OH	–	24*R*
66	*O*-Ara	OAc	+	24*S*
67	*O*-4'-acetoxy-Ara	OH	–	24*R*
68	*O*-4'-acetoxy-Xyl	OH	–	24*R*
69	*O*-2'-acetoxy-Ara	OH	–	24*S*

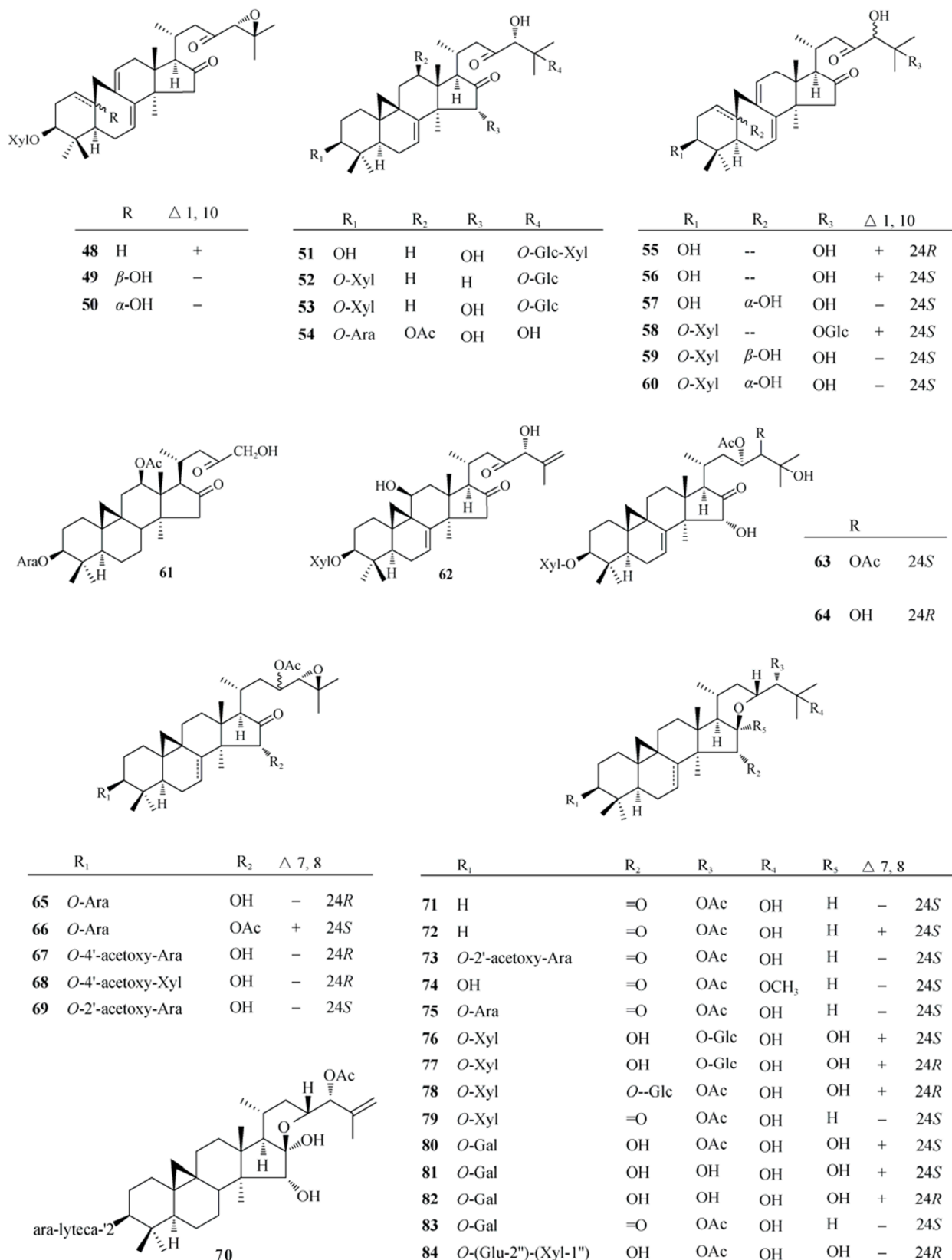|	R_1	R_2	R_3	R_4	R_5	△ 7, 8	
71	H	=O	OAc	OH	H	–	24*S*
72	H	=O	OAc	OH	H	+	24*S*
73	*O*-2'-acetoxy-Ara	=O	OAc	OH	H	–	24*S*
74	OH	=O	OAc	OCH₃	H	–	24*S*
75	*O*-Ara	=O	OAc	OH	H	–	24*S*
76	*O*-Xyl	OH	O-Glc	OH	OH	+	24*S*
77	*O*-Xyl	OH	O-Glc	OH	OH	+	24*R*
78	*O*-Xyl	*O*--Glc	OAc	OH	OH	+	24*R*
79	*O*-Xyl	=O	OAc	OH	H	–	24*S*
80	*O*-Gal	OH	OAc	OH	OH	+	24*S*
81	*O*-Gal	OH	OH	OH	OH	+	24*S*
82	*O*-Gal	OH	OH	OH	OH	+	24*R*
83	*O*-Gal	=O	OAc	OH	H	–	24*S*
84	*O*-(Glu-2")-(Xyl-1")	OH	OAc	OH	OH	–	24*R*

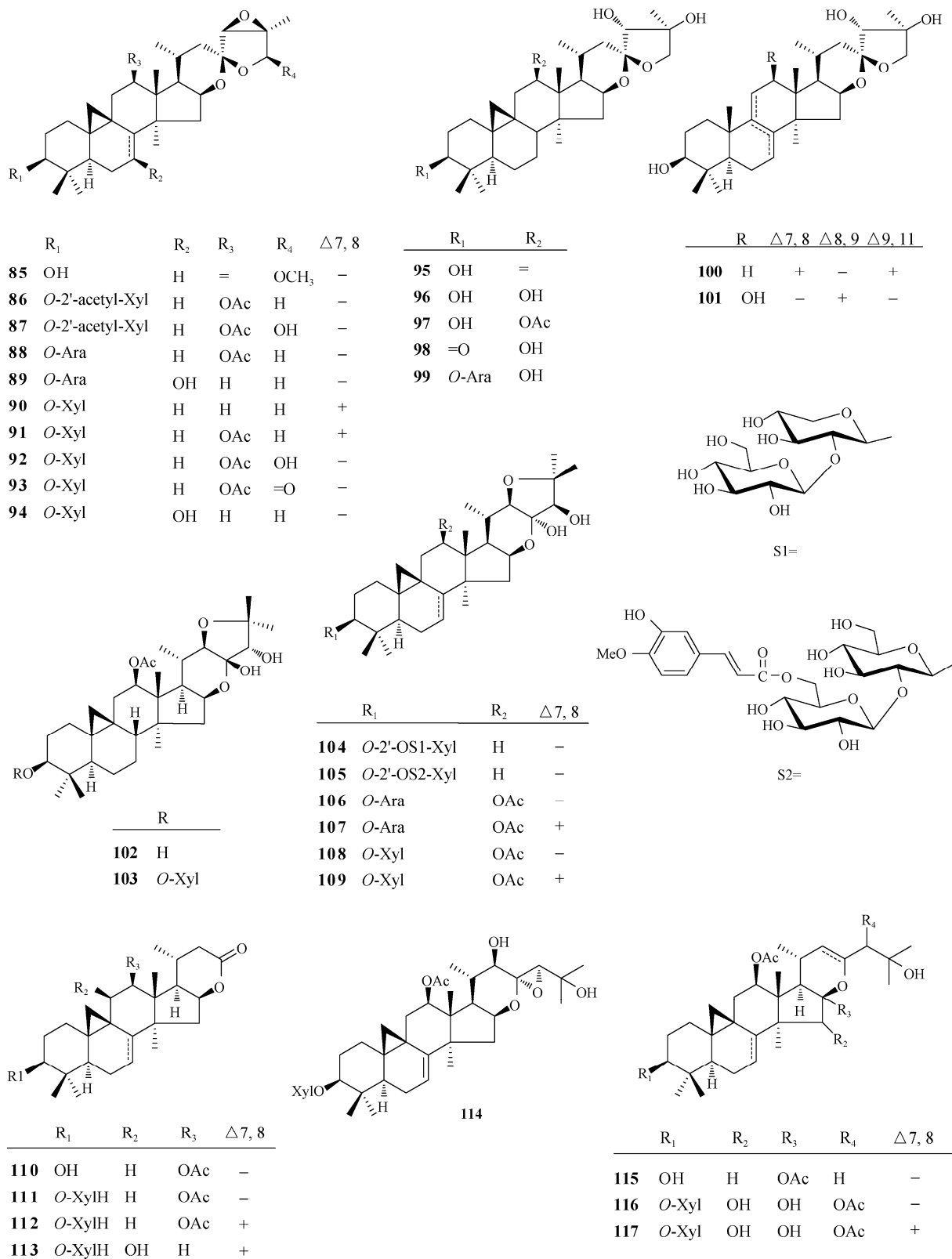**Fig. 2   Structures of compounds 48−84**

Fig. 3   Structures of Compounds 85−117

23-diketo structure, 16-ketone-23-*O*-acetylshengmanol only has one ketone group located on C-16 and one acetyl group located in C-23 instead of ketone group, which reflect in δ_C 72.0 of C-23 and δ_C 220 of C-16, respectively. To our best knowledge, only 7 new compounds in this class (**63–69**) are identified between 2000 to 2014. 23-*O*-acetylshengmanol-3-*O*-α-L-
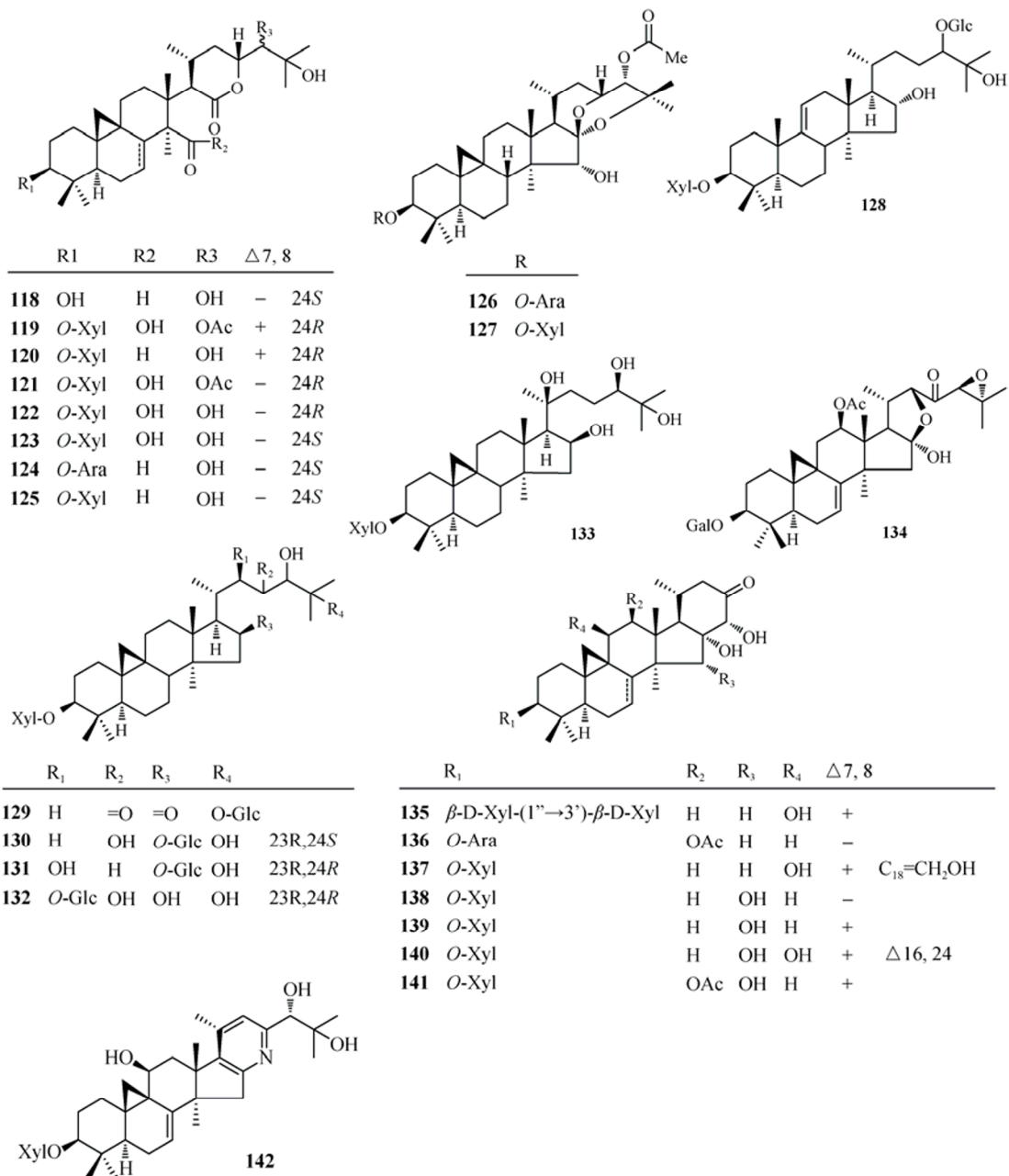
	R1	R2	R3	△7, 8	
118	OH	H	OH	−	24*S*
119	*O*-Xyl	OH	OAc	+	24*R*
120	*O*-Xyl	H	OH	+	24*R*
121	*O*-Xyl	OH	OAc	−	24*R*
122	*O*-Xyl	OH	OH	−	24*R*
123	*O*-Xyl	OH	OH	−	24*S*
124	*O*-Ara	H	OH	−	24*S*
125	*O*-Xyl	H	OH	−	24*S*

	R
126	*O*-Ara
127	*O*-Xyl

	R₁	R₂	R₃	R₄	
129	H	=O	=O	*O*-Glc	
130	H	OH	*O*-Glc	OH	23R,24*S*
131	OH	H	*O*-Glc	OH	23R,24*R*
132	*O*-Glc	OH	OH	OH	23R,24*R*

	R₁	R₂	R₃	R₄	△7, 8	
135	β-D-Xyl-(1"→3')-β-D-Xyl	H	H	OH	+	
136	*O*-Ara	OAc	H	H	−	
137	*O*-Xyl	H	H	OH	+	C₁₈=CH₂OH
138	*O*-Xyl	H	OH	H	−	
139	*O*-Xyl	H	OH	H	+	
140	*O*-Xyl	H	OH	OH	+	△16, 24
141	*O*-Xyl	OAc	OH	H	+	

Fig. 4 Structures of Compounds 118−142

arabinopyranoside (**65**) [18] exhibits apparent cytotoxicity against HSC-2 cells at the concentration of 63 μmol·L⁻¹ and against HGF cells at 267 μmol·L⁻¹. 2′, 23-*O*-diacetylshengmanol-3-*O*-*α*-L-arabinopyranoside (**69**) [24] only shows weak inhibition activities against HL-60 cell line, with IC₅₀ value being 35.24 μmol·L⁻¹.

24-hydroshengmanol type

The major characteristics of this type are that C-15 often contains oxygen substitute, including hydroxyl, carbonycl, acetyl and methoxyl, and that C-16 has hemiacetal structure. Then, the signals of C-15 and C-16 are stable appearing around δ_C 81.5−83.0 and δ_C 102.2−107.0, respectively without big changes. Meantime, after C-15 glucosidation,

such as heracleifolinosides F (**78**) [34], C-15 moves to lower field around δ_C 95.0 with small influence of C-16 and C-17. Since 2000, 15 new compounds have been found to belong to anhydrohydroshengmanol-3-*O*-*α*-L-arabinopyranoside (**70**) [24]. In this case, C-25 appears between δ_C 142−146, while C-26 is around δ_C 113−116. The immunosuppressive activity of 24-*O*-hydroxy-7, 8-didehydro-hydroshengmanol 3-*O*-*β*-D-galactopyranoside (**81** and **82**) [1] has been studied and the results show that **81** has better immunosuppressive activity. So far, 15 compounds, namely 24-epi-24-*O*-hydroxy-7, 8 (**70–84**), have been isolated. Moreover, the configuration of C-23 is R and C-24 might be R or S. C-25 hydroxyl can also be dehydrated to form double bonds between C-25 and C-26,

such as 2′, 24-di-*O*- acetyl-25-didehydrohydroshengmanol 3-*O*-β-D-galactopyranoside (**82**), providing the highest immunosuppressive activity with IC_{50} value being 14.8 μmol·L^{-1}, although its activity was far lower than that of CsA. These data mean that only small difference in structure could lead to remarkable different immunosuppressive activity, and future work should focus on the correlation between small difference in structures and variations in immunosuppressive activity.

Cimifugenins type

In this type of compounds, C-15, C-16, and C-17 are found in δ_C 44, δ_C 73 and δ_C 56, respectively, which are distinguishable data from other types. H-24 appears around δ_H 3.5−3.8 as an S peak. In addition, chemical shifts value of C-23 and C-25 may be helpful to be used to judge the absolute configuration of C-26. In brief, C-26 might be *R*-OH when C-23 is around δ_C 103.6−104.3 together with C-25 in δ_C 62.4−63.9; while C-26 might be *S*-OH when C-23 is around δ_C 105.8−106.5 together with C-25 in δ_C 64.5−65.6. Since 2000, 16 new compounds have been isolated. All the spectrum data suggest that this kind of compounds is highly oxygenated 9, 19-cycloartane-type triterpene, and a seven-ring structure is required to fulfill the unsaturation requirement. The biggest characteristic is that C-23 is linked with C-16 and C-26 respectively, through oxo-bridging (**85−101**). Besides, oxo-bridging usually exists between C-24 and C-25 (**85−94**) due to the hydroxyl groups of C-24 and C-25, forming an oxygen ring with β configuration. Furthermore, two hydroxyls might be located on C-24 and C-25, respectively (**95−99**), instead of oxo-bridge. Sometimes, C-9 and C-19 are seco-cycloartane (**100−101**). In pharmacological study, the anti-osteoporosis activity screening *in vitro* indicates that 2′-*O*-acetyl-27-deoxyactein (**86**)[41] promotes the proliferation for rat osteoblastoma cell line (UMR106) at the concentration of 10^{-9} kg·L^{-1}, suggesting that 2′-*O*-acetyl-27-deoxyactein (**86**) has anti-osteoporosis activity at relatively low concentration. Howerer, more work is needed to clarify the mechanism of 2′-*O*-acetyl-27-deoxyactein (**86**) on protect osteoporosis, such as the effects on alkaline phosphatase (AKP) or external signal-regulated kinase (ERK) activity (the important signaling pathway in osteoporosis) and so on. WT MEFs and tumorigenic cell lines p53−/− +H-RasV12 and p53−/− +p53 N236S +H-RasV12 are used for testing the active structures, which are targeting p53N236S mutation. The results show that yunnanterpene E (**100**)[42] has non-selective activities against all of these cell lines, with IC_{50} values being 5.8, 8.6, and 6.0 μmol·L^{-1}, respectively. However, yunnanterpene D (**101**)[42] exhibits greater selectivity against the p53−/− +p53N236S +H-RasV12 cells than the WT MEFs cells. Furthermore, yunnanterpene D (**101**) exhibits approximately 3-fold higher selectivity against the WT MEFs cells than yunnanterpene E (**100**). According to these results, the mechanism of action of yunnanterpene D (**101**) is worth studying in a more advanced way in the future.

Cimiacerogenin type

The oxygen bridge between C-16-*O*-C-23 and C-22-*O*-C-25 is an important feature of this kind of compounds, which makes these compounds have six rings. In ^{13}C NMR, the specific chemical shifts are C-16 in δ_C 72, C-23 in δ_C 105, C-22 in δ_C 87.0, and C-25 in δ_C 84.0. Since 2000, only 8 new compounds (**102−109**) have been isolated. It is notable that cimiracemosides G (**107**)[15] shows about 15-fold higher cytotoxic activity against HSC-2 tumor cells than normal HGF 18. 20S, 22R, 23S, 24R-16β, 23, 22, 25-diepoxy- cycloartane-3β, 23, 24-triol 3-*O*-β-D-glucopyranosyl-(1-2)-β-D-glucopyranosyl-(1-2)-β-D-xylopyranoside (**104**) and 20S, 22R, 23S, 24R-16β, 23, 22, 25-diepoxy-cycloartane-3β, 23, 24-triol-3-*O*-(6-*O*-trans-isoferuloyl-β-D-glucopyranosyl)- (1-2)-β-D-glucopyranosyl-(1-2)-β-D-xylo pyranoside (**105**)[43] suppress the proliferation of lymphocytes and the IC_{50} values are 1.03×10^{-4} and 5.56×10^{-5} mol·L^{-1}. Furthermore, they show potent immunosuppressive activity in mouse allogeneic mixed lymphocyte reaction (IC_{50} 5.56×10^{-5} mol·L^{-1} and 9.96×10^{-5} mol·L^{-1}, respectively). These data only mean that these compounds have immunosuppressive activity *in vitro*, so experiments *in vivo* should be further done to demonstrate the whole profile of these compounds on their immunosuppressive activity, such as the inflammatory cytokine or chemokine expression in immunosuppressive mice, including psoriasis or experimental allergic encephalomyelitis (EAE).

Asiaticoside type

In this type, C-16 and C-23 are linked by oxygen bridge, and C-16 always appears in δ_C 72.2−84.3. The side chain is variable. When C-23 has carbonyl group, the C-23 appears in δ_C 173; while if C-23 and C-24 form an oxygen ring 20(S), 22(R), 23(R), 24(S)-12β-acetoxy-16β : 23, 23a : 24- diepoxy-3β, 22β, 25-trihydroxy-9, 19-cyclolanost-7-ene 3-*O*-β-D-xylopyrano side (**114**)[45], C-23 appears in δ_C 105.6. Among these compounds, **110−113** are a little different conventional asiaticoside type, due to their side chains. They only have a ketone group on C-23 instead of the whole side chain. Furthermore, C-15 occasionally has a carbonyl group, such as cimidahuside C (**116**) and cimidahuside D (**117**)[46], and C-12 always has acetyl group. Since 2000, C-3 of all of this kind of compounds has been shown to be glucosidation with xyl and only 8 new compounds (**110−117**) have been found.

15, 16-seco-cycloartane types

This kind of cycloartane glycosides has structural peculiarities, namely, C-C bond cleavage between C-15 and C-16. The most important structure of this type is that D-ring is open and becomes one carbonyl or ketone group on C-15 together with one ketone located on C-16. Furthermore, this type of compounds still possesses C-16-*O*-C-23 structure. C-16 often occurs around δ_C 173.0. When the carboxyl group is substituted at C-15, C-15 is about δ_C 178; when the C-15 is substituted with aldehyde, C-15 is about δ_C 207. Since 2000, 8 new compounds (**118−125**) have been isolated from several species.

Other types

Actually, compounds **129–132** own the basic structure of 9, 19-cycloane cycloartane-type, due to their simple skeleton. In this type, C-16 and C-24 are occasionally glycosides with glucose (**129–130**) [35], such as Xyl. To our best knowledge, 3β, 16α-dihydroxy-12-acetoxy-16, 22-cyclo-23-ketone-24R, 25-epoxy-cycloartane-7-ene3-*O*-β-D-galactopyranoside (**134**) [1] is the only 16, 22-cyclo type glycosidesaponin from Cimicifuga species. In addition, other new compounds (**135–141**) have been isolated. As compared with the control, the amount of ACTH secreted from AtT-20 cells is significantly increased by corticotrophin releasing factor (CRF) stimulation. Co-incubation of neocimicigenosides A (**126**) or neocimicigenosides B (**127**) [49] with CRF significantly enhances the ACTH secretion from AtT-20 cells. Thus, **126** or **127** [49] appear to promote hypothalam opituitary-adrenal (HPA) activity, which may lead to stress resistance being recovered. Foetidinosides A (**128**) [35] exerts moderate inhibition against HL-60 and SMMC-7721 cell growth with IC_{50} values being 12.64–30.59 μ mol·L^{-1}, respectively. Cimicifugadine (**142**) [50] is the only 9, 19-cycloane cycloartane-type compound that has N element. Cimicifugadine (**142**) [50] contains one nitrogen atom as an intrinsic and characteristic part of their aglycone structure, which makes them as a separate group.

Discussion

This review mainly discusses the phytochemistry and biological studies of the 9, 19-cycloartenol triterpenoid saponins isolated from genus Cimicifuga since 2000. Thus, to a certain degree, this review would provide useful data for researchers having an interest in exploring or developing new drugs from Cimicifuga spp., especially in further study of menopausal disorders related to some pure compounds instead of only focusing on ethanolic extract or isopropanolic extract of roots of Cimicifuga spp. Further researches should investigate these aspects for genus Cimicifuga to expand medicinal applications *in vitro* or *in vivo*, and even in clinical patients. To our best knowledge, biological studies of the 9, 19-cycloartenol triterpenoid saponins isolated from genus Cimicifuga are not enough to provide sufficient evidence to make some useful conclusion, and more work needs to be done to describe the whole profile of 9, 19-cycloartenol triterpenoid saponins isolated from genus Cimicifuga from both chemical and biological perspectives and studies should be expanded to immunosuppressive anti-osteoporosis, and other. In this review, we attempted to emphasize a new research direction, namely the 9, 19-cyclolanostane triterpenoid glycosides from genus Cimicifuga, and strongly believe that further biological studies will provide valuable insights regarding this ethnomedically important plant.

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