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Cycloartenol triterpenoid saponins from *Cimicifuga simplex* (Ranunculaceae) and their biological effects

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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 are distributed widely in *Cimicifuga* plants, but not in other members of the Ranunculaceae family, and are considered to be characteristics of the *Cimicifuga* genus. This type of triterpenoid glycoside possesses several important biological activities. More than 120 cycloartane triterpene glycosides have been isolated from *Cimicifuga simplex* Wormsk. The aim of this review article is to summarize all the major findings based on the available scientific literatures on *C. simplex*, with a focus on the identified 9,19-cyclolanostane triterpenoid glycosides. Biological studies of cycloartane triterpene glycosides from *Cimicifuga* spp. are also discussed.

[KEY WORDS] *Cimicifuga simplex*; Ranunculaceae; Cycloartenol triterpenoid saponins; Biological effects

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Introduction

The genus *Cimicifuga* in the family Ranunculaceae consists of 25 species distributed throughout East Asia, Europe, and North America [1]. Among them, *C. dahurica* (Turcz.) Maxim., *C. heracleifolia* Kom., and *C. foetida* L. have been listed in the Chinese Pharmacopoeia, and *C. simplex* has been listed in the Japanese Pharmacopoeia as the original plants of *Cimicifuga* rhizome in Japan [2]. *Cimicifuga* rhizome has long been used in East Asian countries to treat headache, dentalgia, aphtha, swelling and pain in the throat, measles, and prolapse of uterus, along with other crude drugs [3-4]. The constituents of *Cimicifuga* plants have been extensively investigated and the principal metabolites are 9,19-cyclolanostane triterpenoid glycosides, phenolic derivatives, sterols, alkaloids, and chromones [5-8]. Interestingly, among these compound types, the 9,19-cyclolanostane triterpenoid glycosides are considered to be characteristics of the *Cimicifuga* genus, which possess estrogen-like effects and immunosuppressive activities [9]. Recently, more than 120 cycloartane triterpene glycosides have been isolated from *C. simplex* [5]. The aim is to review these cycloartane triterpene glycosides from the chemical and biological perspectives.

Traditional uses

C. simplex, also known as Ku lou ya gen and Long yan gen, is an important species in the original Chinese drug Shengma. In Chinese traditional medicine, as along with other *Cimicifuga* species, it has been used to clear heat, relieve toxicity, disperse exterior pathogen, promote eruption, and lift spirit [3]. Plant-based formulations for various medicinal applications use different preparation methods, including powders, alcohol extracts, water extracts, and honey processed pills. The roots of *C. simplex* have been used to treat headache, toothache, aphtha, sore throat, measles, rectocele, and uterine prolapse [11]. The most important biologically active components of *C. simplex* are the cycloartenol triterpenoid saponins which have good immunosuppressive activities [12].

Cycloartenol triterpenoid saponins from *Cimicifuga simplex* Wormsk

C. simplex Wormsk. ex DC. (Shengma in Chinese) is a deciduous perennial herb, and is widely distributed in China [13]. Currently, more than 120 cycloartane-type triterpenoids from *Cimicifuga simplex* have been isolated by several groups [14-27], including compounds of cycloartanol type, 16,23-dione type, shengmanol type, hydroshengmanol type, cimifugenin type, cimiacerogenin type, and the cimigenol type. The chemical structures of these cycloartenol triterpenoid saponins are shown in Fig.s 1−7 and are listed in Table 1. The isolation scheme

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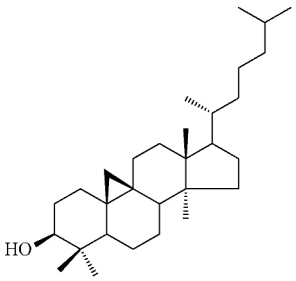
These authors have no any conflict of interest to declare.

for the 9,19-cyclolanostane triterpenoid glycosides from *C. simplex* is shown in Fig. 8.



1 $\Delta^{16,17}$ $\Delta^{24,25}$ 17*S* 20*R*
2 17*R* 20*R*
3 17*S* 20*R*
4 $\Delta^{16,17}$ 17*S* 20*R*

Fig. 1 Cycloartanol-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*

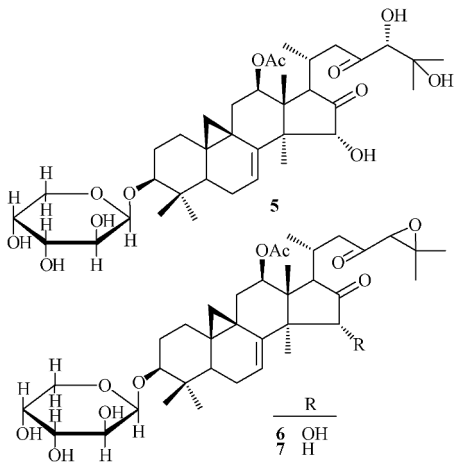
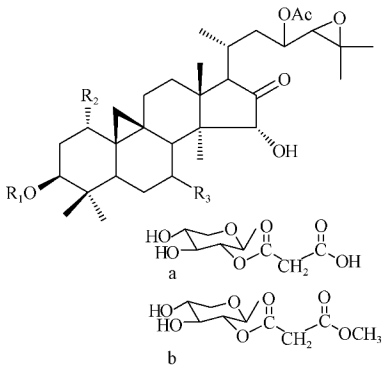
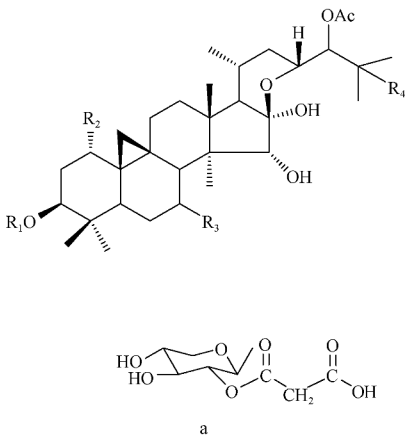


Fig. 2 16,23-Dione-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*

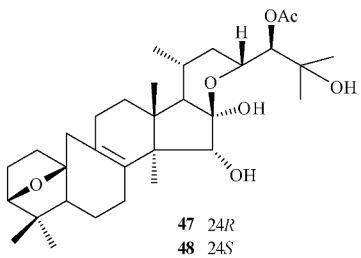


	R_1	R_2	R_3		
8	a	H	H	23*R*	$\Delta^{7,8}$
9	b	H	H	23*R*	$\Delta^{7,8}$
10	Xyl	H	H	23*R*	$\Delta^{7,8}$
11	Gal	H	H	23*R*	$\Delta^{7,8}$
12	Ara	H	H	23*R*	$\Delta^{7,8}$
13	H	H	H	23*R*	$\Delta^{7,8}$
14	Xyl	H	H	23*R*	
15	Xyl	H	OH	23*S*	
16	Xyl	OH	H	23*R*	
17	H	OH	H	23*R*	
18	H	H	OH	23*S*	
19	H	H	H	23*R*	
20	H	H	H	23*S*	
21	Glc-Xyl	H	H	23*R*	
22	a	H	H	23*R*	
23	b	H	H	23*R*	

Fig. 3 Shengmanol-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*

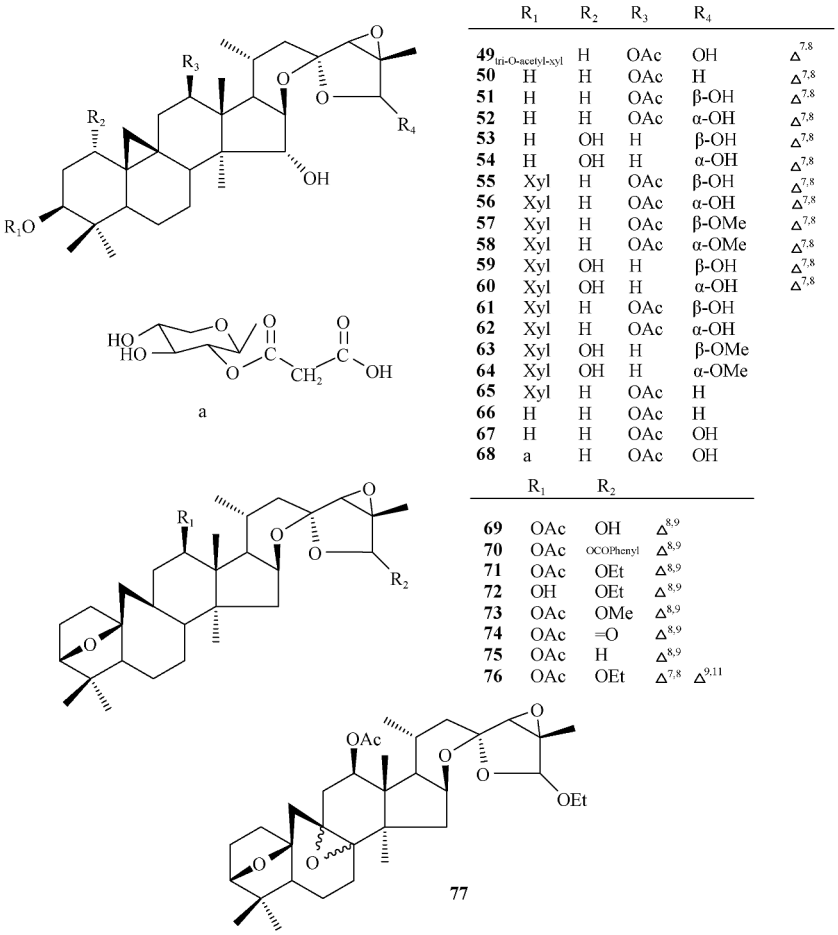


	R_1	R_2	R_3	R_4		
24	Xyl	H	OH	OH	24*R*	
25	Xyl	H	H	OCH_3	24*S*	
26	Xyl	H	OH	OCH_3	24*S*	
27	Xyl	OH	H	OCH_3	24*S*	
28	Xyl	H	H	OH	24*S*	
29	H	H	OH	OH	24*R*	
30	H	H	H	OCH_3	24*S*	
31	H	H	OH	OCH_3	24*S*	
32	H	OH	H	OCH_3	24*S*	
33	H	H	H	OH	24*S*	
34	H	H	H	OH	24*R*	
35	Gal	H	H	OH	24*R*	
36	Gal	H	H	OH	24*S*	$\Delta^{7,8}$
37	Gal	H	H	OH	24*R*	$\Delta^{7,8}$
38	H	H	H	OH	24*R*	$\Delta^{7,8}$
39	Xyl	H	H	OH	24*R*	$\Delta^{7,8}$
40	Xyl	H	H	OH	24*S*	$\Delta^{7,8}$
41	Ara	H	H	OH	24*R*	$\Delta^{7,8}$
42	Ara	H	H	OH	24*S*	$\Delta^{7,8}$
43	a	H	H	OH	24*R*	$\Delta^{7,8}$
44	Xyl	H	H	O	24*S*	$\Delta^{7,8}$
45	H	H	H	OH	24*S*	$\Delta^{7,8}$
46	H	H	H	OCH_3	24*S*	$\Delta^{7,8}$



47 24*R*
48 24*S*

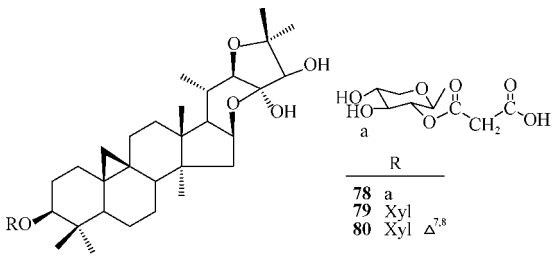
Fig. 4 Hydroshengmanol-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*



	R_1	R_2	R_3	R_4	
49	tri-O-acetyl-xyl	H	OAc	OH	$\Delta^{7,8}$
50	H	H	OAc	H	$\Delta^{7,8}$
51	H	H	OAc	β-OH	$\Delta^{7,8}$
52	H	H	OAc	α-OH	$\Delta^{7,8}$
53	H	OH	H	β-OH	$\Delta^{7,8}$
54	H	OH	H	α-OH	$\Delta^{7,8}$
55	Xyl	H	OAc	β-OH	$\Delta^{7,8}$
56	Xyl	H	OAc	α-OH	$\Delta^{7,8}$
57	Xyl	H	OAc	β-OMe	$\Delta^{7,8}$
58	Xyl	H	OAc	α-OMe	$\Delta^{7,8}$
59	Xyl	OH	H	β-OH	$\Delta^{7,8}$
60	Xyl	OH	H	α-OH	$\Delta^{7,8}$
61	Xyl	H	OAc	β-OH	
62	Xyl	H	OAc	α-OH	
63	Xyl	OH	H	β-OMe	
64	Xyl	OH	H	α-OMe	
65	Xyl	H	OAc	H	
66	H	H	OAc	H	
67	H	H	OAc	OH	
68	a	H	OAc	OH	

	R_1	R_2	
69	OAc	OH	$\Delta^{8,9}$
70	OAc	OCOPhenyl	$\Delta^{8,9}$
71	OAc	OEt	$\Delta^{8,9}$
72	OH	OEt	$\Delta^{8,9}$
73	OAc	OMe	$\Delta^{8,9}$
74	OAc	=O	$\Delta^{8,9}$
75	OAc	H	$\Delta^{8,9}$
76	OAc	OEt	$\Delta^{7,8}$ $\Delta^{9,11}$

Fig. 5 Cimifugenin-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*



	R
78	a
79	Xyl
80	Xyl $\Delta^{7,8}$

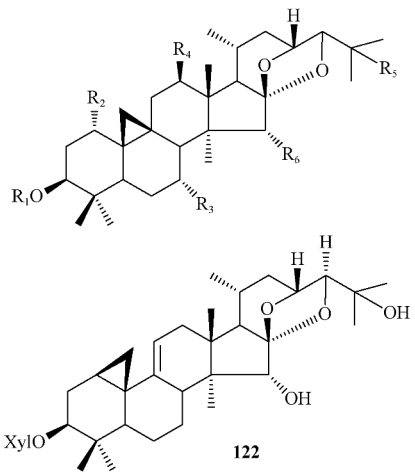
Fig. 6 Cimiacerogenin type cycloartenol triterpenoid saponins from *Cimicifuga simplex*

The 9,19-cyclolanostane triterpenoid glycosides are lanolin alkanol type tetracyclic triterpenoids with a distinctive structure of a 9,19-cyclopropane in the B ring. The side chain possesses a hemiacetal structure and a high level of oxidized functional groups, which react with the D ring into seven groups. There may be a close relationship among the biosynthesis of these seven types, as they all have a high level of oxidation at C-15, C-16, and C-17. Oxygen substituents, such as hydroxy and acetoxy groups, may be located at C-1*α*, C-3*β*, C-6*α*, C-7*β*, C-11*β*, C-12*β*, C-15*α*, C-16*β*, C-18, and C-25; with double bonds at C-7/C-8 and C-25/C-26; and carbonyls located at C-15, C-16, and C-23. The two hydroxyl oxygens of C-24 and C-25 may also be dehydrated to form a ring in these seven types. Glycosidic groups at C-3*β* of the lanolin alkoxides are mostly xylose, and only a few are glucose and arabinose.

Pharmacological studies of cycloartenol triterpenoid saponins on *Cimicifuga* spp.

Immunosuppressive activity

Eduardo *et al.* have evaluated the 9,19-cycloartenol triterpenoid saponins from Cimicifuga Rhizome for their immunosuppressive activity in a mouse allogeneic mixed lymphocyte test [28]. Their results showed that these compounds possessed potent immunosuppressive activity with IC_{50} 1.03 × 10^{-4}, 5.56 × 10^{-5}, and 9.96 × 10^{-5} mol·L^{-1}. Furthermore, their immunosuppressive activities are similar, independent of the sugar moiety [28]. Moreover, Pan *et al* have reported that cycloartenol triterpenoid saponins isolated from *C. foetida* effectively inhibit the proliferation of murine splenocytes induced by concanavalin A, with IC_{50} values ranging from 12.7 to 33.3 nmol·L^{-1}. These results have established that these compounds have good immunosuppressive activity. Thus, they may be excellent candidates for the treatment of immunosuppressive diseases, such as psoriasis, osteoporosis, and myasthenia gravis, as well as some kinds of inflammation [10].



122

	R_1	R_2	R_3	R_4	R_5	R_6		
81	H	OH	H	H	OAc	OH	24*S*	
82	H	OH	H	H	OH	OH	24*S*	
83	H	OH	H	H	OMe	OH	24*S*	
84	H	H	OH	H	OMe	OH	24*S*	
85	H	H	OH	H	OH	OH	24*S*	
86	H	H	OH	H	OH	OH	24*R*	
87	H	H	OH	H	OAc	OH	24*S*	
88	H	H	H	H	OAc	OH	24*S*	
89	H	H	H	H	OMe	OH	24*S*	
90	H	H	H	H	OH	OH	24*S*	
91	H	H	H	H	OH	OH	24*R*	
92	H	H	H	OH	OH	OH	24*S*	
93	Ac	H	OH	H	OH	OH	24*S*	
94	Ac	H	OAc	H	OH	OH	24*S*	
95	Ac	H	H	H	OH	OH	24*S*	
96	Xyl	H	H	H	OAc	OH	24*S*	
97	Xyl	OH	H	H	OAc	OH	24*S*	
98	Xyl	OH	H	H	OH	OH	24*S*	
99	Xyl	H	H	OH	OH	OH	24*S*	
100	Xyl	H	OH	H	OH	OH	24*S*	
101	Xyl	H	OH	H	OAc	OH	24*S*	
102	Ara	H	H	OH	OH	OH	24*S*	
103	Ara	OH	H	H	OH	OH	24*S*	
104	Gal	OH	H	H	OH	OH	24*S*	
105	Gal	H	H	H	OH	OH	24*S*	
106	Gal	H	H	H	OCH3	OH	24*S*	
107	Gal	H	H	H	$OCOCH_3$	OH	24*S*	
108	Glu	H	H	H	$OCOCH_3$	OH	24*S*	
109$_{\text{hexa-O-Ac-Glc-Xyl}}$	H	H	H	OAc	OAc	24*S*		
110	Glc-Xyl	H	H	H	OAc	OH	24*S*	
111	H	H	H	H	OH	OH	24*S*	$\Delta^{7,8}$
112	H	H	H	H	OH	OH	24*R*	$\Delta^{7,8}$
113	Xyl	H	H	H	OH	OH	24*S*	$\Delta^{7,8}$
114	Xyl	H	H	H	OH	OH	24*R*	$\Delta^{7,8}$
115	Xyl	H	H	H	OAc	OH	24*S*	$\Delta^{7,8}$
116	Ara	H	H	H	OH	OH	24*S*	$\Delta^{7,8}$
117	Ara	H	H	H	OAc	OH	24*S*	$\Delta^{7,8}$
118	Ara	H	H	OH	OH	OH	24*S*	$\Delta^{7,8}$
119	Gal	H	H	H	OH	OH	24*R*	$\Delta^{7,8}$
120	Gal	H	H	H	OH	OH	24*S*	$\Delta^{7,8}$
121	Gal	H	H	H	OAc	OH	24*R*	$\Delta^{7,8}$

Fig. 7 Cimigenol-type cycloartenol triterpenoid saponins from *Cimicifuga simplex*

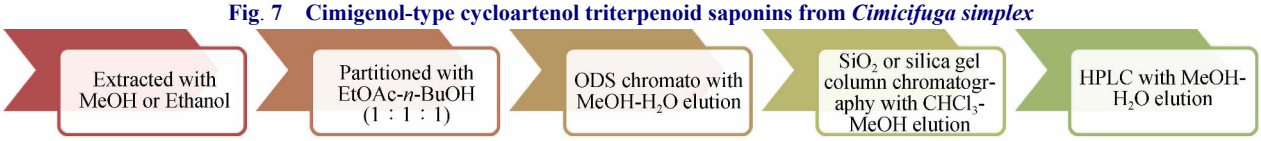


Fig. 8 Isolation scheme for 9,19-cyclolanostane triterpenoid glycosides from *Cimicifuga simplex*

Cytotoxic activity

The rhizomes of *Cimicifuga* species are traditionally the plant part used for medicinal purposes. In order to efficiently utilize this plant, Tian *et al*. extracted the total glycosides, and evaluated its cytotoxicity in HepG2 cells and primary cultured normal mouse hepatocytes using MTT assay [29]. Their results showed that an increase in the ratio of Bax/Bcl-2 was implicated in the total glycosides-induced apoptosis, and this extract inhibited the growth of the implanted mouse H22 tumor in a dose-dependent manner. In view of this, the total glycosides potentially find utility as a new candidate for the treatment of hepatoma. Furthermore, the triterpene glycosides also inhibit breast cancer cells through their apoptotic effects [30-33].

Estrogen-like activity

In traditional Chinese medicine, *Cimicifuga* Rhizome can be used to treat some gynecological diseases, such as prolapse of the uterus, metrorrhagia, and metrostaxis. In Western medicine, it is worth mentioning that the extract of black cohosh (*Cimicifuga racemosa* (L.) Nutt., Remifemin®), which is rich in 9,19-cyclolanostane triterpenoid glycosides, is available as a natural alternative for the treatment of menopausal symptoms, such as hot flashes, anxiety, and depression, and other gynecological complaints. This kind of hormone replacement therapy is a common menopausal treatment for breast cancers due to concerns regarding the potential for breast cell proliferation [34-36].

Other activities

These triterpenoid glycosides also possess several other biological activities, such as, inhibition of thymidine transport into phythoemagglutinin-stimulated lymphocytes [37-38], anti-osteoporosis and anticomplement activities [39-41], detoxification [42], anti-inflammatory, analgesic, and anti-ulcer effects [43], antiviral [44], and hypocholesterolemic effects [45]. Furthermore, this type of triterpenoid may be a candidate for development of new drugs for cardiovascular disorders due to

Table 1 Cycloartenol triterpenoid saponins from *Cimicifuga simplex*

No.	Compound Name	Reference
1	Cycloarta-16,24-dien-3*β*-ol	[25]
2	17-Isocycloartanol	[25]
3	Cycloartanol	[25]
4	16,17-Didehydrocycloartanol	[25]
5	12-Acetoxy-3,15,24*R*,25-tetrahydroxycycloart-16,23-dione-7-en-3-*O*-*α*-L-arabinopyranoside	[27]
6	12-Acetoxy-24*R*,25-epoxy-3,15-dihydroxycycloart-16,23-dione-7-en-3-*O*-*α*-L-arabinopyranoside	[27]
7	12-Acetoxy-24*R*,25-epoxy-3-hydroxy-cycloart-16,23-dione-7-en-3-*O*-*α*-L-arabino pyranoside	[27]
8	23-*O*-Acetyl-7,8-didehydroshengmanol-3-*O*-(2'-*O*-malonyl)-*β*-D-xylopyranoside	[26]
9	23-*O*-Acetyl-7,8-didehydroshengmanol-3-*O*-(2'-*O*-malonyl)-*β*-D-xylopyranoside	[26]
10	23-*O*-Acetyl-7,8-didehydroshengmanol-3-*O*-*β*-D-xylopyranoside	[26]
11	23-*O*-Acetyl-7,8-didehydroshengmanol-3-*O*-*β*-D-galactopyranoside	[24]
12	23-*O*-Acetyl-7,8-didehydroshengmanol-3-*O*-*α*-L-arabinopyranoside	[21]
13	23-*O*-Acetyl-7,8-didehydroshengmanol	[21]
14	23-*O*-Acetylshengmanol-3-*O*-*β*-D-xylopyranoside	[17]
15	7*β*-Hydroxy-23-*O*-acetylshengmanol-3-*O*-*β*-D-xylopyranoside	[16]
16	23-*O*-Acetyl-1*α*-hydroxyshengmanol-3-*O*-*β*-D-xylopyranoside	[18]
17	23-*O*-Acetyl-1*α*-hydroxyshengmanol	[18]
18	7*β*-Hydroxy-23-*O*-acetylshengmanol	[16]
19	23-*O*-Acetylshengmanol	[17]
20	Acetylshengmanol	[16]
21	23-*O*-Acetylshengmanol-3-*O*-*β*-D-glucopyranosyl-(1-3)-*β*-D-xylopyranoside	[17]
22	23-*O*-Acetylshengmanol-3-*O*-(2'-*O*-malonyl)-*β*-D-xylopyranoside	[26]
23	23-*O*-Acetylshengmanol-3-*O*-(2'-*O*-malonyl)-*β*-D-xylopyranoside	[26]
24	24-Epi-24-*O*-acetyl-7*β*-hydroxyhydroshengmanol-3-*O*-*β*-D-xylopyranoside	[20]
25	24-*O*-Acetyl-25-*O*-methyl-hydroshengmanol-3-*O*-*β*-D-xylopyranoside	[20]
26	24-*O*-Acetyl-7*β*-hydroxy-25-*O*-methylhydroshengmanol-3-O-*β*-D-xylopyranoside	[20]
27	24-*O*-Acetyl-1*α*-hydroxy-25-*O*-methylhydroshengmanol-3-O-*β*-D-xylopyranoside	[20]
28	24-*O*-Acetylhydroshengmanol-3-*O*-*β*-D-xylopyranoside	[20]
29	24-Epi-24-*O*-acetyl-7*β*-hydroxyhydroshengmanol	[20]
30	24-*O*-Acetyl-25-*O*-methylhydroshengmanol	[20]
31	24-*O*-Acetyl-7*β*-hydroxy-25-*O*-methylhydroshengmanol	[20]
32	25-*O*-Methyl-1*α*-hydroxy-24-*O*-acetylhydroshengmanol	[20]
33	24-*O*-Acetylhydroshengmanol	[20]
34	24-Epi-24-*O*-acetylhydroshengmanol	[21]
35	24-Epi-24-*O*-acetylhydroshengmanol-3-*O*-*β*-D-galactopyranoside	[21]
36	Shengmaxinside C	[12]
37	24-Epi-24-*O*-acetyl-7,8-didehydrohydroshengmanol-3-*O*-*β*-D-galactopyranoside	[21]
38	24-Epi-24-*O*-acetyl-7,8-didehydrohydroshengmanol	[21]
39	24-Epi-24-*O*-acetyl-7,8-didehydrohydroshengmanol-3-*O*-*β*-D-xylopyranoside	[24]
40	24-*O*-Acetyl-7,8-didehydrohydroshengmanol-3-*O*-*β*-D-xylopyranoside	[24]
41	24-Epi-24-O-acetyl-7,8-didehydrohydroshengmanol-3-*O*-*α*-L-arabinopyranoside	[24]
42	24-*O*-Acetyl-7,8-didehydrohydroshengmanol-3-*O*-*α*-L-arabinopyranoside	[24]
43	24-Epi-24-*O*-acetyl-7,8-didehydrohydroshengmanol-3-*O*-(2'-*O*-malonyl)-*β*-D-xylopyranoside	[26]
44	24-*O*-Acetyl-25-*O*-methyl-7,8-didehydrohydroshengmanol-3-*O*-*β*-D-xylopyranoside	[26]

Continued

No.	Compound Name	Reference
45	24-*O*-Acetyl-7,8-didehydrohydroshengmanol	[24]
46	24-*O*-Acetyl-25-*O*-methyl-7,8-didehydrohydroshengmanol	[26]
47	Heracleifolinol	[24]
48	Proacerinol	[24]
49	Tri-*O*-acetyl- Cimicifugenin A	[14]
50	26-Deoxy-7,8-didehydrocimicifugol	[14]
51	12*β*-Acetoxy-3*β*,26-dihydroxy-24(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
52	12*β*-Acetoxy-3*β*,26-dihydroxy-25(*S*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
53	24(*R*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
54	25(*S*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
55	12*β*-Acetoxy-3*β*,26-dihydroxy-20(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
56	12*β*-Acetoxy-3*β*,26-dihydroxy-23(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
57	12*β*-Acetoxy-3*β*,26-dihydroxy-26(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
58	12*β*-Acetoxy-3*β*,26-dihydroxy-26(*S*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[22]
59	20(*R*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
60	23(*R*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
61	12*β*-Acetoxy-3*β*,26-dihydroxy-20(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanostane 3-*O*-*β*-D-xylopyranoside	[22]
62	12*β*-Acetoxy-3*β*,26-dihydroxy-23(*R*)-16*β*:23;23:26;24:25-triepoxy-9,19-cyclolanostane 3-*O*-*β*-D-xylopyranoside	[22]
63	26(*S*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
64	26(*R*)-16*β*:23;23:26;24:25-Triepoxy-1*α*,3*β*,26-trihydroxy-9,19-cyclolanost-7-ene-3-*O*-*β*-D-xylopyranoside	[23]
65	26-Deoxycimicifugoside	[24]
66	26-Deoxycimicifugol	[24]
67	26-Hydroxycimicifugol	[15]
68	2'-*O*-Malonylcimicifugoside	[26]
69	Cimicifugenin A	[14]
70	26-*O*-Carbonylphenylcimicifugenin A	[15]
71	26-*O*-Ethylcimicifugenin A	[15]
72	12-Hydroxyl-26-*O*-ethylcimicifugenin A	[15]
73	26-*O*-Methylcimicifugenin A	[15]
74	26-*O*-Carbonylcimicifugenin A	[15]
75	26-Hydrogencimicifugenin A	[15]
76	7,8;9,11-Dienyl-26-*O*-ethylcimicifugenin A	[15]
77	8,9-Epoxide-26-*O*-ethylcimicifugenin A	[15]
78	2'-*O*-Malonylcimicifugol	[26]
79	Cimicifugol-3-*O*-*β*-D-xylopyranoside	[26]
80	Cimiaceroside A	[27]
81	25-*O*-Acetyl-1*α*-hydroxycimigenol	[18]
82	1*α*-Hydroxycimigenol	[18]
83	25-*O*-Methyl-1*α*-hydroxycimigenol	[20]
84	25-*O*-Methyl-7*β*-hydroxycimigenol	[16]
85	7*β*-Hydroxycimigenol	[16]
86	24-Epi-7*β*-hydroxycimigenol	[20]
87	25-*O*-Acetyl-7*β*-hydroxycimigenol	[19]
88	25-*O*-Acetylcimigenol	[17]

Continued

No.	Compound Name	Reference
89	25-*O*-Methyl-cimigenol	[16]
90	Cimigenol	[16]
91	24-Epi-cimigenol	[21]
92	12*β*-Hydroxycimigenol	[19]
93	3-*O*-Acetyl-7*β*-hydroxycimigenol	[16]
94	3,7-*O*-Diacetyl-7*β*-hydroxycimigenol	[16]
95	3-*O*-Acetylcimigenol	[16]
96	25-*O*-Acetylcimigenol-3-*O*-*β*-D-xylopyranoside	[17]
97	25-*O*-Acetyl-1*α*-hydroxycimigenol-3-*O*-*β*-D-xylopyranoside	[18]
98	1*α*-Hydroxycimigenol-3-*O*-*β*-D-xylopyranoside	[18]
99	12*β*-Hydroxycimigenol-3-*O*-*β*-D-xylopyranoside	[19]
100	7*β*-Hydroxycimigenol-3-*O*-*β*-D-xylopyranoside	[19]
101	25-*O*-Acetyl-7*β*-hydroxycimigenol-3-*O*-*β*-D-xylopyranoside	[19]
102	12*β*-Hydroxycimigenol-3-*O*-*α*-L-arabinopyranoside	[19]
103	1*α*-Hydroxycimigenol-3-*O*-*α*-L-arabinopyranoside	[24]
104	1*α*-Hydroxycimigenol-3-*O*-*β*-D-galactopyranoside	[24]
105	Cimigenol-3-*O*-*β*-D-galactopyranoside	[21]
106	25-*O*-Methylcimigenol-3-*O*-*β*-D-galactopyranoside	[21]
107	25-*O*-Acetylcimigenol-3-*O*-*β*-D-galactopyranoside	[21]
108	25-*O*-Acetylcimigenol-3-*O*-*β*-D-glucopyranoside	[21]
109	25-*O*-Acetylcimigenol-3-*O*-hexa-acetyl-*β*-D-glucopyranosyl-(1-3)-*β*-D-xylopyranoside	[17]
110	25-*O*-Acetylcimigenol-3-*O*-*β*-D-glucopyranosyl-(1-3)-*β*-D-xylopyranoside	[17]
111	7,8-Didehydrocimigenol	[21]
112	24-Epi-7,8-didehydrocimigenol	[21]
113	7,8-Didehydrocimigenol-3-*O*-*β*-D-xylopyranoside	[24]
114	24-Epi-7,8-didehydrocimigenol-3-*O*-*β*-D-xylopyranoside	[24]
115	25-*O*-Acetyl-7,8-didehydrocimigenol-3-*O*-*β*-D-xylopyranoside	[24]
116	7,8-Didehydrocimigenol-3-*O*-*α*-L-arabinopyranoside	[24]
117	25-*O*-Acetyl-7,8-didehydrocimigenol-3-*O*-*α*-L-arabinopyranoside	[24]
118	Bugbanoside F	[27]
119	Shengmaxinside A	[12]
120	7,8-Didehydrocimigenol-3-*O*-*β*-D-galactopyranoside	[21]
121	Shengmaxinside B	[12]
122	1,10-Epoxide-9,11-didehydrocimigenol-3-*O*-*β*-D-xylopyranoside	[23]

their antioxidant and anti-inflammatory activities [4]. It also have been used by Native Americans to treat a variety of ailments, including diarrhea, sore throat, and rheumatism, [46]. Cimicifugoside, isolated from *C. simplex*, is a novel specific nucleoside transport inhibitor that displays synergistic potentiation of methotrexate cytotoxicity [12]. Thus, cimicifugoside may have some pharmacological effects in immunosuppressive activity. In summary, this type of triterpenoid glycoside from *Cimicifuga* species possesses several biological activities, which makes them excellent candidates for drug development to treat immunosuppressive diseases, tumors, menopausal syndromes, and other disorders.

Discussion

This review discusses the traditional uses, phytochemistry, and biological studies of the cycloartenol triterpenoid saponins isolated from *Cimicifuga simplex*. Thus, this review would provide useful data for researchers having an interest in exploring or developing new drugs from *Cimicifuga simplex*. Presently, there is a growing trend that the worldwide focus has been changed from pure Western drugs to traditional Chinese medicine due to the significant

pharmacological properties of their bioactive ingredients and their ability to treat various diseases [47]. The main components of *Cimicifuga* spp. are available in Remifemin®. The resources of *C. simplex* are substantial in some provinces in China and Japan [48]. However, the pharmacological study and utilization of *C. simplex* remain inadequate to recognize the real effects of these pharmacological activities. There are several other biolological activities of cimicifugosides from other *Cimicifuga* species which have been studied, such as the prevention of metabolic syndromes, and deterioration of cartilage in the knee joint of ovariectomized rats and osteoprotective effects [49]. Further researches should investigate these aspects for *C. simplex* to expand medicinal applications of the *Cimicifuga* genus. In conclusion, there is a need for more researches on the cycloartenol triterpenoid saponins from *C. simplex*, from both chemical and biological perspectives, which can permit determination of the distinctions within the *Cimicifuga* genus and provide a foundation for further research. *C. simplex* is a traditional Chinese medicine plant, and this review has attempted to emphasize a new research direction, namely the 9,19-cyclolanostane triterpenoid glycosides from *C. simplex*. Further biological studies will provide valuable insights regarding this ethnomedically important plant.

References

[1] Eckehard L. Botanical therapy for relieving menopausal symptoms with particular reference to *Cimicifuga Racemosa* [J]. *J Int Obstet Gynecol*, 2010, **37** (4): 230-236.

[2] Gao JC, Peng Y, Yang MS, *et al*. A preliminary pharmaco-phylogenetic study of tribe Cimicifugeae (Ranunculaceae) [J]. *J Systemat Evolut*, 2008, **46** (4): 516-536.

[3] *Pharmacopoeia of the People's Republic of China* [S]. Part I. 2010: 68-69.

[4] Kim HY, Shin HS, Park H, *et al*. *In vitro* inhibition of coronavirus replications by the traditionally used medicinal herbal extracts, Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, and Phellodendron cortex [J]. *J Clin Virol*, 2008, **41** (2): 122-128.

[5] Li JX, Yu ZY. Cimicifugae rhizoma: from origins, bioactive constituents to clinical outcomes [J]. *Curr Med Chem*, 2006, **13** (24): 2927-2951.

[6] Cao P, Pu XF, Peng SL, *et al*. Chemical constituents from *Cimicifuga foetida* [J]. *J Asian Nat Prod Res*, 2005, **7** (2): 145-149.

[7] Li CJ, Li YH, Xiao PG, *et al*. An unusual cycloartane triterpenoid from *Cimicifuga foetida* [J]. *Phytochemistry*, 1996, **42** (2): 489-494.

[8] Sun LR, Qing C, Zhang YL, *et al*. Cimicifoetisides A and B, two cytotoxic cycloartane triterpenoid glycosides from the rhizomes of *Cimicifuga foetida*, inhibit proliferation of cancer cells [J]. *Beilstein J Org Chem*, 2007, **3** (3): 3-8.

[9] Bolle P, Mastrangelo S, Perrone F, *et al*. Estrogen-like effect of a *Cimicifuga racemosa* extract sub-fraction as assessed by *in vivo*, ex vivo and in vitro assays [J]. *J Steroid Biochem Mol Biol*, 2007, **107**(3-5): 262-269.

[10] Pan RL, Chen DH, Si JY, *et al*. Immunosuppressive effects of new cyclolanostane triterpene diglycosides from the aerial part of *Cimicifuga foetida* [J]. *Arch Pharm Res*, 2009, **32** (2): 185-190.

[11] Zhang JK. Formula effect of drug combinations paired by herbs *Cimicifuga as antidote* [J]. *China J Tradit Chin Med Pharm*, 2011, **26** (8): 1844-1846.

[12] Yawata A, Matsuhashi Y, Kato H, *et al*. Inhibition of nucleoside transport and synergistic potentiation of methotrexate cytotoxicity by cimicifugoside, a triterpenoid from *Cimicifuga simplex* [J]. *Eur J Pharm Sci*, 2009, **38** (4): 355-361.

[13] Li M, Chen XL. A Study on the development of the anther and the male gametophyte in *Cimicifuga simplex* Wormsk. [J]. *Acta Sci Nat Univ Pekinensis*, 2000, **36** (2): 186-192.

[14] Genjiro K, Sachiko H, Yoshikazu K, *et al*. Studies on the constituents of *Cimicifuga* spp. XIII. Structure of cimicifugoside [J]. *Chem Pharm Bull*, 1977, **25** (12): 3182-3189.

[15] Genjiro K, Mayumi I, Yoshie S, *et al*. Studies on the constituents of *Cimicifuga* species. XIV. A new xyloside from the aerial parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1994, **42** (5): 1106-1110.

[16] Akiko K, Makio S, Satoshi K, *et al*. Studies on the constituents of *Cimicifuga* species. XV. Two new diglycosides from the aerial parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1994, **42** (9): 1940-1943.

[17] Akiko K, Kei S, Mayumi I, *et al*. Studies on the constituents of *Cimicifuga* species. XVI. Three new cycloartane xylosides from the aerial parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1995, **43** (2): 279-283.

[18] Akiko K, Makio S, Genjiro K. Studies on the constituents of *Cimicifuga* species. XVII. Four new glycosides from the aerial parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1994, **43** (7): 1167-1170.

[19] Akiko K, Makio S, Genjiro K. Studies on the constituents of *Cimicifuga* species. XVIII. Four new xylosides from the aerial parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1996, **44** (1): 167-172.

[20] Akiko K, Makio S, Genjiro K, *et al*. Studies on the constituents of *Cimicifuga* species. XIX. Eight new glycosides from *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1996, **44** (11): 2078-2085.

[21] Akiko K, Masayuki T, Makio S, *et al*. Studies on the constituents of *Cimicifuga* species. XX. Absolute stereostructures of cimicifugoside and actein from *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1998, **46** (3): 467-472.

[22] Akiko K, Masayuki T, Makio S, *et al*. Studies on the constituents of *Cimicifuga* species. XXI. Two new cyclolanostanol xylosides, Bugbanosides A and B from *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1998, **46** (6): 1001-1007.

[23] Akiko K, Masayuki T, Makio S, *et al*. Studies on the constituents of *Cimicifuga* species. XXVI. Twelve new cyclolanostanol glycosides from the underground parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1999, **47** (4): 511-516.

[24] Toshihiro A, Ryuichi H, Kazuo K, *et al*. Cycloarta-16, 4-dien-3*β*-ol: revised structure of cimicifugenol, a cycloartane triterpenoid [J]. *Chem Pharm Bull*, 1999, **47** (8): 1157-1160.

[25] Akiko K, Makio S, Genjiro K. Studies on the constituents of *Cimicifuga* species. XXVII. Malonyl cyclolanostanol glycosides from the underground parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 1999, **47** (8): 1175-1179.

[26] Akiko K, Makio S, Daisuke T, *et al*. Studies on the constituents

of *Cimicifuga* species. XXVIII. Four new cycloart-7-enol glycosides from the underground parts of *Cimicifuga simplex* Wormsk. [J]. *Chem Pharm Bull*, 2001, **49** (4): 437-441.

[27] Kuang HX, Su Y, Yang BY, *et al*. Three new cycloartenol triterpenoid saponins from the roots of *Cimicifuga simplex* Wormsk. [J]. *Molecules*, 2011, **16** (6): 4348-4357.

[28] Eduardo LT, Jay SP. Accuracy of detection of *Trichomonas vaginalis* organisms on a liquid-based papanicolaou smear [J]. *Am J Obstet Gynecol*, 2003, **188** (2): 354-356.

[29] Tian Z, Si JY, Chang Q, *et al*. Antitumor activity and mechanisms of action of total glycosides from aerial part of *Cimicifuga dahurica* targeted against hepatoma [J]. *BMC Cancer*, 2007, **7**: 237-247.

[30] Nesselhut T, Schellhase C, Dietrich R, *et al*. Studies of breast carcinoma cells regarding the proliferaive potential of herbal medication with estrogen-like effects [J]. *Arch Gynecol Obstet*, 1993, **254** (1-4): 817-818.

[31] Dixon DS, Sheikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens [J]. *Oncol Rep*, 1999, **6** (6): 1383-1387.

[32] Katarina H, Thomas N, Johannes F, *et al*. Evaluation of cell death caused by triterpene glycosides and phenolic substances from *Cimicifuga racemosa* extract in human MCF-7 breast cancer cells [J]. *Biol Pharm Bull*, 2004, **27** (12): 1970-1975.

[33] Einbond LS, Shimizu M, Xiao DH, *et al*. Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells [J]. *Breast Cancer Res Tr*, 2004, **83** (3): 221-231.

[34] Cornelia B, Johannes F. Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells [J]. *Breast Cancer Res Tr*, 2002, **76** (1): 1-10.

[35] Beuscher N. *Cimicifuga racemosa* L. Black cohosh [J]. *Phytotherapy*, 1995, **16**: 301-310.

[36] Murray MT. Remifemin: answers to some common questions [J]. *Am J Nat Med*, 1997, **4** (3): 3-5.

[37] Hiromichi H, Fumio K, Nakao I, *et al*. Inhibition of thymidine transport into phytohemagglutinin-stimulated lymphocytes by triterpenoids from *Cimicifuga* species [J]. *J Pharmacobio Dynam*, 1979, **2** (6): 339-349.

[38] Masayuki T, Akiko K, Makio S, *et al*. Antimalarial activity and nucleoside transport inhibitory activity of the triterpenic constituents of *Cimicifuga* spp. [J]. *Biol Pharm Bull*, 1998, **21** (8): 823-828.

[39] Qiu M, Kim JH, Lee HK, *et al*. Anticomplement activity of cycloartane glycosides from the rhizome of *Cimicifuga foetida* [J]. *Phytother Res*, 2006, **20** (11): 945-948.

[40] Tian Z, Pan RL, Si JY, *et al*. Cytotoxicity of cycloartane triterpenoids from aerial part of *Cimicifuga foetida* [J]. *Fitoterapia*, 2006, **77** (1): 39-42.

[41] Tian Z, Pan RL, Chang Q, *et al*. *Cimicifuga foetida* extract inhibits proliferation of hepatocellular cells via induction of cell cycle arrest and apoptosis [J]. *J Ethnopharmacol*, 2007, **114** (2): 227-233.

[42] Yamahara J, Kobayashi M, Kimura H. Biologically active principles of crude drugs. The effect of Cimicifugae Rhizome and constituents in preventive action on the carbon tetrachloride-induced liver disorder in mice [J]. *Shoyakugaku Zasshi*, 1985, **39** : 80-84.

[43] Shibata M, Sakurai N, Onopa M. Pharmacological studies on the crude drug Shoma. II. Anti-inflammatory action of Cimicifuga Rhizome, *Cimicifuga simplex* Wormsk. [J]. *Yakugaku Zasshi*, 1977, **97** (8): 911-915.

[44] Lin X, Cai YY, Xiao PG. Inhibition of SIV *in vitro* by *Cimicifuga dahurica* and its action mechanism [J]. *West China J Pharm Sci*, 1994, **9** (4): 221-224.

[45] Murav'ev IA, Vasilenko YK, Basharov AY. Hypolipidemic properties of cimicilen, isolated from *Cimicifuga dahurica* Maxim. [J]. *Farmatsiya*, 1985, **34** (1): 38-42.

[46] Lieberman S. A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause [J]. *J Womens Health*, 1998, **7** (5): 525-529.

[47] Wang QH, Kuang HX, Su Y, *et al*. Naturally derived anti-inflammatory compounds from Chinese medicinal plants [J]. *J Ethnopharmacol*, 2013, **146** (1): 9-39.

[48] Gao JC, Zhang JC, Zhu GY, *et al*. Advances in studies on pharmacological activity of tribe Cimicifugeae [J]. *Chin Tradit Herbal Drug*, 2006, **37** (10): 3-6.

[49] Danna SW, Gunter S, Markus K, *et al*. Osteoprotective effects of *Cimicifuga racemosa* and its triterpene-saponins are responsible for reduction of bone marrow fat [J]. *Phytomedicine*, 2012, **19** (10): 855-860.

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