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

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

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

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

Fig. 4 Hydroshengmanol-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 acetoxyl groups, may be located at C-1α, C-3β, C-6α, C-7β, C-11β, C-12β, C-15α, C-16β, 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-3β of the lanolin alkanol type tetracyclic triterpenoids 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].
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 phytohemagglutinin-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
| No. | Compound Name                                                                 | Reference |
|-----|-------------------------------------------------------------------------------|-----------|
| 1   | Cycloart-16,24-dien-3β-ol                                                     | [25]      |
| 2   | 17-Isocycloartanol                                                           | [25]      |
| 3   | Cycloartanol                                                                  | [25]      |
| 4   | 16,17-Didehydrocycloartanol                                                   | [25]      |
| 5   | 12-Acetoxy-3,15,24R,25-tetrahydroxyycycloart-16,23-dione-7-en-3-O-α-L-arabinopyranoside | [27]      |
| 6   | 12-Acetoxy-24R,25-epoxy-3,15-dihydroxyycycloart-16,23-dione-7-en-3-O-α-L-arabinopyranoside | [27]      |
| 7   | 12-Acetoxy-24R,25-epoxy-3-hydroxyycycloart-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  | 7β-Hydroxy-23-O-acetylsengmanol-3-O-β-D-xylopyranoside                       | [17]      |
| 15  | 23-O-Acetyl-1α-hydroxyshengmanol-3-O-β-D-xylopyranoside                      | [18]      |
| 16  | 23-O-Acetyl-1α-hydroxyshengmanol-3-O-β-D-xylopyranoside                      | [18]      |
| 17  | 7β-Hydroxy-23-O-acetylsengmanol                                              | [17]      |
| 18  | 23-O-Acetylshengmanol                                                         | [17]      |
| 19  | Acetylsengmanol                                                              | [16]      |
| 20  | 23-O-Acetylsengmanol-3-O-β-D-glucopyranosyl-(1-3)-β-D-xylopyranoside         | [17]      |
| 21  | 23-O-Acetylsengmanol-3-O(2'-O-malonyl)-β-D-xylopyranoside                    | [26]      |
| 22  | 23-O-Acetylsengmanol-3-O(2'-O-malonyl)-β-D-xylopyranoside                    | [26]      |
| 23  | 24-Epi-24-O-acetyl-7β-hydroxyhydroshengmanol-3-O-β-D-xylopyranoside          | [20]      |
| 24  | 24-O-Acetyl-25-O-methylhydroshengmanol-3-O-β-D-xylopyranoside                | [20]      |
| 25  | 24-O-Acetyl-7β-hydroxy-25-O-methylhydroshengmanol-3-O-β-D-xylopyranoside     | [20]      |
| 26  | 24-O-Acetyl-1α-hydroxy-25-O-methylhydroshengmanol-3-O-β-D-xylopyranoside     | [20]      |
| 27  | 24-O-Acetyl-1α-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-7β-hydroxyhydroshengmanol                                  | [20]      |
| 30  | 24-O-Acetyl-25-O-methylhydroshengmanol                                       | [20]      |
| 31  | 24-O-Acetyl-7β-hydroxy-25-O-methylhydroshengmanol                            | [20]      |
| 32  | 25-O-Methyl-1α-hydroxy-24-O-acetylhdroshengmanol                             | [20]      |
| 33  | 24-O-Acetyldydroshengmanol                                                    | [20]      |
| 34  | 24-Epi-24-O-acetyldydroshengmanol                                             | [21]      |
| 35  | 24-Epi-24-O-acetyldhydroshengmanol-3-O-β-D-galactopyranoside                 | [21]      |
| 36  | Shengmaxinside C                                                             | [12]      |
| 37  | 24-Epi-24-O-acetyl-7,8-didehydroshengmanol-3-O-β-D-galactopyranoside         | [21]      |
| 38  | 24-Epi-24-O-acetyl-7,8-didehydroshengmanol                                   | [21]      |
| 39  | 24-Epi-24-O-acetyl-7,8-didehydroshengmanol-3-O-β-D-xylopyranoside            | [24]      |
| 40  | 24-O-Acetyl-7,8-didehydroshengmanol-3-O-β-D-xylopyranoside                  | [24]      |
| 41  | 24-Epi-24-O-acetyl-7,8-didehydroshengmanol-3-O-α-L-arabinopyranoside         | [24]      |
| 42  | 24-O-Acetyl-7,8-didehydroshengmanol-3-O-α-L-arabinopyranoside                | [24]      |
| 43  | 24-Epi-24-O-acetyl-7,8-didehydroshengmanol-3-O(2'-O-malonyl)-β-D-xylopyranoside | [26]      |
| 44  | 24-O-Acetyl-25-O-methyl-7,8-didehydroshengmanol-3-O-β-D-xylopyranoside       | [26]      |
| 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  | 12β-Acetoxy-3β,6β-dihydroxy-24(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 52  | 12β-Acetoxy-3β,6β-dihydroxy-25(S)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 53  | 24(R)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 54  | 25(S)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 55  | 12β-Acetoxy-3β,6β-dihydroxy-20(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 56  | 12β-Acetoxy-3β,6β-dihydroxy-23(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 57  | 12β-Acetoxy-3β,6β-dihydroxy-26(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 58  | 12β-Acetoxy-3β,6β-dihydroxy-26(S)-16β,23;26;24:25-triepoxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [22]      |
| 59  | 20(R)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 60  | 23(S)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 61  | 12β-Acetoxy-3β,6β-dihydroxy-20(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanostane-3-β-D-xylopyranoside | [22]      |
| 62  | 12β-Acetoxy-3β,6β-dihydroxy-23(R)-16β,23;26;24:25-triepoxy-9,19-cyclolanostane-3-β-D-xylopyranoside | [22]      |
| 63  | 26(S)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 64  | 26(R)-16β,23;26;24:25-Triepoxy-1α,3β,26-trihydroxy-9,19-cyclolanost-7-ene-3-β-D-xylopyranoside | [23]      |
| 65  | 26-Deoxyismicificugoside                                                        | [24]      |
| 66  | 26-Deoxyismicificugol                                                          | [24]      |
| 67  | 26-Hydroxismicificugol                                                         | [15]      |
| 68  | 2′:O-Malonylemicificugoside                                                    | [26]      |
| 69  | Cimicifugenin A                                                                | [14]      |
| 70  | 26-O-Carbonylphenylcimicifugenin A                                              | [15]      |
| 71  | 26-O-Ethylcimicifugenin A                                                       | [15]      |
| 72  | 12-Hydroxy-26-O-ethylcimicifugenin A                                            | [15]      |
| 73  | 26-O-Methylcimicifugenin A                                                      | [15]      |
| 74  | 26-O-Carbonylamicificugenin A                                                   | [15]      |
| 75  | 26-Hydrogenemicificugenin 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-Malonylamicificugol                                                       | [26]      |
| 79  | Cimificugol-3-O-β-D-xylopyranoside                                              | [26]      |
| 80  | Cimiaceroside A                                                                | [27]      |
| 81  | 25-O-Acetyl-1α-hydroxycimigenol                                                 | [18]      |
| 82  | 1α-Hydroxycimigenol                                                            | [18]      |
| 83  | 25-O-Methyl-1α-hydroxycimigenol                                                 | [20]      |
| 84  | 25-O-Methyl-7β-hydroxycimigenol                                                 | [16]      |
| 85  | 7β-Hydroxycimigenol                                                            | [16]      |
| 86  | 24-Epi-7β-hydroxycimigenol                                                     | [20]      |
| 87  | 25-O-Acetyl-7β-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  | 12β-Hydroxycimigenol                               | [19]          |
| 93  | 3-O-Acetyl-7β-hydroxycimigenol                    | [16]          |
| 94  | 3,7-DiAcetyl-7β-hydroxycimigenol                  | [16]          |
| 95  | 3-O-Acetylcimigenol                                | [16]          |
| 96  | 25-O-Acetyl-cimigenol-3-O-β-D-xylopyranoside      | [17]          |
| 97  | 25-O-Acetyl-1α-hydroxycimigenol-3-O-β-D-xylopyranoside | [18]      |
| 98  | 1α-Hydroxycimigenol-3-O-β-D-xylopyranoside        | [18]          |
| 99  | 12β-Hydroxycimigenol-3-O-β-D-xylopyranoside       | [19]          |
| 100 | 7β-Hydroxycimigenol-3-O-β-D-xylopyranoside        | [19]          |
| 101 | 25-O-Acetyl-7β-hydroxycimigenol-3-O-β-D-xylopyranoside | [19]      |
| 102 | 12β-Hydroxycimigenol-3-O-α-L-arabinopyranoside    | [24]          |
| 103 | 1α-Hydroxycimigenol-3-O-α-L-arabinopyranoside     | [24]          |
| 104 | 1α-Hydroxycimigenol-3-O-β-D-galactopyranoside     | [21]          |
| 105 | Cimigenol-3-O-β-D-galactopyranoside                | [21]          |
| 106 | 25-O-Methylcimigenol-3-O-β-D-galactopyranoside    | [21]          |
| 107 | 25-O-Acetyl-cimigenol-3-O-β-D-galactopyranoside   | [21]          |
| 108 | 25-O-Acetyl-cimigenol-3-O-β-D-glucopyranoside     | [21]          |
| 109 | 25-O-Acetyl-cimigenol-3-O-hexa-acetyl-β-D-glucopyranosyl-(1-3)-β-D-xylopyranoside | [17]         |
| 110 | 25-O-Acetyl-cimigenol-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. Cimicifugoside, isolated from _C. simplex_, is a novel specific nucleoside transport inhibitor that displays synergistic potentiation of methotrexate cytotoxicity. 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 biologial 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.

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