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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

[CLC Number] R284, R965

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-cycloartenone 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-Cycloartenone 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. |
|-----|----------------------------------------------------|------|
| 1   | Cimigenol-12-one                                   | [24] |
| 3   | 12β-Hydroxy-7(8)-en-cimigenol                     | [26] |
| 5   | 24-Epi-cimigenol-3-one                            | [2]  |
| 7   | 12β-Hydrocimigenol-3-one                          | [24] |
| 9   | Cimicifoetisides A                                | [23] |
| 11  | Cimicifoetisides B                                | [23] |
| 13  | Cimigenol-3-O-[2-O-(E)-2-butenyl]-α-L-arabinopyranoside | [26] |
| 15  | 25-O-Acetylcimigenol-3-O-[4-O-acetyl]-α-L-arabinopyranoside | [26] |
| 17  | Cimicifoetiside IV                                | [19] |
| 19  | Cimiracemosides C                                 | [15] |
| 21  | 3-O-α-L-Arabinopyranosyl-cimigenol-15-0β-D-glucopyranoside | [17] |
| 23  | Bugbanosides F                                    | [16] |
| 25  | Cimiracemosides D                                 | [15] |
| 27  | Cimiracemosides B                                 | [15] |
| 29  | 24-Diepoxy-cycloart-7-en-3β, 12β, 15α, 17α       | [21] |
| 31  | 24-Diepoxy-12β-acetoxy-cycloart-7-en-3β, 24-O-β-D-xylopyranoside | [21] |
| 33  | Cimicifoetiside II                                | [22] |
| 35  | 25-O-Acetyl-7, 8-didehydrocimigenol-3-O-β-D-alactopyranoside | [25] |
| 37  | 12β-Hydroxy-25-anhydrocimigenol                   | [24] |
| 39  | Cimiracemosides J                                 | [28] |
| 41  | Cimicifoetiside III                               | [29] |
| 43  | Bugbanosides D                                   | [16] |
| 45  | Cimidahuside 1                                   | [30] |
| 47  | (3β, 12β, 15α, 24R)-12, 2-Diepoxy-24, 25-epoxy-15-hydroxy-16, 23-dione-3-O-α-L-arabinopyranoside | [31] |
| 49  | Cimiracemosides C                                | [33] |
| 51  | Herculeifolinoside A                             | [34] |
| 53  | Herculeifolinoside C                             | [34] |
| 55  | Cimiracemosides A                                | [33] |
| 57  | (10α, 24R)-10, 24, 25-Trihydroxy-9, 10-seco-9, 19-cycloartenone-7, 9(11)-diene-16, 23-dione | [33] |
| 59  | Cimiracemosides A                                | [33] |
| No. | Compound                                                                 | Ref. |
|-----|--------------------------------------------------------------------------|------|
| 61  | 24-Hydroxy-12β-acetoxy-25, 26, 27-trinorcycloartan-16, 23-dione 3β-O-α-L-arabinopyranoside 23, 24-Diacetylo-3, 15, 23-O-Acetyl-7(8)-en-28-hydroxy-24, 25, 26, 27, 28-diepoxy-cycloartane-3β-O-α-L-arabinopyranoside | [17] |
| 63  | 23, 24-Diacetyle-3, 15, 23-O-Acetyl-7(8)-en-28-hydroxy-24, 25, 26, 27, 28-diepoxy-cycloartane-3β-O-α-L-arabinopyranoside | [36] |
| 65  | 23-O-Acetylsphenoguan-3-O-α-L-arabinopyranoside                              | [18] |
| 67  | Cimiracemoside L                                                            | [28] |
| 69  | 2', 23-O-Diacetylsphenoguan-3-O-α-L-arabinopyranoside                        | [24] |
| 71  | 24-O-Acetylidosahurinol                                                      | [26] |
| 73  | 2', 24-O-Diacetylsphenoguan-3-O-α-L-arabinopyranoside                        | [24] |
| 75  | 24-O-Acetylidosahurinol-3-O-α-L-arabinopyranoside                           | [24] |
| 77  | Heracelfolinosides E                                                         | [34] |
| 79  | Cimiracemoside E                                                            | [15] |
| 81  | Cimiracemoside E                                                            | [1]  |
| 83  | Cimifetidanoside G                                                          | [39] |
| 85  | 26-Methoxy-acetol-12(18)-en                                                | [38] |
| 87  | 2'-O-acetylactein                                                            | [41] |
| 89  | 7β-Hydroxy-23-epi-acteol-3-O-α-L-arabinopyranoside                          | [38] |
| 91  | 7, 8-Didehydro-27-deoxyacteol                                               | [40] |
| 93  | Cimiracemoside P                                                            | [28] |
| 95  | Yunnanterpene G                                                             | [38] |
| 97  | Yunnanterpene C                                                             | [42] |
| 99  | Yunnanterpene F                                                             | [42] |
| 101 | Yunnanterpene D                                                             | [42] |
| 103 | Cimifetidanoside H                                                           | [33] |
| 105 | 25, 24-Diacetyle-3, 15, 23-O-Acetyl-7(8)-en-28-hydroxy-24, 25, 26, 27, 28-diepoxy-cycloartane-3β-O-α-L-arabinopyranoside | [43] |
| 107 | Cimiracemoside G                                                            | [15] |
| 109 | Cimiracemoside F                                                            | [15] |
| 111 | 12β-Acetoxy-3β-hydroxy-24, 25, 26, 27-tetracycloartan-3β-O-α-L-arabinopyranoside | [44] |
| 113 | 3β-O-α-L-arabinopyranoside                                                  | [36] |
| 115 | Cimifetidanoside G                                                           | [38] |
| 117 | Cimidahuside D                                                              | [46] |
| 119 | 24-Acetoxy-15, 16-seco-cycloartan-7-en-3-O-xiloside                          | [47] |
| 121 | 24-Acetoxy-15, 16-seco-cycloartan-3-O-xiloside                               | [48] |
| 123 | 24-Hydroxy-15, 16-seco-cycloartan-3-O-xiloside                              | [48] |
| 125 | 15, 16-Secco-cimterpenes B                                                  | [42] |
| 127 | Neocimicigenosides B                                                        | [49] |
| 129 | Foetidosinosides B                                                          | [35] |
| 62  | Cimifetidanoside E                                                           | [33] |
| 64  | 23-Acetoxy-3, 15, 24, 25-dihydroxy-cycloartan-7-en-16-one-3-O-xiloside       | [36] |
| 66  | 15, 23-O-Diacetylsphenoguan-3-O-α-L-arabinopyranoside                       | [26] |
| 68  | Cimiracemoside M                                                             | [28] |
| 70  | 3', 24-Di-O-acetyl-25-α-anhydrohydroxy-24, 25-epi-acteol-3-O-α-L-arabinopyranoside | [24] |
| 72  | 24-O-acetyl-7(8)-en-isoahurinol                                              | [26] |
| 74  | 25-Methoxy-24-O-acetylsphenoguan                                            | [38] |
| 76  | Heracelfolinosides D                                                         | [34] |
| 78  | Heracelfolinosides F                                                         | [34] |
| 80  | 7, 8-Didehydro-24S-O-acetylsphenoguan-3-O-β-D-galactopyranoside             | [25] |
| 82  | 24-Epi-24-O-hydroxy-7, 8-didehydroxy-23, 24-diacetyle-23, 24-dihydroxy-9, 19-cyclo-3β-yl α-L-arabinopyranoside | [18] |
| 84  | Cimifetidanoside VII                                                         | [39] |
| 86  | 2'-O-Acetyl-27-deoxyacteol                                                   | [41] |
| 88  | Cimiracemoside N                                                             | [28] |
| 90  | Cimiracemoside I                                                             | [28] |
| 92  | Cimiracemoside O                                                             | [28] |
| 94  | 7β-Hydroxy-23-epi-acteol-3-O-β-D-xylosepyranoside                           | [38] |
| 96  | Yunnanterpene B                                                              | [42] |
| 98  | Yunnanterpene A                                                              | [42] |
| 100 | Yunnanterpene E                                                              | [42] |
| 102 | Cimifetidanoside H aglycone                                                  | [33] |
| 104 | 25-Diepoxy-cycloartan-3β-O-α-L-arabinopyranosyl(1-2)-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-(1-2)-β-D-glucopyranosyl | [43] |
| 106 | (22R, 23R, 24R)-12β-acetoxy-16β, 23, 22, 25-diepoxy-3β-ole-24-diepoxy-9, 19-cyclo-3β-yl α-L-arabinopyranoside | [18] |
| 108 | Cimiracemoside H                                                             | [15] |
| 110 | Cimilactone C                                                                | [42] |
| 112 | 12β-Acetoxy-3β-hydroxy-24, 25, 26, 27-tetracycloartan-7-en-23, 16β-olide    | [44] |
| 114 | 20(S), 22(R), 23(R), 24(S)-12β-acetoxy-1β, 23, 23a : 24-diepoxy-3β-β, 25-trihydroxy-9, 19-cyclo-3β-yl α-L-arabinopyranoside | [45] |
| 116 | Cimidahuside C                                                               | [46] |
| 118 | 15, 16-Secco-shengmanol C                                                    | [38] |
| 120 | 24-Hydroxy-15, 16-seco-cycloartan-7-en-3-O-xiloside                          | [47] |
| 122 | 24-Hydroxy-15, 16-seco-cycloartan-3-O-xiloside                              | [48] |
| 124 | 15, 16-Secco-cimterpenes A                                                   | [42] |
| 126 | Neocimicigenosides A                                                         | [49] |
| 128 | Foetidosinosides A                                                           | [35] |
| 130 | Foetidosinosides C                                                           | [35] |
Cimigual type

Cimigual type has an unprecedented 16-O-23R, 24S-O-16 cyclization unit attached to the side chain and represents a significant structural variation in this compound class. In the 13C NMR, C-16 reflects on the δC 112.0. In the 1H NMR, cyclopropane methylene appears at δH 0.27 and 0.58. In the 13C NMR, the signal of C-15, C-16 and C-17 appear in δC 77–81, δC 111–113, δC 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 Cimigual 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.

Furthermore, this type is usually divided into two sub-classes, namely cimicidanol and cimicidol, according to the structures of cimigual-type aglycones, hydrophobic groups, such as cinnamyl and acetoxyl 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 13C NMR data reflect on the δC 220.0 of C-16 and δC 205.0 of C-23. Basically, C-15 is around δC 80.7, and C-20 is around δC 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 δC 205, while cimicidol owns C-24, 25-dihydroxy with C-23, usually appearing in δC 213.0. In addition, C-24, C-25, and C-26 of cimicidanol are around δC 65.5, 60.4, and 18.1, compared with these data of cimicidol that are around δC 84.0, 72.0, and 25.5. In 1H NMR spectrum, cyclopropane methylene signals exhibit at δH 0.61 and 1.1 ppm. Since 2000, 8 new cimicidol 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-12β-acetoxy-25, 26, 27-trincycloarotane-16, 23-dione-3β-O-α-L-arabinopyranoside (61) and one C-24, 25-ene cimicifetidanoside E (62) compound have been isolated from Cimicifuga species. Liu et al. have reported that heraclefolinoside B (52) 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,

| No. | Compound                        | Ref.  |
|-----|--------------------------------|-------|
| 131 | Foetidinosides D                | [35]  |
| 133 | Foetinside                      | [2]   |
| 135 | Foetidinol-3-O-β-D-xylpyranosyl (1′→3′)-β-D-xylpyranoside | [37]  |
| 137 | 28-Hydroxy-foetidinol-3-O-β-D-xylpyranoside | [37]  |
| 139 | 12β-acetoxy-3β, 15α, 16α, 24α-tetrahydroxy-25, 26, 27-trinor, 16-cyclo-cycloart-7-en-23-one 3-O-β-D-xylpyranoside | [36]  |
| 141 | Cimicifugadine                   | [50]  |

Continued
Fig. 1  Structures of compound 1–47
Fig. 2  Structures of compounds 48–84
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 $\delta_{C}$ 72.0 of C-23 and $\delta_{C}$ 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-
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-\(\alpha\)-L-arabinopyranoside (69) \[^{[24]}\] only shows weak inhibition activities against HL-60 cell line, with IC\(_{50}\) 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, carbonyl, acetyl and methoxyl, and that C-16 has hemiacetal structure. Then, the signals of C-15 and C-16 are stable appearing around \(\delta_C\) 81.5–83.0 and \(\delta_C\) 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 \(\delta_C\) 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-\(\alpha\)-L-arabinopyranoside (70) \[^{[24]}\]. In this case, C-25 appears between \(\delta_C\) 142–146, while C-26 is around \(\delta_C\) 113–116. The immunosuppressive activity of 24-O-hydroxy-7, 8-didehydro-hydroshengmanol 3-O-\(\beta\)-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-didehydrodroshengmanol 3-O- β-D-galactopyranoside (82), providing the highest immunosuppressive activity with IC₅₀ 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 δC 44, δC 73 and δC 56, respectively, which are distinguishable data from other types. H-24 appears around δH 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 δC 103.6–104.3 together with C-25 in δC 62.4–63.9; while C-26 might be S-OH when C-23 is around δC 105.8–106.5 together with C-25 in δC 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-cycloartenyl 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 δ 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-cycloartenane (100–101). In pharmacological studies, the anti-osteoporosis activity screening in vitro indicates that 2'-O-acetyl-27-deoxyxestane (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-deoxyxestane (86) has anti-osteoporosis activity at relatively low concentration. However, more work is needed to clarify the mechanism of 2'-O-acetyl-27-deoxyxestane (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 yunnanipene E (100) [42] has non-selective activities against all of these cell lines, with IC₅₀ values being 5.8, 8.6, and 6.0 μmol·L⁻¹, respectively. However, yunnanipene D (101) [43] exhibits greater selectivity against the p53−/− +p53N236S +H-RasV12 cells than the WT MEFs cells. Furthermore, yunnanipene D (101) exhibits approximately 3-fold higher selectivity against the WT MEFs cells than yunnanipene E (100). According to these results, the mechanism of action of yunnanipene E (100) 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 ¹³C NMR, the specific chemical shifts are C-16 in δC 72, C-23 in δC 105, C-22 in δC 87.0, and C-25 in δC 84.0. Since 2000, only 8 new compounds (102–109) have been isolated. It is notable that cimiracemosides G (107) [45] shows about 15-fold higher cytotoxic activity against HSC-2 tumor cells than normal HGF. 20S, 22R, 23S, 24R-16 β, 23, 22, 25-diepoxy- cycloarten-3 β, 23, 24-triol-3-O- β-D-glucopyranosyl-(1-2)- β-D-glucopyranosyl-(1-2)- β-D-glucopyranosyl-(1-2)-β-D-xylopyranoside (104) and 20S, 22R, 23S, 24R-16 β, 23, 22, 25-diepoxy-cycloarten-3 β, 23, 24-triol-3-O-(6-O-trans-isofereuloyl- β-D-glucopyranosyl) - (1-2)-β-D-glucopyranosyl-(1-2)- β-D-xylopyranoside (105) [43] suppress the proliferation of lymphocytes and the IC₅₀ 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 (IC₅₀ 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).

**Astatioside type**

In this type, C-16 and C-23 are linked by oxygen bridge, and C-16 always appears in δC 72.2–84.3. The side chain is variable. When C-23 has carbonyl group, the C-23 appears in δC 173; while if C-23 and C-24 form an oxygen ring δC 56.9 together with C-25 in δC 64.5–65.6. Since 2000, 8 new compounds (110–113) are a little different conventional astatioside 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 ketone group on C-23 instead of the whole side chain. Cimiracemosides G (15) shows about 15-fold higher cytotoxic activity against HSC-2 tumor cells than normal HGF. 20S, 22R, 23S, 24R-16 β, 23, 22, 25-diepoxy- cycloarten-3 β, 23, 24-triol-3-O-(6-O-trans-isofereuloyl- β-D-glucopyranosyl) - (1-2)-β-D-glucopyranosyl-(1-2)- β-D-xylopyranoside (105) [43] suppress the proliferation of lymphocytes and the IC₅₀ 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 (IC₅₀ 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**

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**15, 16-seco-cycloartenane types**

This kind of cycloartenyl 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 δC 173.0. When the carboxyl group is substituted at C-15, C-15 is about δC 178; when the C-15 is substituted with aldehyde, C-15 is about δC 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-cycloartenol triterpenoid-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-di-hydroxy-12-acetoxy-16, 22-cyclo-23-ketone-24R, 25-epoxy-cycloarten-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) [40] 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. Foeotidinosides A (128) [35] exerts moderate inhibition against HL-60 and SMMC-7721 cell growth with IC50 values being 12.64–30.59 μmol·L−1, respectively. Cimicifugadine (142) [50] is the only 9, 19-cycloartenol-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 sapo-nins 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 medical applications in vitro or in vivo, and even in clinical patients. To our best knowledge, biological studies of the 9, 19-cycloartenol triterpenoid sapo-nins 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 tri-terpenoid 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 ethnomedicinally important plant.

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