A Review on Medical Plants of Genus Siegesbeckia: Phytochemical and Pharmacological Studies

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Abstract: Genus Siegesbeckia has been utilized as herbal medicine for treating arthritis, stroke, rash and other diseases for hundreds of years in East Asia. Modern pharmacological researches demonstrated the species of genus Siegesbeckia contains numerous naturally occurring active compounds. Till now, 250 compounds have been separated from Siegesbeckia species, namely 128 diterpenoids, 71 sesquiterpenoids, 14 flavonoids and 37 other compounds. A number of studies showed Siegesbeckia extracts or constituents possessed various therapeutic activities, including anti-inflammation, analgesia, anti-cancer and so on. Some of them have a bright prospect in naturally occurring drug discovery. The information provided by this review is expected to be beneficial for further phytochemical and pharmacological studies of the genus Siegesbeckia.

Keywords: Siegesbeckia; kirenol; diterpenoid; anti-inflammation; sesquitepenoid. © 2022 ACG Publications. All rights reserved.

1. Introduction

The genus Siegesbeckia, as a part of Asteraceae family, consists of 12 species which mainly existed in tropical, subtropical and temperate zones. Some of them have been employed as medicinal herbs in China, Korea and other countries from ancient times. In about 659 AD, the dried aboveground parts of three species, namely S. orientalis, S. pubescens and S. glabrescens, were first documented in Xin Xiu Ben Cao (The newly-revised materia medica) in ancient China by the name of “Xi xian cao” for treatment of arthritis, stroke, rash, edema and so on. Besides, S. pubescens is also used for the treatment of hypertension, headache and vertigo disease as “Huiryeom” in Korea [1]. Recent pharmacology researches reported that plants of genus Siegesbeckia exhibited significant therapeutic effects on anti-inflammation, analgesia, anti-thrombosis, anti-cancer and other diseases.

In recent years, the genus Siegesbeckia attracted large attention of pharmaceutical scientists. This review summarizes the phytochemical profile, pharmacological value and proposed further perspectives on genus Siegesbeckia based on the literature over the past decades.

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A review on medical plants of genus *Siegesbeckia*

2. Chemical Constituents

To date, 250 compounds with various chemical structures have been identified from genus *Siegesbeckia*, which include *ent*-kaurane and *ent*-pimarane diterpenoids, sesquiterpenoids, flavonoids and other compounds. The structures and sources were depicted in Table 1-4 and Figure 1-5, respectively. Amongst, *ent*-kaurane and *ent*-pimarane diterpenoids are often considered as the active compounds of this genus.

2.1. Diterpenoids

Diterpenoid, a terpene with a 20-carbon skeleton, is derived from the assembly of four isoprene units. Diterpenoid is one of the most prevalent classes of genus *Siegesbeckia*. A total of 128 diterpenes have been identified from *S. orientalis*, *S. pubescens* and *S. glabrescens*. They are structurally categorized into four groups, namely *ent*-pimarane diterpenoids, *ent*-kaurane diterpenoids, chain diterpenes and *ent*-strobase diterpenoids, respectively.

The *ent*-pimarane diterpenoid is the most common diterpenoids in genus *Siegesbeckia*. Totally 83 of them (1-83) have been identified up to date. The *ent*-pimarane diterpenoid is a tricyclic diterpene with β-CH₃ at C-17, α-CH₃ at C-19 and C-20, and β-H at C-5, C-8 and C-9. A small number of *ent*-pimarane diterpenoids from genus *Siegesbeckia* contains an epoxy group between C-14 and C-16 (42, 43, 58, 59) or C-12 and C-16 (44, 45). Furthermore, four *ent*-pimarane diterpenoids contain an acetonide group at C-15 and C-16 (33-35, 40). The glycosyl group usually appears at C-18 (8, 9, 12, 21, 22, 27, 33), C-3 (2, 16, 17, 20, 32, 35, 36, 39), C-15 (2), C-16 (30) and C-2 (7). Amongst, the neodorutoside (2) is the only disaccharide glycoside of *ent*-pimarane diterpenoid from genus *Siegesbeckia*. Recently, three diterpenoid dimers (81-83) were isolated and identified from *S. S. glabrescens* [2].

The *ent*-kaurane diterpenoid is another prevalent diterpenoid from genus *Siegesbeckia* with a tetracyclic structure. A total of 33 *ent*-kaurane diterpenoids (84-116) have been identified from this genus. Except of common substituted groups such as hydroxyl, carboxyl, and methoxyl groups, isobutyroloxy group appeared at C-17 of *ent*-kaurane diterpenoid (109) and C-18 of compound (92). Furthermore, compounds (111, 112) contain an acetonide group between C-16 and C-17. Besides, compounds (113-116) are the only four glucopyranosides of *ent*-kaurane diterpenoids from genus *Siegesbeckia*. As for other diterpenoids, only ninechain diterpenoids (117-125) and threent-strobase diterpenoids (126-128) were reported from genus *Siegesbeckia* till now.

**Table 1. *ent*-pimarane diterpenoids isolated from genus *Siegesbeckia***

| No. | Compounds       | Plants       | Ref. | No.       | Compounds                             | Plants       | Ref.               |
|-----|-----------------|--------------|------|-----------|---------------------------------------|--------------|--------------------|
| 1   | darutigenol     | *S. orientalis* | [3]  | 43        | *ent*-14β,16-epoxy-8- pimar-ene-3β,15α-diol | *S. orientalis* | [4]                |
| 2   | neodorutoside   | *S. glabrescens* | [5]  | 44        | *ent*-12α,16-epoxy-2β,15α, 19-trihydroxypimar-8(14)-ene | *S. orientalis* | [6]                |
| 3   | 12-hydroxykirenol | *S. pubescens* | [7]  | 45        | *ent*-12α,16-epoxy-2β,15α,19-trihydroxypimar-8-ene | *S. orientalis* | [6]                |
| 4   | orientalin A    | *S. orientalis* | [8]  | 46        | *ent*-16-nor-3-oxo-pimar-8(14)-en-15-al | *S. pubescens* | [9]                |
| 5   | orientalin B    | *S. orientalis* | [8]  | 47        | 19-hydroxy-15-devinyl-ent-pimar-8,11,13-triene-2,7-dione | *S. pubescens* | [10]               |
| 6   | kirenol         | *S. orientalis* | [8]  | 48        | 2β,19-dihydroxy-15-devinyl-ent-pimar-8,11,13-triene | *S. pubescens* | [10]               |
|   | Compound Description                                      | Plant Species          | Reference |
|---|----------------------------------------------------------|------------------------|-----------|
| 7 | ent-2α,15,16-trihydroxypimar-8(14)-en-2-O-β-D-glucopyranoside | *S. pubescens*         | [11]      |
| 8 | ent-15,16,19-trihydroxypimar-8(14)-en-19-O-β-D-glucopyranoside | *S. orientalis*        | [12]      |
| 9 | ent-2β,15,16-trihydroxypimar-8(14)-ene                 | *S. orientalis*        | [6]       |
| 10 | ent-2α,15,16,19-tetrahydroxy pimar-8(14)-ene           | *S. orientalis*        | [16]      |
| 11 | ent-2β,15,16,19-tetrahydroxypimar-8(14)-ene           | *S. orientalis*        | [16]      |
| 12 | 16-O-acetyldarutigenol                                 | *S. orientalis*        | [6]       |
| 13 | 7β-hydroxydarutigenol                                 | *S. orientalis*        | [4]       |
| 14 | 9β-hydroxydarutigenol                                 | *S. orientalis*        | [4]       |
| 15 | 16-O-acetyldarutigenol                                 | *S. orientalis*        | [4]       |
| 16 | 15,16-dihydroxypimar-8(14)-ene                        | *S. orientalis*        | [4]       |
| 17 | 15,16-di-O-acetyldarutigenol                          | *S. orientalis*        | [4]       |
| 18 | darutoside                                             | *S. orientalis*        | [4]       |
| 19 | ent-2β,15,16-trihydroxypimar-8(14)-en-19-oic acid     | *S. orientalis*        | [14]      |
| 20 | hythiemoside B                                        | *S. orientalis*        | [16]      |
| 21 | ent-(15R),16,19-trihydroxypimar-8(14)-ene             | *S. orientalis*        | [16]      |
| 22 | hydroxy-pimar-8(14)-ene                               | *S. orientalis*        | [17]      |
| 23 | ent-2α,3β,15,16-pentahydroxyoxypimar-8(14)-ene        | *S. orientalis*        | [10]      |
| 24 | ent-2α,7α,15,16-pentahydroxyoxypimar-8(14)-ene        | *S. orientalis*        | [10]      |
| 25 | ent-2α,7β,15,16-pentahydroxyoxypimar-8(14)-ene        | *S. orientalis*        | [10]      |
| 26 | 2-keto-16-acetyloxykirenol                            | *S. orientalis*        | [7]       |
| 27 | ent-2-oxo-15,16,19-trihydroxy pimar-8(14)-en-19-O-β-D-glucopyranoside | *S. orientalis*        | [11]      |
| 28 | 15,16-dihydroxy-2-oxo-pimar-8(14)-ene                 | *S. orientalis*        | [12]      |

Table 1 continued...

|   | Compound Description                                      | Plant Species          | Reference |
|---|----------------------------------------------------------|------------------------|-----------|
| 49 | ent-3β,15R,16-trihydroxypimar-8(14)-diene              | *S. pubescens*         | [10]      |
| 50 | ent-2α,15R,16,19-tetrahydroxy pimar-8(14)-ene         | *S. pubescens*         | [10]      |
| 51 | ent-2β,15,16,19-tetrahydroxy pimar-8(14)-ene          | *S. pubescens*         | [10]      |
| 52 | ent-2α,15,16,18-tetrahydroxy pimar-8(14)-ene          | *S. pubescens*         | [10]      |
| 53 | ent-15,16-dihydroxy-18-noroxypimar-8(14)-en-3-one    | *S. pubescens*         | [10]      |
| 54 | ent-1β,3β,15,16-tetrahydroxy pimar-8(14)-ene         | *S. pubescens*         | [10]      |
| 55 | ent-3β,15,16-trihydroxy pimar-6,8(14)-diene          | *S. pubescens*         | [10]      |
| 56 | ent-2α,15,16,19-tetrahydroxy pimar-6,8(14)-diene     | *S. pubescens*         | [10]      |
| 57 | ent-15,16-dihydroxyoxypimar-1,8(14)-dien-3-one       | *S. pubescens*         | [10]      |
| 58 | 14β,16-epoxy-ent-3β,15α,19-trihydroxypimar-7-one   | *S. pubescens*         | [10]      |
| 59 | 14β,16-epoxy-ent-3α,15α,19-trihydroxypimar-7-one   | *S. pubescens*         | [10]      |
| 60 | ent-2β,15R,16-trihydroxy-19-oxo pimar-8(14)-ene      | *S. pubescens*         | [13]      |
| 61 | siegesbeckia A                                        | *S. glabrescens*       | [15]      |
| 62 | siegesbeckia B                                        | *S. glabrescens*       | [15]      |
| 63 | siegesbeckia C                                        | *S. glabrescens*       | [15]      |
| 64 | siegesbeckia D                                        | *S. glabrescens*       | [15]      |
| 65 | siegesbeckia E                                        | *S. glabrescens*       | [15]      |
| 66 | siegesbeckia F                                        | *S. glabrescens*       | [15]      |
| 67 | siegesbeckia G                                        | *S. glabrescens*       | [15]      |
| 68 | siegesbeckia H                                        | *S. glabrescens*       | [15]      |
| 69 | siegesbeckia I                                        | *S. glabrescens*       | [15]      |
| 70 | siegesbeckia J                                        | *S. glabrescens*       | [18]      |
A review on medical plants of genus *Siegesbeckia*

| No. | Structure                                      | Plant          | Reference | Key            | Plant          | Reference |
|-----|-----------------------------------------------|----------------|-----------|----------------|----------------|-----------|
| 29  | 15,16,18-trihydroxy-2-oxo-pimar-8(14)-ene      | *S. orientalis* | [12]      | 71             | *S. orientalis* | [19]      |
|     | *ent*-2-oxo-15,16-dihydroxy pimar-8(14)-ene   | *S. orientalis* | [6]       | 72             | *S. orientalis* | [19]      |
|     | *ent*-2-oxo-15,16,19-trihydroxy pimar-8(14)-ene | *S. orientalis* | [6]       | 73             | *ent*-16-nor-2-oxopimar-8(14)-ene | *S. orientalis* | [19]      |
|     | *ent*-2-oxo-3β,15,16-trihydroxy pimar-8(14)-ene | *S. orientalis* | [6]       | 74             | *ent*-16-nor-2α,19-dihydroxypimar-8-en-15-al | *S. orientalis* | [19]      |
| 30  | 2-oxo-15,16,19-trihydroxy pimar-8(14)-ene      | *S. orientalis* | [11]      | 75             | 3-O-acetyldarutigenol | *S. orientalis* | [20]      |
| 31  | 15,16-trihydroxypimar-8(14)-ene               | *S. orientalis* | [14]      | 76             | 19-O-acetylkirenol | *S. orientalis* | [20]      |
| 32  | 15,16-trihydroxypimar-8(14)-ene               | *S. orientalis* | [14]      | 77             | *ent*-16-nor-3β,15-dihydroxypimar-8(14)-ene | *S. orientalis* | [20]      |
| 33  | 15,16,19-dihydroxy pimar-8(14)-ene            | *S. orientalis* | [14]      | 78             | 1R,3R,15R,16-tetrahydroxy-pimar-8(14)-ene | *S. orientalis* | [21]      |
| 34  | 15,16,19-dihydroxy pimar-8(14)-ene            | *S. orientalis* | [14]      | 79             | 1R,3R,15R,16-tetrahydroxy-pimar-8(14)-ene | *S. orientalis* | [21]      |
| 35  | 3α-O-β-glucopyranoside-15,16-acetonide        | *S. orientalis* | [14]      | 80             | 3β,15R,16-tetrahydroxy-pimar-8(14)-ene | *S. orientalis* | [21]      |
| 36  | 3α-O-β-glucopyranoside-15,16-acetonide        | *S. orientalis* | [14]      | 81             | *S. orientalis* | [2]       |
|     | 3α-O-β-glucopyranoside                        | *S. orientalis* | [14]      | 82             | *S. orientalis* | [19]      |
| 38  | 3α-O-β-glucopyranoside-15,16-acetonide        | *S. orientalis* | [14]      | 83             | *S. orientalis* | [19]      |
| 39  | 3α-O-β-glucopyranoside                        | *S. orientalis* | [14]      | 84             | *S. orientalis* | [19]      |

Table 1 continued..
(To be continued)
A review on medical plants of genus *Siegesbeckia*

Figure 1. The structures of *ent*-pimarane diterpenoids (1-83) isolated from genus *Siegesbeckia*

Table 2. The structures of *ent*-kaurane diterpenes, chains, and *ent*-strobane diterpenoids isolated from genus *Siegesbeckia*

| No. | Compounds                              | Plants          | Ref. | No. | Compounds                              | Plants          | Ref. |
|-----|----------------------------------------|-----------------|------|-----|----------------------------------------|-----------------|------|
| 84  | siegesbeckiol                           | *S. pubescens*  | [22] | 107 | *ent*-16αH-kauran-17,19-dioic acid     | *S. pubescens*  | [14] |
| 85  | siegesbeckioside                        | *S. pubescens*  | [22] | 108 | siegesmethyletheric acid                | *S. orientalis* | [23] |
| 86  | siegesbeckic acid                       | *S. pubescens*  | [22] | 109 | *ent*-16βH,17-isobutyryloxy-kauran-19-oic acid | *S. glabrescens* | [24] |
| 87  | *ent*-kauran-16β,17,18-triol             | *S. pubescens*  | [22] | 110 | grandifloric acid                      | *S. pubescens*  | [22] |
| 88  | *ent*-16β,17-dihydroxy-kauran-19-oic acid | *S. pubescens*  | [22] | 111 | *ent*-19-methyl-16α,17-dihydroxy kauran-19-oic acid 16α,17-acetonide of | *S. pubescens*  | [14] |
| 89  | *ent*-16αH,17-hydroxy-kauran-19-oic acid | *S. pubescens*  | [22] | 112 | *ent*-19-methyl-16R,17-dihydroxy kauran-19-oic acid 2-O-β-D-apiofuranosyl-(1→3)-2-O-β-D-apiofuranosyl-(1→3)-4-epi-atracyligenin | *S. pubescens*  | [14] |
| 90  | *ent*-16β,17,18-trihydroxy-kauran-19-oic acid | *S. pubescens*  | [25] | 113 | 2-O-(3-methylpentanoyl)-β-D-glucopyranosyl-4-epi-atracyligenin | *S. pubescens*  | [26] |
| 91  | *ent*-16β,17-dihydroxy-kauran-19-oic acid | *S. pubescens*  | [25] | 114 | 2-O-(3-methylpentanoyl)-β-D-glucopyranosyl-4-epi-atracyligenin | *S. pubescens*  | [26] |
Table 2 continued...

| Entry | Compound Description | Source | Reference |
|-------|----------------------|--------|-----------|
| 92    | siegesesteric acid I | S. orientalis | [27] |
| 93    | siegesetheric acid II | S. orientalis | [27] |
| 94    | ent-kauran-19β,17-diol | S. glabrescens | [28] |
| 95    | 16αH-siegesmethyletheric acid | S. pubescens | [28] |
| 96    | ent-18-acetoxy-17-hydroxy-16βH-kauran-19-oic acid | S. pubescens | [14] |
| 97    | ent-18-acetoxy-16α,17-dihydroxykauran-19-oic acid | S. pubescens | [14] |
| 98    | oxy-16/16H-kauran-19-oic acid | S. pubescens | [14] |
| 99    | -17-isobutryloxykauran-19-oic acid | S. pubescens | [14] |
| 100   | ent-16R,17,18-trihydroxykauran-19-oic acid | S. pubescens | [14] |
| 101   | ent-17,18-dihydroxy-16H-kauran-19-oic acid | S. pubescens | [14] |
| 102   | ent-17-isobutryloxy-18-hydroxykauran-19-oic acid | S. pubescens | [14] |
| 103   | ent-16α,17-dihydroxykauran-19-oic acid | S. pubescens | [14] |
| 104   | ent-17-hydroxy-16αH-kauran-19-oic acid | S. pubescens | [14] |
| 105   | ent-19-methyl-17-hydroxy-16αH-kauran-19-oic acid | S. pubescens | [14] |
| 106   | 17-dihydroxy-kauran-19-oate | S. glabrescens | [31] |

2.2. Sesquiterpenoids

Sesquiterpeneis the second most prevalent class of bioactive compounds (129-199) from genus *Siegeseckia*. Germacraneolide is the most common sesquiterpenoid among them, which contains an α-methylene-γ-lactonicring linked with a 10-carbon ring, often oxidized atC-8, C-9 C-14 or C-15 [32]. Wu et al. identified two sesquiterpenoids (151, 152) with a bicycle[6,3,0]-γ-lactone structure in their skeleton [33]. The sesquiterpenoid (155) was identified with a rare 11(7→6)abeo-14-norcarabane structure [34]. Besides, the compound (195) is a guaiane-type sesquiterpenoid from *S. pubescens* [21]. Recently, Hang et al. also isolated four undescribed guaianolide sesquiterpenes from the aerial parts of *S. orientalis* (196-199) [35].
A review on medical plants of genus *Siegesbeckia*

Figure 2. The structures of ent-kaurane diterpenes (84-116), chains (117-125), and ent-strobane diterpenoids (126) isolated from genus *Siegesbeckia*. 
Table 3. The structures of sesquiterpenes isolated from genus *Siegesbeckia*

| No. | Compounds                                      | Plants          | Ref. | No. | Compounds                                      | Plants          | Ref. |
|-----|-----------------------------------------------|-----------------|------|-----|-----------------------------------------------|-----------------|------|
| 129 | orientalide                                   | *S. orientalis* | [36] | 165 | vomifoliol                                    | *S. pubescens*  | [34] |
| 130 | melampolide 1b                                | *S. orientalis* | [3]  | 166 | (1β,6α)-eudesm-4(14)-ene-1,6-diol             | *S. pubescens*  | [34] |
| 131 | melampolide 4a                                | *S. orientalis* | [3]  | 167 | (9β)-caryolane-1,9-diol                       | *S. pubescens*  | [34] |
| 132 | orientin                                      | *S. pubescens*  | [28] | 168 | (10α)-hydroxyamorph-4-en-3-one                | *S. pubescens*  | [34] |
| 133 | 9β-hydroxy-8β-isobutyryloxycostunolide        | *S. orientalis* | [12] | 169 | epiloliolide                                  | *S. pubescens*  | [13] |
| 134 | 9β-hydroxy-8β-methacryloxyloxycostunolide     | *S. orientalis* | [12] | 170 | loliolide                                     | *S. pubescens*  | [13] |
| 135 | 14-hydroxy-8β-isobutyryloxycostunolide        | *S. orientalis* | [12] | 171 | dehydrovomifoliol                             | *S. pubescens*  | [13] |
| 136 | 8β-isobutyryloxy-14-al-costaunolide            | *S. orientalis* | [12] | 172 | (4β,10E)-6α,15-dihydroxy-8β-(isobutyroxyloxy)-14-oxogermacre-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 137 | 9β,14-dihydroxy-8β-isobutyryloxycostunolide  | *S. orientalis* | [12] | 173 | (4β,10E)-6α,15-dihydroxy-8β-(methacryloxyloxy)-14-oxogermacre-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 138 | germacranolide                                | *S. orientalis* | [12] | 174 | (4β,10E)-6α,15-dihydroxy-8β-(anhydroxyloxy)-14-oxogermacre-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 139 | 8β-isobutyryloxy-1β,10α-epoxyloxycostunolide  | *S. orientalis* | [12] | 175 | (4β,10E)-6α,15-dihydroxy-8β-(tigloyloxy)-14-oxogermacre-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 140 | 9β-hydroxy-8β-isobutyryloxyl-β,10α-epoxyloxycostunolide | *S. orientalis* | [12] | 176 | (4β,10E)-6α,15-dihydroxy-8β-(isobutyryloxyloxy)-14-oxogermacre-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 141 | 9β-dihydroxy-1β,10α-epoxyloxy-11β,13-dihydrocostunolide | *S. orientalis* | [12] | 177 | (4β,10E)-6α,14,15-trihydroxy-8β-(tigloyloxy)-germacra-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 142 | 14-hydroxy-8β-isobutyryloxyl-β,10α-epoxyloxycostunolide | *S. orientalis* | [12] | 178 | (4β,10E)-6α,14,15-trihydroxy-8β-(seneicryloxyloxy)-germacra-1(10),11(13)-dieno-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 143 | 15-hydroxy-9α-acetoxy-8β-isobutyryloxyl-14-oxo-melampolide | *S. orientalis* | [12] | 179 | (1(10)E,4Z)-9α-acetoxy-6α,15-dihydroxy-8β-(tigloyloxy)-14-oxogermacre-1(10),4,11(13)-triene-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
| 144 | 9α,15-dihydroxy-8β-isobutyryloxyl-14-oxo-melampolide | *S. orientalis* | [12] | 180 | (1(10)E,4Z)-6α,9α,15-trihydroxy-8β-(tigloyloxy)-14-oxogermacre-1(10),4,11(13)-triene-12-0ic acid,12,6-lactone | *S. orientalis* | [32] |
### Table 3 continued.

|   | Name and Description                                                                 | Source                         |   | Name and Description                                                                 | Source                         |   |
|---|------------------------------------------------------------------------------------|--------------------------------|---|------------------------------------------------------------------------------------|--------------------------------|---|
|145| 15-hydroxy-8β-isobutyryloxy-14-oxo-melampolide S. orientalis [12]                  | [32]                           | 181| (1(10)E,4Z)-9α-acetoxyloxy-6α,14,15-trihydroxy-8β-(tigloxyloxy)-germacra-1(10),4,11(13)-triene-1-2-oic acid 12,6-lactone (1(10)E,4Z)-6α,8β,15-trihydroxy-9α-(methacryloxy)-14-oxogermacra-1(10),4,11(13)-triene-12-oic acid 12,6-lactone | [32]                           |   |
|146| the melampolide S. orientalis [12]                                                 | [32]                           | 182| (4β,10E)-6α,14,15-trihydroxy-8β-(isobutyryloxy)germacra-10,11(13)-diene-12-oic acid 12,6-lactone 2-propenoic acid, 2-methyl-2,3,4,5,8,9,10,11,11α-decahydro-6,10-bis(hydroxymethyl)-3-methylen-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|147| siegesbeckialide A S. pubescens [13]                                               | [32]                           | 183| 9α-ethoxy-8β-(2-isobutyryloxy)-14-oxo-acanthospermolide (2Z)-2-methylbut-2-enolic acid (3aS,4S,5S,6E,10Z,11αR)-5-(ethoxy)-6-formyl-2,3,3a,4,5,8,9,11α-octahydro-10-(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|148| siegesbeckialide B S. pubescens [13]                                               | [32]                           | 184| (1(10)E,4β)-8β-(angelyloxy)-6α,14,15-trihydroxygermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone | [32]                           |   |
|149| 4,11(13)-trien-12-oic acid 12,6-lactone S. pubescens [13]                         | [32]                           | 185| 9α-ethoxy-8β-(2-isobutyryloxy)-14-oxo-acanthospermolide (2Z)-2-methylbut-2-enolic acid (3aS,4S,5S,6E,10Z,11αR)-5-(ethoxy)-6-formyl-2,3,3a,4,5,8,9,11α-octahydro-10-(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|150| pubetalin S. pubescens [13]                                                        | [32]                           | 186| (3aS,4S,5S,6Z,10Z,11αR)-5-(acetyloxy)-2,3,3a,4,5,8,9,11α-octahydro-6,10-bis(hydroxymethyl)-3-methylen-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|151| siegenolide A S. pubescens [33]                                                     | [32]                           | 187| (3aS,4S,5S,6Z,10Z,11αR)-5-(acetyloxy)-2,3,3a,4,5,8,9,11α-octahydro-6,10-bis(hydroxymethyl)-3-methylen-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|152| siegenolide B S. pubescens [33]                                                     | [32]                           | 188| lecocarpinolide F S. orientalis [32]                                               | [32]                           |   |
|153| 2-methylbut-2-enolic acid,2,3,3a,4,5,8,9,10,11,11α-decahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester | [32]                           | 189| (3αS,4S,5S,6Z,10Z,11αR)-5-(acetyloxy)-2,3,3a,4,5,8,9,11α-octahydro-6,10-bis(hydroxymethyl)-3-methylen-2-oxocyclodeca[b]furan-4-yl ester | [32]                           |   |
|154| 1α-decahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester | [32]                           | 190| lecocarpinolide B S. orientalis [32]                                               | [32]                           |   |
|155| pubescone S. pubescens [34]                                                        | [32]                           | 191| (6R,8S,9S)-9-ethoxy-6-hydroxy-8-methacryloxy-14-oxogermacra-1(10)E,14E,11(13)-triene-12,6-lactone | [32]                           |   |

A review on medical plants of genus *Siegesbeckia*
Table 3 continued...

| No. | Compound Name | Source | Reference |
|-----|---------------|--------|-----------|
| 156 | (1(10)E,4Z,6a,8b,9a)-6,9,15-trihydroxy-8-(2-methylnonoyloxy)-14-oxogerma-1(10),4,11(13)-triene-12,6-lactone | S. pubescens | [34] |
| 157 | (1(10)E,4Z,6a,8b,9a)-9-ethyl-6,15-dihydroxy-8-(2-methylacycloxy)-14-oxogerma-1(10),4,11(13)-triene-12,6-lactone | S. pubescens | [34] |
| 158 | (3E,6a,8β)-6,14,15-trihydroxy-8-(2-methylacycloxy)germa-3,11(13)-dieno-12,6-lactone | S. pubescens | [34] |
| 159 | (E,E)-abscisic acid | S. pubescens | [34] |
| 160 | (Z,E)-abscisic acid | S. pubescens | [34] |
| 161 | 4H-carabrone | S. pubescens | [34] |
| 162 | 4H-carabrone | S. pubescens | [34] |
| 163 | 2,3-dihydroaromaticin | S. pubescens | [34] |
| 164 | 2-deoxy-4-epipulchellin | S. pubescens | [34] |

(To be continued)
A review on medical plants of genus *Siegesbeckia*

2.3. Flavonoids and Other Compounds

The content of flavonoids from *Siegesbeckia* species was relatively low compared with terpenes, and only 14 flavonoids were isolated and identified from genus *Siegesbeckia* (200-213). A total of 37 other types of compounds were also isolated from genus *Siegesbeckia*, including steroids, fatty acids and alcohols, phenylpropanoids, alkaloids and so on. It was worth to note that seven rare oxylipins (233-239) [37] and six new lignanoids (240-245) [38] with complex chemical structures were isolated from *S. glabrescens*.

**Table 4.** Flavonoids and other compounds isolated from genus *Siegesbeckia*

| No. | Compounds            | Plants    | Ref. | No. | Compounds                  | Plants          | Ref.          |
|-----|----------------------|-----------|------|-----|-----------------------------|-----------------|---------------|
| 200 | quercetin            | *S. pubescens* | [39] | 226 | epoxyligan                  | *S. pubescens*  | [39]          |
| 201 | 3,7-dimethylquercetin| *S. orientalis* | [8]  | 227 | (E)-3-(3-oxobut-1-enyl)phenyl| *S. pubescens*  | [40]          |
| 202 | 3,4′-O-dimethylquercetin | *S. glabrescens* | [41] | 228 | ursolic acid                | *S. pubescens*  | [42]          |
| 203 | 3-O-methylquercetin  | *S. glabrescens* | [41] | 229 | N-(N-benzoyl-L-phenylalanine)-O-acetyl-L-phenylalanol | *S. pubescens* | [42]          |
| 204 | 3,7,4′-O-trimethylquercetin | *S. glabrescens* | [41] | 230 | tetracosa-carbonic acid     | *S. pubescens*  | [42]          |
Table 4 continued...

| 205 | 3',5',β-trihydroxy-3,4,4',α-tetramethoxy-chalcone | S. pubescens | 231 | 3-dodecanoyloxy-2-isobutyroxy-4'-methylpentanoic | S. glabrescens |
| 206 | 3,4-dimethoxy-2',4'-dihydroxy chalcone | S. glabrescens |
| 207 | 7-O-(β-D-glucopyranosyl)-galaclin | S. glabrescens |
| 208 | 7,3',4'-trihydroxy flavone | S. glabrescens |
| 209 | 5,6,7,3',4',5'-hexamethoxyflavone | S. glabrescens |
| 210 | 8,3',4'-trihydroxy-7-methoxyflavone | S. glabrescens |
| 211 | 5,4'-diomethoxy-7,3'-dimethoxyflavone | S. glabrescens |
| 212 | 7,4'-dihydroxy-3'-methoxyflavone | S. glabrescens |
| 213 | hesperidin | S. pubescens |
| 214 | β-sitosterol | S. orientalis |
| 215 | β-sitosterol glucoside | S. orientalis |
| 216 | methyl arachidate | S. orientalis |
| 217 | heneicosanol | S. orientalis |
| 218 | glycerol monopalmitate | S. glabrescens |
| 219 | stigmasterol | S. pubescens |
| 220 | succinic acid | S. pubescens |
| 221 | ferulic acid | S. pubescens |
| 222 | heptacosanol | S. glabrescens |
| 223 | syringic aldehyde | S. pubescens |
| 224 | D-mannitol | S. pubescens |
| 225 | 2-amino-3-(3'-hydroxy-2'-methylphenoxy)-1-propanol | S. pubescens |

(To be continued)
A review on medical plants of genus *Siegesbeckia*

**Figure 4.** The flavonoids (200-213) and other compounds (214-250) isolated from genus *Siegesbeckia*
3. Pharmacological Activities

In recent years, more and more attention has been paid to Siegesbeckia species for prevention and treatment of diseases. Both the extracts and constituents of Siegesbeckia species have been investigated for their anti-thrombotic, anti-inflammatory, anti-allergic, immune-suppressive, anti-microbial, anti-oxidant and other therapeutic activities.

3.1. Anti-inflammation and Analgesia

Plants of genus Siegesbeckia has been used as a medicinal herb for treatment of various inflammatory diseases in ancient China. Hong and colleagues proved that the ethanol extract of S. orientalis possesses in vitro and in vivo anti-inflammatory effects via blocking the mitogen-activated protein kinases (MAPKs) and NF-κB pathways [51]. Meanwhile, S. glabrescens extract could attenuate the collagen-induced arthritis by the inhibition of synovial hyperplasia and inflammation via blocking NF-κB pathway [52]. Furthermore, Guo et al. further investigated the 50% ethanol extract of S. orientalis on the involvement of TLR4 signaling cascades on inflammatory mediators in murine macrophages. They found the extract inhibited inflammatory mediators regulated by AP-1, NF-κB and IRF3 [53]. In another study, S. orientalis extract was found to alleviate cartilage injury in rats with knee osteoarthritis, repair joint function and other clinical symptoms by upregulating sirt1 expression and downregulating FOXO1 acetylation level [54]. Moreover, the 50% ethanol extract of S. pubescens attenuated Pam:Csk-κB-mediated inflammatory via inhibition of TLR 1/2-mediated NF-κB activation [55]. Additionally, Quan et al. developed a transdermal patch containing S. pubescens extract used for rheumatoid arthritis therapy. The new patch exhibited desirable anti-inflammatory and analgesic activity in chronic inflammation model [56]. Besides, several reports showed the plants of genus Siegesbeckia also had potent neuroprotective activity. Akanda and co-workers reported the neuroprotective effect of S. pubescens on glutamated-induced oxidative stress in HT22 cells, and found that S. pubescens downregulated MAPK/caspase-3 pathway [57]. In addition, S. orientalis also showed attenuation of systemic and neuroinflammation, as well as cognitive dysfunction in postoperative experimental animals [58].

Comparing with three common Siegesbeckia herbs, S. pubescens, S. orientalis and S. glabrescens for the inhibitory effect on nitric oxide (NO) production and IL-6 expression in lipopolysaccharide (LPS)-induced RAW264.7 cells, S. glabrescens showed the most potent among them [59]. In addition, Zhong et al. conducted an in vitro and in silico investigation, proving that S. glabrescens exerted significant anti-inflammatory in LPS-stimulated RAW264.7 cells by inactivation of NF-κB without influencing MAPK pathway [60]. Recently, Linghu and co-workers conducted a comparison in the anti-inflammatory effect of three Siegesbeckia herbs, and S. glabrescens was weaker than the other two herbs but similar inhibitory activity on NF-κB and MAPKs signaling of three herbs were observed [61]. As for essential oils from different Siegesbeckia plants, Gao et al. proved that the essential oil of S. pubescens could reduce the NO production of LPS-induced RAW264.7 cells, and that of S. orientalis significantly reduced the release of cytokine IL-6 [62].

Kirenol (6), a main ent-pimarane diterpenoid in genus Siegesbeckia plants, is considered as one of the main anti-inflammatory constituents. Recently, Ibrahim et al. provided a detailed review on the pharmacological activities of kirenol [63]. The anti-inflammatory effect of kirenol at concentration of 0.4–0.5% was comparable with piroxicam gel in a carrageenan-induced rat acute inflammation model [64]. Compared with prednisolone, kirenol did not lead to adrenal corticotropin or glucocorticoids receptor downregulation [65]. The effect might be owing to reduction of the expression of IL-1 and TNF-α [64], suppression of some essential markers like iNOS and COX-2 [66], upregulation of nuclear Annexin-1 to inhibit NF-κB pathway [65]. Furthermore, Wu et al. found kirenol suppressed the migration of rheumatoid arthritis-associated synovial fibroblasts and IL-6 expression. It also inhibited proinflammatory cytokines secretion, synovium hyperplasia in arthritis mouse models [67]. Additionally, kirenol showed desirable wound management in hyperglycemic mouse models through suppression anti-inflammatory NF-κB pathways, which made it potential for dealing unceasing lesions of diabetic patients [66].
A review on medical plants of genus *Siegesbeckia*

In addition to kirenol, another diterpene, *ent*-16αH,17-hydroxy-kauran-19-oic acid (89) also showed favorable anti-inflammatory and anti-nociceptive compound by activity-guided extraction. The mechanism was considered to be associated with inactivating NF-κB binding capability [68]. Similarly, activity-guided extraction afforded a series of *ent*-kaurane diterpenoids and kirenol from 90% methanol fraction of *S. pubescens*. Amongst, kirenol markedly inhibited LPS-induced NO release in BV2 microglia, and *ent*-16αH,17-hydroxy-kauran-19-oic acid and kirenol dose-dependently suppressed the expression of iNOS and COX-2 [69]. Recently, Gao et al. obtained nine new *ent*-pimarane-type diterpenoids and some of them (62, 66, 68) exhibited comparable inhibitory effect of NO release in LPS-stimulated BV2 microglia [15]. Furthermore, three new *ent*-pimarane diterpenoid dimers were identified from *S. glabrescens*. Amongst, glabreside C (83) dose-dependently promoted the production of heme oxygenase-1 (HO-1), suppressed iNOS and COX2 in LPS-exposed BV2 cells [2].

Apart from the studies on anti-inflammatory diterpenoids of *Siegesbeckia*, which are the major compounds from the herbs [69], latest studies demonstrated that sesquiterpenoids and flavonoids also showed anti-inflammatory activity. Wang and co-workers investigated the anti-inflammatory activity of a series of sesquiterpenoids and diterpenoids from *S. pubescens*. Sesquiterpenoids showed more potent in inhibiting NO production than tested diterpenoids [70]. Furthermore, Li and colleagues analyzed the anti-inflammatory mechanism of a sesquiterpenoid lactone (184). It downregulated the expression of iNOS and COX-2 through inhibition of NF-κB pathway in LPS-stimulated macrophages [71]. Additionally, Engels et al. found a new bioactive sesquiterpene lactone (128) from *S. orientalis* with promising anti-inflammatory activity [30]. Moreover, a flavonoid (204) from *S. pubescens* showed anti-neuroinflammatory effect as well. It markedly suppressed the oxidative stress of glutamate-induced cell damage via activating HO-1 in HT22 cells [1]. Besides, Lim reported four quercetin derivatives from *S. glabrescens* for treatment of neuro-inflammatory diseases, namely 3,7-dimethylquercetin (201), 3,4′-O-dimethylquercetin (202), 3-O-methylquercetin (203), 3,7,4′-O-trimethylquercetin (204). The flavonoids dose-dependently suppressed PGE2 release and COX-2 in LPS-induced microglia [72]. Also, 3,7-dimethylquercetin (201) could suppress NO release and iNOS protein production in rodent macrophages by inhibition of IL-6, IL-1β, TNF-α. Besides, this flavonoid inhibited iNOS, COX-2 and IL-8 in HT-29 cells, which indicated that compound it might be promising for treatment of inflammatory bowel disease [73]. Recently, hesperidin (213), together with kirenol and darutoside (18), was found to suppress the nociceptive stimulus-activated inflammatory infiltrates and the expression of COX-2 [46].

3.2. Antibacterial Activity

Genus *Siegesbeckia* has been proved to be a valuable source of natural anti-microbial products. Kim and co-workers investigated the anti-bacterial compounds from the *S. glabrescens* extract, from which 3-dodecanoyloxy-2-isobutyryloxy-4-methylpentanoic acid (231) was identified with minimal inhibitory concentration (MIC) of 3.12 μg/mL against *Staphylococcus aureus* [44]. Besides, kaurene diterpenoids (88, 98, 99, 101) from *S. orientalis* also exhibited striking anti-microbial activity against methicillin-resistant *Staphylococcus aureus* [23]. In addition, Wu and colleagues reported that rare oxylinips, siegesbeckin A (233) and siegesbeckin E (237) exhibited moderate anti-bacterial activity against gram-positive strains [37].

3.3. Anti-allergic Activity

The elevated release of immunoglobulin E (IgE) was found to be related to immediate allergic reactions. Hwang et al. found that the water extract from *S. orientalis* could exert inhibitory effect on the interleukin (IL)-4-related IgE production in whole spleen cells and U266B1 cells. Furthermore, *S. orientalis* also suppressed the formation of IgE induced by LPS or LPS plus IL-4 [74]. Similarly, the water extract of *S. glabrescens* showed inhibitory effect on IgE production in rodents, which was related to the inhibition of systemic anaphylaxis and serum IgE [75]. Moreover, oral administration of *S. glabrescens* exhibited strong anti-allergic capacity via suppression of histamine production in mast cells [76].
3.4. Antiplatelet and antithrombotic Activity

The kaurene diterpenoid, ent-16,17-dihydroxy-kauran-19-oic acid (88), is an anti-thrombotic component extracted from S. pubescens which was known to exhibit vasodilating activity, hypotensive effect and alleviate the weight of thrombus [77]. Another study showed that it had anti-thrombotic effect and significantly reduced blood viscosity, promoted circulation and suppressed blood stasis [78]. Furthermore, the anti-platelet and anti-thrombotic effects of this diterpenoid (88) were investigated by Wang et al. The mechanism was related with the anti-coagulatory effect and cAMP induction. In arterio-venous shunt model, it decreased thrombus weight and increased plasma cAMP level [79].

3.5. Anticancer Activity

Some compounds isolated from plants of genus Siegesbeckia showed potent anti-cancer activity. The sesquiterpene lactone (154), isolated from S. glabrescens, showed great potential as an inhibitor of the transcription factor glioma-associated oncogene (Gli) mediated transcription. Gli has been proved to play an essential role in Hedgehog signaling pathway, which is closely related with the proliferation of pancreatic cancer cells. This sesquiterpenoid could inhibit Gli homolog 1-mediated transcriptional activity in mesenchymal C3H10T1/2 stem cells [80]. Meanwhile, kirenol have also shown considerable cytotoxic activities against various cancer cells. Liu found that kirenol significantly decreased the incidence as well as the growth of gastric tumor via a significant suppression of lipid peroxidation [81]. Besides, the broad-spectrum anti-cancer activity of S. glabrescens extract has also been proved against breast cancer, ovarian cancer, non-small cell lung cancer cell lines [82]. The aqueous extract of S. pubescens could inhibited the proliferation of breast carcinoma cells through two pathways, including the intrinsic signal in MCF-7 cells and the extrinsic signal in MDA-MB-231 cells [83].

3.6. Immunosuppressive Activity

The ethanol extract of S. orientalis could inhibited immunoreaction induced by ovalbumin in mice. It dose-dependently inhibited concanavalin A (Con A)- and LPS-induced splenocyte in vitro proliferation with the reduction of IgG, IgG1, and IgG2b levels. Notably, compared with cyclosporin A, S. orientalis extract exhibited stronger reducing activity in IgG1 [84]. Furthermore, Xiao et al. investigated the effects of kirenol on experimental autoimmune encephalomyelitis. The treatment with kirenol improved condition through suppressing Th1/Th17 cell differentiation and promoting apoptosis of MOG-specific CD4+ T cells via a mitochondrial pathway [85]. Moreover, kirenol showed its potential anti-arthritis capacity in mice on the modulation of T cells [86].

3.7. Other Activities

The extract from genus Siegesbeckia were reported to be effective in epidermal regeneration and skin damage. Sung and co-workers investigated the epidermal regenerative potential of ent-16α,17-dihydroxykauran-19-oic acid (103) from S. pubescens using KSC cells. The compound stimulated KSC cells and increased the proliferation and migration through Akt /ERK pathway, accelerating the heal of epidermal wounds [87]. Furthermore, Kim et al. evaluated the anti-photoaging effects of S. glabrescens extract and kirenol in mice. Both the water extract of aerial parts from S. glabrescens and kirenol upregulated the mRNA levels related with collagen synthesis genes, while downregulated matrix metalloproteinase (MMP) expression [88]. Recently, Shim et al. demonstrated S. glabrescens contains anti-melanogenesis compounds, such as kirenol and methyl ent-16α, 17-dihydroxy-kauran-19-oate (106), for prevention of oxidation-induced hyperpigmentation [31]. Moreover, airborne particulate matter (PM10) may cause oxidative damages and inflammation in skin. It was found that S. pubescens extract increased the cellular antioxidant capacity by activation of defense genes, mitigation of oxidative stress and also enhancement of cell survival rate under
A review on medical plants of genus *Siegesbeckia*

PM10-based environment. This study also indicated that chlorogenic acid (250) might be one of the active ingredients with antioxidant and cytoprotective effects [50].

As for hepa-to-protection, Sun and colleagues investigated the activity of kirenol both in vivo and in vitro. Results showed that kirenol inhibited ROS level in HepG2 cells. Furthermore, kirenol exhibited powerful in vivo antioxidant and anti-inflammatory abilities via reducing uric acid, inhibiting lipid peroxidation as well as ameliorating liver tissue abnormality in rats [89].

Several researchers provided the scientific evidence for plants of genus *Siegesbeckia* could be helpful in protecting the body against endocrine disorders like obesity. The methanol extracts of *S. pubescens* was found to possess anti-oxidative and anti-obesity capacities. It exhibited DPPH radical scavenging effect with an IC₅₀ value of 47.79 µg/mL. The anti-obesity activity was regulated via cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding proteins α (C/EBPα), C/EBPβ, and peroxisome proliferator-activated receptor (PPAR) gene and proteins expression [90]. Recently, Kim and co-workers found the high hydrostatic pressure extract of *S. orientalis* also showed anti-adipogenic activity, which was associated with the promotion of Wnt/β-catenin pathway [91]. Moreover, Kim et al. proved that kirenol could suppress intracellular lipid accumulation through downregulating C/EBPα, PPARγ, lipid-synthesis enzymes and adipocytokines. It also activated the Wnt/β-catenin signaling by increasing the expression of low density lipoprotein receptor related protein 6 (LRP6) and inactivating glycogen synthase kinase 3β (GSK3β) [92]. Besides, an activity-guided extraction provided two diterpenes with potential anti-obesity effect, ent-16βH,17-isobutyryloxy-kauran-19-oic acid (109) and siegesesteric acid I (92). They were found to be non-competitive inhibitors of PTP1B [24].

As for fracture healing, Kim and colleagues investigated the activity of kirenol on treating or preventing osteoporosis. Results showed that it could enhance osteoblast differentiation of MC3T3-E1 cells through stimulating BMP expression and activating Wnt/β-catenin signaling pathways [93]. Furthermore, the treatment of kirenol enhanced a concentration-dependent acceleration of fracture healing, which was associated with the promotion of Wnt/β-catenin and Runx-2 pathways [94]. In an in vivo study, kirenol inhibited osteoclastogenesis and bone-resorption through suppression of Cav-1/NFATc1 and NF-κB/MAPKs/c-Fos pathways [95]. Moreover, a recent study showed that sesquiterpenoids from *S. pubescens* (185, 191, 194) exhibited potential inhibitory effect against RANKL-induced osteoclast formation with IC₅₀ value of less than 1.0 µM, respectively [21].

Besides, the extracts or constituents of genus *Siegesbeckia* were also proved to be active in treatment of diabetes. The ethanol extract of *S. orientalis* showed protective effect in pancreatic β-cells under glucometoxic environment. The treatment of *S. orientalis* extract significantly downregulated the formulation of ROS, upregulated the level of glutathione and antioxidant enzymes [96].

4. Conclusion

Genus *Siegesbeckia* has been utilized for treatment of various diseases for hundreds of years in east Asia with desirable therapeutic effects. There is growing interest in exploring active compounds or extracts from genus *Siegesbeckia* in recent years. The modern pharmacological researches revealed the underlying mechanism of the traditional uses of *Siegesbeckia* and afforded some promising lead compounds like kirenol and several terpenoids. The potential for the development of new drugs from genus *Siegesbeckia* continues to grow, particularly in the field of anti-inflammation and analgesia. However, there still remains quite a few problems. Most studies were limited to in vitro pharmacological experiments so far. The in vivo tests and clinical studies are still scarce for further confirmation of the therapeutic effects. Furthermore, the structure-activity relationship of compounds from genus *Siegesbeckia* should be paid more attention, which is essential for finding potential new therapeutic agent. Depending on the available literature, the potential therapeutic activities of different kinds of compounds can be categorized generally, such as diterpenoids with anti-inflammatory, anti-cancer, anti-platelet activities and so on, sesquiterpenoids with anti-inflammatory and anti-cancer activities, flavonoids with anti-inflammatory activity. Nevertheless, there are still few reports on more specific structure-activity relationship based on single active compound and its analogues. Moreover, the interaction between bioactive compounds and extracts of genus *Siegesbeckia* with other herbs was
not studied in detail, although *Siegesbeckia* is usually used accompanied with many other herbs as an integrated recipe. Besides, the *in vitro* and *in vivo* toxicity profiles of compounds or extracts from genus *Siegesbeckia* should be also investigated. The toxicity profiles of genus *Siegesbeckia* should be further studied for its applications in clinics practice, especially when it is utilized as a long-term drug for chronic diseases. Overall, there is a bright future for the clinical application of genus *Siegesbeckia*.

**Author Contributions**

Wang Dexia conceptualized the review and completed the initial version of the manuscript. Dong Xin and Nie Yanyan help with database search for the literature. Yang Wenting and Li Chengshou contributed in gathering of information and revision of the manuscript. All authors read and approved the final manuscript.

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**References**

[1] D.S. Lee, M. Lee, S.H. Sung and G.S. Jeong (2016). Involvement of heme oxygenase-1 induction in the cytotoxic protective and neuroinflammatory activities of *Siegesbeckia pubescens* isolated from 5,3'-dihydroxy-3,7,4'-trimethoxyflavone in HT22 cells and BV2 cells, *Int. Immunopharmacol.* 40, 65-72.

[2] X.X. Gao, Y.Y. Zheng, X.Y. Zhang, G.S. Hu, J.M. Jia and A.H. Wang (2021). Ent-pimarane diterpenoid dimers from *Siegesbeckia glabrescens* with potent anti-inflammatory activities, *Chin. J. Chem.* 39, 3315-3321.

[3] R.N. Barua, R.P. Sharma, G. Thyagarajan, W. Herz and S.V. Govindan (1980). New melampolides and darutigenol from *Siegesbeckia orientalis*, *Phytochemistry* 19, 323-325.

[4] F. Wang, X.L. Cheng, Y.J. Li, S. Shi and J.K. Liu (2009). Ent-pimarane diterpenoids from *Siegesbeckia orientalis* and structure revision of a related compound, *J. Nat. Prod.* 72, 2005.

[5] X.Y. Dong, M. Chen, W. Jin, D.X. Huang, S.M. Shen and H.T. Li (1989). Studies on antifertility constituents of *Siegesbeckia glabrescens* Mak, *Acta Pharm. Sin.* 24, 833-836.

[6] Y. Xiang, H. Zhang, C.Q. Fan and J.M. Yue (2004). Novel diterpenoids and diterpenoid glycosides from *Siegesbeckia orientalis*, *J. Nat. Prod.* 67, 1517-1521.

[7] H.Z. Fu, R. Feng, Z.H. Du, Z.C. Miao, X.Z. Yan and G.Y. Li (1997). Studies on chemical constituents of *Siegesbeckia pubescens* (II), *Chin. Trad. Herb. Drugs* 28, 327-329.

[8] J. Xiong, Y. Ma and Y. Xu (1997). The constituents of *Siegesbeckia orientalis*, *Nat. Prod. Sci.* 3, 14-18.

[9] K. Xie, J. Wang, R. Yang, Q. Wu, X. Pi and H. Fu (2013). A new ent-pimarane diterpenoid from *Siegesbeckia pubescens*, *J. Chin. Pharm. Sci.* 22, 197-200.

[10] J.B. Wang, H.Q. Duan, Y. Wang, B.W. Pan, C. Gao, C.Y. Gai, Q. Wu and H.Z. Fu (2017). ent-strobane and ent-pimarane diterpenoids from *Siegesbeckia pubescens*, *J. Nat. Prod.* 73, 17-21.

[11] J. Xiong, Q. Jin and Y. Xu (2001). New diterpenoid glucosides from *Siegesbeckia pubescens*, *Chin. Chem. Lett.* 12, 51-54.

[12] C. Zdero, F. Bohlmann, R.M. King and H. Robinson (1991). Sesquiterpene lactones and other constituents from *Siegesbeckia orientalis* and *Guizotia scabra*, *Phytochemistry* 30, 1579-1584.

[13] H. Jang, J.W. Lee, J.G. Kim, H.R. Hong, T.P.L. Le, J.T. Hong, Y. Kim, M.K. Lee and B.Y. Hwang (2018). Nitric oxide inhibitory constituents from *Siegesbeckia pubescens*, *Bioorg. Chem.* 80, 81-85.

[14] R. Wang, W.H. Chen and Y.P. Shi (2010). ent-kaurane and ent-pimarane diterpenoids from *Siegesbeckia*.
A review on medical plants of genus *Siegesbeckia*

pubescens, *J. Nat. Prod.*, **73**, 17-21.

[15] X. Gao, Z. Rong, G. Long, G. Hu, T. Yan, N. Li, J. Jia and A. Wang (2020). Ent-pimarane diterpenoids from *Siegesbeckia pubescens* with anti-inflammatory activity, *Bioorg. Chem.*, **99**, 103854.

[16] P.M. Giang, P.T. Son and H. Otsuka (2005). ent-pimarane-type diterpenoids from *Siegesbeckia orientalis* L., *Chem. Pharm. Bull.*, **53**, 232-234.

[17] F.Q. Xu, H.P. Hu, Y. Li, Y.S. Ren, H.S. Zhao, Q. Huang and J.T. Wang (2018). A new ent-pimarane-type diterpenoid glycoside from *Siegesbeckia pubescens*, *Rec. Nat. Prod.*, **12**, 493-497.

[18] X.X. Gao, S.Z. Jiang, J. Wang, J.M. Jia and A.H. Wang (2021). A novel ent-pimarane-type diterpenoid from *Siegesbeckia pubescens* with anti-inflammatory activity, *J. Asian Nat. Prod. Res.*, **23**, 1-11.

[19] G. Hu, X. Gao, D. Wang, G. Long, J. Jia and A. Wang (2021). Siegesbeckia K and L, two new diterpenoids from *Siegesbeckia pubescens* with anti-inflammatory activity, *Nat. Prod. Res.*, **35**, 1-8.

[20] J. Wang, K. Xie, Q. Wang, W. Li and H. Fu (2021). Isolation and characterization of ent-pimarane diterpenoids from *Siegesbeckia pubescens*, *Nat. Prod. Res.*, **35**, 1510-1517.

[21] Z.J. Sun, Y.T. Zhang, H.H. Zhou, J. Xu and Q. Gu (2021). Diverse diterpenoids and sesquiterpenoids from *Siegesbeckia pubescens* and their activity against RANKL-induced osteoclastogenesis, *Bioorg. Chem.*, **107**, 104537.

[22] J. Xiong, Y. Ma and Y. Xu (1992). Diterpenoids from *Siegesbeckia pubescens*, *Phytochemistry* **31**, 917-921.

[23] Y. Yang, H. Chen, J.C. Lei and J.Q. Yu (2016). Biological activity of extracts and active compounds isolated from *Siegesbeckia orientalis* L., *Ind. Crop. Prod.*, **94**, 288-293.

[24] S. Kim, M. Na, H. Oh, J. Jang, C.B. Sohn, B.Y. Kim, W.K. Oh and J.S. Ahn (2006). PTP1B inhibitory activity of kaurane diterpenes isolated from *Siegesbeckia glabrescens*, *J. Enzym. Inhib. Med. Chem.*, **21**, 379-383.

[25] G. Hui, L.P. Ya, L.D. Kun and D.X. Ping (2002). Studies on chemical constituents of *Siegesbeckia pubescens* (I), *Chin. Trad. Herb. Drugs* **33**, 495-496.

[26] J. Liu, L. Feng, H.D. Li, Q.L. Dong and R. Chen (2012). Three new ent-kaurane diterpenoids from *Siegesbeckia pubescens*, *Helv. Chim. Acta.*, **95**, 221-226.

[27] D. Guo, Z. Zhang, G. Ye and Z. Lou (1997). Studies on liposoluble constituents from the aerial parts of *Siegesbeckia orientalis*, *Acta Pharm. Sin.*, **32**, 282-285.

[28] Y. Xu, J. Xiong, Q. Jin and S. Wang (2001). Research advancement of *Siegesbeckia, Nat. Prod. Res. Dev.*, **13**, 80-85.

[29] D.T. Trang, P.T.T. Huong, N.T. Cuc, D.T. Dung, B.T.T. Trang, N.X. Nham, B. Huu Tai and P. Van Kiem (2021). Four new acyclic diterpenes from *Siegesbeckia orientalis*, *Nat. Prod. Com.*, **16**, 1-6.

[30] N.S. Engels, B. Gierlikowska, B. Waltenberger, F.-R. Chang, A.K. Kiss and H. Suppner (2020). A new diterpene and anti-inflammatory sesquiterpene lactone from *Siegesbeckia orientalis*, *Planta Medica* **86**, 1108-1117.

[31] S.-Y. Shim, Y.E. Lee and M. Lee (2021). Antioxidant compounds, kirenoil and methyl ent-16α, 17-dihydroxy-kauran-19-olate bioactivity-guided isolated from *Siegesbeckia pubescens* attenuates MITF-mediates melanogenesis via inhibition of intracellular ROS production, *Molecules* **26**, 1940.

[32] N. Liu, C. Wu, J.H. Yu, K.K. Zhu, M.N. Song, F.Y. Yang, R.L. Feng, Y.Y. Zhang, W.Q. Chang and H. Zhang (2019). Germacrane-type sesquiterpenoids with cytotoxic activity from *Siegesbeckia orientalis*, *Bioorg. Chem.*, **92**, 103196.

[33] Q. Wu, H. Li, S.Y. Lee, H.J. Lee and J.H. Ryu (2015). New cytotoxic sesquiterpenoids from *Siegesbeckia glabrescens*, *Molecules* **20**, 2850-2856.

[34] R. Wang, L.-L. Liu and Y.-P. Shi (2010). Pubescone, a Novel 11(7→6)Abeo-14-norcarabran Sesquiterpenoid from *Siegesbeckia orientalis*, *Helv. Chim. Acta.*, **93**, 2081-2085.

[35] H.D.T. Thuy, D.D. Thi, Y.D.T. Hai, H.N. Huy, B.N. Anh, C.N. Thi, N.N. Xuan, H.P.T. Thanh, T.B. Huu and V.K. Phan (2021). Guaianolide sesquiterpenes and benzoate esters from the aerial parts of *Siegesbeckia orientalis* L. and their xanthine oxidase inhibitory activity, *Phytochemistry* **190**, 112889.

[36] R. Baruah, R. Sharma, K. Madhusudanan, G. Thyagarajan, W. Herz and R. Murari (1979). A new melampolide from *Siegesbeckia orientalis*, *Phytochemistry* **18**, 991-994.

[37] C. Wu, Q.Q. Zhang, F.Y. Yang, M.N. Song, Y.L. Sun, Y.Y. Zhang, X.B. Li, D. Ge, N. Liu and H. Zhang (2020). New oxylipins from *Siegesbeckia glabrescens* as potential antibacterial agents, *Fitoterapia* **145**, 104613.

[38] X.X. Gao, Y.N. Gao, D.D. Wang, G.S. Hu, T. Yan, J.M. Jia and A.H. Wang (2021). Six novel lignanoids with complex structures from *Siegesbeckia glabrescens* Makino with their cytotoxic activities, *Fitoterapia* **148**, 104799.

[39] H.Z. Fu, Y.S. Li, D.A. Guo and Z.C. Lou (1999). Studies on chemical constituents of *Siegesbeckia pubescens* (III), *Chin. Trad. Herb. Drugs*, **30**, 491-492.
Wang et al., Rec. Nat. Prod. (202X) X:X XX-XX

[40] J. Liu, R. Chen, Y. Nie, L. Feng, H.D. Li and J.Y. Liang (2012). A new carbamate with cytotoxic activity from the aerial parts of Siegesbeckia pubescens, Chin. J. Nat. Med. 10, 13-15.

[41] J.Y. Kim, H.J. Lim and J.H. Ryu (2010). In vitro anti-inflammatory activity of 3-O-methyl-flavones isolated from Siegesbeckia glabrescens, Bioorg. Med. Chem. Lett. 19, 1511-1514.

[42] K. Zhao, K. Liu and F. Zhao (2012). Active constituents from Siegesbeckia pubescens, Asia-Pac. Trad. Med. 8, 40-42.

[43] C.G. Xin and W.Z. Tao (2006). Study on chemical constituents of Herba Siegesbeckiae, Chin. Pharm. J. 41, 1854-1857.

[44] Y.S. Kim, H. Kim, E. Jung, J.H. Kim, W. Hwang, E.J. Kang, S. Lee, B.J. Ha, J. Lee and D. Park (2012). A novel antibacterial compound from Siegesbeckia glabrescens, Molecules 17, 12469-12477.

[45] L. Zeng, J. Xu, L. Xu, L. Zhu and H. Liu (2017). Separation and identification of flavonoids from Siegesbeckia glabrescens, Chin. J. Exp. Trad. Med. Form. 23, 74-77.

[46] Y.S. Li, J. Zhang, G.H. Tian, H.C. Shang and H.B. Tang (2021). Kirenol, darutoside and hesperidin contribute to the anti-inflammatory and analgesic activities of Siegesbeckia pubescens makino by inhibiting COX-2 expression and inflammatory cell infiltration, J. Ethnopharmacol. 268, 113547.

[47] H.Z. Fu, S.Q. Cai, R. Feng and Z.C. Lou (1998). Chemical Constituents of Siegesbeckia glabrescens (II) Chin. Pharm. J. 33, 276-278.

[48] H.Z. Fu, Z.C. Lou, X.W. Yang, S.Q. Cai, D.A. Guo, J. Yu, X.P. Yang and Y.S. Li (1997). Studies on chemical constituents of Siegesbeckia glabrescens (I) Chin. Trad. Herb. Drugs 28, 259-262.

[49] H.Z. Fu, Z.C. Lou, S.Q. Cai, X.J. Hu and Z.W. Zhang (1998). Chemical constituents of Siegebeckia glabrescens (I), Chin. Pharm. J. 33, 140-142.

[50] J.W. Ha and Y.C. Boo (2021). Siegesbeckiae herba extract and chlorogenic acid ameliorate the death of HaCaT keratinocytes exposed to airborne particulate matter by mitigating oxidative stress, Antioxidants 10, 1762.

[51] Y.H. Hong, L.W. Weng, C.C. Chang, H.F. Hsu, C.P. Wang, S.W. Wang and J.Y. Houng (2014). Anti-inflammatory effects of Siegesbeckia orientalis ethanol extract in vitro and in vivo models, Biomed. Res. Int. 2014, 329712.

[52] Q.S. Ma, K.G. Linghu, T. Zhang, G.D. Zhao, W. Xiong, S.H. Xiong, M. Zhao, W. Xu, J. Yu and H. Yu (2020). Siegesbeckia glabrescens Makino extract attenuated the collagen-induced arthritis through inhibiting the synovial hyperplasia and inflammation, Chin. Med. 15, 1-12.

[53] H. Guo, Y. Zhang, B.C. Cheng, X. Fu, P. Zhu, J. Chen, Y. Chan, C. Yin, Y. Wang and M. Hossen (2018). An ethanolic extract of the aerial part of Siegesbeckia orientalis L. inhibits the production of inflammatory mediators regulated by AP-1, NF-kB and IRF3 in LPS-stimulated RAW 264.7 cells, Biosci. Trends 12, 330-337.

[54] X.D. Tang, Q. Zhao, X.F. Lan, N.N. Ge, Z.H. Tang and C.H. Fan (2020). Effect of Siegesbeckia orientalis on cartilage damage in knee osteoarthritis rats by regulating sirt1/FOXO1 pathway, Chin. J. Immunol. 36, 439-444.

[55] W. Sang, Z.F. Zhong, K.G. Linghu, W. Xiong, A.K.W. Tse, W. San Cheang, H. Yu and Y.T. Wang (2018). Siegesbeckia pubescens Makino inhibits Pam 3 CSK 4-induced inflammation in RAW 264.7 macrophages through suppress TLR1/TLR2-mediated NF-kB activation, Chin. Med. 13, 1-10.

[56] P. Quan, B. Jiao, R. Shang, C. Liu and L. Fang (2021). Alternative therapy of rheumatoid arthritis with a novel transdermal patch containing Siegesbeckiae Herba extract, J. Ethnopharmacol. 265, 113294.

[57] M.R. Akanda, M.J. Kim, I.S. Kim, D. Ahn, H.J. Tae, M.M. Rahman, Y.G. Park, J.W. Seol, H.H. Nam, B.K. Choo and B.Y. Park (2017). Neuroprotective effects of Siegesbeckia pubescens extract on glutamate-induced oxidative stress in HT22 cells via downregulation of MAPK/caspase-3 pathways, Cell. Mol. Neurobiol. 38, 497-505.

[58] J.M.T. Chu, W. Xiong, K.G. Linghu, Y. Liu, Y. Zhang, G.D. Zhao, M.G. Irwin, G.T.C. Wong and H. Yu (2018). Siegesbeckia orientalis L. extract attenuates postoperative cognitive dysfunction, systemic inflammation, and neuroinflammation, Exp. Neurobiol. 27, 564-573.

[59] H. Guo, Y. Zhang, B.C.Y. Cheng, M.Y. Lau, X.Q. Fu, T. Li, T. Su, P.L. Zhu, Y.C. Chan, A.K.W. Tse, T. Yi, H.B. Chen and Z.L. Yu (2018). Comparison of the chemical profiles and inflammatory mediator-inhibitory effects of three Siegesbeckia herbs used as Herba Siegesbeckiae (Xixiancao), BMC Complement. Altern. Med. 18, 141.

[60] Z.F. Zhong, Q.R. Zhang, H.X. Tao, W. Sang, L. Cui, W.A. Qiang, W. San Cheang, Y.J. Hu, H. Yu and Y.T. Wang (2019). Anti-inflammatory activities of Siegesbeckia glabrescens Makino: combined in vitro and in silico investigations, Chin. Med. 14, 1-12.

[61] K.G. Linghu, G.D. Zhao, W. Xiong, W. Sang, S.H. Xiong, A.K.W. Tse, Y. Hu, Z. Bian, Y. Wang and H. Yu (2020). Comprehensive comparison on the anti-inflammatory effects of three species of Siegesbeckia plants based on NF-kB and MAPKs signal pathways in vitro, J. Ethnopharmacol. 250, 112530.
A review on medical plants of genus Siegesbeckia

[62] X.X. Gao, J.C. Wei, L.N. Hong, S.P. Fan, G.S. Hu and J.M. Jia (2018). Comparative analysis of chemical composition, anti-inflammatory activity and antitumor activity in essential oils from Siegesbeckia orientalis, S. glabrescens and S. pubescens with an ITS sequence analysis, Molecules 23, 2185.

[63] S.R. Ibrahim, A.E. Altyar, I.A. Sindi, D.S. El-Agamy, H.M. Abdallah, S.G. Mohamed and G.A. Mohamed (2021). Kirenol: A promising bioactive metabolite from siegesbeckia species: A detailed review, J. Ethnopharmacol. 281, 114552.

[64] J.P. Wang, Y.M. Zhou, Y.J. Ye, X.M. Shang, Y.L. Cai, C.M. Xiong, Y.X. Wu and H.X. Xu (2011). Topical anti-inflammatory and analgesic activity of kirenol isolated from Siegesbeckia orientalis, J. Ethnopharmacol. 137, 1089-1094.

[65] Z.M. Wang, S.G. Zhu, Z.W. Wu, Y. Lu, H.Z. Fu and R.Q. Qian (2011). Kirenol upregulates nuclear Annexin-1 which interacts with NF-κB to attenuate synovial inflammation of collagen-induced arthritis in rats, J. Ethnopharmacol. 137, 774-782.

[66] J. Ren, M.J. Yang, J.W. Chen, S.L. Ma and N. Wang (2020). Anti-inflammatory and wound healing potential of kirenol in diabetic rats through the suppression of inflammatory markers and matrix metallopeinase expressions, Biomed. Pharmacother. 129, 110475.

[67] J. Wu, Q. Li, L. Jin, Y. Qu, B.B. Liang, X.T. Zhu, H.Y. Du, L.G. Jie and Q.H. Yu (2019). Kirenol inhibits the function and inflammation of fibroblast-like synoviocytes in rheumatoid arthritis in vitro and in vivo, Front. Immunol. 10, 1304.

[68] H. Park, I. Kim, J.H. Jeong, E. Park, J. Nam, J. Choi and K. Lee (2007). Anti-inflammatory activities of ent-16β,17-dihydroxy-kauran-19-oic acid isolated from the roots of Siegesbeckia pubescens are due to the inhibition of iNOS and COX-2 expression in RAW 264.7 macrophages via NF-κB inactivation, Eur. J. Pharmacol. 558, 185-193.

[69] L. Mina, K. Seung Hyun, L. Hee Young, C. Yekyung, K. Jimmy and S.S. Hyun (2014). ent-kauran and ent-pterarane diterpenes from Siegesbeckia pubescens inhibit lipopolysaccharide-induced nitric oxide production in BV2 microglia, Biol. Pharm. Bull. 37, 152.

[70] R. Wang, Y.Q. Liu, W. Ha, Y.P. Shi, T.L. Hwang, G.J. Huang, T.S. Wu and K.H. Lee (2011). In vitro anti-inflammatory effects of diterpenoids and sesquiterpenoids from traditional Chinese medicine Siegesbeckia pubescens, Bioorg. Med. Chem. Lett. 24, 3944-3947.

[71] H. Li, J.Y. Kim, J. Hyeon, H.J. Lee and J.H. Ryu (2011). In vitro antiinflammatory activity of a new sesquiterpene lactone isolated from Siegesbeckia glabrescens, Phytother. Res. 25, 1323-1327.

[72] H.J. Lim, H. Li, J.Y. Kim and J.H. Ryu (2011). Quercetin derivatives from Siegesbeckia glabrescens inhibit the expression of COX-2 through the suppression of NF-κB activation in microglia, Biomol. Theor. 19, 27-32.

[73] S.G. Lee, M. Kim, C.E. Kim, J. Kang, H. Yoo, H.S. Sang and M. Lee (2016). Quercetin 3,7-O-dimethyl ether from Siegesbeckia pubescens suppress the production of inflammatory mediators in lipopolysaccharide-induced macrophages and colon epithelial cells, Biosci. Biotechnol. Biochem. 80, 2080-2086.

[74] W.J. Hwang, E.J. Park, C.H. Jang, S.W. Han, G.J. Oh, N.S. Kim and H.M. Kim (2001). Inhibitory effect of immunoglobulin E production by Jin-Deuk-Chal (Siegesbeckia orientalis), Immunopharm. Immunoto. 23, 555-563.

[75] H.M. Kim, J.H. Lee, J.H. Won, E.J. Park, H.J. Chae, H.R. Kim, C.H. Kim and S.H. Baek (2001). Inhibitory effect on immunoglobulin E production in vivo and in vitro by Siegesbeckia glabrescens, Phytother. Res. 15, 572-576.

[76] B.K. Kang, E.H. Lee and H.M. Kim (1997). Inhibitory effects of Korean folk medicine ‘Hi-Chum’ on histamine release from mast cells in vivo and in vitro, J. Ethnopharmacol. 57, 73-79.

[77] H.M. Kim, C.Y. Kim, M.H. Kwon, T.Y. Shin and E.J. Lee (1997). Suppression of anaphylactic reaction in murine by Siegesbeckia pubescens, Arch. Pharm. Res. 20, 122-127.

[78] H. Gao, P.Y. Li, D.K. Li and G.Y. Ji (2001). Effects of ent-16β,17-dihydroxy-kauran-19-oic acid on decompression and blood viscosity, J. Norman Bethune Univ. Med. Sci. 27, 472-474.

[79] J.P. Wang, H.X. Xu, Y.X. Wu, Y.J. Ye, J.L. Ruan, C.M. Xiong and Y.L. Cai (2011). Ent-16β,17-dihydroxy-kauran-19-oic acid, a kaurane diterpene acid from Siegesbeckia pubescens, presents antiplatelet and antithrombotic effects in rats, Phytomedicine 18, 873-878.

[80] H.J. Lee, Q. Wu, H. Li, G. Bae, A.K. Kim and J. Ryu (2016). A sesquiterpene lactone from Siegesbeckia glabrescens suppresses Hedgehog/Gli-mediated transcription in pancreatic cancer cells, Oncol. Lett. 12, 2912-2917.

[81] W. Liu, Y. Li and C. Li (2020). Kirenol exhibits the protective role against N-methyl-N-nitrosourea-induced gastric cancer in rats via modulating the oxidative stress and inflammatory markers, J. Environ. Pathol. Tox. 39, 345-355.

[82] H.X. Tao, G.D. Zhao, K.G. Linghu, W. Xiong, W. Sang, Y. Peng, Y. Wang and H. Yu (2021). Botany,
traditional use, phytochemistry, pharmacology and toxicology of Sigesbeckia herba (Xixiancao): a review, *Phytochem. Rev.* **20**, 569-587.

[83] S.Y. Jun, Y.H. Choi and H.M. Shin (2006). *Siegesbeckia glabrescens* induces apoptosis with different pathways in human MCF-7 and MDA-MB-231 breast carcinoma cells, *Oncol. Rep.* **15**, 1461-1467.

[84] H.X. Sun and H. Wang (2006). Immunosuppressive activity of the ethanol extract of *Siegesbeckia orientalis* on the immune responses to ovalbumin in mice, *Chem. Biodivers.* **3**, 754-761.

[85] J. Xiao, R. Yang, L. Yang, X. Fan, W. Liu and W. Deng (2015). Kirenol attenuates experimental autoimmune encephalomyelitis by inhibiting differentiation of Th1 and th17 cells and inducing apoptosis of effector T cells, *Sci. Rep.* **5**, 9022.

[86] Y. Lu, J. Xiao, Z.W. Wu, Z.M. Wang, J. Hu, H.Z. Fu, Y.Y. Chen and R.Q. Qian (2012). Kirenol exerts a potent anti-arthritic effect in collagen-induced arthritis by modifying the T cells balance, *Phytomedicine* **19**, 882-889.

[87] S.H. Sung, S.H. Park, S.Y. Song, S.J. Lee, H.W. Lee, S.H. Kim, M.A. Lee, I.S. Yoon, D.D. Kim, S. Kang and J.H. Sung (2011). Epidermal regeneration by ent-16α, 17-dihydroxy-kauran-19-oic acid isolated from *Siegesbeckia pubescens*, *Cell Proliferat.* **44**, 527–536.

[88] J. Kim, M.B. Kim, J.G. Yun and J.K. Hwang (2016). Protective effects of standardized *Siegesbeckia glabrescens* extract and its active compound kirenol against UVB-induced photoaging through inhibition of MAPK/NF-κB pathways, *J. Microbiol. Biotech.* **242-250**.

[89] D. Sun, Y. Li, H. Cao, H. Guo, T.A. Alahmadi, S.A. Alharbi and J. Yu (2021). Hepatoprotective potential of kirenol on ethanol-induced liver toxicity in albino rats and acetaminophen-induced oxidative stress-mediated apoptosis in hepatic HepG2 cells, *J. Biochem. Mol. Toxicol.* **35**, e22786.

[90] J.A. Park, K.S. Jin, Y.L. Ji, H.J. Kwon and B.W. Kim (2013). Anti-oxidative and anti-obesity activities of tetrapanax papyriferus and *siegesbeckia pubescens* extracts and their synergistic anti-obesity effects, *Kor. J. Microbiol. Biotechn.* **41**, 341-349.

[91] M.-B. Kim, C. Kim and J.-K. Hwang (2020). High hydrostatic pressure extract of *Siegesbeckia orientalis* inhibits adipogenesis through the activation of the Wnt/β-catenin signaling pathway, *Food Sci. Biotechnol.* **29**, 977-985.

[92] M.B. Kim, Y. Song, C. Kim and J.K. Hwang (2014). Kirenol inhibits adipogenesis through activation of the Wnt/β-catenin signaling pathway in 3T3-L1 adipocytes, *Biochem. Biophys. Res. Co.* **445**, 433-438.

[93] M.B. Kim, Y. Song and J.K. Hwang (2014). Kirenol stimulates osteoblast differentiation through activation of the BMP and Wnt/β-catenin signaling pathways in MC3T3-E1 cells, *Fitoterapia* **98**, 59-65.

[94] I. Karaman, A.E. Günay, M.B. Yerer, E. Demirpolat, S. Doğan, A.H. Yay and İ.H. Kafadar (2020). Effect of kirenol on the interaction between the WNT/β-Catenin and RUNX2/TCF/LEF1 pathways in fracture healing in vivo, *Acta Orthop. Traumat.* **54**, 320-329.

[95] B. Zou, J. Zheng, W. Deng, Y. Tan, L. Jie, Y. Qu, Q. Yang, M. Ke, Z. Ding and Y. Chen (2021). Kirenol inhibits RANKL-induced osteoclastogenesis and prevents ovariectomized-induced osteoporosis via suppressing the Ca2+-NFATc1 and Cav-1 signaling pathways, *Phytomedicine* **80**, 153377.

[96] C.C. Chang, J.Y. Houng, S.W. Wang, C.F. Hsuam, Y.C. Lu, T.H. Chang and Y.L. Chen (2021). Protective effect of *Siegesbeckia orientalis* on pancreatic β-cells under high glucose-induced glucotoxicity, *Appl. Sci.* **11**, 10963.