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•Review•

Research progress on naturally-occurring and semi-synthetic ocotillol-type ginsenosides in the genus *Panax L.* (*Araliaceae*)

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[ABSTRACT] Ocotillol (OT)-type ginsenosides, one subtype of ginsenosides, consist of a dammarane skeleton and a tetrahydrofuran ring. Most naturally-occurring OT-type ginsenosides exist in *Panax* species, particularly in *Panax quinquefolius*, which may be attributed to the warm and humid climate of its native areas. Till now, merely 28 types of naturally-occurring OT-type ginsenosides have been isolated. In contrast, semi-synthesized OT-type ginsenosides are attracted considerable attentions. These ginsenosides can be obtained through oxidation and cyclization of side chains of dammarane-type ginsenosides, and other methods, which may change their physical and chemical properties and further improve their bioavailabilities. It is also notable that the pharmacological activities of ginsenosides are closely related to the stereoisomers caused by the configuration at C-20. Semi-synthesis of OT-type ginsenosides can facilitate our understanding of the biosynthesis, transformation and metabolism of OT-type ginsenosides in the body. This review will systematically summarize the research progress on naturally-occurring and semi-synthetic OT-type ginsenosides, which provides a theoretical basis for their bioactivity-guided research.

[KEY WORDS] Ocotillol-type ginsenosides; *Panax* species; *Panax quinquefolius*; Structure-activity relationship
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Introduction

Potential pharmacological activities of ginseng species are to a great extent attributable to its saponin constituents, also known as ginsenosides [1]. Ginsenosides can be classified into the following groups: dammarane-type [including protopanaxadiol (PPD)-type and protopanaxatriol (PPT)-type], ocotillol (OT)-type (a tetracyclic triterpenoid with a tetrahydrofuran ring in the side chain), oleanolic acid (OA)-type (pentacyclic triterpenoid saponins with oleanolic acid as an aglycone) and others, owing to their different chemical structures [2, 3]. According to previous studies, most naturally-occurring OT-type ginsenosides were isolated from *Panax* species, particularly *P. quinquefolius* (PQ), *P. pseudo-ginseng* subsp. *Himalaicus* (PPGH), *P. japonicus* (PJ), *P. vietnamensis* (PV), and *P. japonicus* var. *major* (PJM), but some were also reported from *Gynostemma* and *Gomphogyne* species, such as *Gynostemma pentaphyllum* (Thunb.) Makino [4-6] and *Neoalsomitra inlegrifoliola* (Cogn.) Hutch [7, 8].

Ocotillol (showed in Fig. 1A) was originally isolated from the resinous bark of ocotillo (*Fouquieria spendens*) in 1963 [9] and elucidated as (20*S*, 24*R*)-epoxydammarane-3*β*, 25-diol [10]. In 1978, the first OT-type ginsenoside, pseudoginsenoside F_{11} (PF_{11}), was isolated from the leaves of PPGH [11], indicating the emergence of a new type ginsenoside in the genus *Panax*. However, (20*S*, 24*R*)-epoxydammarane-3*β*, 6*β*, 12*β*, 25-tetrol (See Fig. 1B), the aglycone of PF_{11}, might be occasionally taken by researchers as ocotillol [12-17]. As shown in the picture below, these two structures are clearly different.

It was reported that PPT- and PPD-type ginsenosides were metabolized by CYP3A4 into OT-type ginsenosides, the final substances circulating in the bloodstream [18-20]. Thus, it's reasonably speculated that natural ginsenosides may act as prodrugs and microsomes-oxygenated products, while OT-type ginsenosides is the real agent exerting therapeutic activities. Yet, in contrast to remarkable pharmacological potential, less studies concerning OT-type ginsenosides have been performed. Here, this review is aimed to summarize the research progress on naturally-occurring and semi-synthesized OT-type ginsenosides, along with their corresponding bioactivities.

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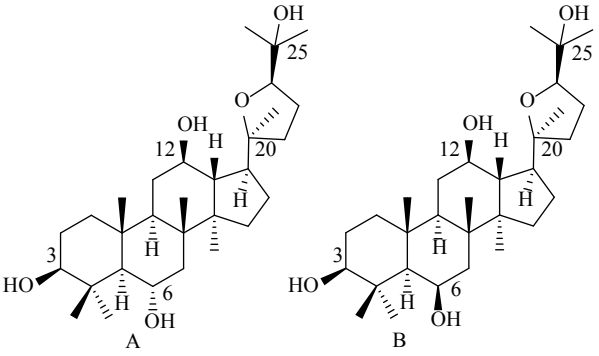
These authors have no conflict of interest to declare.
Dedicated to the 90th Anniversary of the Founding of Shenyang Pharmaceutical University



A: (20*S*, 24*R*)-Epoxydammarane-3*β*, 6*α*, 12*β*, 25-tetrol (ocotillol)
B: (20*S*, 24*R*)-Epoxydammarane-3*β*, 6*β*, 12*β*, 25-tetrol

Fig. 1 Structures of ocotillol and (20*S*, 24*R*)-epoxydammarane-3*β*, 6*β*, 12*β*, 25-tetrol

Comparison of Naturally-occurring OT-type Ginsenosides

Composition of naturally-occurring OT-type ginsenosides

It is widely accepted that OT-type ginsenosides do not exist in *Panax ginseng* (PG) at the initial stage of chemical isolation. The famous OT-type ginsenosides PF_{11} (**4**) was first isolated from the leaves of PPGH, and then found remarkably high in PQ [21], while no one had ever isolated or even detected it in PG over long period of time. Therefore, PF_{11} was used as a distinctive component for differentiating the medical products of PQ and PG. However, a trace level of PF_{11} was detected in the root of PG by LC-MS/MS in 2000 [22]. It should be noted that the difference between PQ and PG lies in the fact that ginsenoside Rf only exits in PG, while PF_{11} is considered as the characteristic component of PQ. Actually, PF_{11} and ginsenoside Rf are a pair of isomers with equal formula weight. It is difficult to distinguish between them through HPLC separation due to their similar retention characteristics in chromatographic column [23]. In Stavrianidi's report, a multiple reaction monitoring method was utilized to quantify PF_{11} and ginsenoside Rf in authentic Asian ginseng based on their particular mass spectrum. PF_{11} was detected with a result of less than 0.0001% (*W*/*W*) and ginsenoside Rf was 700 times or more than PF_{11} in Asian ginseng. Thus, it is reasonably implied that PF_{11} might be neglected in the previous isolation of Asian ginseng. Till now, 28 OT-type ginsenosides (**1**–**28**) have been naturally isolated from *Panax* species (listed in Table 1), and their structures are shown in Fig. S1. Taking all these together, the long-accepted assumption that there are no OT-type ginsenosides in PG has been reframed.

Characteristics of naturally-occurring OT-type ginsenosides

Naturally-occurring OT-type ginsenosides have some characteristics in common (Fig. 2). Briefly, for **1**–**6** & **8**–**19**, the sapogenin moieties share the same skeleton: epoxydammarane-3*β*, 6*α*, 12*β*, 25-tetrol. For **7** & **20**–**28**, some slight changes occurred in the basic skeleton, such as 12- or 3-hydroxyl acylation, hydroxyl substitution on C-27, or formation of 11, 12-epoxy. Particularly, pseudo-ginsenoside RT_9 (**20**), pseudo-ginsenoside RT_{10} (**21**) and vina-ginsenoside R_{14} (**22**) have dammar-20, 24-epoxy-3*β*, 6*α*, 12*β*, 25, 26-pentaol as their skeleton. For the absolute configurations of C-20 and C-24, most of them are *S* configuration except for (20*R*)-PF_{11} (**6**).

Most glycosyl of OT-type ginsenosides that have been naturally isolated so far is *β*-D-glucopyranosyl; besides, there are *α*-D-glucopyranosyl, *α*-L-rhamnopyranosyl and *β*-D-xylopyranosyl. Up to now, there is no arabinosyl. With regard to the relative configuration of D-glucopyranosyl, they are *β*-configuration in most cases, except for vina-ginsenoside R_5 (**15**), vina-ginsenoside R_6 (**16**), and yesanchinoside B (**18**) with *α*-D-glucopyranosyl as their tailing glycosyl. The monoglycosyl or sugar chains of **1**–**23** are attached to the 6-OH of the tetracyclic triterpenoid skeleton. However, the glycosidic linkages of (24*R*)-pseudo-ginsenoside G_1 (**25**), (24*R*)-pseudo-ginsenoside G_2 (**26**) and ginsenoside B (**28**) are formed by the condensation between their glucosyl and the 3-OH of their aglycone. Interestingly, for the linkage between two sugars in these OT-type ginsenosides, they are all 1→2 linkage between *β*-D-glucopyranosyl (inner) and *β*-D-glucopyranosyl (terminal), *α*-L-rhamnopyranosyl and *β*-D-xylopyranosyl. And *α*-D-glucopyranosyl (as a branched terminal glycosyl) linked to *β*-D-glucopyranosyl (inner) *via* 1→6 linkage, for example, vina-ginsenoside R_6 (**16**) and yesanchinoside B (**18**). Moreover, there is 1→4 linkage between *β*-D-xylopyranosyl and *α*-D-glucopyranosyl in vina-ginsenoside R_5 (**15**). In addition, the 6-OH of the inner glucose is easily to be acetylated, such as vina-ginsenoside R_1 (**12**), vina-ginsenoside R_2 (**14**), and yesanchinoside A (**17**).

Selective distribution of naturally-occurring OT-type ginsenosides

In order to determine the distribution of the above mentioned naturally-occurring OT-type ginsenosides among the *Panax* species, a straightforward comparison was drawn in Fig. 3. It can be seen that these OT-type ginsenosides are mostly found in PQ, followed by PJ and PV, while the least in PG. Moreover, it should be noted that the content of OT-type ginsenosides in PV is at an upper level than those of other *Panax* species [3]. Van *et al.* reported that the ratios of PPT- : PPD- : OT-type ginsenosides from the rhizome, radix, and fine roots of PV were 1 : 1.7 : 7.8, 1 : 1.6 : 5.5, and 1 : 4.8 : 3.3, respectively. And on the whole OT-type ginsenosides accounted for 36%–75% of total saponins. In addition, majoroside R_2 is the main OT-type saponin in PV, whose content is more than 5% [58]. Certainly, the quantity of OT-type ginsenosides in PQ is also at a broad level, even if less than those in PV. Liu *et al.* [59] established a method for determining four ginsenosides from flower buds of PQ by Waters Acquity UPLC H-Class with Xevo TQD. Results showed that the content of PF_{11} was 47.67 ± 0.57 $mg \cdot g^{-1}$ (approximately 4.7%), higher than the other three PPT- & PPD-type ginsenosides. PF_{11} distributed in the flower, stem, fruit, leaves and root of PQ at a content of 2.34%, 1.93%, 1.54%, 0.97% and 0.28%, respectively, indicating its remarkably high content in PQ. Hence, it is necessary to comprehensively upgrade the level standards for discriminating them in terms of the content of

Table 1 Naturally-occurring OT-type ginsenosides and their distribution

No.	Name	Source	Used part	References
1	Majoroside R_1	*P. japonicus*	Rhizomes, leaves	[24-26]
		P. vietnamensis	Roots, rhizomes	[27]
2	(24*R*)-Majoroside R_1	*P. japonicus*	Roots, rhizomes	[28, 29]
3	Majoroside R_2	*P. japonicus*	Rhizomes, leaves, underground part	[24-26, 30]
		P. pseudo-ginseng	Rhizomes	[31, 32]
		P. vietnamensis	Roots, rhizomes	[27]
4	Pseudo-ginsenoside F_{11}	*P. pseudo-ginseng*	Leaves, rhizomes	[11, 32-35]
		P. ginseng	Roots	[22]
		P. quinquefolius	Roots, rhizomes, stems, Leaves, flower, fruit	[21, 36-42]
5	(24*S*)-Pseudo-ginsenoside F_{11}	*P. japonicus*	Rhizomes, leaves, underground part	[30, 43]
		P. pseudo-ginseng	Rhizomes	[31, 32]
		P. quinquefolius	Flowers	[41]
		P. vietnamensis	Roots, rhizomes	[27]
6	(20*R*)-Pseudo-ginsenoside F_{11}	*P. quinquefolius*	Roots	[37]
7	12-One-pseudoginsenoside F_{11}	*P. quinquefolius*	Stems, leaves	[44]
8	Pseudo-ginsenoside RT_2	*P. pseudo-ginseng*	Rhizomes	[32, 33]
		P. japonicus	Rhizomes	[45]
9	Pseudo-ginsenoside RT_4	*P. pseudo-ginseng*	Rhizomes	[33]
		P. japonicus	Underground part	[30]
		P. vietnamensis	Roots, rhizomes	[27]
		P. quinquefolius	Stems, leaves	[46]
10	Pseudo-ginsenoside RT_5	*P. pseudo-ginseng*	Rhizomes	[33]
		P. quinquefolius	Roots, flowers, leaves, fruit	[12, 36, 41, 47, 48]
		P. ginseng	Leaves, fruit pedicels	[49, 50]
11	Pseudo-ginsenoside RT_8	*P. ginseng*	Seeds	[51]
12	Vina-ginsenoside R_1	*P. vietnamensis*	Roots, rhizomes	[27]
		P. japonicus	Underground part	[30]
13	(24*R*)-Vina-ginsenoside R_1	*P. quinquefolius*	Flower buds	[41]
14	Vina-ginsenoside R_2	*P. vietnamensis*	Roots, rhizomes	[27]
		P. japonicus	Underground part	[30]
15	Vina-ginsenoside R_5	*P. vietnamensis*	Roots, rhizomes	[52]
16	Vina-ginsenoside R_6	*P. vietnamensis*	Roots, rhizomes	[52]
		P. japonicus	Underground part	[30]
17	Yesanchinoside A	*P. japonicus*	Underground part	[30]
18	Yesanchinoside B	*P. japonicus*	Underground part	[30]
19	Yesanchinoside C	*P. japonicus*	Underground part	[30]
20	* Pseudo-ginsenoside RT_9	*P. japonicus*	Rhizomes	[29]
21	* Pseudo-ginsenoside RT_{10}	*P. japonicus*	Rhizomes	[29]
22	Vina-ginsenoside R_{14}	*P. vietnamensis*	Roots, rhizomes	[53, 54]
23	Pseudo-ginsenoside RT_6	*P. quinquefolius*	Stems, leaves	[55]
24	Pseudo-ginsenoside R_1	*P. quinquefolius*	Stems, leaves	[55]
25	(24*R*)-Pseudo-ginsenoside G_1	*P. quinquefolius*	Roots	[56]
26	(24*S*)-Pseudo-ginsenoside G_2	*P. quinquefolius*	Roots	[56]
27	* Ginsenoside A	*P. ginseng*	Roots, rhizomes	[57]
28	* Ginsenoside B	*P. ginseng*	Roots, rhizomes	[57]

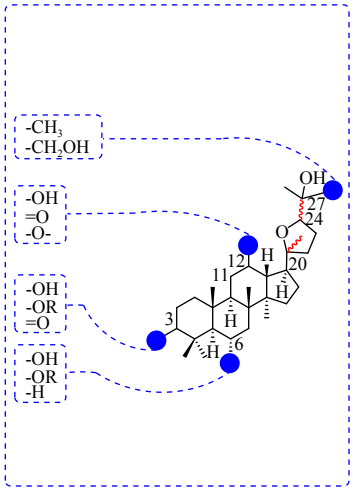
* Pseudo-ginsenoside RT_9: (20*S*, 24*S*, 25*R*)-6-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl]-dammar-20, 24-epoxy-3*β*, 6*α*, 12*β*, 25, 26-pentaol; * Pseudo-ginsenoside RT_{10}: (20*S*, 24*R*, 25*R*)-6-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl]-dammar-20, 24-epoxy-3*β*, 6*α*, 12*β*, 25, 26-pentaol; * Ginsenoside A: 3-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl]-11, 12-epoxy-dammar-20*S*, 24*R*-epoxy-3*β*, 12*β*, 25-triol; * Ginsenoside B: 3-*O*-[*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl]-11, 12-epoxy-dammar-20*S*, 24*S*-epoxy-3*β*, 12*β*, 25-triol

OT-type ginsenosides.

Semi-synthesis of OT-type ginsenosides

Many researchers have extensively explored the transformation from PPD- and PPT-ginsenosides to OT-type ginsenosides by oxidizing the side chain usually with hydrogen peroxide, peroxyacetic acid, benzo-hydroperoxide, potassium permanganate, and p-chloro-peroxybenzoic acid [60-66]. Table 2 summarizes 18 semi-synthesized OT-type ginsenosides, and their structures are showed in Fig. S2.

In Liu's experiment [61], hydrogen peroxide, peroxyacetic acid, and benzo-hydroperoxide were used to oxidize the



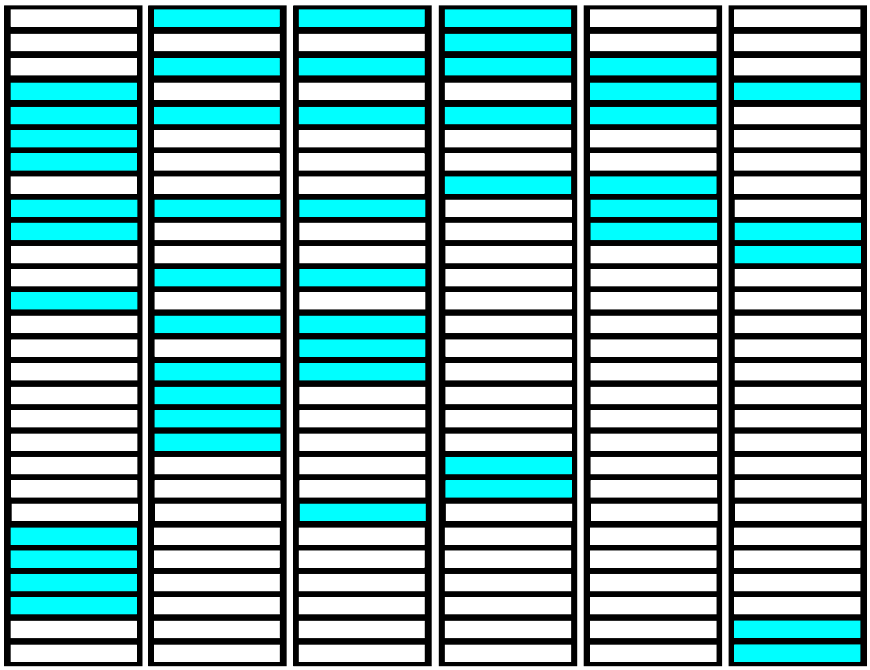
Basic skeleton:
For **1**−**6** & **8**−**19**, the sapogenin moieties share the same skeleton: cpoxydammarane-3β, 6α, 12β, 25-tetrol; for **7** & **20**−**28**, some slight changes occurred in the basic skeleton, such as 12- or 3-hydroxyl acylation, hydroxyl substitution on C-27, or formation of 11, 12-epoxy.

Absolute configurations of C-20 and C-24:
Most of their C-20 and C-24 are in *S* configuration, except for (20*R*)-PF11 (**6**), namely 20*R* configuration.

Types and relative configurations of glycosyls:
Most glycosyl of OT-type ginsenosides that have been naturally isolated so far is β-D-glucopyranosyl; besides, there are also α-D-glucopyranosyl, α-L-thamnopyranosyl and β-D-xylopyranosyl. Up to now, there is no arabinose. With regard to the relative configuration of D-glucopyranosyl, they are β-configuration in most cases, except for **15**, **16**, and **18** with α-D-glucopyranosyl as their tailing glycosyl.

Types of glycosidic linkages:
1) The mono-glycosyl or sugar chains of **1**−**23** are attached to the 6-OH of the tetracyclic triterpenoid skeleton. However, the glycosidic linkages of **25**, **26** and **28** are formed by the condensation between their glucosyl and the 3-OH of their aglycone.
2) For the linkage between two sugars in these OT-type ginsenosides, they are all 1→2 linkage between β-D-glucopyranosyl (inner) and β-D-glucopyranosyl (terminal), α-L-rharmnopyranosyl and β-D-xylopyranosyl. And α-D-glucopyranosyl (as a branched termnal glycosyl) linked to β-D-glucopyranosyl (inner) *via* 1→6 linkage, for example **16** and **18**. Moreover,there is 1→4 linkage between β-D-xylopyranosyl and α-D-glucopyranosyl, which only exists in **15**.

Fig. 2 Structure characteristics of natural OT-type ginsenosides isolated from the *Panax* species



*A filled blue box means the compound has been isolated from the corresponding *Panax* species.

Fig. 3 Selective distribution of naturally-occurring OT-type ginsenosides from the *Panax* species

side chain of (20*R*)-Rg$_3$ and (20*R*)-Rh$_2$ for achieving four OT-type ginsenosides: **36**, **37**, **40** and **41**. Furthermore, the 20*S* epimers of the two ginsenosides mentioned and 20*S*-PPD were also investigated under the same conditions, affording **31**, **35** and **39**. In the light of these different outcomes, Liu proposed that S_N1 occurred in the oxidation of 20*R* configuration while S_N2 in 20*S* [61]. However, in 2016, Yang proposed a new point that the stereo configuration of C-20 was coincident with different oxidants used during the synthesis [60], and concluded that when hydrogen peroxide was used as an oxidant, the stereo configuration of the resultant OT-type ginsenosides at C-20 remained the same with reagents. Moreover, S_N1 featured the mechanism of this oxidative reaction whatever the C-20 configurations of the reagent ginsenosides are, so both 24*S* and 24*R* OT-type ginsenosides were produced. In the same year, in order to determine the exact mechanisms and the possibility of stereoselectivity during the synthesis, 12β-hydroxyl-ocotillol and its epimer were synthesized from two routes [68]. One was oxidation with meta-chloroperbenzoic acid (m-CPBA) at a yield of 44.1% and 28.6%, respectively. The other was acetylation, oxidation and saponification at a yield of 16.4% and 16.2%, respectively. After repeating these two routes many times, the researchers deduced that oxidation was involved in the mechanism of action. In route one, due to the interaction of intramolecular hydrogen bonds, the chemical environments on both sides of the C24(25) double bond in (20*S*)-PPT were different, leading to the different yields of 12β-hydroxyl-ocotillol and its epimer.

Table 2 Structure of semi-synthesized OT-type ginsenosides (29−46)

No.	Name	References
29	(*R*, *S*)-Pseudo-ginsenoside F11	[60]
30	(*S*, *R*)-Pseudo-ginsenoside DQ	[10]
31	(*S*, *S*)-Pseudo-ginsenoside DQ	[10]
32	(*R*, *R*)-Pseudo-ginsenoside DQ	[61, 67]
33	(*R*, *S*)-Pseudo-ginsenoside DQ	[61]
34	(*S*, *R*)-Pseudo-ginsenoside HQ	[67]
35	(*S*, *S*)-Pseudo-ginsenoside HQ	[67]
36	(*R*, *R*)-Pseudo-ginsenoside HQ	[61, 67]
37	(*R*, *S*)-Pseudo-ginsenoside HQ	[61, 67]
38	(*S*, *R*)-Pseudo-ginsenoside GQ	[67]
39	(*S*, *S*)-Pseudo-ginsenoside GQ	[67]
40	(*R*, *R*)-Pseudo-ginsenoside GQ	[61, 67]
41	(*R*, *S*)-Pseudo-ginsenoside GQ	[61, 67]
42	M1 *	[60]
43	M2 *	[60]
44	(20*S*, 24*R*)-3-*O*-acetyl-dammar-20, 24-epoxy-3*β*, 12*β*, 25-triol	[67]
45	(20*R*, 24*R*)-3-*O*-formyl- dammar-20, 24-epoxy-3*β*, 25-diol	[67]
46	(20*R*, 24S)-3-*O*-formyl-dammar-20, 24-epoxy-3*β*, 25-diol	[67]

M1 *: (20*R*, 24*R*)-6-*O*-*β*-D-glucopyranosyl-dammar-(20, 24)-epoxy-3*β*, 6*α*, 12*β*, 25-tetrol; M2 * : (20*R*, 24*S*)-6-*O*-*β*-D-glucopyranosyl-dammar-(20, 24)-epoxy-3*β*, 6*α*,12*β*, 25-tetrol

As for route 2 (synthesized *via* oxidation with m-CPBA, intramolecular S_N2 and saponification), the absence of intramolecular hydrogen bonds in the acetylated (20*S*)-PPT meant that the chemical environments on both sides of the C24(25) double bond were the same, resulting in almost equal yields of the pair of epimers [68]. In 2012, Tian *et al.* [69] reported six OT-type ginsenosides which were obtained through oxidizing the alkaline degradation products of total ginsenosides in PQ stems and leaves with m-CPBA, namely (20*S*/*R*, 24*R*)-PF_{11}, (20*S*, 24*S*)-pseudo-ginsenoside RT_4, (20*S*, 24*R*)-pseudo-ginsenoside RT_5, (20*S*, 24*R*)-pseudo-ginsenoside HQ (**34**), and (20*S*, 24*S*)-pseudo-ginsenoside HQ (**35**). Apart from the oxidative method, some researchers also obtained other OT-type ginsenosides by modifying the current methods. In a previous study [70], the modified products of PF_{11} under acidic conditions were further separated by normal and reversed-phase thin-layer chromatography to obtain (*S*, *R*)-RT_5, (*R*, *R*)-12*β*-hydroxyl-ocotillol, and (*S*, *R*)-12*β*-hydroxyl-ocotillol. Bi *et al.* semi-synthesized a series of ocotillol derivatives through three steps: first, acetylating the hydroxyls of PPD- or PPT-type ginsenosides to protect the hydroxyls free from the next oxidation, followed by the oxidation and cyclization of sidechian, and finally removing the acyl-group through base treatment. Additionally, substitution reactions were performed at 3-OH of pseudo-ginsenoside DQ using several kinds of aromatic, various furoxan, long-chain amino acid, and nitrated aliphatic esters, achieving a series of 3-substituted OT-type triterpenoid derivatives [63, 71-73].

Biological Activities of OT-type Ginsenosides

Intervention effect on the nervous system

The pharmacological researches of OT-type ginsenosides, especially PF_{11}, mainly placed emphasis on the intervention activity induced by opioids and its mechanisms. Early in 1999, it was proposed that PF_{11} antagonized the memory impairment induced by scopolamine [74]. In addition, pretreatment with PF_{11} antagonized the memory impairment, analgesia, analgesia, as well as the development of reverse tolerance induced by morphine [75]. In addition, PF_{11} inhibited the morphine-induced reduction of glutamate in the medial prefrontal cortex (mPFC), which indicated that PF_{11} can prevent the development of behavioral sensitization by affecting the glutamatergic system in mPFC [76]. These findings suggested that PF_{11} can act as a potential intervention agent for the addiction to opioids. The anti-amnesic effect of PF_{11} on Alzheimer's disease (AD) was tested with two types of AD mice models, where oral treatment with PF_{11} significantly relieved learning and memory impairment in AD mice through inhibiting the accumulation of A*β* (1–40), restoring oxidation resistance in the cortex, and downregulating the expression of JNK2, p53 and cleaved caspase 3 in the hippocampus [77]. Recently, a study reported that PF_{11} facilitated the clearance of A*β* by repairing the endosomal lysosomal system which was interrupted by A*β* [78, 79]. In addition, PF_{11} produced anti-neuritis effects on LPS-activated microglial cells through restricting the TLR4-mediated TAK1/IKK/NF-*κ*B, MAPKs and Akt signaling pathways [80]. Also, majoroside R_2 was a positive modulator of GABA receptors, which reversed social isolation stress and pregnenolone sulfate-induced decreases in pentobarbital sleep of mice [81].

Protective effect on the cardiovascular and cerebrovascular systems

Early researches found that pseudo-ginsenoside GQ improved the heart function of rats with myocardial ischemia induced by intravenous injection of isoproterenol. Previous studies suggested that pseudo-ginsenoside GQ, pseudo-ginsenoside HQ and PF_{11} exert cardioprotective effects on rats with myocardial ischemia induced by isoproterenol [82-85]. Furthermore, the cardioprotective effect of ocotillol's epimer, (20*S*, 24*S*)-ocotillol, (*S*, *R*)-pseudo-ginsenoside DQ's epimer, (*S*, *S*)-pseudo-ginsenoside DQ were also assessed. The (*S*, *R*)-configuration showed good cardioprotective effect, while no statistical difference was observed in pathological examination and determination of biochemical markers between the (20*S*, 24*S*) group and the model group, suggesting that the configuration of C-24 of the furan ring was involved in ocotillol and pseudo-ginsenoside DQ's cardioprotective effect [63, 83, 86]. Subsequently, PF_{11} was found to significantly decrease the level of active *β*1-adrenoceptor in H9c2 cardiomyocytes [84]. Meanwhile, molecular docking verified that PF_{11} had binding sites for *β*1-adrenoceptor. Some research demonstrated OT-type ginsenosides ameliorated not only heart injury, but cerebral injury induced by ischemia. Furthermore, PF_{11} improved lysosomal function and lysosome/autophagosome fusion after permanent middle cerebral artery occlusion (pMCAO), which were then reversed by chloroquine (a lysosomal inhibitor). (*S*, *R*)-Pseudo-ginsenoside DQ exhib-

ited ameliorated effects on the viability of H9c2 cells with anoxia/reoxygen injury [72] and shortened the duration of barium chloride-induced cardiac arrhythmias of rats [85]. Furthermore, ocotillol [15] and pseudo-ginsenoside GQ [87] were investigated as to their protective against heart dysfunction caused by doxorubicin-induced injury. Results showed that pseudo-ginsenoside GQ acted better than dexrazoxane, an FDA-authorized drug used to protect the heart against doxorubicin-induced injury, through protecting the membrane and mitochondria of myocardia. It was proposed that ocotillol may protect myocardia against cell toxicity induced by doxorubicin without compromising anticancer activity *via* enhancing the antioxidative potency.

Anti-tumor activity

PPT- and PPD-type ginsenosides exert excellent anti-tumor activity through inhibiting cancer cell proliferation, inducing cancer cell apoptosis and exhibiting anti-metastasis effects. However, the current researches were not limited to this, and it has been found that OT-type ginsenosides also have good anti-cancer activity. Majoroside R_2 exhibited an inhibitory effect on early antigen of Epatein-Barr virus induced by 12-*O*-tetrade-canoylphorbol-13-acetate and phorbol acetate in Raji cells [88, 89], and it also had effective anti-tumor activity in two-stage carcinogenesis test of mouse hepatic tumor and mouse skin [54]. A study investigated the inhibited activity of several ocotillol derivatives against Ehrlich carcinoma ascites as well as the structure-activity relationship. Results showed that the cytotoxic activity of epoxy-dammarane-triol with an 11α-OH group was slightly higher than that of epoxy-dammarane-triol with a 12β-OH group. Epoxy-dammarane-triol with an 11α-OH group and epoxy-dammarane-diol with a 3α-OH group were more active than those with a 3β-OH group [79]. Recently, researches showed that some OT-type ginsenosides coadministered with anti-tumor agents ameliorated their side effects without compromising antitumor activities [14]. Moreover, PF_{11} was shown to improve the nephrotoxicity induced by cisplatin without sacrificing the antitumor activity, and further study showed pretreatment of PF_{11} suppressed the expression of p53 in renal tissue and inhibited tubular cell apoptosis [16]. What's confusing, ocotillol and PF_{11} have the same sapogenin-epoxy dammar, when co-administrated with antitumor agents, ocotillol made doxorubicin more sensitive to p53, so as to accelerate the apoptosis of cancer cells. In contrast, PF_{11} suppressed p53 and ameliorated the apoptosis of tubular cell apoptosis. Whether they can be co-administered with antitumor agents to ameliorate side effects or enhance antitumor activity remains to be investigated.

Antibacterial activity

Bi *et al*. has been investigating the anti-bacterial activity of OT-type ginsenosides as well as their derivatives [73, 90-92]. Most of them showed excellent anti-bacterial activity against gram-positive bacteria. Particularly, (20*S*, 24*S*)-epoxy-dammarane-3β, 12β, 25-triol and (20*S*, 24*S*)-epoxy-25-hydroxy-dammarane-3, 12-dione showed anti-bacterial activity against CA-MRSA strain USA300. Meanwhile, the structure-activity relationship of these derivatives were studied. It was found that the substitution of 3-OH of the steroid backbone was a key determinant of antibacterial activity against gram-positive bacteria [73] and the 24*S*-configuration was preferred for antibacterial activity of compounds when the 3-OH was of no substitution.

Discussion and Conclusion

For medicinal plants, climate conditions (including temperature, sunlight and precipitation) are a key factor that directly affects their growth, development and reproduction. Here, it is clear that OT-type ginsenosides have more content and varieties in PQ than PV, PG and others. The native areas of PQ in the United States and Canada, ranging from 30 to 47 degrees north latitude, have a warm and humid climate on account of the influence of the Mexican warm current and the adjustment of the Pacific Ocean and the Great Lakes. All the advantages above lead to the higher expression of key genes (such as squalene synthase, squalene epoxidase and 2, 3-oxidosqualene cyclase) during the biosynthesis of ginsenosides [93]. In addition, previous studies also showed the content of ginsenoside F_2 was strongly negatively correlated with the percentage of sunshine and sunshine hours [94]. Since there are few naturally occurring OT-type ginsenosides, the current researches mainly focus on the semi-synthesis of them through some methods (for example, side chain oxidation and cyclization of dammarane-type ginsenosides), which may change their physical and chemical properties and further improve their bioavailability. Lately, researches demonstrated that the pharmacological activity of ginsenosides is closely related to the stereoisomers produced by the C-20 configuration. Furthermore, recent research showed novel nitrated compounds synthesized by attaching nitric oxide releasing groups to OT-type triterpenoids exerted stronger bioactivities. For example, (20*S*, 24*R*)-epoxy-3β-*O*-(6-nitrooxy hexanoyl)-dammarane-12β, 25-diol significantly inhibited the growth of both gram-positive and negative bacteria [90]. Overall, bioactivity-guided semi-synthesis of OT-type ginsenosides through various methods can assist researchers to well understand the mechanism of biosynthesis, transformation and metabolism of OT-type ginsenosides in *vivo*, and accordingly promote the research and development of novel nitrated derivatives of OT-type ginsenosides.

Supporting Information

Supporting information of this paper can be requested by sending E-mails to the corresponding authors.

References

[1] Wang MY, Li HN, Liu WW, *et al*. Dammarane-type leads panaxadiol and protopanaxadiol for drug discovery: biological activity and structural modification [J]. *Eur J Med Chem*, 2020, **189**: 112087.
[2] Piao X, Zhang H, Kang J, *et al*. Advances in saponin diversity of *Panax ginseng* [J]. *Molecules*, 2020, **25**(15): 3452.
[3] Minh NH, Truong NH, Vu HKL, *et al*. Antimelanogenic activity of ocotillol-type saponins from *Panax vietnamensis* [J]. *Chem Biodivers*, 2020, **17**(5): e2000037.
[4] Bai MS, Gao JM, Fan C, *et al*. Bioactive dammarane-type triterpenoids derived from the acid hydrolysate of *Gynostemma pentaphyllum* saponins [J]. *Food Chem*, 2010, **119**(1): 306-310.
[5] Liu X, Ye W, Mo Z, *et al*. Five new ocotillone-type saponins from *Gynostemma pentaphyllum* [J]. *J Nat Prod*, 2004, **67**(7): 1147-1151.
[6] Piacente S, Pizza C, De TN, *et al*. New dammarane-type glycosides from *Gynostemma pentaphyllum* [J]. *J Nat Prod*, 1995, **58**(4): 512.

[7] Fujita S, Kasai R, Ohtani K, *et al*. Dammarane glycosides from aerial part of *Neoalsomitra integrifoliola* [J]. *Phytochemistry*, 1995, **38**(2): 465-472.

[8] Qiu MH, Ryoji K. A new dammarane triterpenoid from *Neoalsomitra integrifoliola* [J]. *Acta Bot Yunnan*, 1992, **14**(4): 442-444.

[9] Halls CMM, Warnhoff EW. The constitution of ocotillol [J]. *Chem Ind (London, U K)*, 1963, **51**: 1986.

[10] Nagai M, Tanaka N, Tanaka O, *et al*. Triterpenes of Japanese white birch and the configuration at C-24 of ocotillol II and its related compounds [J]. *Chem Pharm Bull*, 1973, **21**(9): 2061-2065.

[11] Tanaka O, Yahara S. Dammarane saponins of leaves of *Panax pseudo-ginseng* subsp. *himalaicus* [J]. *Phytochemistry*, 1978, **17**(8): 1353-1358.

[12] Liu CD. Research on the chemical constituents of flower buds of *Panax quinquefolium* L. [D]. Shenyang Pharmaceutical University, 2008.

[13] Wang ZJ, Sun L, Peng W, *et al*. Ginseng derivative ocotillol enhances neuronal activity through increased glutamate release: a possible mechanism underlying increased spontaneous locomotor activity of mice [J]. *Neuroscience*, 2011, **195**: 1-8.

[14] Wang HB, Yu PF, Bai J, *et al*. Ocotillol enhanced the antitumor activity of doxorubicin *via* p53-dependent apoptosis [J]. *Evid Based Complement Alternat Med*, 2013, **2013**: 468537.

[15] Fu XY, Kong L, Tang MT, *et al*. Protective effect of ocotillol against doxorubicin-induced acute and chronic cardiac injury [J]. *Mol Med Rep*, 2014, **9**(1): 360-364.

[16] Wang HB, Kong L, Zhang JQ, *et al*. The pseudoginsenoside F_{11} ameliorates cisplatin-induced nephrotoxicity without compromising its anti-tumor activity *in vivo* [J]. *Sci Rep*, 2014, **4**: 4986.

[17] Lee SY, Jeong JJ, Le THV, *et al*. Ocotillol, a majonoside R_2 metabolite, mmeliorates 2, 4, 6-trinitrobenzenesulfonic acid-induced colitis in mice by restoring the balance of Th17/Treg cells [J]. *J Agric Food Chem*, 2015, **63**(31): 7024-7031.

[18] Hao H, Lai L, Zheng C, *et al*. Microsomal cytochrome P450-mediated metabolism of protopanaxatriol ginsenosides: metabolite profile, reaction phenotyping, and structure-metabolism relationship [J]. *Drug Metab and Dispos*, 2010, **38**(10): 1731-1739.

[19] Li L, Chen XY, Zhou JL, *et al*. *In vitro* studies on the oxidative metabolism of 20(*S*)-ginsenoside Rh2 in human, monkey, dog, rat, and mouse liver microsomes, and human liver S9 [J]. *Drug Metab Dispos*, 2012, **40**(10): 2041-2053.

[20] Wang JR, Tong TT, Yau LF, *et al*. Characterization of oxygenated metabolites of ginsenoside Rg1 in plasma and urine of rat [J]. *J Chromatogr B*, 2016, **1026**: 75-86.

[21] Wei JX, Wang JF, Li ZR. Studies on the chemical constituents of Xi Yang Shen (*Panax quinquefolius*) (I) [J]. *Chin Tradit Herb Drugs*, 1983, **14**(9): 389-391.

[22] Li W, Gu C, Zhang H, *et al*. Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish *Panax ginseng* C. A. Meyer (Asian ginseng) and *Panax quinquefolius* L. (North American ginseng) [J]. *Anal Chem*, 2000, **72**(21): 5417-5422.

[23] Stavrianidi AN, Rodin IA, Braun AV, *et al*. HPLC-MS/MS determination of biomarkers of *P. quinquefolius* in plant materials and commercial products [J]. *J Anal Chem*, 2014, **69**(14): 1323-1329.

[24] Wang DQ, Yang CR, Ning YC. Saponins of the rhizome of *Panax japonicus* C. A. Meyer *var. major* (Burk.) Wu et Feng collected in Qinling Mountain (Shaanxi) [J]. *Acta Bot Sin*, 1988, **30**(4): 403-408.

[25] Yang TR, Wu MZ, Zhou J. Triterpenoid saponins of leaves of *Panax japonicus* C. A. Meyer *var. major* (Burk.) Wu et Feng [J]. *Acta Bot Yunnan*, 1984, **6**(1): 118-120.

[26] Morita T, Kasai R, Tanaka O, *et al*. Saponins of Zu-Tziseng, rhizomes of *Panax japonicus* C. A. Meyer *var. major* (Burk.) C. Y. Wu et K. M. Feng, collected in Yunnan, China [J]. *Chem Pharm Bull*, 1982, **30**(12): 4341-4345.

[27] Nguyen MD, Nguyen TN, Kasai R, *et al*. Saponins from Vietnamese ginseng, *Panax vietnamensis* Ha et Grushv. collected in central Vietnam. I [J]. *Chem Pharm Bull*, 1993, **41**(11): 2010-2014.

[28] Shi XL, Wang JF, Yao H, *et al*. Chemical constituents of roots of *Panax japonicus* C. A. Mey. *var. major* (Burk.) C. Y. Wu et K. M. Feng [J]. *Chem J Chin U*, 2013, **34**(2): 381-385.

[29] Li M, Jin YR, Wang XZ, *et al*. Five new triterpenoid saponins from the rhizomes of *Panacis majoris* and their antiplatelet aggregation activity [J]. *Planta Med*, 2017, **83**(3-04): 351-357.

[30] Zou K, Zhu S, Tohda C, *et al*. Dammarane-type triterpene saponins from *Panax japonicus* [J]. *J Nat Prod*, 2002, **65**(3): 346-351.

[31] Namba T, Matsushige K, Morita T, *et al*. Saponins of plants of *Panax* species collected in central Nepal and their chemotaxonomical significance. I [J]. *Chem Pharm Bull*, 1986, **34**(2): 730-738.

[32] Morita T, Kong YC, But PPH, *et al*. Saponins of plants of *Panax* species collected in Central Nepal and their chemotaxonomic significance. II [J]. *Chem Pharm Bull*, 1986, **34**(10): 4368-4372.

[33] Tanaka O, Morita T, Kasai R, *et al*. Study on saponins of rhizomes of *Panax pseudo-ginseng* subsp. *himalaicus* collected at Tzatogang and Pari-la, Bhutan-Himalaya [J]. *Chem Pharm Bull*, 1985, **33**(6): 2323-2330.

[34] Shukla YN. Studies on Indian ginseng. Part VII. Rhizome saponins of *Panax pseudo-ginseng* subsp. *himalaicus* and its var. *bipinnatifidus* [J]. *Planta Med*, 1989, **55**(4): 396.

[35] Shukla YN, Thakur RS. Investigation of *Panax* Part IV. Saponins of *Panax pseudo-ginseng* subsp. *himalaicus* var. *angustifolius* rhizomes [J]. *Planta Med*, 1988, **54**(4): 367-368.

[36] Su J, Li HZ, Yang CR. Studies on saponin constituents in roots of *Panax quinquefolium* [J]. *China J Chin Mater Med*, 2003, **28**(9): 830-833.

[37] Liu JP, Wang F, Li PY, *et al*. A new ocotillol-type triterpenoid saponin from red American ginseng [J]. *Nat Prod Res*, 2012, **26**(8): 731-735.

[38] Zheng YL, Li XG, Bao JC, *et al*. Studies on chemical constituents of rhizoma of *Panax quinquefolius* [J]. *Chin Pharm J*, 2005, **40**(11): 815-816.

[39] Zhang CX, Bao JC, Liu G, *et al*. Protective effect of ocotillol on acute myocardial injury induced by LAD in rat [J]. *Chin Tradit Patent Med*, 2006, **28**(5): 757-759.

[40] Ma XY, Sun P, Wang LL, *et al*. Triterpenoid saponins in stems and leaves of American ginseng [J]. *Chin Pharm J*, 1993, **28**(12): 718-720.

[41] Nakamura S, Sugimoto S, Matsuda H, *et al*. Medicinal flowers. XVII. New dammarane-type triterpene glycosides from flower buds of american ginseng, *Panax quinquefolium* L. [J]. *Chem Pharm Bull*, 2007, **55**(9): 1342-1348.

[42] Li XG, Zhang LX, Meng XY, *et al*. Isolation, identification and content determination of pseudogisenoside F_{11} in American ginseng [J]. *J Jilin Agric Uni*, 2005, **27**(6): 645-648.

[43] Wang DQ, Fan J, Li SR, *et al*. Saponins of the rhizome of *Panax japonicus* var. *bipinnatifidus* and their significance for chemotaxonomy [J]. *Acta Bot Yunnan*, 1988, **10**(1): 101-104.

[44] Qi Z, Wang ZZ, Zhou BS, *et al*. A new ocotillol-type ginsenoside from stems and leaves of *Panax quinquefolium* L. and its anti-oxidative effect on hydrogen peroxide exposed A549 cells [J]. *Nat Prod Res*, 2020, **34**(17): 2474-2481.

[45] Li M, Jin YR, Wang XZ, *et al*. Studies on triterpenoid glycosides from rhizomes of *Panacis majoris* and their antiplatelet aggregation activity [J]. *Chem Res Chin Univ*, 2016, **32**(6): 943-946.

[46] Qiu NN. Studies on the chemical constituents and bioavailability of saponins from the leaves and stems of *Panax quinquefolium* L. [D]. Jilin University, 2010.

[47] Yang YW, Xu XL, Qiu JQ, *et al*. Nuclear magnetic resonance studies of ginsenoside (I). Structural elucidation of an ocotillol-type saponin separated from the leaves of *Panax quinquefolium* L. [J]. *J Spectrosc*, 1991, **3**: 283-290.

[48] Wang LJ, Li PY, Zhao CF, *et al*. Chemical constituents in the fruit of *Panax quinquefolius* [J]. *Chin Tradit Herb Drugs*, 2000, **31**(10): 723-724.

[49] Dou DQ, Chen Y. Ocotillone-type ginsenoside from leaves of *Pannax ginseng* [J]. *J Chin Pharm Sci*, 2002, **11**(4): 119-121.

[50] Han WJ, Lu SK, Wen HL, *et al*. Chemical constituents from fruit pedicels of *Panax ginseng* [J]. *Chin Herb Med*, 2018, **8**: 1751-1760.

[51] Rho TW, Yoon KD, Jeong HW, *et al*. Identification of a novel triterpene saponin from *Panax ginseng* seeds, pseudoginsenoside RT8, and its antiinflammatory activity [J]. *J Ginseng Res*, 2020, **44**(1): 145-153.

[52] Nguyen MD, Ryoji K, Ohtani K, *et al*. Saponins from Vietnamese ginseng, *Panax vietnamensis* Ha et Grushv. Collected in central Vietnam II [J]. *Chem Pharm Bull*, 1994, **42**(1): 115-122.

[53] Nguyen MD, Nguyen TN, Ryoji K, *et al*. Saponins from Vietnamese ginseng, *Panax vietnamensis* Ha et Grushv. collected in central Vietnam III [J]. *Chem Pharm Bull*, 1994, **42**(3): 634-640.
[54] Yamasaki K. Bioactive saponins in Vietnamese ginseng, *Panax vietnamensis* [J]. *Pharm Biology*, 2000, **38**(Suppl 1): 16-24.
[55] Liu JP, Tian X, Liu HY, *et al*. Two novel dammarane-type compounds from the leaves and stems of *Panax quinquefolium* L. [J]. *J Asian Nat Prod Res*, 2013, **15**(9): 974-978.
[56] Liu JP, Lu D, Li PY. Two new dammarane-type triterpene saponins from red American ginseng [J]. *J Asian Nat Prod Res*, 2011, **13**(3): 198-204.
[57] Zhong FL. Studies on the chemical constituents and bioactivities of *Panax ginseng* C. A. Meyer cv. Silvatica [D]. Jilin University, 2008.
[58] Van LTH, Lee GJ, Vu HKL, *et al*. Ginseng saponins in different parts of *Panax vietnamensis* [J]. *Chem Pharm Bull*, 2015, **63**(11): 950-954.
[59] Liu P, Wang SW, Xia GP. Determination of ginsenoside Re, pseudo-ginsenoside F11, ginsenoside Rb3, and ginsenoside Rd from flower buds of *Panax quinquefolium* [J]. *Chin Tradit Herb Drugs*, 2018, **49**(17): 4144-4147.
[60] Yang J. *Study on semi synthesis and biological activity of octanone type ginsenosides* [D]. Jilin University, 2016.
[61] Liu JP. *Studies on isolation, structure modification and pharmacological activities of saponins from the leaves and stems of Panax quiquefolium L. cultivated in China* [D]. Shenyang Pharmaceutical University, 2005.
[62] Dai L. *Studies on isolation, modification and bioactivities of protopanaxatriol saponins in leaves and stems of Panax quinquefolium L.* [D]. Jilin University, 2010.
[63] Bi Y, Wang T, Meng QG, *et al*. Synthesis and myocardial ischemia protective effect of ocotillol-type derivatives [J]. *Rec Nat Prod*, 2012, **6**(3): 242-254.
[64] Liu HY. *Studies on the preparation process and the related substances of pseudo-ginsenoside F_{11}* [D]. Jilin university, 2015.
[65] Meng QG, Bi Y, Liang W, *et al*. Synthesis, structural determination of a new ocotillol derivative and its epimer [J]. *Lett Org Chem*, 2011, **8**(9): 682-685.
[66] Ren YY. *Studies on the preparation process and the related substances of pseudo-sapogenin DQ* [D]. Jilin University, 2012.
[67] Yang J, Li XW, Sun T, *et al*. Semisynthesis and bioactive evaluation of oxidized products from 20(*S*)-ginsenoside Rg3, Rh2, protopanaxadiol (PPD) and their 20(*R*)-epimers as cytotoxic agents [J]. *Steroids*, 2016, **106**: 26-34.
[68] Wang WZ. Synthesis and formation mechanism of ocotilol and its epimer [J]. *J China Pharm Uni*, 2016, **47**(3): 282-287.
[69] Tian X. *Studies on ocotillol-type ginsenoside and its related compounds* [D]. Jilin University, 2012.
[70] Wang CC. *Studies on the structural modification of pseudo-ginsenoside-F_{11}* [D]. Jilin University, 2011.
[71] Bi Y, Tian JW, Ji CM, *et al*. Ocotillol-type derivatives (II) synthesis and protective effects on cultured anoxia/reoxygen injury myocardiocytes [J]. *J Med Plants Res*, 2011, **5**(31): 6731-6737.
[72] Bi Y, Tian JW, Wang L, *et al*. Synthesis, structural determination and protective effects on cultured anoxia/reoxygen injury myocardiocytes of ocotillol-type derivatives [J]. *J Med Plants Res*, 2011, **5**(11): 2424-2429.
[73] Bi Y, Ma C, Zhou ZW, *et al*. Synthesis and antibacterial evaluation of novel hydrophilic ocotillol-type triterpenoid derivatives from 20(*S*)-protopanaxadiol [J]. *Rec Nat Prod*, 2015, **9**(3): 356-368.
[74] Li Z, Guo YY, Wu CF, *et al*. Protective effects of pseudoginsenoside-F11 on scopolamine-induced memory impairment in mice and rats [J]. *J Pharm Pharmacol*, 1999, **51**(4): 435-440.
[75] Li Z, Wu CF, Pei G, *et al*. Antagonistic effect of pseudoginsenoside-F_{11} on the behavioral actions of morphine in mice [J]. *Pharmacol Biochem Behav*, 2000, **66**(3): 595-601.
[76] Hao Y, Yang JY, Wu CF, *et al*. Pseudoginsenoside-F_{11} decreases morphine-induced behavioral sensitization and extracellular glutamate levels in the medial prefrontal cortex in mice [J]. *Pharmacol Biochem Behav*, 2007, **86**(4): 660-666.
[77] Wang CM, Liu MY, Wang F, *et al*. Anti-amnesic effect of pseudoginsenoside-F_{11} in two mouse models of Alzheimer's disease [J]. *Pharmacol Biochem Behav*, 2013, **106**: 57-67.
[78] Yao XC, Xue X, Zhang HT, *et al*. Pseudoginsenoside-F_{11} alleviates oligomeric β-amyloid-induced endosome-lysosome defects in microglia [J]. *Traffic*, 2019, **20**(1): 61-70.
[79] Prokof'eva NG, Chaikina EL, Pokhilo ND, *et al*. Hemolytic and cytotoxic activity of dammarane-type triterpenoids [J]. *Chem Nat Compd*, 2007, **43**(1): 72-75.
[80] Wang XX, Wang CM, Zhao SQ, *et al*. Pseudoginsenoside-F_{11} (PF_{11}) exerts anti-neuroinflammatory effects on LPS-activated microglial cells by inhibiting TLR4-mediated TAK1/IKK/NF-κB, MAPKs and Akt signaling pathways [J]. *Neuropharmacology*, 2014, **79**: 642-656.
[81] Nguyen TT, Matsumoto K, Yamasaki K, *et al*. Majonoside-R_2 reverses social isolation stress-induced decrease in pentobarbital sleep in mice: possible involvement of neuroactive steroids [J]. *Life Sci*, 1997, **61**(4): 395-402.
[82] Liu JP, Zhao CF, Li PY, *et al*. Ameliorative efects of pseudoginsenoside GQ on isoproterenol-induced acute myocardial ischemia in rats [J]. *J Jilin Univer (Med Edit)*, 2006, **32**(1): 64-67.
[83] Wang T, Meng Q, Zhang J, *et al*. Study on the structure-function relationship of 20(*S*)-panaxadiol and its epimeric derivatives in myocardial injury induced by isoproterenol [J]. *Fitoterapia*, 2010, **81**(7): 783.
[84] Zhang NQ, Wang CZ, Wang ZZ, *et al*. Anti-myocardial ischaemic effect of pseudoginsenoside F_{11} by inhibiting expression of beta1-adrenoceptor in rats with coronary artery ligation [J]. *J Funct Foods*, 2017, **36**: 224-232.
[85] Li W. *The structural modification and biological activity of ginsenoside* [D]. Jilin University, 2010.
[86] Han B, Meng QG, Li Q, *et al*. Effect of 20(*S*)-protopanaxatriol and its epimeric derivatives on myocardial injury induced by isoproterenol [J]. *Arzneimittelforschung*, 2011, **61**(03): 148-152.
[87] Jin X, Shen WZ, Jin LF, *et al*. Protective efect of pseudo-ginsenoside GQ on doxorubicin-induced acute myocardial injury in rats [J]. *J Jilin Univer (Med Edit)*, 2013, **39**(6): 1164-1168.
[88] Tian M, Li LN, Zheng RR, *et al*. Advances on hormone-like activity of *Panax ginseng* and ginsenosides [J]. *Chin J Nat Med*, 2020, **18**(7): 546-535.
[89] Konoshima T, Takasaki M, Tokuda H, *et al*. Anti-tumor-promoting activity of majonoside-R_2 from Vietnamese ginseng, *Panax vietnamensis* Ha et Grushv. (I) [J]. *Biol Pharm Bull*, 1998, **21**(8): 834.
[90] Bi Y, Yang X, Zhang TT, *et al*. Design, synthesis, nitric oxide release and antibacterial evaluation of novel nitrated ocotillol-type derivatives [J]. *Eur J Med Chem*, 2015, **101**: 71-80.
[91] Bi YX. Application of ocotillol in preparation of drugs for treatment of senile dementia: CN, 103830256 [P]. 2014-06-04.
[92] Zhou ZW, Ma C, Zhang HY, *et al*. Synthesis and biological evaluation of novel ocotillol-type triterpenoid derivatives as antibacterial agents [J]. *Eur J Med Chem*, 2013, **68**: 444-453.
[93] Liu WC, Wang Y, Sun CY, *et al*. Correlation between ginsenoside accumulation and SQS and SQE gene expression in different organs of *Panax quinquefolius* [J]. *Chin Tradit Herb Drugs*, 2011, **42**(3): 579-584.
[94] Sun X, Qian QY, Zheng SH, *et al*. Quality ecotype of *Panax quinquefolium* L. based on heredity chemistry-ecology characteristics [J]. *Acta Pharm Sin*, 2019, **54**(9): 1695-1705.

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