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

NIU Xue-Ni, LUO Wen, LV Chong-Ning, LU Jin-Cai

Department of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang 110016, China
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[ABSTRACT] Octillol (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] Octillol-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], octillol (OT)-type (a tetracyclic triterpenoid with a tetrahydrofuran ring in the side chain), oleamonic acid (OA)-type (pentacyclic triterpenoid saponins with oleamonic 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. Himalicus (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 integrifoliola (Cogn.) Hutch [7,8].

Octillol (showed in Fig. 1A) was originally isolated from the resinous bark of ocotillo (Fouquieria sp. pendens) in 1963 [9] and elucidated as (20S, 24R)-epoxydammarane-3β, 25-diol [10]. In 1978, the first OT-type ginsenoside, pseudo-ginsenoside F11 (PF11), was isolated from the leaves of PPGH [11], indicating the emergence of a new type ginsenoside in the genus Panax. However, (20S, 24R)-epoxydammarane-3β, 6β, 12β, 25-tetrol (See Fig. 1B), the aglycone of PF11, might be occasionally taken by researchers as octillol [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 produgs 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.
have dammar-20, 24-epoxy-3β, 6α, 12β, 25, 26-pentaol as their skeleton. For the absolute configurations of C-20 and C-24, most of them are S configuration except for (20R)-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-xylpyranosyl. 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$_4$ (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 (24R)-pseudo-ginsenoside G$_1$ (25), (24R)-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-xylpyranosyl. And α-D-glucopyranosyl (as a branched terminal glycosyl) linked to β-D-glucopyranosyl (inner) via 1→6 linkage, for example, vina-ginsenoside R$_8$ (16) and yesanchinoside B (18). Moreover, there is 1→4 linkage between β-D-xylpyranosyl 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$_4$ (12), vina-ginsenoside R$_9$ (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 (9). 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% (18). 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. (9) 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 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
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...
Fig. 2  Structure characteristics of natural OT-type ginsenosides isolated from the Panax species

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*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 (20R)-Rg₃ and (20R)-Rh₂ for achieving four OT-type ginsenosides: 36, 37, 40 and 41. Furthermore, the 20S epimers of the two ginsenosides mentioned and 20S-PPD were also investigated under the same conditions, affording 31, 35 and 39. In the light of these different outcomes, Liu proposed that S₁0,1 occurred in the oxidation of 20R configuration while S₁₀,2 in 20S [60]. However, in 2016, Yang proposed a new point that the stereo configuration of C-20 was coincident with different oxidants during the synthesis [61] 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, S₁0,1 featured the mechanism of this oxidative reaction whatever the C-20 configurations of the reagent ginsenosides are, so both 24S and 24R 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 [60]. 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 (20S)-PPT were different, leading to the different yields of 12β-hydroxyl-ocotillol and its epimer.

As for route 2 (synthesized via oxidation with m-CPBA, intramolecular S-O and saponification), the absence of intramolecular hydrogen bonds in the acetylated (20S)-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 [60]. In 2012, Tian et al. [60] 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 (20S,R, 24R)-PF11, (20S, 24S)-pseudo-ginsenoside RTs, (20S, 24R)-pseudo-ginsenoside RTs, (20S, 24R)-pseudo-ginsenoside HQ (34), and (20S, 24S)-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 [60], the modified products of PF11 under acidic conditions were further separated by normal and reversed-phase thin-layer chromatography to obtain (S, R)-RTs, (R, R)-12β-hydroxy-ocotillol, and (S, R)-12β-hydroxy-ocotillol. Bi et al. semi-synthesized a series of ooc tilol derivatives through three steps: first, acetyaling the hydroxyls of PPD- or PPT-type ginsenosides to protect the hydroxyls free from the next oxidation, followed by the oxidation and cyclization of sidechain, 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 PF11, mainly placed emphasis on the intervention activity induced by opioids and its mechanisms. Early in 1999, it was proposed that PF11 antagonized the memory impairment induced by scopolamine [74]. In addition, pretreatment with PF11 antagonized the memory impairment, analgesia, as well as the development of reverse tolerance induced by morphine [73]. In addition, PF11 inhibited the morphine-induced reduction of glutamate in the medial prefrontal cortex (mPFC), which indicated that PF11 can prevent the development of behavioral sensitization by affecting the glutamatergic system in mPFC [70]. These findings suggested that PF11 can act as a potential intervention agent for the addiction to opioids. The anti-amnesic effect of PF11 on Alzheimer’s disease (AD) was tested with two types of AD mice models, where oral treatment with PF11 significantly relieved learning and memory impairment in AD mice through inhibiting the accumulation of Aβ (1–40), restoring oxidation resistance in the cortex, and downregulating the expression of JNK2, p53 and cleaved caspase 3 in the hippocampus [75]. Recently, a study reported that PF11 facilitated the clearance of Aβ by repairing the endosomal lysosomal system which was interrupted by Aβ [78, 79]. In addition, PF11 produced anti-neuritis effects on LPS-activated microglial cells through restricting the TLR4-mediated TAK1/IKK/NF-κB, MAPKs and Akt signaling pathways [80]. Also, majoroside R3 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 PF11 exert cardioprotective effects on rats with myocardial ischemia induced by isoproterenol [82-85]. Furthermore, the cardioprotective effect of ocotillol’s epimer, (20S, 24S)-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 (20S, 24S) 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, PF11 was found to significantly decrease the level of active β1-adrenoceptor in H9c2 cardiomyocytes [84]. Meanwhile, molecular docking verified that PF11 had binding sites for β1-adrenoceptor. Some research demonstrated OT-type ginsenosides ameliorated not only heart injury, but cerebral injury induced by ischemia. Furthermore, PF11 improved lysosomal function and lysosome/auto-phagosome fusion after permanent middle cerebral artery occlusion (pMCAO), which were then reversed by chloroquine (a lysosomal inhibitor). (S, R)-Pseudo-ginsenoside DQ exhib-
mented 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 [81]. Furthermore, ocofilol [14] 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 ocofilol 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$_{3}$ exhibited an inhibitory effect on early antigen of Epatine-Barr virus induced by 12-O-tetradecanoylphorbol-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 [40]. A study investigated the inhibited activity of several ocofilol 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 [19]. Moreover, PF$_{11}$ was shown to improve the nephrotoxicity induced by cisplatin without sacrificing the antitumor activity, and further study showed pre-treatment of PF$_{11}$ suppressed the expression of p53 in renal tissue and inhibited tubular cell apoptosis [16]. What’s confusing, ocofilol and PF$_{11}$ have the same sapogenin-epoxy dammar, when co-administered with antitumor agents, ocofilol 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 [79, 90-92]. Most of them showed excellent anti-bacterial activity against gram-positive bacteria. Particularly, (20S, 24S)-epoxy-dammarane-3β, 12β, 25-triol and (20S, 24S)-epoxy-25-hydroxyl-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 24S-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 3-oxidosqualene cyclase) during the biosynthesis of ginsenosides [80]. 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 nitratred compounds synthesized by attaching nitric oxide releasing groups to OT-type triterpenoids exerted stronger bioactivities. For example, (20S, 24R)-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 nitratred derivatives of OT-type ginsenosides.

**Supporting Information**

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

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