J Ginseng Res xxx (2017) 1–6

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Review article

Discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins

Juan Liu, Yangrong Xu, Jingjing Yang, Wenzhi Wang, Jianqiang Zhang, Renmei Zhang, Qingguo Meng*

School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Yantai, China

ARTICLE INFO

Article history:
Received 10 September 2016
Received in Revised form
31 December 2016
Accepted 2 January 2017
Available online xxx

Keywords:
biological activity
discovery
metabolism
ocotillol-type saponin
semisynthesis

ABSTRACT

Ocotillol-type saponins are one kind of tetracyclic triterpenoids, sharing a tetrahydrofuran ring. Natural ocotillol-type saponins have been discovered in *Panax quinquefolius* L., *Panax japonicus*, *Hana mina*, and Vietnamese ginseng. In recent years, the semisynthesis of 20(*S*/*R*)-ocotillol-type saponins has been reported. The biological activities of ocotillol-type saponins include neuroprotective effect, antimyocardial ischemia, antiinflammatory, antibacterial, and antitumor activities. Owing to their chemical structure, pharmacological actions, and the stereoselective activity on antimyocardial ischemia, ocotillol-type saponins are subjected to extensive consideration. In this review, we sum up the discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins.

1. Introduction

Ginseng, a perennial plant belonging to the genus *Panax* of the Araliaceae family, is well known for its medicinal properties that help alleviate pathological symptoms, promote health, and prevent potential diseases. Ginseng saponins are often classified into several groups: protopanaxadiol (PPD) type, protopanaxatriol (PPT) type, oleanolic acid type, and ocotillol type.

There are numerous chemical components present in *Panax quinquefolius* L., such as saponins, amino acids, saccharides, volatile oils, alkaloids, aliphatic acids, and mineral elements, among which ginsenosides are thought to be the main active ingredients. Ocotillol-type saponins (Fig. 1) are often used as phytochemical markers of *P. quinquefolium* L. to distinguish it from ginseng [1,2].

Ocotillol-type saponins, sharing a tetrahydrofuran ring and a dammarane skeleton, are one class of rare ginsenosides, which are very rarely found in natural products. We find that stereoselectivity plays a key role in pharmacological action as well as pharmacokinetics.

2. Discovery of ocotillol-type saponins

Natural ocotillol-type saponins mainly include PF11, RT2 (**3**), RT4 (**5**), RT5 (**4**), 24(*S*)-PF11 (**12**), vina-ginsenoside R1 (VR1; **6**), VR2 (**7**), VR5 (**8**), VR6 (**9**), majonoside R1 (MR1; **10**), MR2 (**11**), yesanchinoside A (**13**), B (**14**), and C (**15;** Table 1). The content of PF11 in American ginseng flower, pedicel, stems and leaves, pulp, and roots is 2.34%, 1.93%, 0.97% 1.54%, and 0.28%, respectively [19].

Tanaka and Yahara [3] and Chen et al [4] isolated and further identified new dammarane saponin PF11 (**1**) from dried leaves of *Panax pseudo-ginseng* subsp. *himalaicus*, whose sapogenin was identified as (20*S*,24*R*)-dammarane-20,24-epoxy-3β,6α,12β,25-tetraol, ocotillol (**17**).

Panax japonicus saponins MR1 and MR2 were afforded from Yunnan Rhizoma panacis majoris and identified by ^{13}C nuclear magnetic resonance (NMR) and mass spectrometry (MS). Hydroxyls at C-6 of (20*S*,24*S*)-ocotillol were connected with glc2-1glc and glc2-1xyl disaccharide chain [16].

* Corresponding author. School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, 30, Qingquan RD, Laishan District, Yantai 264005, China.
E-mail address: qinggmeng@163.com (Q. Meng).

http://dx.doi.org/10.1016/j.jgr.2017.01.001
p1226-8453 e2093-4947/$ – see front matter

PF11 and ocotillol-type saponins RT2, RT4, and RT5 were collected from the rhizomes of *P. pseudo-ginseng* subsp. *himalaicus* [10]. RT5 was also obtained from the stems and leaves of American ginseng by Ma et al [11]. 24(*S*)-PF11, RT2, MR2, and 24(*R*)-PF11 were separated from wild *Panax notoginseng* subspecies in central of Nepal [5,17].

VR1 and VR2 were first isolated from Vietnam ginseng rhizome, and were formulated as monoacetylated 24(*S*)-PF11 and monoacetylated MR2. Rare ocotillol saponin vina-ginsenoside R5 and R6 with α-glucan chains were also split by Nguyen et al [13,15]. Yesanchinosides A, B, C and 24(*S*)-PF11 (**12**), RT4, VR1 and VR2, and MR2 were isolated from the underground part of *P. japonicus* collected in the south of Yunnan Province, China [14].

Ocotillol was isolated from the alkaline degradation products of American ginseng total saponins by Ma et al [6]. The C-20 configuration of ginsenosides was not changed during alkaline degradation. The ^{1}H NMR and ^{13}C NMR chemical shifts of ocotillol were acquired using two-dimensional NMR.

Liu et al [9] extracted 20(*R*)-PF11 (**2**) from American red ginseng, and applied patent for its extracting method and pharmaceutical activity. Compared with Asian white ginseng, steamed ginseng has stronger anticancer activities. In addition, a new minor C-3 epimer of ocotillol, 3α-ocotillol (**16**), was isolated from *P. quinquefolium* L. along with ocotillol. Its structure was elucidated as (20*S*,24*R*)-dammarane-20,24-epoxy-3α,6α,12β,25-tetraol [18].

3. Semisynthesis of 20(*S*)-ocotillol-type saponins

24,25-Epoxy intermediates were gained by oxidation with *m*-chloroperoxybenzoic acid from 20(*S*)-PPD and 20(*R*)-PPD. Tetrahydrofuran ring was formed by Baldwin's rules of molecular open-loop and close-loop response by 5-exo-tet cyclization [20–23].

The ocotillol-type saponins were first semisynthesized by Liu [24] with combinatorial chemistry. PGQ (**18**), PHQ (**19**), and PDQ (**20;** Table 2) were obtained with oxidation cyclization of the side chain on 20(*S*)-Rg3, 20(*S*)-Rh2, and 20(*S*)-PPD).

Gao et al [25] isolated four major compounds—20(*S*)-PPD, **17**, 20(*S*)-PPT, and (20*S*,24*R*)-PDQ (**23**)—from the oxidative residue of American ginseng's total saponins. In 2008, (12*R*,20*S*,24*R*)-20,24;12,24-beisopropyl-dammarane-3β-ol (**25**) and **23** were obtained from the oxidative alkaline degradation products of Canadian *P. quinquefolium* saponins.

PF11 was afforded from 20(*S*)-Rg2 in yield 80% and could be used to prepare medicine for the therapy of attention deficit hyperactivity disorder, fatigue, allomnesia, etc. [7].

17 and its C-24 epimer (**21**) were semisynthesized from 20(*S*)-PPT by acetylation, oxidization, and saponification. Structures of the two epimers were identified by electrospray ionization-MS, ^{1}H NMR, ^{13}C NMR, and single X-ray crystal diffraction [26,27,31].

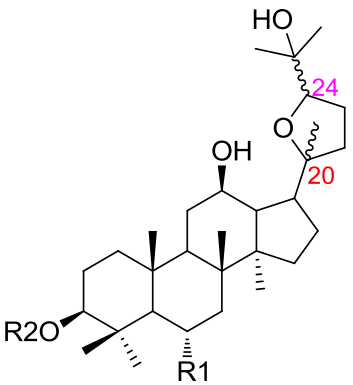

Figure 1. Structure of ocotillol-type saponins.

Table 1
Natural ocotillol-type saponins

No.	Ingredient name	R1	R2	C-20	C-24	Refs.
1	20(*S*)-PF11	-O-glc-rha	H	*S*	*R*	[3–8]
2	20(*R*)-PF11	-O-glc-rha	H	*R*	*R*	[8,9]
3	RT2	-O-glc-xyl	H	*S*	*R*	[5,10]
4	RT5	-O-glc	H	*S*	*R*	[8,10–12]
5	RT4	-O-glc	H	*S*	*S*	[8,10,13,14]
6	VR1	-O-glc(-Ac)-rha	H	*S*	*S*	[13,14]
7	VR2	-O-glc(-Ac)-xyl	H	*S*	*S*	[13,14]
8	VR5	-O-glc-xyl-αrha	H	*S*	*S*	[15]
9	VR6	-O-glc(-αglc)-xyl	H	*S*	*S*	[15]
10	MR1	-O-glc-glc	H	*S*	*S*	[13,16]
11	MR2	-O-glc-xyl	H	*S*	*S*	[5,13,14,16]
12	24(*S*)-PF11	-O-glc-rha	H	*S*	*S*	[5,13,14,17]
13	Yesanchinoside A	-O-glc(-Ac)-glc	H	*S*	*S*	[14]
14	Yesanchinoside B	-O-glc(-αglc)-glc	H	*S*	*S*	[14]
15	Yesanchinoside C	-O-glc-glc-xyl	H	*S*	*S*	[14]
16	3α-ocotillol	-OH	H	*S*	*R*	[18]

Ac, acetyl; αglc, α-D-glucopyranosyl; glc, β-D-glucopyranosyl; rha, α-L-rhamnopyranosyl; xyl, β-D-xylopyranosyl

Table 2
Semisynthetic 20(*S*)-ocotillol-type saponins

No.	Ingredient name	R1	R2	C-20	C-24	Refs.
17	ocotillol	-OH	-H	*S*	*R*	[6,8,12,25–27]
18	20(*S*)-PGQ	-H	-glc-glc	*S*	*S*	[24]
19	20(*S*)-PHQ	-H	-glc	*S*	*S*	[8,24]
20	20(*S*)-PDQ	-H	-H	*S*	*S*	[24,28,29]
21	24(*S*)-Ocotillol	-OH	-H	*S*	*S*	[8,26,27]
22	24(*R*)-PHQ	-H	-glc	*S*	*R*	[8]
23	24(*R*)-PDQ	-H	-H	*S*	*R*	[25,28,29]
24	24(*R*)-PHQ	-H	-glc-glc	*S*	*R*	[30]

glc, β-D-glucopyranosyl

Meanwhile, the crystal results indicated that C24 configurations were *R*-form and *S*-form, respectively.

Ren [28] had carried out the synthesis of PDQ by (20*S*)-PPD. **20** and **23** were achieved in a molar ratio of 3.6:1, whereas Meng et al [11] obtained **20** and **23** in nearly 1:1 molar ratio with acetylation, oxidization, and saponification of (20*S*)-PPD.

Wang [12] has studied the residue of PF11 degradation under acidic condition using chromatography and recrystallization. Ocotillol, (12*R*,20*S*,24*S*)-20,24;12,24-diepoxy-dammarane-3β,6α-diol (**26**), (20*R*,24*R*)-ocotillol (**27**), and **4** were obtained.

Tian [8] acquired **1**, **4**, **5**, **17**, **19**, (20*R*,24*R*)-PF11, **21**, and **22** by alkaline degradation and oxidation from total saponins of *P. quinquefolium* stems and leaves.

Compared with other ginseng plants, *Panax vietnamensis* has been found to have a high content of MR2, which is more than 5% of the dried rhizome, and exhibited antitumor and hepatocyte-protective activities. Zhang et al [32] conducted transcriptome sequencing of this species using Illumina next-generation sequencing, which prepared a certain amount of target compounds. The large number of transcripts provided in this study not only facilitates the study of ocotillol-type saponins biosynthesis but could also provide opportunities to engineer microorganisms for the *de novo* production of active ingredients. Furthermore, numerous simple sequence repeats (SSRs) were identified and will be very useful for marker-assisted selection breeding of this herb [32].

4. Semisynthesis of 20(*R*)-ocotillol-type saponins

20(*R*)-PPD (**28**) was degraded from *P. quinquefolium* L. with 50% citric acid and sodium hydrate in glycerol, respectively. Two C24 epimeric 20(*R*)-ocotillol type saponins, 20*R*,24*S*-epoxy-dammarane-3β,12β,25-triol (**M1**, **29**) and 20*R*,24*R*-epoxy-dammarane-

Please cite this article in press as: Liu J, et al., Discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins, Journal of Ginseng Research (2017), http://dx.doi.org/10.1016/j.jgr.2017.01.001