J Ginseng Res 41 (2017) 373–378

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

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ARTICLE INFO

Article history:
Received 10 September 2016
Received in Revised form
31 December 2016
Accepted 2 January 2017
Available online 13 January 2017

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].

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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].

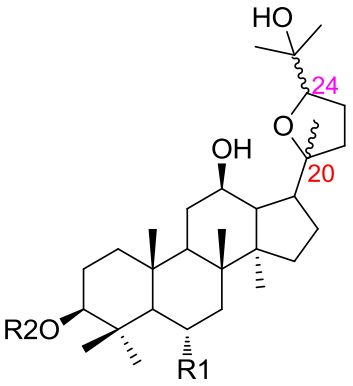

Figure 1. Structure of ocotillol-type saponins.

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-

Table 3
Semisynthetic 20(*R*)-ocotillol-type saponins

No.	Ingredient name	R1	R2	C-20	C-24	Refs.
27	20(*R*)-ocotillol	-OH	-H	*R*	*R*	[12]
29	**M1**	-H	-H	*R*	*S*	[33]
30	**M2**	-H	-H	*R*	*R*	[33]
31	**M3**	-H	-Ac	*R*	*S*	[33]
32	**M4**	-H	-Ac	*R*	*R*	[33]

3β,12β,25-triol (**M2**, **30;** Table 3), were synthesized from 20(*R*)-PPD. Suitable crystals of **29** and **30** were obtained by open-air evaporation of an acetone solution. The configurations of **29** and **30** were established as (20*R*,24*S*) and (20*R*,24*R*), respectively, using X-ray single crystal diffraction [33].

Two C24 epimeric 3-acetyled ocotillol-type sponins, (20*R*,24*S*)-epoxy-dammarane-3β,12β,25-triol acetate (**M3**, **31**) and (20*R*,24*R*)-epoxy-dammarane-3β,12β,25-triol acetate (**M4**, **32;** Table 3), were obtained from 20(*R*)-PPD, which made it possible to isolate **29** and **30**. The results indicated that the configurations of **31** and **32** were (20*R*,24*S*) and (20*R*,24*R*), respectively [34].

5. Biological activities

5.1. Effect on nervous system

Li et al [35] found that PF11 could antagonize the memory dysfunction induced by scopolamine in tests. The additional study demonstrated that morphine-induced allomnesia was markedly inhibited by PF11, and the conditioned place preference to morphine was significantly blocked [36]. Moreover, morphine-stimulated opioid receptor signaling could be antagonized directly at the cellular level by orally administered PF11 [37]; behavior sensitization was antagonized and glutamate decrease in the medial prefrontal cortex induced by morphine was blocked [38]. Meanwhile, PF11 showed no similarity to opioids, sedative-hypnosis, and stimulants because of its physical and psychological independence [39].

Wu et al [40] and Fu et al [41] reported that PF11 showed effective protection on methamphetamine-induced neurotoxicity through many experiments.

PF11 was proposed to play an important role in anti-Parkinson affection, in that it inhibited free radical formation and stimulated endogenous antioxidant release [42].

The results demonstrated that PF11 could antagonize Alzheimer disease, as measured in the Morris water maze and step-through tests, and it might serve as a promising agent for Alzheimer disease [43].

PF11 exerted antineuroinflammatory effects on lipopolysaccharide (LPS)-activated microglial cells by inhibiting TLR4-mediated transforming growth factor β activated kinase 1 (TAK1)/IkB kinases (IKK)/nuclear factor kB (NF-κB), mitogen-activated protein kinases (MPKs), and Akt signaling pathways, indicating its therapeutic implication for neurodegenerative diseases associated with neuroinflammation [44].

Peroxisome proliferator-activated receptor gamma (PPARγ) was activated with modest adipogenic activity by PF11, adiponectin oligomerization and secretion in 3T3-L1 adipocytes were promoted, and obesity-linked phosphorylation of PPARγ at Ser-273 by Cdk5 were inhibited [45].

Wang et al [46] discovered that the increased release of glutamate could mediate the ocotillol-evoked neuronal excitability, which resulted in the increased release of spontaneous locomotor activities *in vivo*.

MR2 exerted reversing effect on the social isolation stress-induced decrease in pentobarbital sleep, which was mediated by the neurosteroid site on the gamma aminobutyric acid (GABAA) receptor complex in mice [47].

Accumulating evidence strongly suggested that communication box paradigm-induced psychological stress- and conditioned fear stress-induced antinociception was attenuated by MR2. Numerous lines of evidence markedly indicated the involvement of central opioid, GABAA receptor, and corticotropin-releasing factor mechanisms in the effect of MR2 [48].

5.2. Protective effects on cardiovascular system

PGQ showed ameliorative effects on isoproterenol-induced and doxorubicin (DOX)-induced acute myocardial ischemia and hemorrhagic shock in rats, and transparently increased mean arterial pressure and blood oxygen content and decreased serum lipoperoxidase. In addition, it could enhance the superoxide dismutase (SOD) activities [49–51].

Previous experiments in our laboratory results indicated that ocotillol had a protective effect on myocardial ischemic injury; it significantly reduced the area of myocardial ischemia, necrosis, and level of lactate dehydrogenase (LDH) in serum, and enhanced the antifree-radical actions of heart tissues [52,53]. Further study indicated that **17** and **23** showed better effect on myocardial injury induced by isoproterenol than **21** and **20**, respectively [54,55]. In addition, Bi et al [30,56] found that **23** exhibited a potent protective effect on cultured myocardiocytes with anoxia/reoxygen injury, which was superior to 20(*S*)-panaxadiol, whereas **20** had none of this activity.

Zhao et al [57] found that ocotillol may be related to antioxidation action. It could reduce the cerebral infarction area, improve ischemic injuries induced by brain tissue pathological changes, decrease the content of malondialdehyde (MDA) in ischemic brain tissue, and increase the activity of SOD.

Cotreatment of ocotillol with DOX significantly alleviated related toxic injury, especially cardiotoxicity, whereas ocotillol alone exhibited no protective activity [58].

PF11 could significantly weaken the heart rate slowed down by posterior pituitrin-induced acute myocardial ischemia in rats, reduce elevation of the electrocardiogram T wave of myocardial ischemia, and improve myocardial ischemia in rats [59].

5.3. Antiinflammatory effects

Lee et al [60] and Jeong et al [61] measured the antiinflammatory effects of VR2, MR2, and their metabolites in LPS-stimulated mouse peritoneal macrophages, and found that only VR2 exhibited cytotoxicity against peritoneal macrophages. MR2, PRT4, and ocotillol could inhibit LPS-stimulated transcription factor (NF)-κB activation and expression of the proinflammatory cytokines tumor necrosis factor-α and interleukin-1, but they did not inhibit peptidoglycan-induced NF-κB activation in the macrophages. Among the tested ginsenosides, ocotillol exhibited a strong inhibitory effect on inflammation. VR2 and MR2 were orally administered and may be metabolized to ocotillol via PRT4. Metabolites, particularly ocotillol, showed antiinflammatory effects by prohibiting the binding of LPS to TLR4 on macrophages.

5.4. Antibacterial effects

Bi et al [62–65] and Zhou et al [66] found that **20** and **23** exhibited excellent antibacterial activity *in vitro* against *Staphylococcus aureus* and *Bacillus subtilis*. When combined with two commercial antibiotics, kanamycin and chloramphenicol, they showed strong synergistic activity against *S. aureus* USA300 and *B. subtilis* 168 at sub–minimum inhibitory concentration levels. In

addition, nitric oxide (NO) and its auto-oxidation products were known to disrupt normal bacterial function and NO releasing molecules, and they may be developed as potential antibacterial leads in drug discovery. Analysis of the *in vitro* data showed that the derivatives bearing the same furoxan group possessed various NO releasing capacity. Stereostructure may affect the NO release of these ocotillol-type furoxans. Compounds with nitrated aliphatic esters at C-3 displayed higher NO release than other analogues, and might be related to good antibacterial activity against both Gram-positive and Gram-negative bacteria.

5.5. Antitumor effects

The experiments suggested that MR2 showed effective influence on antitumor-promoting activity on mouse hepatic tumor and mouse skin [67,68]. MR2 also exhibited significant inhibitory effect on Epstein–Barr virus early antigen induced by the tumor promoter phorbol acetate [69].

Ocotillol could enhance DOX-induced cell death in p53 wild-type cancer cells. Coadministration of ocotillol with DOX could induce much more cell apoptosis and activate p53 to some degree, and enhanced cytotoxic activity was partially blocked [70].

Van Le et al [71,72] found that ocotillol-type saponins with no glycosyl moiety at C-20 were relatively stable in steaming, and the radical scavenging activity was increased continuously up to 20 h of steaming; the antiproliferative activity against A549 lung cancer cells was also improved.

Ma and Yang [73] stated that **17**, **21**, and **27** showed moderate cytotoxic activity against HL-60, NCI-N87, and Hep-G2 at a concentration of 1–200 μM, and indicated that cytotoxicity was related to the substitution of the hydroxyl group of C-25 and C-3, configuration of C-20.

Administration PF11 with cisplatin did not affect its anticancer effect. It could reduce cisplatin-induced renal injury in rats and prevent the DNA breakage of renal proximal tubule cell, and decrease the effects of cisplatin on mitochondrial morphology, function, and the intracellular expression of caspase family, ultimately preventing apoptosis of renal cells [74].

(20*S*,24*R*/*S*)-epoxy-12β,25-dihydroxy-dammarane-3β-amine (ORA and OSA) could inhibit the ABCB1 transporter. The study suggested that ORA had a stronger stimulatory effect on ATPase activity than OSA. ORA also exhibited a higher docking score as compared with OSA inside the transmembrane domain of ABCB1 [75].

Cotreatment of RT5 with CDDP might attenuate the following nephrotoxicity without inhibiting its antitumor efficiency, thereby reducing the renal tubular damage and decreasing the apoptosis by enhancing the antioxidant levels, which could provide one novel strategy for cancer treatment in clinics [76].

6. Metabolism

Wang and Li [77] found that PF11 was relatively stable in artificial gastric juice, feces, bile, and urine, and played a variety of physiological activity in prototype by intraperitoneal injection.

PGQ administered via the sublingual vein was mainly excreted in bile, accounting for 41.60% of the total dose; fecal excretion accounts for 9.97%, and only a small amount of PGQ was detected in urine. PGQ was also given as a prototype drug in the bile, urine, and feces [78].

20, **23**, (20*S*,24*S*)-epoxydammarane-12,25-diol-3-one and (20*S*,24*R*)-epoxydamma rane-12,25-diol-3-one were metabolized from 20(*S*)-PPD in mixed human liver microsomes (HLMs) and human hepatocytes. The predominant metabolic pathway of 20(*S*)-PPD observed was the oxidation of 24,25-double bond to yield 24,25-epoxide, followed by hydrolysis and rearrangement to form the corresponding 24,25-vicinaldiol derivatives and the 20,24-oxide forms. Further sequential metabolites are also detected through hydroxylation and dehydrogenation. Two glucuronide conjugates, **20** and **24**, were detected in human hepatocyte incubations, and their conjugation sites were tentatively assigned to the 25-hydroxyl group. The formation of 25-hydroxyl group is very important for the elimination of 20(*S*)-PPD [79].

After **20** or **23** was orally administered, within 48 h, fecal excretion cumulant was 17.09% and 17.69% of the dosage, respectively, whereas it was scarcely excreted through urine. Meanwhile, the bile excretion cumulant of **20** and **23** was 1.47% and 8.01% of the dosage, respectively; the former was 5.4-fold of the latter, demonstrating obvious stereoselectivity [80].

The *in vitro* and *in vivo* selectivity effects of ocotillol-type side chain and C-24 stereoconfiguration on P-glycoprotein (P-gp) were analyzed; the absolute bioavailability of **23** was about 14-fold higher than that of **20**. 24(*S*)-Ocotillol type epimer processed poor transmembrane permeability and can be distinguished by P-gp [81].

Wang et al [82] observed the *in vitro* and *in vivo* formation and metabolism of **20** and **23**. Stereoselective metabolism isoforms of CYP450 enzymes contributed to the HLMs were elucidated. **20** was the more predominant ingredient in rat plasma after the oral administration of 24(*S*)-PPD. The analysis data indicated that **20** had higher formation rate and lower oxygenation metabolism rate than **23**, and the stereoselective differences were more obvious in HLMs than in rat liver microsomes (RLMs). The chemical inhibitor assay showed that CYP3A was the predominant isoform responsible for the further metabolism of **23** in HLMs. The biliary excretion ratio of **20** glucuronide was more than 28-fold higher than that of **23** glucuronide after intravenous administration to rats, which also indicated that **20** was preferentially metabolized to produce the glucuronide conjugates than **23**.

Wang et al [83] found that the oxidative metabolites of 20(*S*)-PPT were identified in HLMs and rats. Enzyme kinetics experiments showed that the apparent formation V_{max} of **17** was 10.4-fold and 2.4-fold higher than that of **21** in HLMs and RLMs, respectively. The depletion rate of **17** was 11-fold faster than that of **21** in HLMs, and was similar in RLMs. Hence, the remarkable species differences of 20(*S*)-PPT metabolism mainly resulted from the stereoselective formation and further metabolic elimination of **17** and **21**.

7. Conclusion and recommendation

In conclusion, the available data suggest that antiinflammatory activity, inhibiting the increase of MDA, reduction of myocardial ischemia and necrosis area, level of LDH, SOD, glutathione peroxidase, and total antioxidant capacity of ocotillol, play vital role in myocardial ischemia. Among the reported ocotillol-type saponins, ocotillol exhibits excellent and stereoselective activity in configuration against myocardial ischemia reperfusion injury and possesses further research value. However, owing to the lack of clinical studies on ocotillol, it is difficult to make a clear decision. We recommend that further study on ocotillol should concentrate on the following areas: (1) molecular mechanisms underlying the beneficial role of ocotillol on myocardial ischemia; (2) pharmacokinetic research on utilizing different delivery systems to increase its bioavailability; (3) pharmacodynamic study on clinical studies about myocardial ischemia. In addition, it is also necessary to study the scale-up preparation method of ocotillol.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (No. 81473104).

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