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Research progress of the studies on the roots of *Peucedanum praeruptorum* dunn (Peucedani radix)

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Abstract: As a commonly employed traditional Chinese medicine, Peucedani Radix (Qian-hu in Chinese), which consists of the dried roots of *Peucedanum praeruptorum* Dunn, has a long history of application for the treatment of cough with thick sputum and dyspnea, nonproductive cough and upper air-way infections in traditional medicinal practice. The current review aims to summarize the research progress on the botany, phytochemistry, chemical analysis, pharmacological assay, and pharmacokinetic profile of this famous herbal drug. All available information on this traditional medicine was obtained via electronic search (using ACS, PubMed, Web of Science, Google Scholar, Baidu Scholar, and CNKI). Phytochemical investigations revealed that angular-type pyranocoumarins (APs), mainly (±)-praeruptorin A (Pd-Ia), (+)-praeruptorin A, (±)-praeruptorin B, (+)-praeruptorin B (Pd-II) and (+)-praeruptorin E (Pd-III), were the main active components in Qian-hu, while some other types of ingredients were also identified from this herb. The crude extract and pure compounds from Peucedani Radix exhibited a wide spectrum of *in vitro* and *in vivo* pharmacological activities, including vasorelaxant, cardioprotective, hepatoprotective, anti-tumor and anti-platelet aggregative effects. Conversely to the well-defined chemical constituents and activities, the properties of absorption, pharmacokinetics, and metabolism were rarely characterized. However, further investigations are wistful for the development of new drugs and therapies for various diseases, especially cardiovascular disorders. Collectively, the present review on the phytochemistry, chemical analysis, pharmacological evaluation, and pharmacokinetic profile of Peucedani Radix will provide meaningful information for further studies and commercial exploitation of the herbal medicine.

Keywords: Peucedani Radix; angular-type pyranocoumarins; chemical constituents; absolute configuration; pharmacological activities; pharmacokinetics

INTRODUCTION

Peucedani Radix consists of the dried roots of perennial herbaceous plant *Peucedanum praeruptorum* Dunn of Apiaceae family and initially documented in Miscellaneous Records of Famous physicians (Ming Yi Bie Lu). This herbal medicine is named as Qian-hu in Chinese, and also known as: aunt dishes, luo ghost food, water Qian-Hu, udo, chicken feet, *etc*. (Rao *et al*., 1995) in some regions of China. This herbal medicine is acrid and bitter in flavour and slightly cold in nature. It is documented as tropistic to the lung channel.

The original plant is widely distributed in Zhejiang, Anhui, Jiangxi, Fujian, Jiangsu, Henan and Hunan provinces in China. After the Ministry of Agriculture of agricultural products quality and safety center review and expert appraisal, Peucedani Radix cultured in Ningguo country, Anhui province, in accordance with "The measures for the administration of geographical indication of agricultural products" registration protection conditions, which was stipulated by the Ministry of Agriculture in May 2010, formally issued the "Ning hogfennel agricultural product geographical indications registration certificate", the implementation of protection by law (Xiang, 2006).

Following the theory of traditional Chinese medicine, the bitterness of this herbal medicine usually could send down abnormally ascending of Qi, thus resolving cough to stop cough; the acridness is dispersing; and slight coldness can clear heat. Hence, it can send down the adverse Qi, resolve phlegm to stop cough, and disperse wind-heat, indicated the prospects of treatment in cough due to phlegm-heat, and those with cough and sore-throat caused by invasion of lung by wind-heat.

Before 2005, the roots of *Peucedanum decursivum* Maxim. (*Angelica decursive*, Zi-hua Qian-hu) were also listed in Chinese Pharmacopoeia as one of the two original source of Peucedani Radix (Rao *et al*., 1995). This plant was removed owing to the significant difference of appearance and active characteristics between *P. decursivum* and *P. praeruptorum*. Although the sole source was authorized, many kinds of plants are still sold as the counterfeits and substitutes of Peucedani Radix in current material market, such as *P. decursivum* Maxim. (Zi-hua Qian-hu), *P. rubricaule* Shan *et* Sheh (Yun Qian-hu), *P. guangxiense* Shan *et* Sheh (Guang-xi Qian-hu), *P. Mashanense* Shan *et* Sheh (Ma-shan Qian-

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hu), *P. turgeniifolium* Wolff (Chang Qian-hu), *P. japonicum* Thunb. (Bing-hai Qian-hu), *P. wawrae* (Wolff) Su (Tai-shan Qian-hu), *P. medicum* Dunn (Hua-zhong Qian-hu), *P. medicum* Dunn var. gracile Dunn ex Shan *et* Sheh (Yan Qian-hu), *P. dissolutum* (Diels) Wolff (Nan-chuan Qian-hu), *P. wulongense* Shan *et* Sheh (Wu-long Qian-hu), *P. formosanum* Hyata (Tai-wan Qian-hu), *P. terebinthaceum* (Fisch.) Fisch. *ex* Turcz (Shifangfeng), *P. diellsianum* Fedde *ex* Wolff (Zhu-jie Qian-hu), *P. harry-smithii* Fedde *ex* Wolff (Hua-bei Qian-hu), *P. harry-smithii var* suglabrum Shan *et* Sheh (Shao-mao Bei-qian-hu), *etc* (Rao *et al*., 1995). Consequently, it is critically important to review the research progress for the chemical evaluation, qualitative and quantitative analysis of ingredients in Peucedani Radix and metabolic and pharmacokinetic profiles of this herb.

Chemical constituents

A plenty of chemical components have been identified from Peucedani Radix, including coumarins, flavones, sugars, saponins, steroids and volatile oils, while coumarins, in particular angular-type pyranocoumarins (APs), are regarded as the main active constituents contributing to the Qian-hu effect (Kong, 2010). Up to now, more than forty coumarins categorized to this type were identified from the roots of *P. praeruptorum*, and the chemical structures of these APs were summarized in fig. 1.

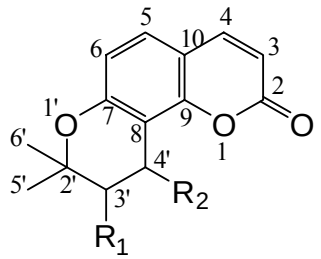
In addition to those angular-type pyranocoumarins, other components including praeroside I (44) (Okuyama *et al*., 1989), rutarin (45) (Kong *et al*., 1994a), isorutarin (46) (Kong *et al*., 1994a), psoralen (47) (Kong *et al*., 1993c), 8-methoxypsoralen (48) (Kong *et al*., 1993c), marmesinin (49) (Okuyama *et al*., 1989), nodakenin (50) (Kong *et al*., 1994a), nodakenetin (51) (Liu and Xu, 2002), decuroside V (52) (Takata *et al*., 1990b), bergapten (5-methoxypsoralen, 53) (Kong *et al*., 1993c), apiosylskimmin (54) (Takata *et al*., 1990b), skimming (55) (Takata *et al*., 1990b), (-)-peucedanol (56) (Kong *et al*., 1993b), scopolin (57) (Takata *et al*., 1990b), scopoletin (58) (Kong *et al*., 1994b), umbelliferone (59) (Chang and Li, 1999b), vanillic acid (60) (Kong *et al*., 1994a), gallic acid (61) (Kong *et al*., 1994a), daucosterol (62), *β*-sitosterol (63) (Kong *et al*., 1993c), galactitol (64) (Kong *et al*., 1993b), acetylatractylodinol (65) (Zhang *et al*., 2005b), tanshinone I (66) (Zhang *et al*., 2005b), tanshinone II (66) (Zhang *et al*., 2005b), (-)-sclerodin (67) (Zhang *et al*., 2006), palmitic acid (68) (Zhang *et al*., 2006), imperatorin (69) (Zhang *et al*., 2006), 2,6-dimethyl quinoline (70) (Zhang *et al*., 2006), tetracosanoic acid (71) (Zhang *et al*., 2006), angelicin (72) (Chang and Li, 1999a), arnocoumarin (73) (Chang and Li, 1999a), 3,4-methylenedioxy-8-methoxy-9,10 -dihydrophenanthrinic acid,9,10-dione (74) (Zhang *et al*., 2010), praeroside VI (75) (Ishii *et al*., 2008), hymexelsin (76) (Ishii *et al*., 2008), isofraxidin (77) (Ishii *et al*., 2008), 8-carboxy-7-hydroxycoumarin (78) (Ishii *et al*., 2008), praeroside VII (79) (Chang *et al*., 2008), peucedanoside A (80) (Chang *et al*., 2007b), peucedanoside B (81) (Chang *et al*., 2007b), apterin (82) (Chang *et al*., 2007b), 5,8-dimethoxypsoralen (83) (Kong *et al*., 1996b), isoscopoletin (84) (Kong *et al*., 1996b), anchoic acid (85) (Kong *et al*., 1996b), isoboconin (86) (Chang and Li, 1999b), aegelinol (87) (Chang and Li, 1999b), falcarindiol (88) (Miyazawa *et al*., 1996), qianhucoumarin F (89) (Kong and Li, 1994), Pd-C-I (90) (Kong *et al*., 1994a), baihuaqianhuoside (91) (Kong *et al*., 1994a), *etc*., were also isolated and identified from the roots of *P. praeruptorum*.

Determination of absolute configuration of angular-type pyranocoumarins

In general, the angular-type pyranocoumarins (APs) consist of the *cis*/*trans*-kellactone skeletons and acyl subsituents at C-3′ and/or C-4′ positions, which were always mentioned as two chiral centers. The identification of acyl groups was traditionally achieved using NMR spectroscopy, yet electron ionization-tandem mass spectrometry (EI-MS/MS) and electrospray ionization-tandem mass spectrometry (ESI-MS/MS) were widely introduced in recently years. The acyl moieties at C-3′ and C-4′ positions would be successively lost in EI-MS/MS (fig. 2) (Swager and Cardellina II, 1985), while the cleavage of C-3′ acyl group was prior to that at C-4′ position in ESI-MS/MS case (fig. 3) (Tao *et al*., 2009).

It is crucial to determine the absolute configurations of these two carbons, since the activities of APs are governed by their absolute chemical structures. In 1980s, ^{1}H-NMR spectroscopy was widely employed to elucidate the relative configurations using some rules of thumb. For *cis*-khellactone derivates, the coupling constant ($J_{3',4'}$) between the two protons at C-3′ and C-4′ position is around 5.0 Hz, and 5′-CH_3 and 6′-CH_3 share almost an identical chemical shift (δ). On the other side, the coupling constant ($J_{3',4'}$) for *trans*-khellactone derivates locates at the range of 3.0 ~ 6.9 Hz, and the difference between the chemical shifts ($\Delta\delta$) of 5′-CH_3 and 6′-CH_3 ranges from 0.08 ppm to 0.20 ppm. However, Okuyama *et al*. (Okuyama and Shibata, 1981) proposed that the ^{13}C-NMR spectroscopy could provide more important information for relative configuration. The chemical shift difference ($\Delta\delta$) between the C-5′ and C-6′ of *trans*-khellactone derivates is between 4.0 ppm and 6.0 ppm, while the C-5′ and C-6′ of *cis*-khellactone derivates almost share an identical chemical shift (δ).

In order to determine the absolute configurations of APs, alkaline hydrolysis is generally adopted as a chemical correlation tool to afford both *cis*-khellactone and *trans*-khellactone (fig. 4), which are generated by epimerization at C-4′ during alkaline treatment. The absolute configuration of (+)-*cis*-khellactone was determined as *R*-configurations for C-3′ and C-4′ using X-ray



No.	Name	Con[b]	R_1	R_2	Reference
1	(±)-praeruptorin A (Pd-Ia)	*cis*	angeloyloxy	acetyloxy	(Okuyama and Shibata, 1981, Chen *et al*., 1979, Lu *et al*., 2001)
2	(±)-praeruptorin B	*cis*	angeloyloxy	angeloyloxy	(Chen *et al*., 1979, Lu *et al*., 2001)
3	(+)-praeruptorin A	*cis*	angeloyloxy (S)	acetyloxy (S)	(Chen *et al*., 1979)
4	(+)-praeruptorin B (Pd-II)	*cis*	angeloyloxy (S)	angeloyloxy (S)	(Okuyama and Shibata, 1981, Chen *et al*., 1979)
5	(-)-praeruptorin A	*cis*	angeloyloxy (R)	acetyloxy (R)	(Xu *et al*., 2010)
6	(-)-praeruptorin B	*cis*	angeloyloxy (R)	angeloyloxy (R)	(Song *et al*., 2012a)
7	(+)-praeruptorin E (Pd-III)	*cis*	angeloyloxy (S)	isovaleryloxy (S)	(Okuyama and Shibata, 1981, Ye *et al*., 1982)
8	Pd-Ib	-	angeloyloxy (R)	oxo	(Wang *et al*., 2006, Okuyama and Shibata, 1981)
9	Qianhucoumarin I	*cis*	acetyloxy (S)	tigloyloxy (S)	(Kong, 1996)
10	(3′S,4′S)-3′-angeloyl-4′-acetylkhellactone	*cis*	angeloyloxy (S)	acetyloxy (S)	(Lou *et al*., 2004)
11	(3′S,4′R)-3′-acetyl-4′-angeloylkhellactone	*trans*	acetyloxy (S)	angeloyloxy (R)	(Lou *et al*., 2004)
12	(3′R,4′S)-3′-acetyl-4′-tigloylkhellactone	*trans*	acetyloxy (R)	tigloyloxy (S)	(Lou *et al*., 2004)
13	(3′R,4′R)-3′-acetyl-4′-angeloylkhellactone (pteryxin)	*cis*	acetyloxy (R)	angeloyloxy (R)	(Lou *et al*., 2004, Takata *et al*., 1990a, Kong *et al*., 1993c)
14	(3′S,4′R)-3′-acetyl-4′-isobutyrylkhellactone	*trans*	acetyloxy (S)	isobutyryloxy (R)	(Lou *et al*., 2004)
15	peucedanocoumarin I	*trans*	isovaleryloxy (S)	acetyloxy (R)	(Takata *et al*., 1990a)
16	peucedanocoumarin II	*trans*	acetyloxy (S)	angeloyloxy (R)	(Takata *et al*., 1990a)
17	peucedanocoumarin IIII	*trans*	acetyloxy (S)	tigloyloxy (R)	(Takata *et al*., 1990a)
18	qianhucoumarin H	*trans*	angeloyloxy (S)	isovaleryloxy (R)	(Kong *et al*., 1996b)
19	(3′R,4′S)-3′-angeloylkhellactone	*trans*	angeloyloxy (R)	hydroxyloxy (S)	(Kong *et al*., 1993a)
20	qianhucoumarin A	*cis*	hydroxyl (R)	tigloyloxy (R)	(Kong *et al*., 1993c)
21	qianhucoumarin B	*cis*	acetyloxy (S)	hydroxyl (S)	(Kong *et al*., 1993a)
22	qianhucoumarin C	*cis*	hydroxyl (S)	acetyloxy (S)	(Kong *et al*., 1993a)
23	qianhucoumarin D	*cis*	acetyloxy (S)	acetyloxy (S)	(Kong *et al*., 1994b)
24	qianhucoumarin E	-	tigloyloxy (R)	oxo	(Kong *et al*., 1994b)
25	(+)-laserpitin	*cis*	hydroxyl (S)	angeloyloxy (S)	(Hou *et al*., 2010)
26	qianhucoumarin J	*cis*	angeloyloxy (S)	propionyloxy (S)	(Hou *et al*., 2010)
27	*cis*-3′,4′-disenecioylkhellactone	*cis*	senecioyloxy	senecioyloxy	(Chang and Li, 1999b)
28	isobocconin	*trans*	acetyloxy	isobutyryloxy	(Chang and Li, 1999b)
29	aegelinol	-	hydroxyl (R)	dihydro	(Chang and Li, 1999b)
30	*trans*-khellactone	*trans*	hydroxyl (R)	hydroxyl (S)	(Chang and Li, 1999b)
31	*cis*-khellactone	*cis*	hydroxyl (R)	hydroxyl (S)	(Willetee and Soine, 1962)

No.	Name	Con[b]	R_1	R_2	Reference
32	3′-acetyl-4′-isovalerylkhellactone	*cis*	acetyloxy (R)	isovaleryloxy (R)	(Willetee and Soine, 1962)
33	*cis*-3′-senecioyl-4′-angeloylkhellactone	*cis*	senecioyloxy (R)	angeloyloxy (R)	(Chang and Li, 1999a)
32	*cis*-3′,4′-diisovalerylkhellactone	*cis*	isovaleryloxy	isovaleryloxy	(Zhang *et al*., 2005b)
35	3′-isovaleryl-4′-keto-khellactone[a]	-	isovaleryloxy	oxo	(Hou *et al*., 2009)
36	3′-angeloyl-4′-propionylkhellactone[a]	-	angeloyloxy	propionyloxy	(Hou *et al*., 2009)
37	praeroside II	*cis*	glucosyloxy (R)	hydroxyl (R)	(Takata *et al*., 1988)
38	praeroside III	*trans*	glucosyloxy (S)	hydroxyl (R)	(Takata *et al*., 1988)
39	praeroside IV	-	glucosyloxy (R)	dihydro	(Takata *et al*., 1988)
40	praeroside V	-	dihydro	glucosyloxy (S)	(Takata *et al*., 1988)
41	praeroside VI	*cis*	apiosyl(1→6)glucosyloxy	hydroxyl (R)	(Chang *et al*., 2008)
42	*cis*-3′-isovaleryl-4′-senecioylkhellactone	*cis*	isovaleryloxy (S)	senecioyloxy (S)	(Jong *et al*., 1992)
43	*cis*-3′-isobutyryl-4′-acetylkhellactone	*cis*	isobutyryloxy (R)	acetyloxy (R)	(Kong *et al*., 2003)

Fig. 1: The chemical structures of angular-type pyranocoumarins (APs, 1-43) identified from the roots of *Peucedanum praeruptorum* Dunn.

[a]the chemical structure was determined using LC-MS/MS and the absolute configurations haven't been indicated.
[b]relative configuration

spectrometry and the identity of (-)-*cis*-khellactone was thus characterized as (-)-(3′S, 4′S)-*cis*-khellactone. The hydrolyzed products were purified and compared with (+)-*cis*-khellactone and (-)-*cis*-khellactone. If (+)-*cis*-khellactone was identified as one of the hydrolyzed product, the configuration of C-3′ should be characterized as *R*, while (-)-*cis*-khellactone only could be yielded by (3′S)-angular-type pyranocoumarin. Further, the configuration of C-4′ was determined by the different NMR spectroscopic data between *cis*- and *trans*-type pyranocoumarins.

In addition, circular dichroism (CD) spectroscopy was recently subjected to carry out the determination of absolute configurations (Lou *et al*., 2004, Xu *et al*., 2010). A practical rule relating the position and absolute stereochemistry of the khellactone derivates to the behavior of their Cotton effects in CD curves was proclaimed by Lou *et al.* (Lou *et al*., 2004).

Chemical analysis and quality control of peucedani radix

Due to the different original herbs in current market, it is significant to identify the germplasm origin of Qian-hu. The microscopic features of the radix of *P. praeruptorum* Dunn were proposed in 1980s. As a widely adopted technique, thin-layer chromatography (TLC) was introduced to authorize this herbal drug by Song *et al* and Zhou *et al.* (Song and Xing, 2000, Zhou, 2008). In previous literatures, ^{1}H-NMR spectroscopy has been employed for chemotaxonomic evaluation of this traditional Chinese herbal drug (Wu *et al*., 1996, Liu *et al*., 1999, Wang *et al*., 1996, Ye *et al*., 1995), and the results revealed that ^{1}H-NMR spectroscopy is a quick, simple and reliable means to distinct Qian-hu from other similar herbal drugs, including *P. decursivi, P. medicun, P. rublicanle* and so on, while praeruptorin A and some other angular-type pyranocoumarins were adopted as the chemical indicators for recognition. In addition, a methodology of sequence characterized amplified regions (SCAR) markers was developed to distinguish of the three similar species of medicinal herbs, including *Angelica decursiva* (*P. decursivum*), *P. praeruptorum* and *Anthricus sylvestris*, based on the random amplified polymorphic DNA (RAPD) and internal transcribed spacer (ITS) sequence, and this SCAR marker could also provide valuable information for verifying whether the official drug was mixed with an adulterate (Choo *et al*., 2009).

High performance liquid chromatography coupled with diode array detection and tandem mass spectrometry (HPLC-DAD-MS/MS) was also subjected as a preferable technique for rapid identification and chemical profiling of *P. praeruptorum* (Tao *et al*., 2009, Zhu *et al*., 2004). In most cases, praeruptorin A, praeruptorin B and praeruptorin E were adopted the indicators for quality control of Peucedani Radix using HPLC-UV (Zhang *et al*., 2005a, Kong *et al*., 1996a, Xu *et al*., 2001a, Wu *et al*., 2009, Xu *et al*., 2007, Wang, 2004) or gas chromatography (GC) (Xu *et al*., 2001b). The quality standard of Peucedani Radix was proposed by Zhang *et al.* adopting HPLC-UV (Zhang *et al*., 2005a).

Pharmacological activities of Peucedani Radix and the chemical components

Pharmacological activities of the crude extract

Extensive pharmacological activities were revealed for this herbal medicine, which was traditionally adopted the treatments of cough with thick sputum and dyspnea, upper respiratory infections, during screening on modern pharmacological models.

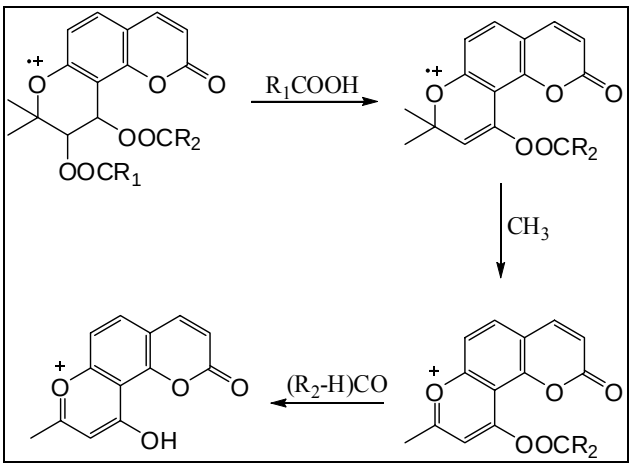


Fig. 2: The proposed ESI-MS^n fragmentation scheme for angular-type pyranocoumarins.

As an anciently employed agent for the treatment of asthma, the crude extract of Qian-hu can significantly restrain OVA-induced airway inflammation, airway hyperreactivity and Th2 predominant response on mice mode (Xiong *et al*., 2012c), and can attenuated the contractions of isolated rabbit trachea smooth muscles by acetylcholine and potassium chloride (Jin *et al*., 1994).

More interesting, this herbal drug shows a great prospect for the treatment of cardiovascular disease. Thus, there are an increasing number of the pharmacological evaluations concerning on the antihypertensive activity of this herbal medicine. The active components were proved mainly distributed in the petroleum ether extract and could relax pulmonary artery smooth muscle directly as a Ca^{2+} antagonist (Wei *et al*., 1994). The crude extract was shown to prevent and reverse hypertrophy of renovascular hypertensive left ventricular hypertrophy (LVH) by decreasing the concentration of $[Ca^{2+}]_i$, up-regulating the ATPase activity, improving cardiac function and myocardial compliance (Rao *et al*., 2002b, Rao *et al*., 2002c, Ji and Rao, 1996, Zhou *et al*., 2001a, Zhou *et al*., 2001b, Zhao *et al*., 1994). Wang *et al.* mentioned that the therapeutic effect of Qian-hu extract on pulmonary hypertension in patients suffered chronic obstructive pulmonary disease (COPD) may be related with the inhibition on the synthesis or secretion endothelin-1 (ET-1), abnormality of which may provide important contribution in the development of chronic hypoxic pulmonary hypertension (Wang *et al*., 2001). Wang *et al.* regarded that Qian-hu extract could down-regulat the pulmonary artery pressure without predominant influencing the systemic artery pressure, decrease the right heart index and reduce the thickness of small pulmonary artery media significantly. The composition of tenascin-C (TN-C) decreased obviously in pulmonary vasculature in rats after treatment of the extract (Wang *et al*., 2000).

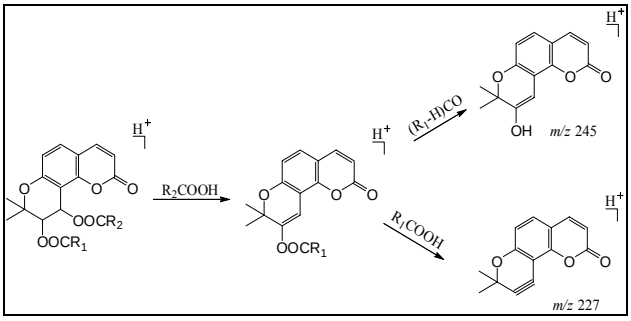


Fig. 3: The proposed ESI-MS^n fragmentation scheme for angular-type pyranocoumarins.

The anti-myocardial ischemia action was also revealed in existing reports. Administration of *P. praeruptorum* extract could result in a decrease of the size of acute myocardial ischemia injury (AM1), and the activities of lactate dehydrogenase (LDH), aspartate amino transferase (AST), superoxide dismutase (SOD), methyl diaidehyde (MDA), creatine kinase MB (CK-MB) and creatine kinase (CK), suggesting that the crude extract of Qian-hu exhibited protective effects on AM1 (Jiang *et al*., 2004a, Jiang *et al*., 2004c, Jiang *et al*., 2002). The expression of IL-6, Fas, bax and bcl-2 could be modify by the extract of Peucedani Radix (Chang *et al*., 2003, Liu *et al*., 2002). In addition, significant protection of the microstructure and ultrastructure from reperfusion injury was also observed for Qian-hu extract (Jiang *et al*., 2004b).

The low polar fraction of Peucedani Radix showed cytotoxic activity on *Artemia saline* test and antimicrobial activity on *Streptococcus agalactiae*, *Staphylococcus aureus*, *Escherichia coli*, *Shigella flexneri* and *Salmonella typhi*, while the *n*-butanol and aqueous extracts exhibited none or low activities on these models (Lu *et al*., 2001, Chen *et al*., 2002). Moreover, herbal extract was proved pharmacological actions including suppression of hepatic microsomal drug-metabolism enzymes activity in mice (Wang *et al*., 2004), definite cytotoxic and anti-proliferative action on SGC7901 cells (Liang *et al*., 2010), oxygen radicals elimination and lipid peroxidation inhibition (Wang *et al*., 2008).

Pharmacological properties of the major angular-type pyranocoumarins in Qian-hu

Angular-type pyranocoumarins, that were observed as the major constituent of *P. praeruptorum* Dunn, in particular praeruptorin A (PA) and praeruptorin B (PB), were

universally regarded to be responsible for the effects of Qian-hu extract mentioned above.

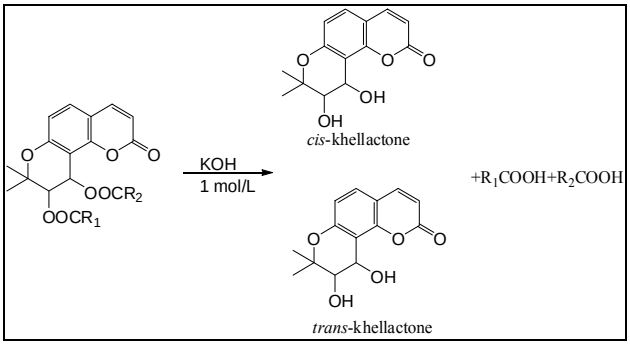


Fig. 4: Representative alkaline hydrolysis pathways of angular-type pyranocoumarins

(±)-Praeruptorin A (PA) could relax the tracheal smooth muscle isolated from rabbits through blocking the potential-dependent Ca^{2+} channels and inhibiting the release of Ca^{2+} from intracellular Ca^{2+}-pool (Guan *et al*., 1994). This active component could also suppress respiratory tract inflammation, remodel hyperresponsive airway, decrease the levels of IL-4 and IL-13 in BALF along with IgE in serum, increase the level of INF-γ in BALF, down-regulate the expression of pSmad2/3 and TGF-β1, and up-regulate the expression of Smad7 in pulmonary tissue, as well as inhibit eotaxin protein and mRNA expression, IκBα degradation, NF-κB nuclear translocation, NF-κB DNA-binding activity and RelA/p65 phosphorylation in lung. Above all, PA significantly suppressed airway inflammation and airway remodeling induced by ovalbumin stimulation, thus showing great therapeutic potential for allergic asthma (Xiong *et al*., 2012a, Xiong *et al*., 2012b).

PA and (+)-praeruptorin A (*d*PA) were widely highlighted as anti-hypertensive drug candidates. PA was usually documented cardiovascular pharmacological activities as a Ca^{2+} antagonist and a K^+ channel opener (Zhang *et al*., 2001, Li *et al*., 1994, Wang *et al*., 1997, Wang *et al*., 1995), while *d*PA was commonly mentioned due to the Ca^{2+} antagonistic activity (Rao *et al*., 1988, Rao *et al*., 2002a, Yang and Rao, 1997). Interestingly, *d*PA was found to increase coronary blood flow on isolated guinea pig heart (Chen *et al*., 1979), yet the corresponding effect was absence for PA. Distinct relaxant effects of the levorotatory and dextrorotatory enantiomers of PA was proved by Xu *et al*. on the isolated rat aorta rings, which might be mainly attributed to nitric oxide synthesis mediated by endothelial nitric oxide synthase (Xu *et al*., 2010).

PA and *d*PA could also prevent and treat ischemic reperfusion injury that was related to the effect of Qian-hu extract, typically through blocking the calcium channels and/or opening the potassium channels (Liu and Chang, 2002, Yang *et al*., 1995, Chang *et al*., 2007a, Chang *et al*., 1994, Chang, 2002).

Moreover, pyranocoumarins, such as PA, *d*PA, (+)-praeruptorin B and (+)-praeruptorin E, exerted anti-inflammatory effects in LPS-stimulated RAW264.7 macrophages through inhibiting NF-κB and STAT3 activation (Yu *et al*., 2012, Yu *et al*., 2011). PA could regulate the multiple drug resistant (MDR), differentiation and apotosis of cancer cells, when it was screened on a couple of cell lines (Fong *et al*., 2004, Zhang *et al*., 2003, Wu *et al*., 2003).

Absorption, Distribution and metabolism of angular-type pyranocoumarins from peucedani radix

In contrast to extensive pharmacologic studies, the pharmacokinetic properties of the coumarin-type components of Peucedani Radix have scarcely been studied, hence their contribution to the herbal action and active forms *in vivo* remain unclear.

As an herbal medicine, Peucedani Radix is usually taken orally by convention, indicating that it is needed to clarify the intestinal absorption of those active constituents. A couple of *in vitro* models have been developed for permeability and absorption screening, of which the Caco-2 cell (human colon adenocarcinoma cell line) monolayer model is widely mentioned as a preferable tool (Yee, 1997). The transport of (±)-praeruptorin A (PA), (+)-praeruptorin B (*d*PB) and (3′R,4′R)-3′,4′-diangeloylkhellactone (*l*PB, anomalin) was evaluated on this model (Zhao *et al*., 2011, Yue *et al*., 2012, Jing *et al*., 2011). The transport property and metabolism of *dl*-PA in Caco-2 cells was characterized under the assistance of a well-developed chiral HPLC-UV method. PA showed a rapid transport across the Caco-2 monolayers, partially bound to cell membranes and underwent hydrolysis during transport. The hydrolysis of PA catalyzed by carboxylesterases was demonstrated, and it implicates extensive first-pass intestinal and hepatic hydrolysis of the tested compound. Slight enantioselectivity was observed in the transport process (Jing *et al*., 2011). Anomalin [(3′R,4′R)-3,4′-diangeloyl khellactone] was demonstrated as a well-absorbed compound, and the transport mechanism was indicated as passive diffusion (Zhao *et al*., 2011). At the meanwhile, the P_{app} values of *d*PB for apical (AP) to basolateral (BL) or BL to AP were between 2.0×10^{-6} cm/s and 5.0×10^{-6} cm/s, along with P_{app}(BL-AP)/P_{app}(AP-BL) less than 1.5. As a consequence, *d*PB was proved as a drug candidate with relatively bad absorption, which absorbed mainly by passive diffusion approach through intestinal tract (Yue *et al*., 2012). The data displayed in literatures also indicated enantiospecific absorption of praeruptorin B enantiomers.

In vitro metabolic models were introduced to characterize the metabolic features of APs in rat liver microsomes and human liver microsomes (RLMs and HLMs) (Jing *et al*., 2013, Ruan *et al*., 2011, Song *et al*., 2012b, Song *et al*., 2011, Song *et al*., 2012a). Metabolic pathways including

hydrolysis, oxidation and intra-molecular acyl migration were detected as the main reaction types for *d*PA, *d*PA, *d*PB and *d*PE (Song *et al*., 2012b, Song *et al*., 2011). Extensive metabolism was observed for all the screened components in RLMs or HLMs and CYP3A4 was demonstrated to be the main isoenzyme mediating both hydrolysis and oxidation of *d*PA in HLMs, yet CYP 3A1 and/or 3A2 for PA metabolism in RLMs (Jing *et al*., 2013, Ruan *et al*., 2011).

PA was revealed that it was rapidly distributed and eliminated from rat plasma and demonstrated linear dynamics in dose range of 5-20 mg/kg following i.v. administration. The mean elimination half-life ($t_{1/2}$) of PA dosing of 5, 10 and 20 mg/kg were approximal 1.0 h. Spleen, heart and lung were observed as the major distribution tissues in rats, and the existence of PA in brain was also revealed since low polarity enabled PA to cross the blood–brain barrier (BBB). No long-term accumulation was detected for PA in all tissues. Low total recoveries were demonstrated for this compound within 24 h (0.120% in urine, 0.097% in bile and 0.009% in feces), which might be caused by significant liver-mediated first pass effect. When PA was i.v. administrated to liver cirrhosis (LC) rats at a single dose of 5 mg/kg, the area under curve (AUC) was significantly greater than that of the control group which could be owing to the slower hepatic blood flow rate and subsequently significant slower hepatic Cl_{int} in LC rats. In addition, the decrease of PA metabolic clearance might be at least partly arouse by the decreased expression and/or activity levels of CYP3A1 and 3A2 in LC rats, which were responsible for PA metabolism (Zhang *et al*., 2011). Pteryxin [(3′R,4′R)-3′-acetyl-4′-angeloylkhellactone], which is the regio-isomer of *l*PA, also showed rapidly distribution and elimination from mouse plasma ($t_{1/2}$ =1.463 h). Surprisingly, liver was detected as the major distribution tissue for pteryxin in mice, and the transport of the BBB was observed for pteryxin owing to its low polarity. As was expected, long-term accumulation wasn't observed for pteryxin in all mouse tissues (Wang *et al*., 2012). Moreover, in the case of *d*PB, the pharmacokinetic profile fitted well into a typical two-compartment model including a fast distribution phase coupled with a relative slow elimination phase. Tissue distribution results proved that the highest concentration of proto drug was detected in pulmonary tissue, followed by tissues of heart, liver and kidney, successively. As a low polar component, *d*PB was detectable in the brain after i.v. administration without surprise, indicating transport across the BBB for *d*PB (Liang *et al*., 2012).

CONCLUSION

Overall, although many studies were performed on this famous, there are still some shortcomings in these literatures. Enantioselective activities, absorption and metabolism were observed for the main components in Qian-hu, suggesting that it is crucial to develop enantiospecific method to monitor enantiomers separately for the purpose of quality control and pharmacokinetic study. Moreover, it is also necessary to characterize the chemical profile of this herbal medicine and characterized the herb-related components *in vivo* after oral administration of this plant.

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