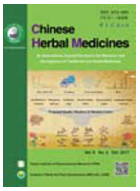

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Original article

Research on Quality Markers of *Moutan Cortex*: Quality Evaluation and Quality Standards of *Moutan Cortex*

Zhi-qiang Wang[1, 2, 3], Jie Shen[1, 2], Pei Li[1, 2], Shuang-shuang Liu[1, 2], Fan Yi[1, 2], Hai-bo Liu[1, 2], Fan-rong Wu[3], Chun-nian He[1, 2*], Fei-hu Chen[3*], Pei-gen Xiao[1, 2]

1. Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100193, China

2. Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Beijing 100193, China

3. School of Pharmacy, Anhui Medical University, Hefei 230032, China

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ABSTRACT

Objective To identify the quality markers of *Moutan Cortex* (MC) and establish the quality evaluation methods for multi-component assay and fingerprinting of MC. **Methods** The chemical constituents in MC were identified by HPLC-QTOF-MS. UPLC was employed for the multi-component assay and fingerprinting of MC. Furthermore, text mining was carried out to review the biosynthesis pathways and pharmacological and pharmacokinetic studies related to MC, and *in silico* target fishing was conducted to construct compound-target networks for MC. **Results** Sixteen compounds were clearly identified in MC and their structures were confirmed through comparison with literature data. In addition, the biosynthetic pathways and component specificities of the identified compounds were summarized and confirmed by text mining. Pharmacological activities, including traditional usage and modern pharmacological studies were summarized. A total of 282 targets from *Homo sapiens* were fished for 13 compounds. In addition, pharmacokinetic studies of different compounds were synopsized. Finally, multi-component assay and fingerprint of MC were established. **Conclusion** Eight major components are selected as quality markers of MC, such as oxypaeoniflorin, apiopaeonoside, albiflorin, paeonolide, paeoniflorin, 1,2,3,4,6-penta-*O*-galloyl-β-*D*-glucose, mudanpioside C and paeonol. These eight quality markers are successfully applied to the quality evaluation of MC, and could be useful in improving the current quality standards of MC.

Key words

Moutan Cortex; multi-component assay; network pharmacology; quality evaluation; quality marker

* **Corresponding authors: He CN** Tel/Fax: +86-10-5783 3165 E-mail: cnhe@implad.ac.cn

Chen FH Tel/Fax: +86-551-6516 1116 E-mail: cfhchina@sohu.com

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1. Introduction

Moutan Cortex (MC), the dried root bark of *Paeonia suffruticosa* Andr. (family Ranunculaceae), shows the functions of clearing the heat, cooling the blood, promoting the blood circulation, and removing blood stasis according to the traditional Chinese medicine (TCM) theory. MC is one of the commonly used crude drugs in TCM that has a variety of chemical components and a wide spectrum of pharmacological activities. The root is often collected in autumn with the soil cleared away and the rootlets removed, and processed into two kinds of MC, Liandanpi and Guadanpi. Liandanpi is produced by stripping off the root bark and dehydrating the root under the sun; Guadanpi is obtained by scraping off tertia before removal of the root duramen, and then sun-drying the root (Pharmacopoeia Committee of P. R. China, 2015). MC is extensively used in TCM prescriptions and has a long history of use in China and other Eastern countries such as Japan and Korea. Furthermore, MC was first recorded in *Shennong's Classic of Materia Medica* and classified as one of the middle-leveled herbs. Description of the first processing method of MC can be found in *Essential Prescriptions from the Golden Cabinet* (*Jingui Yaolue*), composed by Zhong-jing Zhang (150−219 AD) at the end of the Eastern Han Dynasty (Zhao et al, 2008). Since then, various classical clinical books in China from the Han Dynasty to the Qing Dynasty have described several processing methods for MC, such as wine-frying (*jiu zhi*), stir-frying (*chao zhi*), boiling (*zhu zhi*), roasting (*tan chao*) and charcoaling (*zhi tan*). MC was produced in different areas in China, e.g., Anhui, Henan, Shandong and Sichuan provinces. Among them, Fengdanpi, produced in Tongling, Anhui province, was reported to be of the highest quality, and Tongling was commonly regarded as a *daodi* area, or a specific eco-geographic region. In addition, *P. delavayi* Franch, called Diandanpi, was commonly used in Yunnan province as a substitute for MC due to morphological resemblance.

Thus far, more than 120 compounds have been isolated from and identified in MC; These can be divided into seven classes such as monoterpene glycosides, flavonoids, tannins, triterpenes, phenols, and others (He et al, 2010; Wang et al, 2017). The principal components are paeonol, paeoniflorin, apiopaeonoside, oxypaeoniflorin, 1,2,3,4,6-penta-*O*-galloyl-β-*D*-glucose (PGG), benzoylpaeoniflori and gallic acid among others. Pharmacological studies have suggested that MC has a wide spectrum of activity, e.g. anti-inflammatory, anti-oxidative, anti-allergic, hepatoprotective, cardioprotective, and neuroprotective effects (Wu et al, 2010; Zhao et al, 2016). Moreover, MC is recorded in the pharmacopoeias of several countries, such as China, Japan, Korea, and Vietnam. All these pharmacopoeias stipulate the assay of only one component, paeonol. Additionally, quality standards in Hong Kong and Taiwan include content determination of paeonol and paeoniflorin.

However, holistic quality standards for MC are still lacking and quantitative markers of MC have not been properly specified. A single marker approach, by only determining the content of paeonol, cannot fully reflect the quality of MC. Based on the current problems associated with the quality evaluation of crude drugs and decoction slices, Liu et al (2016a; 2017) proposed the concept of quality marker, which combines the biosynthetic pathway analysis of secondary metabolites and quantitative or qualitative approaches together with pharmacological research results. Quality markers should have the features of transferability and traceability throughout the whole production and processing chain, from herbs, decoction pieces, processed pieces, extracts, and intermediates to finished products. (Liu et al, 2016b) In order to study the therapeutic effects and chemical constituents, and for the quality control of MC, literature review and *in silico* target fishing were employed to determine the quality markers of MC. In addition, content determination based on UPLC and fingerprint methods was established.

2. Materials and methods

2.1 Chemicals

The reference substances such as gallic acid, methyl gallate, catechin, oxypaeoniflorin, apiopaeonoside, albiflorin, paeonolide, paeoniflorin, benzoic acid, galloylpaeoniflorin, PGG, mudanpioside C, benzoyloxypaeoniflorin, paeonol, benzoylpaeoniflorin and kaempferol were purchased from Chengdu Pusi Bio-technology Co., Ltd. (China), and their purities were not less than 95%. MeOH and CH_3CN of HPLC-grade were purchased from Honeywell (USA). Deionized water was prepared using a Millipore purification system (USA) and filtered through a 0.22-μm membrane. The solvents of analytical-grade for extraction and chromatography were purchased from Beijing Beihua Fine Chemicals Co., Ltd. (China).

2.2 Sample collection and preparation

The MC decoction slices derived from the root cortex of *P. suffruticosa* were purchased from Anguo and Bozhou TCM markets. Fresh *P. suffruticosa* root barks were collected from Bozhou and Tongling in Anhui province. All samples were authenticated by Dr. Chun-nian He, and the voucher samples were deposited in Prof. Xiao's laboratory at Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences in Beijing, China. Samples were pulverized and filtered through a 60-mesh sieve. Samples (0.25 g) were macerated with MeOH-H_2O (25 mL, 3:1, v/v) and placed in an ultrasonic water bath for 30 min. After cooling to room temperature, the extractions were filtered through a 0.22-μm membrane, and three aliquots (2 μL) were used for analysis.

2.3 HPLC-QTOF-MS

Mass spectrometry was performed on a Waters Q-TOF analyzer in a UPLC I-class Xevo G2 QT of system (Waters Corporation, USA) in both negative and positive ion modes. The flow rate of nebulization gas was set at 800 L/h at 300 ^oC