Phytomedicine 38 (2018) 166–174

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Original Article

Plasma pharmacokinetics and cerebral nuclei distribution of major constituents of *Psoraleae fructus* in rats after oral administration

Yan-Fang Yang[a], You-Bo Zhang[a,b], Zhi-Jing Chen[a], Ying-Tao Zhang[a,*], Xiu-Wei Yang[a,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, Department of Natural Medicines, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China
[b] Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, United States

ARTICLE INFO

Keywords:
Psoraleae fructus
Pharmacokinetics
Cerebral nuclei distribution
Coumarins
Prenylflavonoids
LC-MS/MS

ABSTRACT

Background: The fruit of *Psoralea corylifolia* L., *Psoraleae fructus* (PF), is widely used in traditional Chinese medicine as a well-known herbal tonic. Previous studies have shown that PF and its major constituents may have potential values in the treatment of Parkinson and Alzheimer diseases, though their pharmacokinetics and brain distribution were largely unknown.

Purpose: To develop a liquid chromatographic–tandem mass spectrometry (LC–MS/MS) method for simultaneous studies of the plasma pharmacokinetics and cerebral nuclei (including cerebellum, thalamus, brainstem, hippocampus, corpus striatum and cortex) distribution in rats of eleven known PF compounds following as psoralen, isopsoralen, psoralidin, bavachin, bavachinin, isobavachin, isobavachalcone, bavachalcone, neobavaisoflavone, corylifol A, and corylin.

Methods: Rats were orally administered via gavage at a single dose of PF extract at 1.2 g/kg. The eleven known PF compounds were extracted from rat plasma and cerebral nuclei at different time points, and then determined by the established LC–MS/MS method. Non-compartmental pharmacokinetic profiles were calculated, and the distribution in rat plasma and cerebral nuclei were compared.

Results: The results showed that all the tested compounds were quickly absorbed into rat plasma and distributed almost evenly to the cerebral nuclei. The distribution concentrations at different nuclei varied at one determined time point, but the overall trends were basically similar to the plasma concentration-time results. Psoralen and isopsoralen, the two highest coumarins contained in PF, displayed far higher plasma concentrations ($AUC_{0\rightarrow\infty,\ plasma} \approx 53{,}884 \sim 65{,}578$ ng·h/ml) and central nervous system penetration ($AUC_{0\rightarrow\infty,\ brain\ nuclei} \approx 44{,}659 \sim 65{,}823$ ng·h/g) than the prenylflavonoids (other compounds except psoralidin, $AUC_{0\rightarrow\infty,\ plasma} \approx 69 \sim 324$ ng·h/ml; $AUC_{0\rightarrow\infty,\ brain\ nuclei} \approx 119 \sim 3662$ ng·h/g). However, the total brain-to-plasma ratios of the prenylflavonoids were higher than the coumarins, suggesting the prenylflavonoids can more readily enter the brain than the coumarins.

Conclusion: The established LC–MS/MS method is sensitive and specific for the simultaneous quantitation of the eleven PF compounds in rat plasma and cerebral nuclei. The results of plasma pharmacokinetics and cerebral nuclei distribution may reveal the possible substance basis for the CNS activities of PF, and highlight the application possibility of PF and its major constituents in the treatment of Parkinson and Alzheimer diseases.

Introduction

Psoraleae Fructus (PF), known as Bu-gu-zhi in China, is the dried fruit of *Psoralea corylifolia* L. (family Fabaceae). It is used as a well-known herbal tonic in traditional Chinese medicine, especially for the treatment of erectile dysfunction and kidney diseases (Chinese Pharmacopoeia Commission, 2015). It possesses multiple biological properties, including antioxidant (Haraguchi et al., 2002), anti-inflammatory (Szliszka et al., 2011), immunomodulating (Latha et al., 2000), anti-tumor (Kim et al., 2014), bone-strengthening

Abbreviations: ACN, acetonitrile; AUC, area under curve; Aβ42, β-amyloid 42; CE, collision energy; C_{max}, maximum drug concentration; CMC-Na, carboxymethyl cellulose sodium; CNS, central nervous system; DP, declustering potential; ESI, electrospray ionization; ESI^+, positive ion mode of electrospray ionization; EtOAc, ethyl acetate; FA, formic acid; IS, internal standard; LC–MS/MS, liquid chromatographic–tandem mass spectrometry; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MeOH, methanol; MRM, multiple reaction monitoring; MRT, mean residue time; MS, mass spectrometry; MW, molecular weight; PF, *Psoraleae Fructus*; PFE, *Psoraleae Fructus* extract; Q1, precursor ion; Q3, product ion; QC, quality control; Q-trap, quadrupole-linear ion trap; RSD, relative standard deviation; RT, retention time; SD, standard deviation; S/N, signal-to-noise ratio; $t_{1/2}$, elimination half-life; TIC, total ion chromatography; t_{max}, time to reach maximum drug concentration

* Corresponding authors.
E-mail addresses: zytao@bjmu.edu.cn (Y.-T. Zhang), xwyang@bjmu.edu.cn (X.-W. Yang).

https://doi.org/10.1016/j.phymed.2017.12.002
Received 18 July 2016; Received in revised form 2 October 2017; Accepted 3 December 2017

(Miura et al., 1996), antibacterial (Khatune et al., 2004; Yin et al., 2004), and estrogenic (Lim et al., 2011) activities. Recent studies have also shown that PF extract (PFE), as well as one or more of its active components, has effects on the central nervous system (CNS), such as BACE1 (β-secretase) inhibition (Choi et al., 2008), neuroprotection and antiparkinsonism (Im et al., 2014; Zhao et al., 2009), acetylcholinesterase (Somani et al., 2015) and monoamine oxidases (Zarmouh et al., 2015) inhibition activities. Phytochemical examinations revealed that PF contains monoterpene phenols, coumarins and prenylflavonoids, in addition to unidentified volatile oil, lipids and resins (Chopra et al., 2013). The major constituents of PF have been characterized and quantified, including bakuchiol, psoralen (**1**), isopsoralen (**2**), psoralenoside, isopsoralenoside, psoralidin (**3**), bavachin (**4**), bavachinin (**5**), isobavachin (**6**), isobavachalcone (**7**), bavachalcone (**8**), neobavaisoflavone (**9**), corylifol A (**10**), and corylin (**11**) (Wang et al., 2009; Zhao et al., 2005) etc. While plasma pharmacokinetic studies of psoralen, isopsoralen, psoralenoside, isopsoralenoside, and bakuchiol have been reported (Feng et al., 2010; Wang et al., 2014; Yan et al., 2010), little is known about the absorption and brain distribution of the prenylflavonoids.

Previously we have reported the inhibitory effect of PFE on β-amyloid 42 (Aβ42) aggregation, and identified prenylflavonoids **5** and **7** as the major active compounds effectively inhibiting the on-pathway aggregation of Aβ42 through two different mechanisms (Chen et al., 2013). These findings, along with the CNS activities summarized above, suggested that PFE and its constituents may be valuable to the treatment of Parkinson and Alzheimer diseases. The brain penetration abilities of these compounds were critical determining factors for their in vivo CNS effects. Unfortunately, only limited information about the brain bioavailability of the two coumarins, psoralen and isopsoralen, is available today (Feng et al., 2010). In the present study, we established a highly sensitive and reliable liquid chromatographic–tandem mass spectrometry (LC–MS/MS) method and analyzed the rat plasma pharmacokinetics and cerebral nuclei distribution of the eleven major constituents in PFE (**1–11**, the chemical structures listed in Fig. 1) after oral administration. The aim of the study was to systematically examine the pharmacokinetics of PF components and the possible substance basis for its CNS activity.

Materials and methods

Materials and reagents

PF was purchased from Beijing Tong Ren Tang Pharmacy (Beijing, China, No. 20,140,912) and identified by Prof. Ying-Tao Zhang from Peking University. Eleven reference standards for the compounds of interest were obtained from Shanghai Yuanye Bio-Tech. Co. Ltd. (Shanghai, China) with purities above 98.0%. Scoparone (internal standard, IS) was purchased from the National Institutes for Food and Drug Control (Beijing, China). LC-MS grade methanol (MeOH) and acetonitrile (ACN) were purchased from J. T. Backer (Center Valley, PA, USA). HPLC grade formic acid (FA) (Dikma, Lake Forest, CA, USA) and Milli-Q water (Millipore, Bedford, MA, USA) were used throughout the study. All other chemicals and solvents used were of analytical grade.

Animals

The animal study was in accordance with the guidelines for the Care and Use of Laboratory Animals in Beijing and was approved by the Animal Care and Use Committee of Peking University (approval No.: LA 2,014,161, approved in 27 February 2014). Sprague-Dawley rats were supplied by the Laboratory Animal Center of Peking University Health Science Center (Beijing, China) (license No. SCXK (Jing) 2011–0012) and maintained under controlled environmental conditions (temperature 24 ± 2 °C; relative humidity 60 ± 5%; 12 h light/dark cycle). The rats were used for the study after 1-week acclimatization with free access to water and standard food.

Apparatus and operation conditions

LC analysis was performed with a DIONEX Ultimate 3000 HPLC system equipped with an Ultimate 3000 Pump and a DIONEX Ultimate

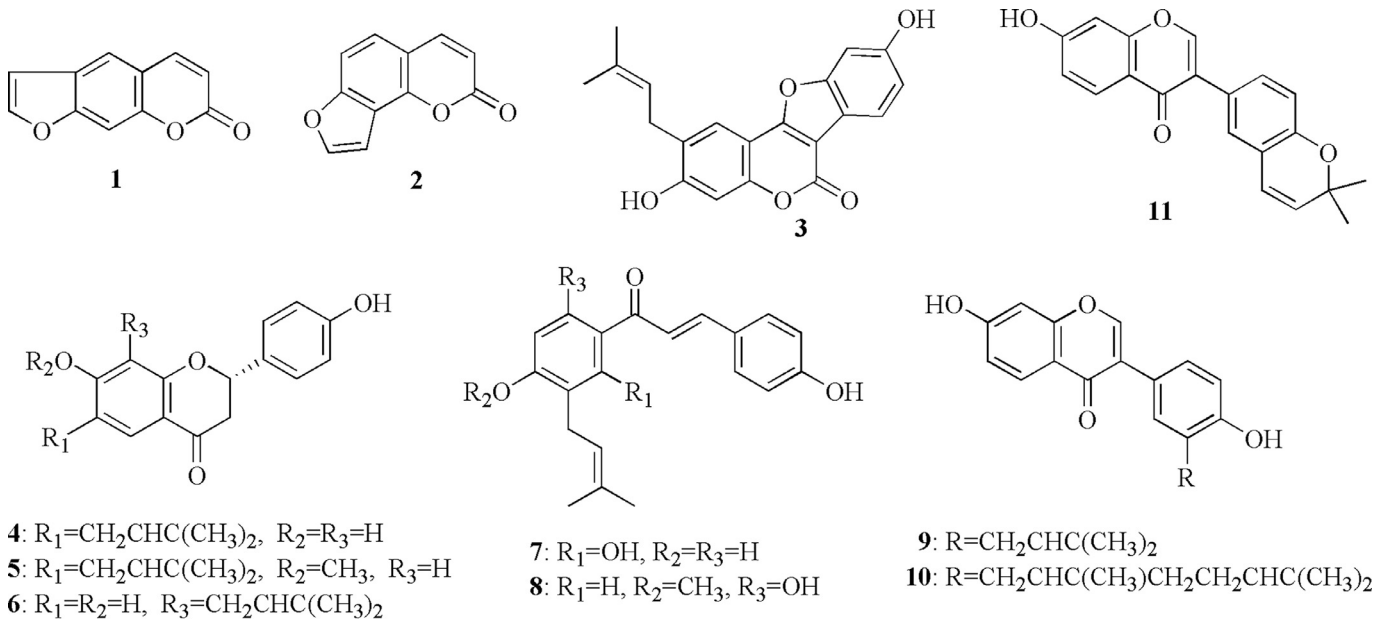

Fig. 1. Chemical structures of main components from PF.
(**1**) psoralen, (**2**) isopsoralen, (**3**) psoralidin, (**4**) bavachin, (**5**) bavachinin, (**6**) isobavachin, (**7**) isobavachalcone, (**8**) bavachalcone, (**9**) neobavaisoflavone, (**10**) corylifol A, (**11**) corylin.