ARTICLE IN PRESS
+ MODEL
Journal of Traditional Chinese Medical Sciences (2017) xx, 1–9

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: http://www.elsevier.com/locate/jtcms

Characteristics of the anti-dementia drug system of *Zisu Fang* preparations based on pharmacokinetic and pharmacodynamic analysis

Jianye Quan [a], Shujuan Yang [a], Fang Zhang [a], Li Tan [a], Jing Kong [a], Yanyan Jiang [a,b], Rendi Sun [c], Renbing Shi [a,b,*]

[a] *School of Chinese Pharmacy, Key Unit of Exploring Effective Substances of Classical and Famous Formulas of State Administration of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100102, China*
[b] *Quality Control Technology and Engineering Center of Chinese Medicine, Beijing Municipal Commission of Education, Beijing 100102, China*
[c] *Shanghai Green Valley Pharmaceutical Life Park Co. Ltd, Shanghai 201707, China*

Received 30 December 2016; received in revised form 27 September 2017; accepted 27 September 2017
Available online ■ ■ ■

KEYWORDS
Index components;
Pharmacokinetics;
Pharmacodynamics;
Characteristics of anti-dementia drug system

Abstract *Objectives:* To investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of index components of *Zisu Fang* preparations and additionally analysis the anti-dementia drug system characteristics.
Methods: A PK-PD-drug interaction (DI) method was applied to determine the characteristics of index components of *Zisu Fang* preparations *in vivo*.
Results: In the PK study, maximum plasma concentration, area under the plasma concentration–time curve, and mean residence time of index components of *Zisu Fang* preparations were higher in the memory-deficit model group than in the control group. This suggested that the index components of *Zisu Fang* preparations had an affinity for the state of dementia in this model. In the PD study, at the peak time points of anti-dementia efficacy (0.17 h and 1 h), the plasma concentrations of index components of *Zisu Fang* preparations reached the first or second largest plasma concentration peak or were close to the plasma concentration peak, and showed positive correlation between these two peaks, indicating that the index components of *Zisu Fang* synergistically exerted an anti-dementia effect. According to the association analysis of PK-PD-DI, baicalin, rosmarinic acid, salvianolic acid B, matrine, and tanshinone IIA were the main active ingredients of the anti-dementia drug system of *Zisu Fang*

* Corresponding author. School of Chinese Pharmacy, Key Unit of Exploring Effective Substances of Classical and Famous Formulas of State Administration of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100102, China.
E-mail address: shirb@126.com (R. Shi).
Peer review under responsibility of Beijing University of Chinese Medicine.

https://doi.org/10.1016/j.jtcms.2017.09.004

Please cite this article in press as: Quan J, et al., Characteristics of the anti-dementia drug system of *Zisu Fang* preparations based on pharmacokinetic and pharmacodynamic analysis, Journal of Traditional Chinese Medical Sciences (2017), https://doi.org/10.1016/j.jtcms.2017.09.004

preparations *in vivo*, but were only efficacious against dementia when all five components were present at a specific concentration and proportion.
Conclusions: Based on the PK and PD correlation analysis, baicalin, rosmarinic acid, salvianolic acid B, matrine, and tanshinone IIA are the main active ingredients of *Zisu Fang* preparations with regard to its anti-dementia effects, and represent the basic characteristics of drug system: natures, synergy, and affinity.

Introduction

Zisu Fang is clinically prescribed based on the formulation of the academician Yongyan Wang and is composed of perilla root (perilla frutescens (L.) BRITT.), salvia root (*Salvia miltiorrhiza BHE.*), Scutellariae root (*Scutellaria baicalensis GEORGI.*), and sophora root (*Sophora flavescens AIT.*).[1] It has been shown to exert a wide range of biological activities, including antibacterial effects, antioxidant effects, anti-allergic effects, free radical-scavenging activity, anti-dementia effects, and neuronal protection.[1–9] The results of a previous efficacy study showed that *Zisu Fang* preparations in the natural ratio showed significant anti-dementia effects, and significantly decreased the acetylcholinesterase (AchE) content in the cerebral cortex of a mouse model of dementia. Acetylcholine is a neurotransmitter that plays an important role in learning and memory processes in the brain.[10,11] AchE is the primary enzyme that degrades acetylcholine and can affect learning and memory. Therefore, the reversible inhibition of AchE activity in the brain can reduce the metabolism of acetylcholine, thus improving learning and memory function in patients with dementia.[12,13] In our study, the pharmacokinetics (PK) of the components of *Zisu Fang* preparations were analyzed. Screening indicated that the content of baicalin, rosmarinic acid, salvianolic acid B, matrine, and tanshinone IIA was high, and that the metabolism of these components was representative of *in vivo* metabolism. Therefore, we selected these five compounds as potential anti-dementia index components of *Zisu Fang*. The purpose of the present study was to investigate the PK and pharmacodynamics (PD) profile of these index components in normal and memory-deficit model rats, and to further characterize this drug system.

Ethical approval

The experiment was approved by the animal ethics committee of Beijing university of Chinese medicine.

Experimental reagents

Baicalin (batch number: 110715-201318; purity: 93.3%), rosmarinic acid (batch number: 111871-201505; purity: 98.5%), salvianolic acid B (batch number: 111562-201615; purity: 96.2%), matrine (batch number: 110805-200508; purity: 98.5%), tanshinone IIA (batch number: 110766-201520; purity: 98.9%), chloramphenicol (batch number: 130555-201203; purity: 93.5%), and pentoxifylline (batch number: 100591-201502; purity: 99.7%) were purchased from the National Institute for Food and Drug Control (Beijing, China). Scopolamine hydrobromide was purchased from the Chengdu Institute of Biology, Chinese Academy of Sciences (batch number: MUST-16031708; purity: 99.8%). Piracetam was purchased from Guangdong Huanan Pharmacy (Dongguan, China).

Zisu Fang preparations, composed of perilla root, salvia root, Scutellariae root, and sophora root were prepared by the School of Chinese Pharmacy, Beijing University of Chinese Medicine (Beijing, China). The herbs were mixed in a specific ratio and then separated by macroporous resin. The content of baicalin, rosmarinic acid, salvianolic acid B, matrine, and tanshinone IIA was 22.84%, 17.77%, 0.78%, 2.47%, and 0.45%, respectively.

Acetonitrile and methanol were purchased from Fisher Scientific (Bridgewater, NJ). Formic acid was purchased from Sinopharm Chemical Reagent Beijing (Beijing, China). All other reagents were of analytical grade or higher.

Experimental animals

Healthy male Sprague–Dawley rats [weighing (220–250) g] were purchased from Beijing Vital River Laboratory Animal Technology (animal license no. SCXK Beijing 2012-0001, Beijing, China). All the rats were housed in a common animal room at a temperature of 18–24°C and humidity of 40–60%, and free access to conventional food and water.

Rat oral dose conversion

Zisu Fang preparations: normal dose D = 1.8 g/60 kg × 7 × 1000 = 210 mg/kg.

Piracetam (positive control drug): normal dose D = 1.2 g/60 kg × 7 × 1000 = 140 mg/kg.

In the PK study, the dosage given to each rat was 630 mg/kg, which is three times of normal experimental dosage (210 mg/kg).

Groups and sample collection

After adaptive feeding for 1 week, 75 healthy rats were orally administered the *Zisu Fang* preparations (0.63 g/kg), and blood samples were collected from the abdominal aorta at 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1.5 h,

Please cite this article in press as: Quan J, et al., Characteristics of the anti-dementia drug system of *Zisu Fang* preparations based on pharmacokinetic and pharmacodynamic analysis, Journal of Traditional Chinese Medical Sciences (2017), https://doi.org/10.1016/j.jtcms.2017.09.004