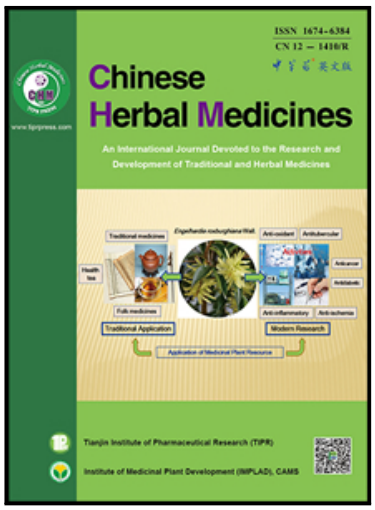

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Original article

Toxicity-efficacy converting of ginseng combined with Fuzi Banxia incompatibility in heart failure stage of Cor pulmonale

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Abstract **Objective** Fuzi Banxia is one of eighteen antagonisms, previous studies have shown that the incompatibility could play special effects in the specific condition of diseases and appropriate compatible environment. The present study aims to evaluate the toxicity-efficacy of ginseng combined with Fuzi Banxia incompatibility intervening in the heart failure stage of cor pulmonale and to explore its mechanism. **Methods** Monocrotaline (MCT)-induced cor pulmonale were used in this study. Ultra high-resolution small animal ultrasound real-time imaging system and the right heart catheterization were used to estimate cardiac function. Semi automatic biochemical analyzer was used to test myocardial enzyme LDH, CK, and CK-MB in serum. The heart tissues were stained with HE, and TUNEL assay was used to assess the pathomorphological changes and myocardial apoptosis. The expression of hypertrophy and apoptosis associated genes: ANP, BNP, β-MHC, Bax, and Bcl-2 in the right ventricle were determined by RT-PCR. **Results** Fuzi Banxia combined with ginseng obviously attenuated mortality, decreased RVHI, and increased cardiac index; RVSP and mPAP were significantly reduced, and EF and FS were raised obviously; Myocardial enzymes LDH, CK, and CK-MB were pronounced attenuated; heart diameter reduced, right ventricular dilatation was significantly decreased, inflammatory cell infiltration notably reduced, and cardiac apoptosis rate was decreased obviously. Meanwhile the expression of hypertrophy-related ANP, BNP, and β-MHC mRNA were up-regulated, the expression of apoptosis-related Bax mRNA was down-regulated, and the expression of anti-apoptosis-related Bcl-2 mRNA and Bcl-2/Bax ratio were up-regulated. **Conclusion** Ginseng compatible environment could attenuate cardiac toxicity of Fuzi Banxia incompatibility intervening in the heart failure stage of cor pulmonale, and improve cardiac function, which may be related to the expression of hypertrophy and apoptosis associated genes, and thus delay the occurrence and development of heart failure.

[Keywords]

apoptosis; cardiac function; Fuzi Banxia; incompatibility; ginseng compatibility; hypertrophy

1. Introduction

Thousands of years clinical practice in traditional Chinese medicines (TCM) has led to a series of theories and principles to guide the appropriate use of TCM. Among them, "Eighteen antagonisms" is one of the fundamental principles on TCM incompatibility. However, the application of the incompatibility in a prescription was not uncommon since Han Dynasty, the usage was not absolutely forbidden (Bian et al, 2012; Zuo et al, 2015). As sorting out and analyzing literatures, we found that under the specific condition of diseases and appropriate compatible environment, the incompatibility could play special effects, and severe adverse effects are the key manifestation of its toxicity in the process of taking effect, which made the clinical usage of Chinese medicine complicated and confused, especially in the incompatibility related to toxicity and efficiency (Duan et al, 2012; Fan et al, 2015; Zhuang et al, 2016).

Aconiti Lateralis Radix Praeparata (Fuzi) and *Pinellae Rhizoma* (Banxia), one of “Eighteen antagonisms”, are widely used in clinic to treat asthma and chest obstruction with pain. In addition, ginseng usually combined with Fuzi Banxia incompatibility when treating various pulmonary and heart diseases (Zhang et al, 2010; Zhang et al, 2011; Jia et al, 2015). Our previous study have shown that MCT-induced cor pulmonale eventually can cause heart failure, and the early stage of cor pulmonale was the indication of Fuzi Banxia incompatibility, but at the late stage of cor pulmonale, heart failure stage, Fuzi Banxia incompatibility cannot be used for its serious heart adverse effects. It suggested that different symptom conditions would be one of the key terms leading to toxicity or efficacy of the co-use of the incompatibility (Zhuang et al, 2016). The present experiment based on the contraindication of Fuzi Banxia incompatibility and heart failure stage of cor pulmonale to explore whether and why ginseng compatibility caused toxicity-attenuated and efficacy-produced effects, which would provide a theoretical basis for the clinical application of ginseng combined with Fuzi Banxia incompatibility.

2. Materials and Methods

2.1 Drugs and reagents

Aconiti Lateralis Radix Praeparata (Fuzi), *Pinellae Rhizoma* (Banxia) and *Ginseng Radix* et *Rhizoma* (Ginseng) were purchased from Beijing Huamiao Pharmaceutical Co., Ltd. DNase I and proteaseK were bought from Roche Biosciences, and DAB staining kit and hematoxylin were obtained from Beijing CellChip Biotechnology Co., Ltd. Creatine kinase (CK), CK-MB and lactate dehydrogenase (LDH) Assay Kit were purchased from Nanjing Jiancheng Bioengineering Institute.

2.2 Animal model and experiment design

The experimental protocol was approved by the Ethics Committee for Animal Experimentation of Tianjin University of Traditional Chinese Medicine and was conducted according to the NIH Guide for the Care and Use of Laboratory Animals. Adult male Wistar rats (180-200) g, Certificate No. SCXK 2012-0001, Beijing Vital River Laboratory Animal Technology Co., Ltd. were used in this study. The rats were housed under controlled conditions with a temperature at (22 ± 2) °C, a 12 h light/dark cycle (lights on at 8:00 AM), and humidity at (60-70) % for at least one week before experiment.

Cor pulmonale rat model was induced by a single intraperitoneal injection of monocrotaline (MCT, 60 mg/kg b.wt. GR-133-151019, Guangrun Bio Technology, Co. Ltd. Nanjing, China) previously dissolved in 1 mol/L HCl and pH adjusted to 7.4 using 1 mol/L NaOH, after three weeks, eventually developed to heart failure. Rats were randomly divided into four groups: control group (Control, n = 10), model group (Model, n = 26), Fuzi Banxia combination group (1:1) (FB, n = 26, ig 5g/kg/d), ginseng combined with Fuzi Banxia group (1:1:1) (GFB, n = 25, ig 5g/kg/d) and ginseng alone group (Gins, n = 25, ig 5g/kg/d). Administration was last for two weeks. 5g/kg/d is four fold of clinical equivalent dose.