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Pharmacological and safety evaluation of fibrous root of *Rhizoma Coptidis*

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ABSTRACT

The aim of this study was to investigate the pharmacological activities and safety of fibrous root of *Rhizoma Coptidis* (FRC). FRC not only protected Kunming mice from the minimal lethal dose of *Escherichia coli*, but also protected rabbits from hyperpyrexia induced by lipopolysaccharid (LPS). The acute toxicity study showed that oral median lethal dose (LD₅₀) of FRC was greater than 7000 mg/kg body weight in Kunming mice. The sub-chronic toxicity study showed that the no-observed-adverse effect level (NOAEL) of FRC was 1.88 g/kg body weight in Sprague-Dawley rats, whereas FRC at higher dose (3.76 g/kg body weight) resulted in damage to liver and lung. Negative results were present in Ames test, mouse micronucleus test and mouse sperm abnormality test. These findings support the use of FRC in veterinary medicine.

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1. Introduction

Rhizoma Coptidis (RC) is widely used in veterinary clinics because of its antibacterial and antipyretic activities (Commission of Chinese Veterinary Pharmacopoeia, 2010). RC mainly consists of various alkaloids, including berberine, coptisine, epiberberine and palmatine (Fig. 1), which are used

as standard for its quality control in China (Chen et al., 2012). The fibrous root of *Rhizoma Coptidis* (FRC) is usually discarded during the processing of RC. However, our previous researches showed that alkaloids also exist in FRC (Liu et al., 2010). The presence of alkaloids suggests that FRC may have similar pharmaceutical use as RC in veterinary clinics. And we found that FRC in combination with other herbs were effective in the

Abbreviations: 2-AA, 2-aminoanthracene; 2-AF, 2-aminofluorene; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFDA, China Food and Drug Administration of the People's Republic of China; CMC, sodium carboxymethylcellulose; CPA, cyclophosphamide; FAS, fenaminosulf; FRC, fibrous root of *Rhizoma Coptidis*; HPLC, high-performance liquid chromatography; ICR, Institute of Cancer Research; LD₅₀, median lethal dose; LPS, lipopolysaccharides; MMS, methyl methanesulphonate; MNPCE, micronucleated polychromatic erythrocytes; MOH, Ministry of Health of the People's Republic of China; NCE, normochromactic erythrocyte; NOAEL, no-observed-adverse effect level; OECD, Organization for Economic Co-operation and Development; PCE, polychromatic erythrocytes; RBC, red blood cell count; RC, *Rhizoma Coptidis*; SA, sodium azide; WBC, white blood cell count.

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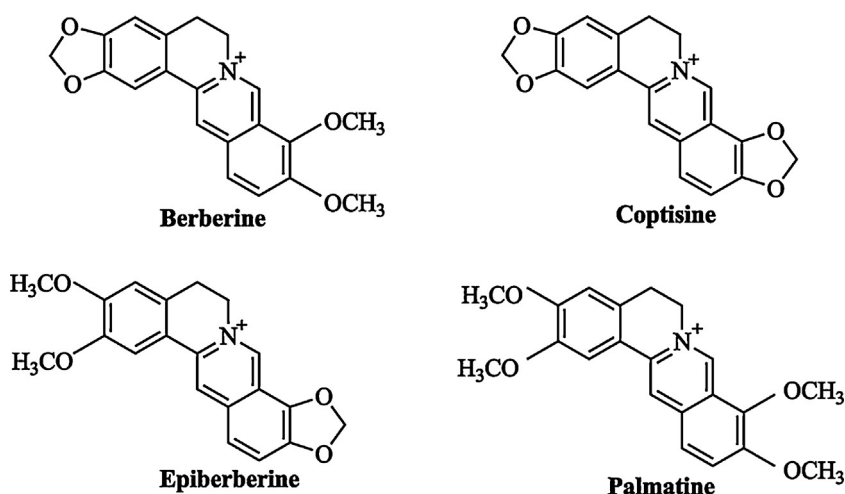


Fig. 1 – The chemical structures of berberine, coptisine, epiberberine and palmatine.

treatment of dysentery as well as the fever in animals (Sun et al., 2010; Wang et al., 2010). However, there is little information about its pharmacological activities and safety.

To contribute to the use of FRC in veterinary clinics, we study its pharmacological activities (antibacterial and antipyretic activities) and safety. And the safety was evaluated by acute oral toxicity study, sub-chronic 90-day toxicity study, Ames test, mouse micronucleus test and mouse sperm abnormality test.

2. Materials and methods

2.1. Preparation of FRC and RC

Fibrous root and rhizome of *Coptis chinensis* Franch. were harvested from the Good Agricultural Practices Base in Shizhu (Chongqing, China). They were authenticated by Professor Lvjiang Yuan at Southwest University. The voucher specimens of FRC (No. 20110314) and RC (No. 20110315) were deposited in a herbarium at the School of Pharmaceutical Sciences, Southwest University. Both of them were washed with water and air dried. The coarse powder of FRC or RC, as the final product, was obtained after crush and filtration (150 mesh).

2.2. Characterization of FRC and RC

The powder of FRC (0.2 g) or RC (0.1 g) was extracted once with 50 ml of methanol and hydrochloric acid (100:1; v/v) at room temperature for 30 min under ultrasonic treatment (power 250 W, frequency 40 kHz). The extract was filtered, diluted, and then used for the high-performance liquid chromatography (HPLC).

HPLC analysis was performed on a Agilent 1100 HPLC system (Agilent, USA) using a Hypersil ODS C-18 column (25 cm × 4.6 mm, 5 μm). The mobile phase consisted of acetonitrile and 0.05 mol/l potassium dihydrogen phosphate buffer (50:50, v/v, pH 4.0) containing 0.4% (w/v) sodium dodecyl sulfate. The eluates were monitored at 345 nm with a flow rate of 1 ml/min and sample size of 10 μl was carried out at column

oven temperature 30 ± 2 °C. The reference standards of berberine and palmatine were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China); coptisine and epiberberine were purchased from Chengdu Biopurify Phytochemicals Ltd. (Chengdu, China). The purities of all standards were not less than 98.0%.

2.3. Animals

The animal experimental protocols were approved by the Ethical Committee of Animal Care of the Third Military Medical University. All procedures were conducted in accordance with the Guidance Suggestions for the Care and Use of Laboratory Animals, formulated by the Ministry of Science and Technology of the People's Republic of China in 2006.

Adult male New Zealand White rabbits (2.5–3.0 kg), Kunming mice (18–22 g) of both sexes, and Sprague-Dawley rats (95–115 g) of both sexes were supplied by the Animal Breeding Center of the Third Military Medical University (Chongqing, China). Institute of Cancer Research (ICR) mice (18–20 g) of both sexes were supplied by the Comparative Medicine Centre of Yangzhou University (Yangzhou, China). New Zealand White rabbits were used for study of antipyretic activity. Kunming were used for studies of antibacterial activity and acute toxicity. Sprague-Dawley rats were used for study of sub-chronic toxicity. ICR mice were used for mouse micronucleus test and mouse sperm abnormality test. All animals were housed under a 12-h light/dark cycle, and allowed free access to food and water. The room temperature was maintained at 21–23 °C and relative humidity at 40–60%.

2.4. Antibacterial activity in mice

The antibacterial activity of FRC was studied in Kunming mice by infecting the minimal lethal dose of *Escherichia coli* according to the China Food and Drug Administration of the People's Republic of China (CFDA) guideline (No. [Z] GPT1-1) (CFDA, 2005a). In the preliminary experiment, the minimal lethal dose of chicken *E. coli* CVCC 249 (China Veterinary Culture Collection Center, Beijing, China) that caused 90–100% mortality

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