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Comparative study of pharmacokinetics and tissue distribution of osthole in rats after oral administration of pure osthole and *Libanotis buchtormensis* supercritical extract

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ABSTRACT

Ethnopharmacological relevance: Libanotis buchtormensis is the source of an important traditional medicine from Shaanxi province of China used in the treatment of many illnesses. *Libanotis buchtormensis* supercritical extract (LBSE) has analgesic, sedative and anti-inflammatory qualities. Osthole is one of the major bioactive components of LBSE; it is known for its significant anti-tumor, analgesic, and anti-inflammatory properties, it also alleviates hyperglycemia.

Aim of the study: The purpose of the present study was to compare the pharmacokinetics and tissue distribution of osthole in Sprague-Dawley (SD) rats after oral administration of pure osthole and LBSE. The two preparations were administered at the same osthole dose (approximately 130 mg/kg). The results should provide some guidance for the clinical applications of *Libanotis buchtormensis*.

Materials and methods: Comparative pharmacokinetics and tissue distribution of osthole in SD rats after oral administration of pure osthole and LBSE were analyzed using reversed-phase high-performance liquid chromatography (RP-HPLC). All pharmacokinetic data were analyzed using 3P97 software. Samples of blood and internal organs (heart, liver, spleen, lungs and kidney) were collected and pretreated according to the experimental schedule. After pretreatment, plasma and tissue samples were extracted using ether–ethyl acetate mixture (3:1, v/v). The concentration of osthole in the plasma and tissues were determined using the RP-HPLC method.

Results: The procedure described in this paper shows good precision and stability and is suitable for the osthole assays in biological samples. We found that the average plasma concentration-time profile of osthole after oral administration of osthole and LBSE showed a single peak. There were also clear differences between plasma concentrations of osthole after oral administration of pure osthole and LBSE. Non-osthole ingredients in LBSE showed some pharmacokinetic interactions with osthole and hence decreased its absorption levels ($p < 0.05$). Our results show different tissue distribution of osthole in the single and composite administration regimens.

Conclusions: This study compares the pharmacokinetic characteristics and tissue distribution of osthole in rats after oral administration of pure osthole and LBSE; the results might be useful in clinical application of this traditional Chinese herbal medicine.

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1. Introduction

Libanotis buchtormensis (Fisch.) DC. belongs to the Umbelliferae family and is found in Shaanxi, Gansu and Sichuan provinces of China. Dried root and rhizomes of this plant are used in traditional folk medicine to alleviate many disease symptoms. Some of the typical examples are: general aching, headache, toothache, traumatic injury, pain after traumatic injuries, joint pain and swelling, bone and muscle pain caused by rheumatism, and pain associated with other diseases (Jiangsu New Medical College, 1985). The therapeutic effects of this medicine are thought to be a result of complex interactions of its various ingredients. Recently, pharmacological studies have also shown that *Libanotis buchtormensis* extract has an analgesic effect (Shi et al., 2006). Our previous study of pharmacology of LBSE (containing 65% of osthole) have demonstrated excellent analgesic, sedative and anti- inflammatory properties of this extract (Shi et al., 2011a).

Osthole (structure A in Fig. 1), a coumarin compound isolated from the dried root and rhizome of *Libanotis buchtormensis*, is one of the main bioactive ingredients important for the integral effect

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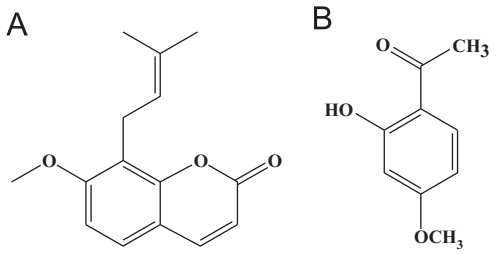

Fig. 1. Chemical structure of osthole (A) and paeonol (B).

of *Libanotis buchtormensis* (Song et al., 2007; Shi et al., 2011b). This compound displays many beneficial properties, such as alleviation of hyperglycemia (Liang et al., 2009), hypolipidemic effect (Song et al., 2006), and protective effect in focal cerebral ischemia-reperfusion injury (He et al., 2009). It prevents atherosclerosis and suppresses the hepatic lipid accumulation (Ogawa et al., 2007). Several studies have reported its role as a seizure suppressant, anticonvulsant and its involvement in the alleviation of acute neurotoxic effects (Jarogniew et al., 2009a,b). Its inhibitory effect in alcohol-induced fatty liver disease (Sun et al., 2009) and a neuroprotective effect (Chao et al., 2010; Liu et al., 2010; He et al., 2012) has been also demonstrated. Osthole improves neurobehavioral functions and reduces infarct volume and matrix metalloproteinase-9 activity (Mao et al., 2011), has an anti-tumor effect (Zhou et al., 2002), improves chronic cerebral hypoperfusion-induced cognitive deficits and reduces neuronal damage in hippocampus (Ji et al., 2010). Attenuation of experimental autoimmune encephalomyelitis in C57 BL/6 mice (Chen et al., 2010), anti-coagulation (Zhou et al., 2006) and elimination of oxygen free radicals by this compound (Wang et al., 2004a) have been also reported. Some pharmacological studies have shown that osthole shares the anti- inflammatory and analgesic effects with LBSE (Liu et al., 2005; Hu et al., 2007). Osthole can be used as a phytochemical marker for the quality control of *Libanotis buchtormensis*.

The pharmacokinetics of osthole in rat plasma has been studied after its intravenous and oral administration in the rat (Tsai et al., 1996; Zhou et al., 2008). Pharmacokinetic analysis of this compound has been also performed by HPLC in rat plasma after oral administration of *Fructus Cnidii* extract (Li et al., 2005) and has been studied in the plasma of the rats with cerebral ischemia hypoperfusion (Zhou et al., 2011). Osthole pharmacokinetics has been also studied in rabbits (An et al., 2003; Wang et al., 2004b). Tissue distribution of osthole in rats (Zheng et al., 2006), and the pharmacokinetics and tissue targeting of this compound (Zheng et al., 2011) have been also reported. Some *in vivo* studies have indicated that the therapeutic effect of herbal products might be caused by multi-ingredient synergism rather than the independent actions of individual ingredients (Ma et al., 2009). To improve our understanding of those complex processes, it is necessary to study the differences in the pharmacokinetics and tissue distribution of osthole and other ingredients of herbal preparations.

Osthole is one of the constituents of *Libanotis buchtormensis*; its therapeutic effects have been usually reported after an oral administration of multi-compound mixtures extracted from *Libanotis buchtormensis*. In this study, we used LBSE containing 65% of osthole to determine the pharmacokinetic profiles associated with its analgesic, sedative and anti-inflammatory activities (Liu et al., 2005; Hu et al., 2007; Shi et al., 2011a).

LBSE is more efficacious than a pure preparation of osthole, probably because of positive synergistic interactions between osthole and other components. LBSE mimics better the traditional mode of treatment where the water decoction and alcohol infusion of this herb were commonly applied (Jiangsu New Medical College, 1985). The pharmacokinetics of osthole has been extensively studied; however, plasma pharmacokinetics and tissue distribution of osthole from *Libanotis buchtormensis* extract, and comparative plasma pharmacokinetics and tissue distribution data of osthole after oral administration of pure osthole and LBSE have been scarcely reported. The interactions between osthole and other components of LBSE, their efficacy, and the relative significance of those compounds as well as their effect on pharmacokinetic behavior and tissue distribution of osthole remain unknown. Therefore, in this study, an analytical method was established, validated, and employed to compare the pharmacokinetics and tissue distribution of osthole in rats after oral administration of pure osthole and LBSE.

2. Materials and methods

2.1. Materials and reagents

Libanotis buchtormensis (Fisch.) DC. was purchased from Taibai Mountains (Shaanxi, China), and was authenticated by Xiezhimin, the chief pharmacist from Xi'an Food and Drug Inspection Institute. A voucher specimen was deposited at the Faculty of Pharmacy, School of Medicine, Xi'an Jiaotong University, China. LBSE, containing 65.0% of osthole, was prepared by supercritical extracting, standing and sedimenting. Osthole (purity 98.0%) was purchased from Xi'an Thinleaf Milkwort Stem and Leaf Plants Technology Limited Company. The internal standard (IS), paeonol (batch number: 110708-200505, $>99\%$ purity), was purchased from National Institute for the Control of Pharmaceutical and Biological Products (Ministry of Health, Beijing, China). The structure of paeonol is shown in Fig. 1(B). Methanol was of chromatographic grade (Kermel Company, Tianjing, China); all other reagents were of analytical grade. Triple-distilled water was prepared by Molelement 1805b Element Model Ultrapure Water Instrument (Mole Company, Shanghai, China) and used throughout the study.

2.2. Animals

Male and female Sprague-Dawley (SD) rats (weight 250–300 g) were obtained from the Laboratory Animal Center of Xi'an Jiaotong University (Xi'an, China). Rats were fasted for 12 h and allowed free access to water prior to the experiments. All rats were processed according to suggested ethical guidelines for the care of laboratory animals.

2.3. Instruments and conditions

The analysis was performed on a Shimadzu Scientific Instruments (Kyoto, Japan) liquid chromatographic system with SPD-20A pump, LC-20AT UV detector and a computer system for data acquisition (CS-light chromatography workstation, Shimadzu Corporation). The analyte was determined at ambient temperature using an analytical column (Kromasil, ODS, 150 mm × 4.6 mm i.d., 5 μm particle size, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China) with a guard C_{18} column (10 mm × 4.6 mm i.d., 5 μm. Scienhome Scientific, Inc., Tianjin, China). The mobile phase consisted of a methanol–water mixture (75:25, v/v). The analysis was performed at a flow rate of 1.0 ml/min with the detection wavelength of at 322 nm.

2.4. Treatment of animals

All SD rats were randomly divided into three groups. The first group was used to prepare control plasma and tissue samples, the second for the pharmacokinetic studies (two subgroups, $n=6$ in

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