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Transdermal permeation of geniposide in the herbal complex liniment in vivo and in vitro

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ABSTRACT

Zhongtong Caji, a kind of liniment, is a traditional Chinese medicinal formula that is widely used for clinical treatment of inflammation and sprains. In this study, the principal effective compound of this formula, geniposide, was used as a criterion to represent the transdermal permeability of the whole formula. A passive diffusion of Zhongtong Caji through the stratum corneum was discovered by an in vitro experiment. The dosage–content relationship detected in subcutaneous tissue after in vivo drug administration was further evidence of its permeation. Blood analysis after different dosages showed that the geniposide could be absorbed and accumulated by subcutaneous tissue within 1 h after drug administration, and it would be eliminated by blood circulation 1 h after drug treatment.

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1. Introduction

Transdermal drug delivery (TDD) is a commonly used and convenient method of drug administration enabling physicians to provide controlled delivery of drugs to patients with local injury, such as a wrench or sprain. Zhongtong Caji is a kind of liniment for external transdermal medicine that is made from more than ten kinds of various herbal drugs, such as gardenia fruit, borneol, schefflera arboricola hayata, ampelopsis delavayana, menthol and so on. Gardenia fruit is the principal effective element in this formula. This formula has been widely used among the Yi population of southwest China for its anti-inflammatory activities and analgesic effects.

Gardenia fruit has been traditionally used as a Chinese medicine for centuries in China, as well as in other Asian countries. It has been included in traditional medical formulas for the treatment of inflammation, sprain, jaundice headache, edema, fever, hepatic disorders, and hypertension (Aburada et al., 1976; Chen et al., 2009; Miyasita, 1976; Tseng et al., 1995). Modern clinic pharmacological research has revealed that gardenia fruit has several other activities, such as anti-inflammatory properties, cytotoxic effects, as well as protective activity against oxidative damage (Tseng et al., 1995; Lee et al., 2009; Jung et al., 2009; Jagedeeswaran et al., 2000).

Geniposide (Fig. 1), one of the major iridoid glycosides and active compounds of gardenia fruit, was previously shown to inhibit 5-lipoxygenase (Nishizawa et al., 1988), ovalbumin-induced junction permeability, and inhibit recovery of transepithelial electrical resistance in guinea pig trachea, which shows its potential as an anti-asthma therapeutic drug (Liaw and Chao, 2001). Additionally, geniposide was shown to have activity against the tumor-promoting factor, 12-O-tetradecanoylphorbol-13-acetate (TPA), which activates protein kinase C (Lee et al., 1995), as well as display anti-angiogenic activity (Park et al., 2003; Koo et al., 2004). Recent reports have demonstrated that geniposide can prevent PC12 cells from oxidative damage via the MAP kinase pathway (Liu et al., 2007). It is also reported that geniposide has anti-inflammatory activities in carrageenan-induced rat paw edema and it can also inhibit vascular permeability induced by acetic acid in a dose-dependent manner (Koo et al., 2006).

To find the pharmacological performance of this formula, geniposide was used as a criterion to evaluate its transdermal penetration of this liniment. The permeability of geniposide of the liniment was first observed in vitro. The distribution and concentration of geniposide in subcutaneous tissue was determined in a dose-dependent manner in vivo. Finally, high performance liquid chromatography (HPLC) was used to observe the blood concentration of geniposide after external use of the liniment with different dosages and to explore the correlation between geniposide concentrations in both blood and subcutaneous tissue at different dosages and time.

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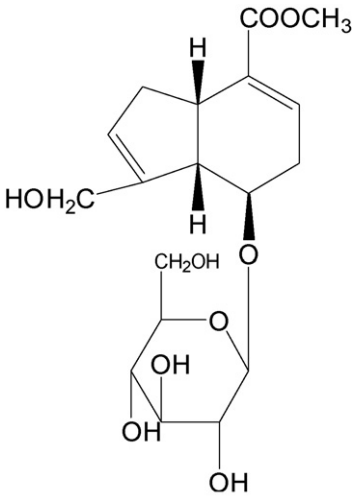

Fig. 1. Chemical structure of geniposide.

2. Materials and methods

2.1. Animals

ICR mice (male, weighing 25–28 g) were purchased from Vital River Experimental Animal Center, license number: SCXK 2005-0003. The experimental protocol was in accordance with the guidelines of China for animal care, which was conformed to the internationally accepted principles in the care and use of experimental animals. All experiments were performed in accordance with international standards on the ethical treatment of animals, and the minimum number of animals was used to minimize suffering. Mice were housed under climate-controlled conditions with a 12-h light/dark cycle and provided standard food and water ad libitum. To eliminate the effect of epidermal hairs on drug absorption, 25% (m/v) Na_2S was used to remove the epidermal hair at the dorsal region 2 days before experimentation.

2.2. Chemicals

Geniposide standard was obtained from the National Institute for the Control of Pharmaceutical and Biological Products, China (batch number: 110749-200613); methanol and acetonitrile were purchased from the Beijing Chemical Reagent Company; Zhongtong Caji (the liniment) was obtained from the Institute of Materia Medica of Yunnan Province (batch number: 090721), containing geniposide 0.064% (w/v) detected by HPLC assay; purified water was made from distilled water.

2.3. Drug administration and sampling

2.3.1. The permeation in vitro

Drug administration and sampling in vitro was modified based on previous references (Li et al., 2009; Sonavanea et al., 2008). Full-thickness mouse skin was excised from the dorsal region of the 25% Na_2S treated mouse. The subcutaneous fat, tissue and blood vessel were carefully removed. The treated skin was mounted on the donor compartment with the stratum corneum side facing downward into the receptor compartment. 15 mL of normal saline (pH 7.4) was used as the receptor medium. The donor compartment was filled with 5 mL of drug solution. The available diffusion area between compartments was 2.98 cm^2. The temperature of the whole system was kept at 37 °C. To stabilize the whole system, two compartments were connected to each other 15 min before drug solution was administered into the donor partition, and 1 mL of receptor medium was sampled before the moment of drug administration as control. 0.25, 0.5, 1, 2, 4 and 6 h were set as time points to collect samples from the receptor compartment from the moment of drug administration. Every sample was 1 mL of the receptor medium, and 1 mL of normal saline was added into the receptor compartment after each sampling. Each time point included triplicate analysis.

2.3.2. The permeation in vivo

Drug administration and sampling in vivo was modified based on a previous reference (Morris et al., 2009). The mice were divided into 4 groups; each group had 3 mice. 1 group was control, which was administered with normal saline. And the others were trial groups, which were liniment-administered 1, 2 and 3 times, respectively. The drug was administered on the epidermal hair-removed skin, and each administration had intervals of 0.5 h. The animal was killed and the subcutaneous tissue of the drug-administered region was collected immediately 0.5 h after the last drug administration. Samples were weighed, and stored at −20 °C to prepare for analysis. The experimental procedure was as displayed in Table 1.

2.4. Determination of geniposide in blood

The groups of mice and the method of drug administration were the same as above. For each group, the blood of each mouse was collected 30 min after the last administration. Blood plasma was isolated from the blood sample and stored at −20 °C for analysis.

2.5. HPLC analytical methods (Lv et al., 2008)

2.5.1. HPLC system

The HPLC system for geniposide analysis included a Waters 600 pump, a Waters 7725 sample processor, and a Waters 2487 double-UV–vis detector. A Zorbax SB-C18 reverse column (5 μm, 4.6 mm × 150 mm, Agilent) was used. The mobile phase was an acetonitrile:purified water (15:85) mixture at a flow rate of 1.0 mL/min. The detector was set to 238 nm, and the column temperature was controlled at 25 °C. The volume of each injection was 10 μL.

2.5.2. Preparation of samples for HPLC analysis

0.4 mL of plasma from each sample was added to 2 mL of methanol in glass test tubes to denature and deposit protein, and then the mixture was vortexed for 1 min and was subject to 30 min of ultrasonic treatment followed by a 10-min centrifuge at the speed of 1500 rpm. The supernatant was removed to a clear penicillin bottle. After the methanol evaporated at 37 °C, the residue was dissolved in 200 μL of methanol. The solution was moved to an eppendorf tube to centrifuge at 14,000 rpm for 20 min, after which then the supernatant was injected into the HPLC system to be analyzed.

About 300 mg of subcutaneous tissue from each sample was mixed with 2 mL of methanol and homogenized. The homogenate was subject to ultrasonic treatment in a 10 mL glass test tube for 30 min followed by a 15-min centrifuge at a speed of 1500 rpm. The supernatant was removed to a penicillin bottle. The previous step was repeated again with 2 mL of methanol, and the supernatant was removed to the same penicillin bottle. Methanol was evaporated at 37 °C, and the residue was dissolved in 200 μL of methanol. The supernatant, after a 20-min centrifuge at the speed of 14,000 rpm, could be injected into the HPLC system to be analyzed.

2.5.3. Presentations of testing criteria

To determine the quantity of drug release (μg/cm^2) (Wang et al., 2008), a linear equation was used to compute the released drug quantity of each sample. The data from the in vitro experiment was

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