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ORIGINAL ARTICLE

Pharmacokinetic study of eplerenone in rats after long-term coadministration with buckwheat tea

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Abstract The aim of this study was to investigate the effect of long-term intake of Tartary buckwheat tea on the pharmacokinetics (PK) of eplerenone in rats. A validated high-performance liquid chromatography-mass spectrometry (HPLC-MS) method was established to determine the eplerenone in plasma, and the portal vein absorption model was applied to conduct the pharmacokinetic study. Two groups of animals—buckwheat tea group and control group—were involved in this study. Plasma samples were obtained at different time points after administration, and were separated on Shimadzu HPLC-MS 2020 instruments. The method showed good linearity ($r = 0.9988$) over a wide dynamic range (0.20–50 μg/mL). Within- and between-batch precisions ranged from 2.13% to 7.90%. The extraction recovery rates ranged from 91.96% to 94.96%. The data showed that in the Tartarian buckwheat group the area under the curve and maximum concentration of eplerenone were reduced compared with those of the blank group ($p < 0.01$), but the time to reach peak concentrations of eplerenone ($p < 0.01$) was prolonged. The results suggested that long-term consumption of Tartary buckwheat tea might induce the activities of the hepatic drug metabolizing enzyme, which can accelerate the metabolism of eplerenone. According to the results, the dosage of eplerenone should be adjusted in hypertension treatment trials when administered with Tartary buckwheat or Tartary buckwheat-containing dietary supplements to avoid potential drug interactions.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Tartary buckwheat, a dried mature seed of *Fagopyrum genera* in the Polygonaceae family, is mainly produced in southwestern and northern China. It is rich in flavonoids, oleic acid, vitamins, niacin, and dietary fiber [1,2]. The amount of flavonoids in Tartary buckwheat is 10—100 times higher than that of other buckwheat species, in which rutin makes up 70—90%.

Previous studies reported that flavonoids in Tartary buckwheat have hypoglycemic, serum lipid-lowering, and antihypertensive effects [3,4]. As a result, Tartary buckwheat tea has become a popular healthy drink in recent years. It is reported that the main bioactive ingredients of Tartary buckwheat—rutin, quercetin, kaempferol, and naringin [5,6], are inhibitors or activators of CYP3A4, CYP1A1, and CYP1A2 of the cytochrome P450 (CYP450) system [7—10]. Eplerenone, a type of a selective aldosterone receptor blocker, is mainly metabolized by CYP3A4 and has been used for the treatment of hypertension for a long time [11,12]. In clinics, rutin and quercetin frequently result in the emergence of drug—drug interactions by affecting the activities of drug-metabolizing enzymes [13—15]. If eplerenone is simultaneously coadministered with buckwheat tea to patients, the bioavailability and metabolism of eplerenone can be affected.

The purpose of this study is to investigate whether the long-term administration of buckwheat tea could affect the pharmacokinetic (PK) profile of eplerenone in rats. A validated high-performance liquid chromatography-mass spectrometry (HPLC-MS) method was established to determine the eplerenone in plasma, and the portal vein absorption model was applied to conduct the pharmacokinetic study. Two groups of animals, the buckwheat tea group and the control group, were used in the study. The result of this study was expected to provide an experimental foundation for the coadministration of eplerenone and buckwheat tea in the clinical treatment of hypertension.

Materials and methods

Chemicals and reagents

Tartarian buckwheat tea was purchased from Zhengzhong Food Co., Ltd (Xichang, China). Eplerenone, rutin, and quercetin, were purchased from the National Institutes for Food and Drug Control (Beijing, China). Astragaloside (IS) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). β-Cyclodextrin, sodium phosphate buffer solution, and sodium chloride were purchased from Beijing Chemical Corporation (Beijing, China). HPLC-grade acetonitrile and methanol were obtained from Fisher Scientific (Iowa, USA). HPLC-grade formic acid was purchased from Kelong Chemical Industry (Chengdu, China), and ultrapure water was produced using a Millipore Milli-Q system (Millipore, Billerica, MA, USA). All the other reagents used were of reagent grade. The chemical structures of eplerenone and IS are shown in Figure 1.

Animal

Male Sprague—Dawley rats of specified pathogen free (SPF) grade were obtained from the Laboratory Animal Center of Sichuan Health Science Academy (Certificate No. SCXK 2004-6). The rats were housed in an animal room with air conditioning (22—24°C) and free access to food and water. Treatment of all animals was in accordance with the National Institutes of Health Guide to the Care and Use of Laboratory Animals. The experiments were carried out under the approval of Experiment Administration Committee of Sichuan Health Science Academy.

Drug administration

The Tartarian buckwheat water solution for the experiment was prepared by boiling 17.8 g Tartarian buckwheat with 10 times of water for 5 minutes, followed by another 10-minute boiling cycle with 5 times of water. The solution was combined and concentrated to 100 mL. After centrifugation at 13,500*g* for 5 minutes, the clear supernatant was filtered by 0.22-μm (pore size) membrane. The filtrate was considered Tartarian buckwheat test solution, with a concentration of 0.178 g/mL.

We also prepared a lower concentration of Tartarian buckwheat solution as a substitute for the drinking water of the animals. Specifically, 5.34 g Tartarian buckwheat was treated under two boiling cycles (40 times of water for 5 minutes and 45 times of water for 10 minutes). The combined solution was concentrated to 300 mL, with a concentration of 0.0178 g/mL.

Eplerenone physic liquor was prepared by dissolving 1 g of eplerenone in 100 mL of a mixed solution that consisted of 15% β-cyclodextrin, 0.07 mol/L sodium phosphate buffer solution (pH 7.4), and 0.5% sodium chloride.

Animal experiment and drug administration

After 1 week of acclimatization, 20 male Sprague—Dawley rats (200—220 g) were randomly divided into the blank group and the Tartarian buckwheat group (10 rats in each group). Rats in the Tartarian buckwheat group were administered with Tartarian buckwheat water solution [1.78 g/kg, intragastric gavage (i.g.)] twice a day for 29 days. During these days, the lower concentration buckwheat solution substituted for the animals' drinking water. Rats were fasted for 12 hours prior to the experiment with drinking water supply as usual. Rats in the two groups were orally administered with eplerenone solution (100 mg/kg). The blood samples (0.2 mL) were obtained 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 6 hours, 8 hours, and 10 hours after the administration. The blood samples were preserved in a 37°C water bath for 20 minutes and then centrifuged at 3500 rpm for 10 minutes. The upper phase was transferred and preserved in a refrigerator (at −80°C) for future analysis.

Sample preparation

Rat plasma sample (20 μL) was transferred into 4-mL tubes prior to adding 20 μL IS. The mixture was vortexed for 10 seconds, and acetonitrile (2 mL) was then added to form an emulsion. The emulsion was vortexed for 3 minutes followed by centrifugation at 4000 rpm for 8 minutes. The