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Research article

Effect of a soluble prebiotic fiber, NUTRIOSE, on the absorption of ginsenoside Rd in rats orally administered ginseng

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ABSTRACT

Background: There is limited understanding of the effect of dietary components on the absorption of ginsenosides and their metabolites into the blood.
Methods: This study investigated the pharmacokinetics of the ginseng extract and its main constituent ginsenoside Rb1 in rats with or without pretreatment with a prebiotic fiber, NUTRIOSE, by liquid chromatography tandem mass spectrometry. When ginsenoside Rb1 was incubated with rat feces, its main metabolite was ginsenoside Rd.
Results: When the intestinal microbiota of rat feces were cultured *in vitro*, their ginsenoside Rd-forming activities were significantly induced by NUTRIOSE. When ginsenoside Rb1 was orally administered to rats, the maximum plasma concentration (Cmax) and area under the plasma drug concentration–time curve (AUC) for the main metabolite, ginsenoside Rd, were 72.4 ± 31.6 ng/mL and 663.9 ± 285.3 μg·h/mL, respectively. When the ginseng extract (2,000 mg/kg) was orally administered, Cmax and AUC for ginsenoside Rd were 906.5 ± 330.2 ng/mL and 11,377.3 ± 4,470.2 μg·h/mL, respectively. When ginseng extract was orally administered to rats fed NUTRIOSE containing diets (2.5%, 5%, or 10%), Cmax and AUC were increased in the NUTRIOSE receiving groups in a dose-dependent manner.
Conclusion: These findings reveal that intestinal microflora promote metabolic conversion of ginsenoside Rb1 and ginseng extract to ginsenoside Rd and promote its absorption into the blood in rats. Its conversion may be induced by prebiotic diets such as NUTRIOSE.

1. Introduction

Orally administered herbal medicines and functional foods inevitably come in contact with intestinal microbiota [1,2]. The intestinal microbiota are influenced by endogenous and exogenous factors, such as diet, drugs, stress, etc, and they metabolize endogenous compounds secreted into the gastrointestinal tract and orally administered exogenous xenobiotics, such as constituents of herbal medicines and functional foods [3–5]. Thus, intestinal microbiota transform constituents of herbal medicines and functional foods to bioactive compounds prior to absorption [2,6,7].

Ginseng (the root of *Panax ginseng* Meyer, Araliaceae) is frequently used as a herbal medicine and functional food, and ginsenosides, the major constituents, exhibit a spectrum of biological effects, including anti-inflammatory and antitumor activity [2,8,9]. Ginsenosides need to be metabolically activated by human intestinal microbes to express their biological effects [10,11].

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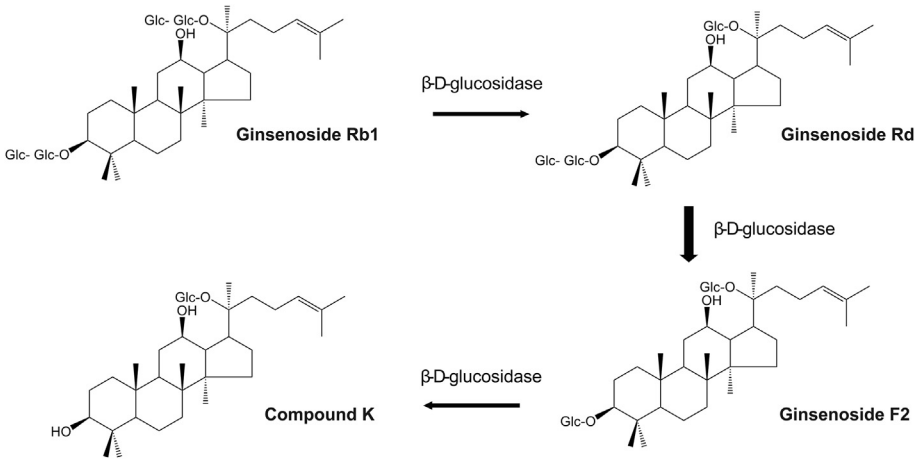

Fig. 1. Metabolic pathway of protopanaxadiol-type ginsenosides metabolized by intestinal bacteria.

Ginsenosides Ra, Rb1, Rb2, and Rc are metabolized primarily to ginsenoside Rd by human intestinal microbiota (Fig. 1) [6,7,12]. Ginsenoside Rd exhibits potent anti-inflammatory, antiobesity, and anti-ischemic effects [13–15], and it is further metabolized to ginsenoside F2 and compound K, which also possess pharmacological activity. Intestinal microbes, therefore, play an important role in the observed pharmacological effects of ginseng. Furthermore, the gastrointestinal absorption of ginseng constituents and metabolites in humans and animals is influenced by regulators of intestinal microbiota such as diet and drugs. Therefore, the effect of diet and subsequent alterations in intestinal bacterial metabolic activities on the pharmacokinetic behaviors of ginsenosides needs to be studied in detail.

NUTRIOSE, used as a food ingredient, is a soluble prebiotic fiber derived from wheat and corn. NUTRIOSE administered orally to healthy men is partially digested (up to 15%) in the small intestine and progressively fermented (up to 75%) in the colon [16]. NUTRIOSE also increased colony counts of intestinal *Lactobacillus* spp. [16–18]. In human individuals given short- and long-term NUTRIOSE supplementations, fecal α/β-glucosidase activities were significantly increased and symptoms of intestinal bowel disease were improved through a protective immune effect.

In the present study, we studied the pharmacokinetics of ginsenoside Rd after oral administration of ginsenoside Rb1 or ginseng extract with or without NUTRIOSE pretreatment in rats, to understand the effect of diet on the relationship between intestinal bacterial metabolic conversion of ginsenosides to ginsenoside Rd and the absorption of ginsenoside Rd into the blood.

2. Materials and methods

2.1. Materials

Ginseng extract was prepared according to the method described by Bae et al [12]. Briefly, the dried root of *Panax ginseng* Meyer (1 kg) produced at Kumsan (Chungnam, Korea) was extracted with 70% ethanol twice, concentrated, and freeze-dried (yield, 18%). The extracted powder contained 8.9% ginsenoside Rb1 and 1.4% ginsenoside Rd. The ethanol extract was suspended in water and successively extracted with hexane and butanol. The butanol fraction was separated by silica gel column chromatography to yield ginsenosides Rb1 (purity > 92%, 52 mg) and Rd (purity > 94%, 8 mg).

NUTRIOSE, a mixture of glucose polymers with a fairly narrow molecular weight range (number-average molecular weight, 200–4000 Da; weight-average molecular weight, 4000–6000; degree of polymerization, 12–25), was kindly donated from Roquette (Lestrem, France).

2.2. Assay of fecal metabolism of ginsenoside Rb1 to ginsenoside Rd

Rat fecal specimens ($n = 5$, approximately 0.2 g) were collected in plastic cups and suspended in 1.8 mL cold saline [19]. The fecal bacterial suspension was centrifuged at 500 × *g* for 5 min, and the resultant supernatant was sonicated and centrifuged at 10,000 × *g* for 30 min. The resultant supernatant was used as a crude enzyme solution.

To investigate the effect of diet on the metabolic activation of ginsenoside Rb1 to ginsenoside Rd by intestinal microbiota cultured in Gifu anaerobic broth (GAM broth), the fresh stool specimen was suspended in GAM broth and centrifuged at 500 × *g*. The resultant supernatant was inoculated in dextrose (1%) or NUTRIOSE (1%) containing GAM broth (glucose-free broth) and cultured for 24 h. The cultured media was collected by centrifugation (10,000 × *g*, 20 min). The precipitate was used as the crude enzyme for assaying the metabolism of ginsenoside Rb1 to Rd. The generated Rd was assayed by high performance liquid chromatography (HPLC).

For assaying the contribution of fecal activity in the metabolism of ginsenoside Rb1 to ginsenoside Rd, a reaction mixture (2 mL) containing 0.2 mL of the fecal culture prepared from freshly collected rat feces ($n = 5$) and 0.2 mL of 0.1mM ginsenoside Rb1was incubated at 37°C for 1 h, which was followed by the addition of 2 mL of MeOH to stop the reaction. The reaction mixture was centrifuged at 3000 × *g* for 10 min, and the levels of ginsenoside Rb1 and its metabolite ginsenoside Rd in the resultant supernatant were analyzed by HPLC. The HPLC system was as follows: a Hewlett Packard series 1050 module, a UV detector (Ramsey, MN, USA) set at 203 nm, a Hypersil ODS column (4.6 × 150 mm i.d., 5.0 μm; Agilent, Santa Clara, CA, USA), linear-gradient mixture of 30% water and 70% acetonitrile for 15 min as elution solvent, flow rate of 1.0 mL/min, and injection volume of 20 μL.

2.3. Animals

Male Sprague–Dawley rats (210–240 g) were supplied by the Orient Experimental Animal Breeding Center (Gyunggi-do, Korea). All animals were housed in wire cages (2 rats per cage) kept at a temperature of 20–22°C and 50 ± 10% humidity, fed standard laboratory chow (Samyang Co., Seoul, Korea), and allowed water *ad libitum*. All experiments were performed in accordance with the National Institutes of Health and Kyung Hee University Guides for

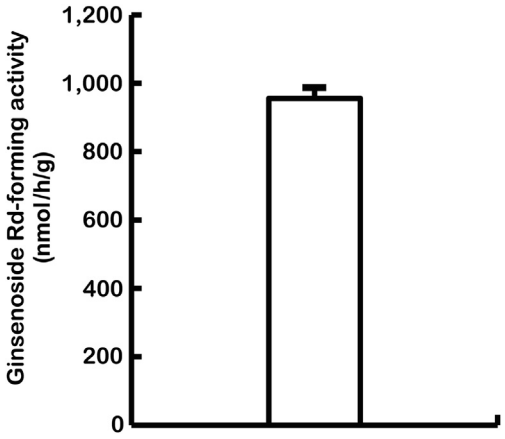

Fig. 2. The metabolic conversion of ginsenoside Rb1 to ginsenoside Rd by rat feces. All values are presented as mean ± standard deviation ($n = 5$).

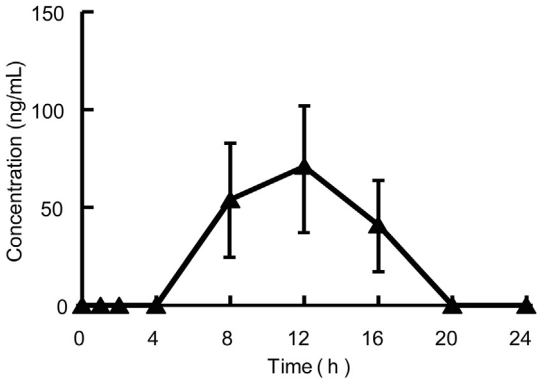

Fig. 3. Plasma concentrations of ginsenoside Rd after oral administration of ginsenoside Rb1 (200 mg/kg) in rats. All values are presented as mean ± standard deviation ($n = 5$).

Laboratory Animals Care and Use and approved by the Committee for the Care and Use of Laboratory Animals in the College of Pharmacy, Kyung Hee University (KHP-2012-04-06-R1).

2.4. Pharmacokinetic study

Each rat was orally fed ginsenoside Rb1, ginseng extract, or vehicle 2 h after the last dose of a 2-wk administration of a NUTRIOSE-containing control diet. Blood was collected (0.2 mL) from the tail vein at 0 h, 1 h, 2 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h after ginseng extract administration.

The rats were divided into 2 groups [either treated with vehicle alone (normal control, $n = 5$) or test agent (200 mg/kg ginsenoside Rb1, $n = 5$)] in a preliminary study and the remaining animals were later divided into seven groups as follows for a subsequent study: Group 1, NOR, group fed a control diet, $n = 5$; Group 2, N-NOR, group fed NUTRIOSE (control diet + NUTRIOSE 10%, $n = 5$); Group 3, G0.2, group treated with ginseng extract (200 mg/kg) after feeding a control diet, $n = 5$; Group 4, G2, group treated with ginseng extract (2,000 mg/kg) after feeding a control diet, $n = 5$; Group 5, N2.5-G2, group treated with ginseng extract (2,000 mg/kg) after feeding NUTRIOSE (control diet + NUTRIOSE 2.5%, $n = 5$); Group 6, N5-G2, group treated with ginseng extract (2,000 mg/kg) after feeding NUTRIOSE (control diet + NUTRIOSE 5%, $n = 5$); and Group 7, N10-G2, group treated with ginseng extract (2,000 mg/kg) after feeding NUTRIOSE (control diet + NUTRIOSE 10%, $n = 5$) in a second substudy. The control diet or NUTRIOSE-containing control diet was administered for 2 wk prior to starting treatment with the ginseng extract.

2.5. Sample preparation and calibration curves

Blood samples were centrifuged for 10 min at 4,000 × g to separate the plasma. The plasma samples (20 μL) were deproteinized with the same volume of acetonitrile for ginsenoside Rd detection. The supernatants were evaporated to dryness under a gentle N_2 stream at 50°C. The residue was reconstituted with 100 μL of 70% methanol. A 2-μL aliquot was injected into the liquid chromatography tandem mass spectroscopy (LC–MS/MS) system. Calibration standards were prepared by spiking 10 μL of working solutions into 90 μL of rat blank plasma over a concentration range of 5–1,000 ng/mL. The calibration curves were generated by plotting the peak area ratios of the analytes to the internal standard vs. the concentrations of analytes, by least-square linear regression. Each standard was prepared in triplicate. The correlation coefficients of the calibration curves were greater than 0.99. The calibration curve equation for ginsenoside Rd was $y = 9.94 \times 10^{-6}x + 3.8 \times 10^{-5}$.

2.6. HPLC-MS/MS instrumentation

For the analysis of ginsenoside Rd, HPLC-MS/MS analyses were performed on Agilent Technologies 1260 Infinity HPLC-6460 Triple Quad Mass Spectrometer (Palo Alto, CA, USA). Chromatographic separation of the sample was performed on a Hypersil BDS C18 column (50 mm × 2.1 mm internal diameter, 5 μL; Thermo Scientific, Waltham, MA, USA). For elution, a linear gradient was applied: CH_3CN–H_2O (40:60, v/v) to CH_3CN–H_2O (95:5, v/v) for 10 min. The flow rate was 0.3 mL/min. Mass spectra were acquired in a positive mode using nitrogen gas at a temperature of 300°C, flow rate of 10 L/min, nebulizer pressure of 20 psi, quadruple temperature of 30°C, and capillary voltage of 4000 V. The precursor–product ion pairs monitored were 969→789 for ginsenoside Rd and 409→238 for the internal standard (amlodipine).

2.7. Pharmacokinetic analysis

The maximum plasma concentration (Cmax) and time to reach maximum drug concentration (Tmax) for ginsenoside Rd were estimated directly from the plasma concentration–time profiles. Area under the plasma drug concentration–time curve (AUC) was calculated by using the log-linear trapezoidal rule for the total period and extrapolated to infinity.

Table 1
Pharmacokinetic study of ginsenoside Rd in rats treated with ginsenoside Rb1 or ginseng extract

Group	Ginsenoside Rd		
	Tmax (h)	Cmax (ng/mL)	AUC (ng·h/mL)
Rb0.2	10.6 ± 2.3	72.4 ± 31.6	663.9 ± 285.3
G0.2	9.6 ± 5.3	690.4 ± 473.0	8974.2 ± 379.9
G2	11.2 ± 5.2	906.5 ± 330.2	11377.3 ± 4470.2
N2.5-G2	8.4 ± 5.0	982.2 ± 455.9	12882.3 ± 8086.5
N5-G2	6.0 ± 4.0	1079.5 ± 422.1	12281.0 ± 7062.0
N10-G2	8.0 ± 4.0	1220.3 ± 796.5	15213.3 ± 6086.7

Group labels are as mentioned in Figs. 4 and 5
AUC, area under the blood concentration curve; Cmax, maximum plasma concentration; Tmax, maximum drug concentration time

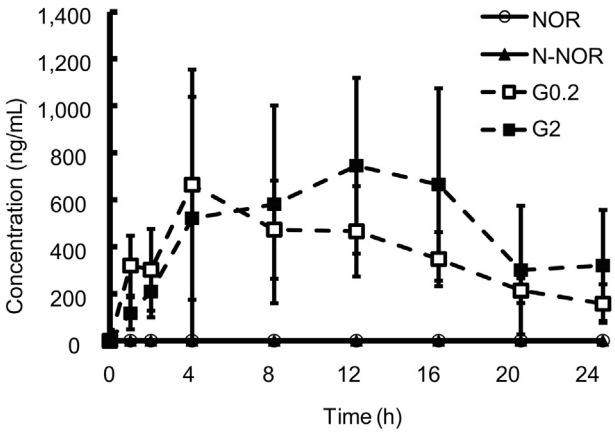

Fig. 4. Pharmacokinetic study of ginsenoside Rd in rats orally administered ginseng extract. Rats were orally administered ginseng extracts at a dose of 200 mg/kg or 2,000 mg/kg after being fed a control diet or NUTRIOSE-containing diet for 2 wk; N-NOR: Group fed with NUTRIOSE (control diet + NUTRIOSE 10%) for 2 wk; G0.2: Group treated with ginseng extract (200 mg/kg) after being fed with a control diet for 2 wk; G2: Group treated with ginseng extract (2,000 mg/kg) after being fed with a control diet for 2 wk. All values are presented as mean ± standard deviation ($n = 5$).

2.8. Statistical analysis

Statistical analysis was performed using a one-way analysis of variance (ANOVA; IBM SPSS version 20.0; IBM Corp., Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Fecal metabolic activities of rats for ginsenoside Rb1 in vitro

To confirm the ability of intestinal microflora to metabolize ginsenosides to ginsenoside Rd, we measured ginsenoside Rd levels after exposure of rat feces to ginsenoside Rb1 (Fig. 2). The activity of feces in metabolizing ginsenoside Rb1to ginsenoside Rd ranged from 927 nmol/h/g to 970 nmol/h/g, and the mean activity was 955 nmol/h/g.

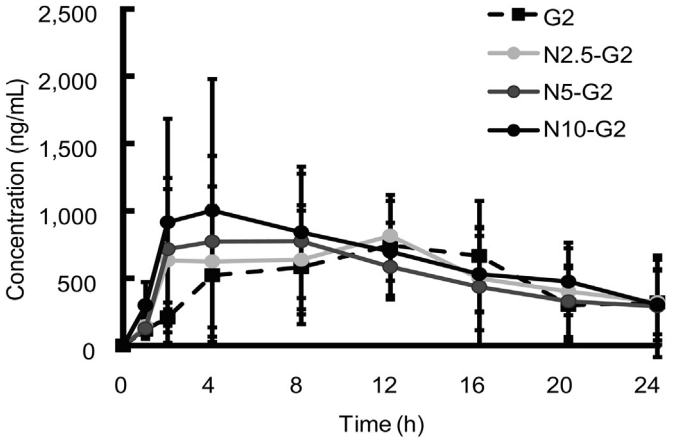

Fig. 5. Pharmacokinetic study of ginsenoside Rd in rats orally administered ginseng extract with or without NUTRIOSE. Rats were orally administered ginseng extracts at a dose of 2,000 mg/kg after being fed a control or NUTRIOSE-containing diet for 2 wk. G2: Group treated with ginseng extract after being fed a control or NUTRIOSE-containing diet for 2 wk; N2.5-G2: Group treated with ginseng extract after being fed with NUTRIOSE (control diet + NUTRIOSE 2.5%) for 2 wk; N5-G2: Group treated with ginseng extract after being fed with NUTRIOSE (control diet + NUTRIOSE 5%) for 2 wk; N10-G2: Group treated with ginseng extract after being fed with NUTRIOSE (control diet + NUTRIOSE 10%) for 2 wk. All values are presented as mean ± SD ($n = 5$).

Fig. 6. Effect of NUTRIOSE on the intestinal bacterial metabolic conversion of ginsenoside Rb1 to ginsenoside Rd in rat fecal microbiota cultured in general anaerobic medium. All values are presented as mean ± standard deviation ($n = 4$). * $p < 0.05$ compared with dextrose.

3.2. Pharmacokinetic study of ginsenoside Rd in rats orally treated with ginsenoside Rb1 or ginseng extract

To investigate whether the metabolite ginsenoside Rd is absorbed into the blood in rats orally administered with ginsenoside Rb1, we orally administered ginsenoside Rb1 (200 mg/kg) or ginseng extract (200 mg/kg or 2,000 mg/kg) to rats and then periodically measured the plasma concentration of ginsenoside Rd, which is a ginsenoside Rb1 metabolite (Fig. 3). When the rats were administered with ginsenoside Rb1 (200 mg/kg), the Tmax of ginsenoside Rd was 10.6 ± 2.3 h and the Cmax and AUC of ginsenoside Rd were 72.4 ± 31.6 ng/mL and 663.9 ± 285.3ng h/mL, respectively (Table 1).

When ginseng extract was administered at 200 mg/kg or 2,000 mg/kg, the Cmax and AUC of ginsenoside Rd were found to be 690.4 ± 473.0 ng/mL and 8974.2 ± 379.9 ng h/mL, respectively, in rats treated with 200 mg/kg ginseng extract, and 906.5 ± 330.2 ng/mL and 11377.3 ± 4470.2 ng h/mL, respectively, in rats treated with 2,000 mg/kg ginseng extract, respectively (Fig. 4, Table 1). However, the differences in Cmax and AUC of ginsenoside Rd between rats treated with 200 mg/kg and 2,000 mg/kg ginseng extract were not significant.

3.3. Effect of NUTRIOSE on the pharmacokinetic parameters of ginsenoside Rd in rats orally treated with ginseng extract

To understand the effect of diet on the absorption of the metabolite ginsenoside Rd into the blood, we measured the plasma concentration of ginsenoside Rd in ginseng extract-treated rats fed with or without pretreatment with NUTRIOSE for 2 wk. We detected ginsenoside Rd when ginseng extract was orally administered in rats both with and without NUTRIOSE pretreatment (Fig. 5). We could detect ginsenoside Rd at 2 h after administration of ginseng extract in rats not fed NUTRIOSE. We also found that NUTRIOSE increased the blood concentration of ginsenoside Rd as compared with to that in the normal control group by up to 30%, although the difference between groups was not statistically significant due to large individual variations (Table 1).

3.4. Effect of NUTRIOSE on the metabolic conversion of ginsenoside Rb1 to ginsenoside Rd by rat fecal microflora cultured in GAM

To further investigate whether NUTRIOSE could induce rat fecal metabolic activity in the conversion of ginsenoside Rb1 to ginsenoside Rd, we cultured fecal microbiota of rats in GAM broth with or without NUTRIOSE for 24 h and measured the ginsenoside Rd-

forming activity (Fig. 6). The cultured fecal microbiota of rats potently hydrolyzed ginsenoside Rb1 to ginsenoside Rd when NUTRIOSE was added. When rat fecal microbiota was cultured in 1% NUTRIOSE-containing GAM broth, the metabolism of ginsenoside Rb1 to ginsenoside Rd was induced 3.4 fold (3.4 ± 1.8, $p = 0.04$) compared with microbiota cultured in dextrose-containing GAM broth.

4. Discussion

Ginseng contains many hydrophilic ginsenosides, which are metabolized to hydrophobic bioactive compounds before absorption into the blood [2]. For example, ginsenosides Ra1, Ra, Rb1, Rb2, Rc, and Rd are metabolized to compound K via ginsenoside Rd by intestinal microbiota of humans and rats. Therefore, to understand the complete spectrum of the pharmacological activities of ginseng, it is important to first understand the metabolism of ginsenosides and study the absorption pattern of the metabolites into systemic circulation. In the present study, we measured ginsenoside Rd, a metabolite of ginsenoside Rb1, in rats orally treated with ginsenoside Rb1. We could also detect the important metabolite ginsenoside Rd after exposure of ginsenoside Rb1 to intestinal microbiota. This metabolite was also detected in rats orally treated with ginseng extract. In previous clinical studies, ginsenoside Rd was detected when G115, a ginseng saponin fraction, was administered orally [20]. We detected ginsenoside Rd 8 h after administration in the blood of ginsenoside Rb1-treated rats. However, in the blood of ginseng extract-treated rats, ginsenoside Rd was detected within 2 h after administration. The rapid absorption of ginsenoside Rd in ginseng extract-treated rats as compared to that in ginsenoside Rb1-treated rats should be due to the higher ginsenoside Rd content in the ginseng extract. We also analyzed the difference in the systemic absorption of the fecal metabolite ginsenoside Rd between rats orally treated with ginsenoside Rb1 and ginseng extract. The Tmax values of ginsenoside Rd were not different between ginsenoside-Rb1-treated and ginseng-extract-treated rats. When the dosage of ginseng extract was increased, Tmax was longer. However, when the same ginsenoside Rb1 and ginseng extract dosage was orally administered, the AUC and Cmax of ginsenoside Rd were 13.5-fold higher in ginseng extract-treated rats than in ginsenoside Rb1-treated rats. These results may be due to ginsenoside Rd contained in the ginseng extract. Furthermore, when the dosage of ginseng extract was increased 10-fold, the AUC of ginsenoside Rd did not significantly increase. These results suggest that when ginsenoside Rb1 was administered orally, the absorption of the metabolite ginsenoside Rd would depend on the metabolic conversion of ginsenoside Rb1 to ginsenoside Rd by intestinal microbiota. Therefore, to increase the rate of absorption of ginsenoside Rd into the blood, intestinal bacterial metabolic activation of ginsenoside Rb1 to ginsenoside Rd may be induced. In the present study, we investigated the effect of a prebiotic, NUTRIOSE, on intestinal bacterial metabolic activity. When the intestinal microbiota of rats were cultured in NUTRIOSE-containing GAM, NUTRIOSE induced the metabolic conversion of ginsenoside Rb1 to ginsenoside Rd. These results suggest that the prebiotic NUTRIOSE may promote the ginsenoside-metabolizing enzyme activity of gastrointestinal microbiota, and that NUTRIOSE-induced microbiota are capable of further potentiating the metabolic conversion of ginsenosides to ginsenoside Rd. We also performed a pharmacokinetic study of ginseng extract in rats fed with NUTRIOSE for 2 wk. Supplementation of NUTRIOSE in the diet significantly increased the AUC and Cmax of ginsenoside Rd in a NUTRIOSE content dependent manner and accelerated this process. Supplementation of 10% NUTRIOSE in the diet caused AUC and Cmax of ginsenoside Rd to increase 1.34-fold. Furthermore, Tmax was shorter in NUTRIOSE-fed rats than in normal diet-treated ones.

In conclusion, the absorption of bioactive metabolite ginsenoside Rd in rats orally administered with ginsenoside Rb1 or ginseng extract was dependent on the metabolic activity of gastrointestinal microflora. Furthermore, oral administration of a prebiotic NUTRIOSE can stimulate the intestinal bacterial metabolic conversion of ginsenoside Rb1 to ginsenoside Rd to improve the absorption of ginsenoside Rd.

Conflicts of interest

All authors declare no conflicts of interest.

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