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Research article

Effect of B-complex vitamins on the antifatigue activity and bioavailability of ginsenoside Re after oral administration

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ABSTRACT

Background: Both ginsenoside Re and B-complex vitamins are widely used as nutritional supplements. They are often taken together so as to fully utilize their antifatigue and refreshing effects, respectively. Whether actually a drug–nutrient interaction exists between ginsenoside Re and B-complex vitamins is still unknown. The objective of this study was to simultaneously investigate the effect of B-complex vitamins on the antifatigue activity and bioavailability of ginsenoside Re after their oral administration. The study results will provide valuable theoretical guidance for the combined utilization of ginseng and B-complex vitamins.

Methods: Ginsenoside Re with or without B-complex vitamins was orally administered to mice to evaluate its antifatigue effects and to rats to evaluate its bioavailability. The antifatigue activity was evaluated by the weight-loaded swimming test and biochemical parameters, including hepatic glycogen, plasma urea nitrogen, and blood lactic acid. The concentration of ginsenoside Re in plasma was determined by liquid chromatography–tandem mass spectrometry.

Results: No antifatigue effect of ginsenoside Re was noted when ginsenoside Re in combination with B-complex vitamins was orally administered to mice. B-complex vitamins caused to a reduction in the bioavailability of ginsenoside Re with the area under the concentration–time curve from zero to infinity markedly decreasing from 11,830.85 ± 2,366.47 h·ng/mL to 890.55 ± 372.94 h·ng/mL.

Conclusion: The results suggested that there were pharmacokinetic and pharmacodynamic drug–nutrient interactions between ginsenoside Re and B-complex vitamins. B-complex vitamins can significantly weaken the antifatigue effect and decrease the bioavailability of ginsenoside Re when simultaneously administered orally.

1. Introduction

Ginseng is the root of *Panax ginseng* Meyer, which has been used as a kind of herbal medicine in the Oriental countries for thousands of years. In 2009, the International Codex Alimentarius Commission in the 32nd session passed the international standards for ginseng, which stipulated that cultivated ginseng can be used in food, thereby allowing ginseng to be more widely used as a kind of herbal medicine and functional food. The main bioactive constituent of ginseng is ginsenoside, which is usually extracted and evaluated in biochemical analysis. So far, over 180 types of ginsenoside have been identified [1,2]. Ginsenoside Re is one of the major constituents of ginsenosides. This exhibits many bioactivities including antifatigue effects, antioxidant effects, protection of endothelial cells, and attenuation of diabetes-associated cognitive deficits [3–5].

B vitamins are water soluble. Adequate levels of vitamin B are essential for the optimal performance and metabolic activity of a host and several studies have also confirmed that they can improve cognitive performance and mood [6–9]. However, they cannot be synthesized by the human body, and thus, daily intakes are necessary. B vitamins mainly include vitamin B_1, vitamin B_2,

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vitamin B_3, vitamin B_5, vitamin B_6, vitamin B_7, vitamin B_9, and vitamin B_{12}. B vitamins as a group are essential for the normal functioning of all living cells. If there is a reduction in the levels of one of the B vitamins, the entire metabolic process rapidly comes to a standstill. To achieve best results, all kinds of B vitamins should be taken together [10]. Therefore, B-complex vitamins are often recommended as nutritional supplements.

Nowadays, both ginsenoside Re and B-complex vitamins are widely used as nutritional supplements. They are often taken together so as to fully utilize their antifatigue and refreshing effects, respectively. However, drug and nutrient as exogenous substances are absorbed into the body and share several common sites of transport, absorption, distribution, metabolism, and elimination, each of which may lead to the drug–nutrient interaction. Whether actually a drug–nutrient interaction exists between ginsenoside Re and B-complex vitamins is still unknown. Drug–nutrient interactions draw less attention than drug–drug interactions [11–13]. The objective of this study was to simultaneously investigate the effect of B-complex vitamins on the antifatigue activity and bioavailability of ginsenoside Re after their oral administration. The study results will provide valuable theoretical guidance for the combined utilization of ginseng and B-complex vitamins.

2. Materials and methods

2.1. Chemicals and reagents

Ginsenoside Re (≥ 98.0% purity) was purchased from School of Chemistry, Jilin University (Changchun, China). Digoxin [internal standard (IS)] with purity of 98.0% or more was purchased from Pure Chemical Standard Co., Ltd. (Chengdu, China). Vitamin B_1 (≥ 99%), vitamin B_2 (≥ 98%), vitamin B_3 (≥ 99%), vitamin B_5 (≥ 99%), vitamin B_6 (≥ 99%), vitamin B_7 (≥ 97%), vitamin B_9 (≥ 97%), and vitamin B_{12} (≥ 98%) were purchased from Shanghai Yuanye Bio-Technology Co., Ltd. (Shanghai, China). Liver glycogen assay kits, urea assay kits, and lactic acid (LA) assay kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Ammonium hydroxide (HPLC grade) was purchased from Beijing Chemical Works (Beijing, China).

Solid-phase extraction (SPE) columns (Oasis HLB 3 cm^3/60 mg) were purchased from Waters (Milford, MA, USA). Methanol and acetonitrile (both HPLC grade) were purchased from Fisher Scientific (NJ, USA). Milli-Q (Millipore) water was used in all experiments. All other chemicals were of HPLC or analytical grade.

2.2. Animals

ICR strain male mice (weight 17–21 g) for the antifatigue experiment were purchased from Yisi Laboratory Animal Technology Co., Ltd. [Qualified No. SCXK (Ji)-2011-0004, Changchun, China] and male Sprague-Dawley rats (weight 230–260 g) for the bioavailability experiment were purchased from Changsheng Bio-Technology Co., Ltd. [Qualified No. SCXK (Liao)-2010-0001, Dalian, China]. Animals were housed under standard conditions in an animal house with free access to food and water, with a 12:12-h light–dark cycle at a consistent temperature (22 ± 2°C) and humidity (50% ± 10%). All experiments were designed in accordance with the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health and approved by the Committee of the Institute of Special Economic Animals and Plants, Chinese Academy of Agricultural Science.

2.3. Antifatigue study

2.3.1. Grouping and treatment

After a 7-d acclimatization to the laboratory conditions, a total of 160 male ICR mice were randomly divided into the following four groups ($n = 40$ per group): control group (normal saline); Re group (5 mg/kg ginsenoside Re); B-complex vitamins group (vitamin B_1 2.25 mg/kg, vitamin B_2 2.25 mg/kg, vitamin B_3 7.50 mg/kg, vitamin B_5 3.45 mg/kg, vitamin B_6 1.50 mg/kg, vitamin B_7 22.50 μg/kg, vitamin B_9 60.00 μg/kg, and vitamin B_{12} 1.50 μg/kg [6–9]); and mixture group, which received both ginsenoside Re and B-complex vitamins. The administration dose, however, in the mixture group was the same as that used in the aforementioned three groups. Each mouse was orally administered with the drug for 30 consecutive days. The health status of the mice was observed each day and all mice were weighed every 2 d. According to the *Technical Standards for Testing and Assessment of Health Food* (2003 edition), the weight-loaded swimming time, hepatic glycogen level, plasma urea nitrogen level, and blood LA level were tested to estimate the antifatigue effect [14].

2.3.2. Loaded swimming test

In brief, the test involved the following steps: 30 min after the last intragastric administration, a lead sheath, weighing 5% of the body weight of the mouse, was tied to the root of the mouse tail. Four tempered glass pools (50 × 40 × 40 cm) were filled with water to a depth of 30 cm. The mice (10/group) were dropped into the water. The swimming time (time from dropping into the water to sinking underwater for over 10 s) was recorded. The water temperature was 25 ± 1°C.

2.3.3. Determination of hepatic glycogen

In brief, determination of hepatic glycogen levels involved the following steps: 30 min after the last intragastric administration, the mice (10/group) were killed by cervical vertebral dislocation and their liver tissues were extracted for further analysis. It is well-known that glycogen in the liver tissues is unstable and loses activity easily *in vivo*; thus, 100 mg liver tissue from each mouse was weighed, cleaned using normal saline, dried with filter paper, and then diluted in lye immediately. To estimate the quantity of glycogen, the anthrone colorimetric method was adapted.

2.3.4. Determination of plasma urea nitrogen

In brief, determination of plasma urea nitrogen involved the following steps: 30 min after the last intragastric administration, the mice (10/group) were forced to swim in pools filled with water maintained at 30 ± 1°C for 90 min without weight loading. After a 60-min resting period, blood was sampled from eyes and collected in tubes containing heparin. Plasma samples were collected by centrifugation for 10 min at 3,800 rpm, and concentrations of plasma urea nitrogen were analyzed using urea assay kits.

2.3.5. Determination of blood LA

In brief, determination of blood LA involved the following steps: 30 min after the last intragastric administration, 20 μL of blood was drawn from the mice (10/group) with a syringe needle using the retro-orbital bleeding method. The mice were then forced to swim for 10 min without weight loading, and blood was drawn immediately after and 20 min after swimming. The LA levels were measured using LA assay kits.

2.4. Bioavailability study

2.4.1. Experimental protocols and blood sampling

After a 7-d acclimatization to the laboratory conditions, the rats were allowed to fast for 12 h with free access to water prior to

experiment. The 10 rats in this group were divided into two subgroups ($n = 5$ per subgroup) randomly, namely, the ginsenoside Re group and the mixture group. The ginsenoside Re group received an oral dose of 200 mg/kg ginsenoside Re, whereas the mixture group received an oral dose of 200 mg/kg ginsenoside Re and B-complex vitamins (vitamin B_1 1.5 mg/kg, vitamin B_2 1.5 mg/kg, vitamin B_3 5 mg/kg, vitamin B_5 2.3 mg/kg, vitamin B_6 1 mg/kg, vitamin B_7 15 μg/kg, vitamin B_9 40 μg/kg, and vitamin B_{12} 1 μg/kg [6–9]).

Aliquots of 0.2-mL blood samples were collected at predetermined time points (0 h, 0.083 h, 0.25 h, 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 5.0 h, 8.0 h, 10.0 h, 12.0 h, 24.0 h, and 48.0 h) via the caudal vein after the administration of respective doses, and the samples were added into tubes containing heparin. Subsequently, plasma samples were prepared by centrifugation for 10 min at 3,800 rpm and stored at −80°C for further analysis.

2.4.2. Blood sample preparation

An aliquot of 50-μL plasma samples was removed from the −80°C storage and thawed under ambient temperature. Preconditioning of the SPE column was performed by washing the column with 3.0 mL methanol and 3.0 mL deionized water successively. Plasma sample was spiked with 10 μL of an IS solution (8 μg/mL digoxin dissolved in water) and then loaded onto a preconditioned SPE column after diluting tenfold with 4% phosphoric acid solution. The column was then washed with 1.0 mL of water and 1.0 mL of methanol successively. The methanol eluent was finally dried under a flow of nitrogen at 37°C and dissolved in 100 μL of water:methanol (50:50, v/v) for liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis.

2.4.3. Liquid chromatography–tandem mass spectrometry analysis

A 5-μL aliquot of the prepared sample solution was used for the LC–MS/MS analysis. The LC–MS/MS analysis was performed on UPLC/XEVO TQ with electrospray ionization source (Waters). The separation was achieved using a BEH C_{18} column (2.1 × 50 mm, 1.7 μm, Waters) with a mobile phase consisting of 0.01% (w/v) ammonium hydroxide–acetonitrile solution as Solvent A and 0.01% (w/v) ammonium hydroxide solution as Solvent B at a flow rate of 0.5 mL/min. A gradient elution system was used as follows: 0–1.0 min, 28–35% A; 1.0–1.5 min, 35–75% A; 1.5–2.5 min, 75% A; 2.5–3.0 min, 75–28% A; 3.0–4.0 min, 28% A. The column temperature was kept constant at 35°C. Mass spectrum analysis was carried out using negative multiple reaction monitoring (MRM) mode. The precursor–product ion pairs, fragmentor voltage (Frag. V in volts), and collision energy (CE in volts) for the analytes were as follows: m/z 945.7735 > 637.6352 for the quantitative ion pair of ginsenoside Re (Frag. 72 V, CE 36 V), m/z 945.7735 > 475.5107 for the qualitative ion pair of ginsenoside Re (Frag. 72 V, CE 44 V) (Fig. 1); m/z 779.6530 > 649.5557 for the quantitative ion pair of IS (Frag. 66 V, CE 32 V), m/z 779.6530 > 475.4506 for the qualitative ion pair of IS (Frag. 66 V, CE 44 V). The detection parameters were optimized as follows: nebulizer pressure, 2.8 kV; source temperature, 150°C; drying gas temperature, 450°C; drying gas flow, 1,000 L/h; nebulizer gas flow, 50 L/h; and collision gas flow, 0.16 mL/min.

2.5. Statistical analysis

All values were presented as the mean ± standard deviation. Pharmacokinetic parameters were estimated by the noncompartmental model using *WinNonlin 6.3* program package (Pharsight Corporation, Mountain View, CA, USA). The parameters include area under the concentration–time curve from zero to the last sampling time or infinity (AUC $_{0-t}$ or AUC $_{0-\infty}$), maximum observed concentration (C_{max}), and maximum observed time (T_{max}). The AUC $_{0-t}$ was calculated using the linear trapezoidal with linear interpolation method and the AUC $_{0-\infty}$ was extrapolated by the AUC $_{0-t}$, while C_{max} and T_{max} were read directly from individual plasma concentration–time data.

All statistical procedures were performed using SAS version 9.2. First, the data were analyzed by homogeneity test for variance. If the data exhibited homoscedasticity, the significance of the mean difference was determined by one-way analysis of variance (ANOVA), followed by a least significant difference (LSD) t test for multigroup comparisons if the ANOVA manifested a significant difference. Otherwise, it was determined by the Kruskal–Wallis test. All p values less than 0.05 were considered to indicate a statistically significant difference; p less than 0.01 was considered highly significant difference.

3. Results

3.1. Effect of B-complex vitamins on the antifatigue activity of ginsenoside Re

3.1.1. Effects on body weight change

The one-way ANOVA results indicated that there were no significant differences in the body weight of mice among the control, Re, B-complex vitamins, and mixture groups during the initial and terminal stages ($p > 0.05$; Table 1).

3.1.2. Effects on weight-loaded swimming test, levels of hepatic glycogen, and levels of plasma urea nitrogen

According to the one-way ANOVA and LSD t test, the weight-loaded swimming time and the hepatic glycogen and plasma urea nitrogen levels of mice in the ginsenoside Re group showed a highly significant difference compared with those in the control group ($p < 0.01$); however, there were no significant differences in these

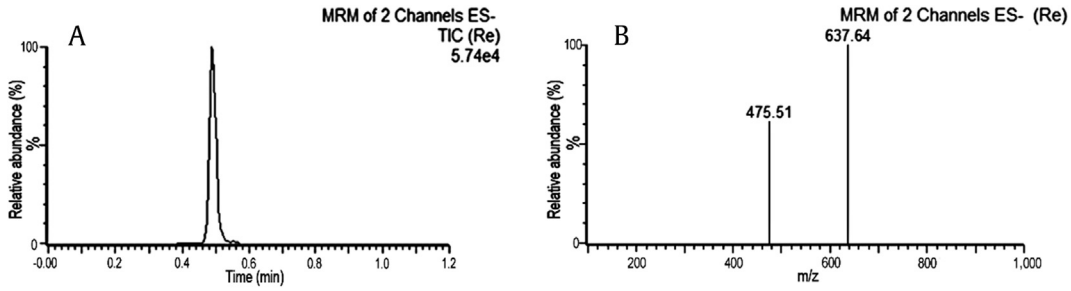

Fig. 1. Multiple reaction monitoring (MRM) chromatograms. (A) MRM chromatogram of ginsenoside Re in the plasma sample after oral administration of ginsenoside Re. (B) MRM mass spectrum of ginsenoside Re in the plasma sample: m/z 945.7735 > 637.6352 for the quantitative ion pair and m/z 945.7735 > 475.5107 for the qualitative ion pair. TIC, total ion current.

Table 1
Effects of ginsenoside Re and B-complex vitamins on body weights in mice

Group	Body weight (g)		
	Initial	Terminal	Increased
Control	20.79 ± 2.36	33.50 ± 3.46	12.71 ± 3.31
Ginsenoside Re	20.55 ± 2.24	33.23 ± 2.35	12.69 ± 2.89
B-complex vitamins	20.71 ± 2.42	34.07 ± 3.41	13.35 ± 3.09
Mixture	21.08 ± 2.17	33.67 ± 2.82	12.59 ± 3.26

Data are presented as mean ± standard deviation.

three indexes among the control, B-complex vitamins, and mixture groups (Table 2).

3.1.3. Effects on blood LA level

According to the one-way ANOVA and LSD *t* test, compared with the control group, only the ginsenoside Re-administrated group demonstrated variations in the levels of blood LA ($p < 0.05$); however, there were no significant differences in the variance of blood LA level among the control, B-complex vitamins, and mixture groups (Table 3).

3.2. Pharmacokinetic profiles

After oral administration of ginsenoside Re (200 mg/kg) and ginsenoside Re (200 mg/kg) in combination with B-complex vitamins to rats, the pharmacokinetic profiles were obtained and analyzed. The results showed that B-complex vitamins significantly reduced the bioavailability of ginsenoside Re after oral administration. Compared with the ginsenoside Re group, the mixture group had lower C_{max1} ($p < 0.01$) and C_{max2} ($p < 0.01$), but higher apparent total clearance/bioavailability ($p < 0.01$). There were no significant differences between T_{max1} ($p > 0.05$), T_{max2} ($p > 0.05$), and $t_{1/2}$ (half-life) ($p > 0.05$) of ginsenoside Re. Meanwhile, the AUC $_{0-t}$ and AUC $_{0-\infty}$ of ginsenoside Re were 14- and 13-fold higher in ginsenoside Re-treated rats than those in rats in the mixture group, respectively (Fig. 2; Table 4).

Table 2
Effects of ginsenoside Re and B-complex vitamins on the loaded swimming time, hepatic glycogen, and plasma urea nitrogen levels in mice

Group	Loaded swimming time (min)	Hepatic glycogen (mg/g)	Plasma urea nitrogen (mmol/L)
Control	5.34 ± 1.14	12.90 ± 3.17	9.17 ± 1.27
Ginsenoside Re	9.67 ± 2.36 **	18.93 ± 3.08 **	7.38 ± 0.64 **
B-complex vitamins	5.02 ± 0.82	14.39 ± 3.26	9.24 ± 2.55
Mixture	5.94 ± 1.10	11.00 ± 1.66	8.43 ± 1.15

Data are presented as mean ± standard deviation.
** $p < 0.01$, compared with the control group.

Table 3
Effects of ginsenoside Re and B-complex vitamins on the variance of blood LA level in mice

Group	Blood LA level (mmol/L)			
	Before swimming	0 min after swimming	20 min after swimming	Variance of blood LA [1)]
Control	2.61 ± 1.47	3.09 ± 0.71	2.55 ± 1.14	78.74 ± 23.93
Ginsenoside Re	2.37 ± 1.63	2.73 ± 0.92	1.09 ± 0.35 *	57.43 ± 9.79 *
B-complex vitamins	2.36 ± 0.57	2.95 ± 0.41	2.89 ± 1.23	72.53 ± 11.48
Mixture	2.55 ± 1.65	3.39 ± 1.14	2.17 ± 0.67	73.08 ± 9.64

Data are presented as mean ± standard deviation.
* $p < 0.05$, compared with the control group.
LA, lactic acid.
[1)] Variance of blood lactic acid = 5 × (lactic acid level before swimming + 3 × lactic acid level 0 min after swimming + 2 × lactic acid level 20 min after swimming).

3.3. Validation of the LC–MS/MS assay

The UPLC/XEVO TQ operated in the MRM mode (for LC–MS/MS assay) was suitable for the quantitative analysis of ginsenoside Re in rat plasma collected at different time points. Calibration standards were prepared by spiking working solutions into 50 μL of rat blank plasma. Ginsenoside Re presented a good linearity with the correlation coefficient (R^2) being higher than 0.99 over the ranges of 1.0–1,000.0 ng/mL. The lower limit of quantitation and lower limits of detection of these analytes using the rat blank plasma were 0.8 ng/mL (S/N = 10) and 0.2 ng/mL (S/N = 3), respectively. The specificity of the method was confirmed by comparing MRM chromatograms of Re and the IS for a blank rat plasma sample with a spiked rat plasma sample. The analytes could be detected without any significant interference. The recoveries of ginsenoside Re ranged from 91.9% to 98.9%, which were estimated using spiked plasma at high, middle, and low concentrations. The precision of the method was determined using the derivation of the peak areas of quality-control (QC) plasma sample at six consecutive sampling times. The relative standard deviation of ginsenoside Re was 1.0%. The intraday precision of the method was 4.5%, which was determined using the derivation of the peak areas of QC plasma sample at different sampling times on the same day. The interday precision of the method was 7.1%, which was determined using the derivation of the peak areas of QC plasma sample on consecutive days.

4. Discussion

Ginsenoside Re has been demonstrated to exhibit antifatigue effect and B-complex vitamins are common nutritional supplements that provide refreshment. Ginsenoside Re and B-complex vitamins are often taken simultaneously. Through the antifatigue experiment in mice, we found that orally administrated Re showed no significant difference in the body weights of mice, but rather it prolonged the weight-loaded swimming time ($p < 0.01$) compared with mice in the control group. An analysis of biochemical parameters related to fatigue also demonstrated that the hepatic glycogen level of mice in the Re group was significantly increased ($p < 0.01$), although the plasma urea nitrogen level and the variance of LA after swimming were significantly decreased compared with those in the control group ($p < 0.01$ and $p < 0.05$, respectively). These results indicated that ginsenoside Re exerts an antifatigue effect. However, there were no significant differences in the weight-loaded swimming time, the hepatic glycogen level, the plasma urea nitrogen level, and the variance of LA after swimming among the mice in the control, B-complex vitamins, and mixture groups, which indicated that B-complex vitamins do not have the antifatigue effect; meanwhile, no antifatigue effect of ginsenoside Re was noted when ginsenoside Re was orally administered to mice in combination with B-complex vitamins.

Recent research has demonstrated that ginsenoside Re has a poor bioavailability (only 0.24%) [15,16]. Drug–drug interactions sometimes can influence the bioavailability of drugs, leading to changes in pharmacodynamic profiles. We speculated that there was a drug–nutrient interaction between ginsenoside Re and B-complex vitamins *in vivo*, resulting in the change of the antifatigue effect of ginsenoside Re. Therefore, ginsenoside Re with or without B-complex vitamins was orally administered to rats in the bioavailability study. Our study results show that B-complex vitamins worsen the bioavailability of ginsenoside Re. Compared with the ginsenoside Re group, the mixture group had markedly reduced

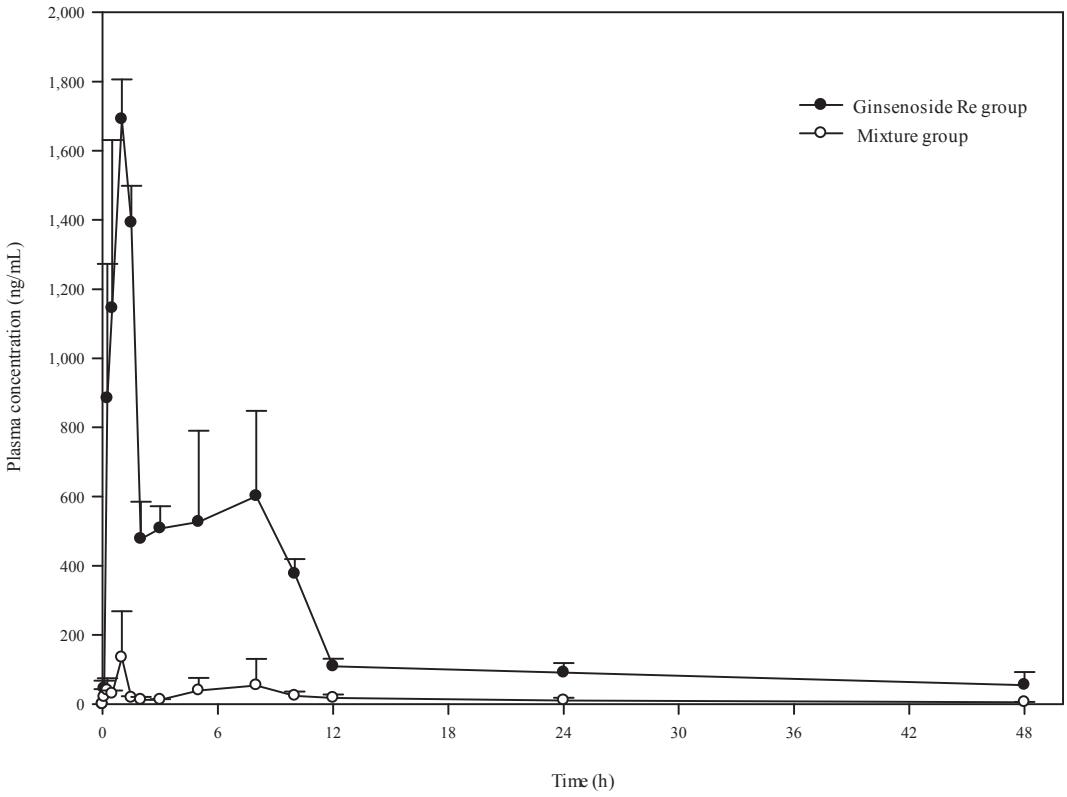

Fig. 2. Mean plasma concentration–time profiles of ginsenoside Re in rats. In the ginsenoside Re group, rats were orally administered ginsenoside Re (dose 200 mg/kg). In the mixture group, rats were orally administered ginsenoside Re in combination with B-complex vitamins (dose 200 mg/kg).

C_{max1} ($p < 0.01$) and C_{max2} ($p < 0.01$). Meanwhile, the AUC $_{0-t}$ and AUC $_{0-\infty}$ of ginsenoside Re in coadministration with B-vitamin complex (mixture-treated rats) became one-fourteenth and one-thirteenth of those noted in rats treated with only ginsenoside Re, respectively. The results proved that there was a drug–nutrient interaction between ginsenoside Re and B-complex vitamins *in vivo*, and this interaction is the most likely cause of reduction of ginsenoside Re antifatigue effect.

As is the case with many other herbal extracts, ginsenoside Re has poor absorption and bioavailability due to its poor membrane permeability [17,18], active biliary excretion [19], and tendency to form self-micelles [20,21]. Oral administration of ginsenoside Re mixed with B-complex vitamins significantly reduced the initial absorption of Re compared with administration of ginsenoside Re alone in terms of C_{max} and AUC. The reduction might be due to the affected absorption of ginsenoside Re in the gastrointestinal tract, rather than due to the decreased clearance as there were no significant differences in the $t_{1/2}$ of Re in plasma [22]. Ginsenoside Re and B vitamins may form some new macromolecular compounds with lower lipid solubility, thus leading to the poorer membrane permeability of ginsenoside Re. By contrast, most of the drug–drug interactions are caused by metabolizing enzymes and P-glycoprotein (P-gp) [23–25]. The levels of cytochrome P_{450} enzymes in the intestines are less than those in the liver. Therefore, we speculated that the change in enzyme activity that contributed to the interactions between ginsenoside Re and B-complex vitamins is limited. Ginsenosides are a good substrate for P-gp [26,27], and it is possible that B-complex vitamins could have enhanced the expression levels of P-gp in intestines, which led to the poorer absorption of ginsenoside Re. Some studies have suggested that the transport mechanism of ginsenosides is passive diffusion [19,28]; by contrast, the main transport mechanism of B vitamins is active transport [29,30]. However, because both passive diffusion and active transport require a specific carrier protein, it is possible that B-complex vitamins might interfere in the role of carrier protein of ginsenoside Re. Nevertheless, elucidating and confirming this role needs additional studies.

In conclusion, the results presented in this work suggest that when ginsenoside Re was orally administered in combination with B-complex vitamins, there was a significant reduction in the bioavailability of ginsenoside Re, which can weaken the antifatigue effect of ginsenoside Re. The results suggested that there were

Table 4
Pharmacokinetic parameters of ginsenoside Re in rats after oral administration of ginsenoside Re with and without B-complex vitamins

Group	Ginsenoside Re	Mixture
T_{max1} (min)	54 ± 13	35 ± 29
C_{max1} (ng/mL)	1,703.85 ± 104.15	129.46 ± 104.04 **
T_{max2} (min)	468 ± 107	492 ± 123
C_{max2} (ng/mL)	623.02 ± 257.82	75.92 ± 68.83 **
AUC $_{0-t}$ (h·ng/mL)	9,896.68 ± 1,234.48	695.22 ± 232.75 **
AUC $_{0-\infty}$ (h·ng/mL)	11,830.85 ± 2,366.47	890.55 ± 372.94 **
$t_{1/2}$ (min)	500.56 ± 368.88	536.70 ± 356.89
CL/F (L/min/kg)	0.32 ± 0.044	3.91 ± 0.46 **
Vd/F (L/kg)	250.73 ± 159.70	3,019.93 ± 2,166.78 **
MRT $_{0-t}$ (min)	664.57 ± 79.16	849.52 ± 341.70
MRT $_{0-\infty}$ (min)	895.45 ± 312.28	974.15 ± 426.34

Data are presented as mean ± standard deviation.
** $p < 0.01$, compared with the ginsenoside Re group.
AUC $_{0-t}$, area under the concentration–time curve from zero to the last sampling time; AUC $_{0-\infty}$, area under the concentration–time curve from zero to infinity; CL/F, apparent total clearance/bioavailability; MRT $_{0-t}$, mean residence time from zero to the last sampling time; MRT $_{0-\infty}$, mean residence time from zero to infinity; Vd/F, apparent volume of distribution/bioavailability.

pharmacokinetic and pharmacodynamic drug–nutrient interactions between ginsenoside Re and B-complex vitamins. Thus, it is better not to orally administer ginsenoside Re and B-complex vitamins simultaneously.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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