Ginseng, an herbal drug, has been extensively used in traditional oriental medicine for preventive and therapeutic purposes for over 2000 years. Ginseng has a wide range of pharmacological activities, including immunomodulatory effects, anti-inflammatory activity, anti-tumor activity, improvement of physical stamina, and stimulation of the appetite, and is also thought to have effects on learning, memory and behavior. Being a “cure-all” or panacea, ginseng is usually used as a general health tonic. Its major active components are ginsenosides, a diverse group of steroidal saponins, which demonstrate the ability to target multitudinous tissues, producing an array of pharmacological responses. Ginsenosides are characterized according to the number and position of sugar moieties on the sterol chemical structure (Fig. 1). Based on their structural differences, ginsenosides are divided into three main categories, the 20(S)-protopanaxadiol, 20(S)-protopanaxatriol and oleanane families. The 20(S)-protopanaxatriol family chemically differs from the 20(S)-protopanaxadiol family by the addition of one hydroxy group at C-6.

Numerous people in many countries have taken ginseng or its derived products, however, little is known about the interactions between ginseng and prescription drugs. Therefore, it is important to evaluate whether ginseng and its active components possess the potential to exert influence on hepatic metabolic enzymes. Cytochrome P450 isoforms (CYPs) are responsible for the majority of the oxidative metabolism of drugs and xenobiotics. The interaction of a new drug with one or more CYPs in vivo would pose a potentially clinically relevant event with other drugs known to be metabolized by the same enzyme. If drug–drug interaction (DDI) studies with form-selective substrates indicate a compound has little affinity for a CYP isozyme, then the need for in vivo interaction studies of these CYPs is not required. Therefore, a study on the effects of drugs on CYP activities may provide valuable information to predict their clinically significant DDI.

There are several reports of the effects of ginseng extract or naturally occurring ginsenosides on CYP activities. However, in most cases, ginseng products are orally administered. Odani et al. have reported that the absorption of naturally occurring ginsenosides Rb1 and Rb2 from the intestines is very poor. Akao et al. also reported that ginsenoside

The intestinal bacterial metabolites of ginsenosides are responsible for the main pharmacological activities of ginseng. The purpose of this study was to find whether these metabolites influence hepatic metabolic enzymes and to predict the potential for ginseng–prescription drug interactions. Utilizing the probe reaction of CYP3A activity, testosterone 6β-hydroxylation, the effects of derivatives of 20(S)-protopanaxadiol and 20(S)-protopanaxatriol families on CYP3A activity in rat liver microsomes were assayed. Our results showed that ginsenosides from the 20(S)-protopanaxadiol and 20(S)-protopanaxatriol family including Rb1, Rb2, Rc, Compound-K, Re, and Rg, had no inhibitory effect, whereas Rg2, 20(S)-panaxatriol and 20(S)-protopanaxatriol exhibited competitive inhibitory activity against CYP3A activity in these microsomes with the inhibition constants (Ki) of 86.4±0.8 μM, 1.7±0.1 μM, and 3.2±0.2 μM, respectively. This finding demonstrates that differences in their chemical structure might influence the effects of ginsenosides on CYP3A activity and that ginseng-derived products might have potential for significant ginseng–drug interactions.

Key words ginseng–drug interaction; intestinal bacterial metabolite; ginsenoside; CYP3A

Fig. 1. Structure of Ginsenosides

20(S)-protopanaxadiol type

Rb1
Rα=glu-gluc,Rβ=H,Rγ=glu-gluc
Rb2
Rα=glu-gluc,Rβ=H,Rγ=glu-threo
Rb
Rα=glu-gluc,Rβ=H,Rγ=glu-threo
Rb1
Rα=H,Rβ=O-gluc-threo,Rγ=glu
Rb2
Rα=H,Rβ=O-gluc-threo,Rγ=glu
Rα=H,Rβ=O-gluc-threo,Rγ=glu

20(S)-protopanaxatriol type

Re
Rα=H,Rβ=glu
C-K
Rα=H,Rβ=O-gluc-threo,Rγ=glu
20(S)-protopanaxatriol (Ptp)
Rα=H,Rβ=O-gluc-threo,Rγ=glu

20(S)-protopanaxadiol (Pd)
20(S)-protopanaxatriol (Pp)

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Compound K (C-K) appears in the plasma of rats after oral administration of Rb1. There are many studies showing that C-K, (also called M-1) is really responsible for the main pharmacological activities of ginseng. For the (20S)-protopanaxatriol ginsenosides, such as Re and Rg1, the intestinal bacterial metabolite is believed to be protopanaxatriol (Ppt), or M-4), which mediates the anticancer actions of ginsenosides. In contrast to the very low absorption rate of Rg1, only 1.9% from intestines, Ppt is easily absorbed.

As the major isozyme of CYPs, CYP3A, which constitutes 30% of the human hepatic P450 complement and 70% of the human small intestine P450 complement and metabolizes 40—50% drugs in clinical use has drawn great attention. Therefore, evaluation of the effect on the activity of CYP3A is important both for drug discovery and in the prediction of potential for herb—drug interactions. In this study, we selected testosterone 6β-hydroxylation (the commonly used specific marker reaction for CYP3A) as the indicator of the activity of CYP3A2, a counterpart of human CYP3A4, in rat liver microsomes. Instead of naturally occurring ginsenosides, this study reported how the ginsenoside intestinal metabolite protopanaxatriol (Ppt), and panaxatriol (Pt) influence the CYP3A-mediated testosterone 6β-hydroxylation in the microsomes.

**MATERIALS AND METHODS**

**Chemicals and Reagents** d-Glucose-6-phosphate, glucose-6-phosphate dehydrogenase, corticosterone, NADP⁺, and 6β-hydroxytestosterone were purchased from Sigma (St. Louis, MO, U.S.A.), EGTA was purchased from Boehringer Mannheim (Mannheim, Germany). Testosterone was obtained from Acros (New Jersey, U.S.A.), and HEPES was obtained from Boehringer Mannheim (Mannheim, Germany). Compound K (C-K), (also called M-1) is really responsible for the main pharmacological activities of ginseng. For the (20S)-protopanaxatriol ginsenosides, such as Re and Rg1, the intestinal bacterial metabolite is believed to be protopanaxatriol (Ppt), or M-4), which mediates the anticancer actions of ginsenosides. In contrast to the very low absorption rate of Rg1, only 1.9% from intestines, Ppt is easily absorbed.

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**Tissue and Microsomes** Healthy male Sprague–Dawlay rats, 210g, were supplied by the Experimental Animal Center of Dalian Medical University. Rat liver microsomes were prepared from liver tissue as described in the literature. Protein concentrations of the microsomal fractions were determined by the Lowry method using bovine serum albumin as a standard.

Protein concentrations of the microsomal fractions were determined by the Lowry method using bovine serum albumin as a standard. In this study, three rat microsomes prepared from three different livers were used.

**Enzymatic Assay** The microsomal incubation conditions used to study testosterone 6β-hydroxylation have been reported. We modified them slightly as follows: each incubation was performed in a 100 μm phosphate buffer at pH 7.4 containing 0.5 mg/ml microsomal protein, 10 μm glucose 6-phosphate, 1 mm NADP⁺, 4 mm magnesium chloride, 1 unit/ml of glucose 6-phosphate dehydrogenase, and testosterone (previously dissolved in methanol, whose final concentration was 1%, v/v) with a range of concentrations in a total volume of 500 μl. There was a 3 min preincubation step at 37°C before the reaction was started by the addition of NADP⁺. After 10 min, the reactions were quenched by adding 500 μl acetonitrile and an internal standard, corticosterone. The incubation mixtures were then centrifuged for 10 min at 20000×g. An aliquot of the supernatant (injection volume of 50 μl) was analyzed by HPLC as described below. The metabolites were quantified using the ratio of 6β-hydroxytestosterone to internal standard, calibration curve.

**HPLC System** The HPLC system (SHIMADZU, Kyoto, Japan) consisted of an SCL-10A system controller, two LC-10AD pumps, a SIL-10A auto injector, a SPD-10A UV detector. The supernatant was analyzed using a SHIMADZU C18 column (4.6×150 mm i.d., 5 μm particle size) and UV detection at 254 nm. A gradient mobile phase consisting initially of 70:30, solvent A (methanol: water: acetonitrile, 39:60:1) versus solvent B (methanol: water: acetonitrile, 80:18:2), was brought to a composition of 30:70 in 15 min and held for 7 min, all at a flow rate of 1 ml/min. Under these conditions, 6β-hydroxytestosterone, corticosterone and testosterone were eluted at 9.3, 14.8, and 19.2 min, respectively.

**Inhibition of Testosterone 6β-Hydroxylation Activity** A typical incubation mixture (final volume, 500 μl) contained 0.5 mg/ml microsomal protein, NADPH-generating system, 50 μm testosterone and different concentrations of ketoconazole, ginsenoside Rb1, Rb2, Re, C-K, Re, Rg1, Rg2, Pt or aglycone Ppt, in a 100 mm phosphate buffer (pH 7.4). Ketoconazole was used as positive control. There was a 3 min preincubation step at 37°C before the reaction was started by the addition of NADP⁺. Testosterone, ketoconazole, and ginsenoside C-K, Re, Rg1, Rg2, Pt and Ppt were previously dissolved in methanol, and the other ginsenosides in water. The final concentration of methanol in the incubation system was 1% (v/v). After 10 min incubation, the reactions were quenched by adding 500 μl of acetonitrile and internal standard. The incubation mixtures were then centrifuged for 10 min at 20000×g. Finally, 50 μl supernatant was used for HPLC analysis.

**Enzymatic Kinetic Analysis** The apparent Kᵢ and Vₑₘᵃₓ values were determined in a range of concentrations of testosterone (20, 40, 60, 80, 100 μm). The apparent inhibition constant (Kᵢ) values were determined in a range of concentrations of testosterone (50, 60, 80, 100 μm) and different concentrations of Rg₁ (0, 10, 20, 50, 100 μm), Pt (0, 1, 5, 10, 20 μm), Ppt (0, 1, 5, 10, 20 μm) or ketoconazole (0, 10, 50, 100, 500, 1000 nm).

**Data Analysis** The apparent kinetic parameters of 6β-hydroxytestosterone formation (i.e., Vₑₘᵃₓ and Kₑₘ) were estimated from the best fit line using least-squares linear regression of inverse substrate concentration versus inverse velocity (Lineweaver–Burk plots), and the mean values were used to calculate kinetic parameters Vₑₘᵃₓ and Kₑₘ. Inhibition data from experiments that were conducted using multiple compound concentrations were graphically represented by Dixon plots and Kₑₘ values were calculated with the use of nonlinear regression according to the equations for competitive inhibition (Eq. 1) and noncompetitive inhibition (Eq. 2),

\[ v = \frac{V_{m} S}{K_{m} + S} + \frac{V_{m} K_{i}}{K_{m} + S} \]  

\[ v = \frac{V_{m} S}{K_{m} + S + K_{i}} \]  

where \( I \) is compound concentration, \( K_{i} \) is the inhibition constant, \( S \) is the substrate concentration, and \( K_{m} \) is the substrate concentration at half the maximum velocity (\( V_{m} \)) of the reaction. The mechanism of inhibition was decided graphically.
from Lineweaver–Burk plots, and from the enzyme inhibition models. The nonlinear regression was made using SPSS v8.0 software (SPSS Inc. Chicago, U.S.A.). IC$_{50}$ values (concentration of inhibitor causing 50% inhibition of original enzyme activity) were determined by Microsoft Excel software (Microsoft Inc, U.S.A.).

RESULTS

Enzymatic Kinetic Parameters for Testosterone 6β-Hydroxylation in Rat Liver Microsomes The apparent $K_m$ and $V_{max}$ values for testosterone 6β-hydroxylation in rat liver microsomes were 29.5±4.4 μM, 4.1±0.3 nmol/min/mg protein, respectively, which were comparable to the values of previous studies.22)

Inhibition of CYP3A Activity by Ginsenosides To investigate whether the ginsenosides can affect the catalytic activity of CYP3A, the testosterone 6β-hydroxylation assay was conducted with varying concentrations of ginsenosides. One specific inhibitor of CYP3A, ketoconazole (KTZ), was used as positive control. The concentrations of 20(S)-protopanaxadiol derivatives Rb$_1$, Rb$_2$, Re, C-K and 20(S)-protopanaxatriol derivatives Re, Rg$_1$, Rg$_2$, Pt and Ppt were 500 μM, 500 μM, 250 μM, 500 μM, 500 μM, 500 μM, 100 μM, 500 μM, and 500 μM, respectively, which approached their maximal soluble concentrations in the incubation system.

Results from our study showed that 20(S)-protopanaxadiol derivatives Rb$_1$, Rb$_2$, Re, and C-K in the adopted concentrations did not exhibit inhibitory activity against the activity of testosterone 6β-hydroxylation in rat liver microsomes. Compared with the control, the testosterone 6β-hydroxylation activities in the presence of Rb$_1$, Rb$_2$, Re, or C-K were 104.9%, 89.0%, 93.7%, or 107.0%, respectively. Among 20(S)-protopanaxatriol derivatives, Re and Rg$_1$ also did not show inhibitory activity against the activity of testosterone 6β-hydroxylation, and compared with the control, the activities of testosterone 6β-hydroxylation in the presence of Re and Rg$_1$ were 95.9% and 96.4%, respectively. However, Rg$_2$, Pt and Ppt exhibited different degrees of inhibition to testosterone 6β-hydroxylation activity in rat liver microsomes. Rg$_2$ weakly inhibited the activity of testosterone 6β-hydroxylation. In the presence of 100 μM Rg$_2$, the activity decreased to 70.6%. Pt and Ppt were found to strongly inhibit the activity of testosterone 6β-hydroxylation. Compared with the control, the remaining activities of testosterone 6β-hydroxylation in the presence (500 μM) of Pt and Ppt were 14.2%, and 19.4%, respectively. We conducted further study in lower concentrations of Pt and Ppt. Compared with the control, the remaining activities of testosterone 6β-hydroxylation in the presence (5 μM) of Pt and Ppt were 48.2%, and 72.9%, respectively (Fig. 2).

Inhibition Kinetic Analysis To further characterize the inhibition of CYP3A activity by Rg$_2$, Pt and Ppt, enzyme inhibition kinetic experiments were performed. We calculated IC$_{50}$ and $K_i$ values of KTZ to compare with previous studies. As positive control, KTZ inhibited testosterone 6β-hydroxylation with an IC$_{50}$ value of 406±112 nM, which was consistent with published data (290 nM) in rat liver microsomes.23) From the relevant data, the $K_i$ value of KTZ calculated was 169.3±10.4 nM.

Rg$_2$ weakly inhibited the activity of testosterone 6β-hydroxylation and diminished the activity to 83.4% at 50 μM and to 71.6% at 100 μM. Pt and Ppt were found to strongly inhibit testosterone 6β-hydroxylation with the remaining activity 54.7% and 76.5% of control, respectively, at 5 μM. At 10 μM, the activity decreased by 62.1% and 51.4%, respectively, which suggested that more than half of the activity had been inhibited by the coexistence of Pt or Ppt at only 10 μM. At 20 μM, the extent of inhibition had reached 73.3% and 63.5%, respectively.

Fig. 2. Inhibitory Effects of Ginsenosides on Activity of Testosterone 6β-Hydroxylation in Rat Liver Microsomes

Reactions were performed in the presence of testosterone (50 μM), without (Ctrl) or with different compounds Rb$_1$ (500 μM), Rb$_2$ (500 μM), Re (250 μM), C-K (500 μM), Rg$_1$ (500 μM), Rg$_2$ (500 μM), Rg$_3$ (100 μM), Ppt (5 μM) and Pt (5 μM) or KTZ (1 μM) in the microsomes (0.5 mg protein/ml) and NADPH-generating system in a 100 μl phosphate buffer (pH 7.4) in a final volume of 500 μl at 37 °C for 10 min. Inhibition data are expressed as percentage of inhibition compared with control incubations (Ctrl) containing no tested compounds. Each point represents the mean of three separate experiments performed in duplicate.

Fig. 3. Representative Lineweaver–Burk Plots and Dixon Plots of the Effect of Rg$_2$ on 6β-Hydroxysteroid Formation in Rat Liver Microsomes

Reactions were performed in the presence of testosterone (50, 60, 80, 100 μM), with various concentrations of ginsenosides Rg$_2$ (0, 10, 20, 50, 100 μM) in the microsomes (0.5 mg protein/ml) and NADPH-generating system in a 100 μl phosphate buffer (pH 7.4) in a final volume of 500 μl at 37 °C for 10 min. Each point represents the mean of three separate experiments performed in duplicate.
The representative Lineweaver–Burk plots for the inhibition of testosterone 6β-hydroxylation by Rg2, Pt and Ppt (Figs. 3—5) and analysis of the parameters of the enzyme inhibition model suggested that the inhibition types of Rg2, Pt and Ppt were competitive. Based on analysis of Dixon plots presented in Figs. 3—5, Rg2 showed a weakly competitive inhibition with $K_i$ of $86.4 \pm 10.0 \mu M$. Pt and Ppt were found to have strongly competitive inhibitory activities against testosterone 6β-hydroxylation with $K_i$ of $1.7 \pm 0.1 \mu M$ and $3.2 \pm 0.2 \mu M$, respectively. These results imply that specific differences in the chemical structure of ginsenosides might influence their effects on CYP3A activities.

**DISCUSSION**

A recent survey in China indicated that 75% of respondents had used traditional Chinese medicine (TCM) during the past year to treat kinds of diseases.23) A similar survey in U.S.A. also showed that in 1997, 42.1% U.S. households used unconventional therapy including herbal medicine, and an estimated 15 million adults took prescription medications concurrently with herbal remedies and/or high-dose vitamins (18.4% of all prescription users).24) This means that numerous persons were at risk for potential herb–prescription drug interactions. Therefore, it is vital to evaluate whether ginseng, one of the most commonly used herbal products, and its active components possess the potential to exert an influence on metabolic enzymes.

CYPs play an important role in the metabolism of exogenous compounds, which catalyze the majority of drugs oxidation, and the effects on CYP activities may result in clinically significant DDI. There are several reports about the effects of ginseng extract or naturally occurring ginsenosides on CYP activities. Based on their in vitro data, Henderson et al. reported that Rd, Rc, and Rf weakly modulate some CYPs activities, while the naturally occurring ginsenosides and eleutherosides tested, including Rb1, Rb2, Rc, Rd, Re, Rf, or Rg1, are not likely to inhibit drug metabolizing enzymes.6) Chang et al. demonstrated that although standardized Panax ginseng extracts (G115) and standardized Panax quinquefolius extracts (NAGE) can decrease human recombinant CYP1A activities, the effects are not due to the naturally occurring ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, or Rg1, are not likely to inhibit drug metabolizing enzymes.6) Other researchers also found that the intestinal absorption of naturally occurring ginsenosides is very poor,7,14) and that the intestinal bacterial metabolites of ginsenosides are really responsible for the main pharmacological activities of ginseng.9–13) To the best of our knowledge, there are still no reports about the effects of intestinal bacterial metabolites of ginsenosides on metabolism enzymes.

The CYP3A subfamily is a major contributor to the elimination of orally administered drugs and also has been recognized to be the most important isoform in drug metabolism. CYP3A2, a counterpart of human CYP3A4, is the constitu-
tive testosterone 6β-hydroxylase in male rat liver,26) and testosterone 6β-hydroxylation best fits a one-enzyme model in rat liver microsomes.23) There are some studies reporting that the metabolism of several compounds, such as docetaxel, Ecteinascidin 743 and so on, was catalyzed by cytochrome P450 isozymes CYP3A2 in rats and CYP3A4 in humans, respectively.27,28) Ghosal et al. reported that anti-rat CYP3A2 antibody inhibited the metabolism of Midazolam, a CYP3A4 probe substrate, in rat, human, and cDNA-expressed human CYP3A4 microsomes.29) In this study, we chose testosterone 6β-hydroxylation as a probe of CYP3A activity.

Our results show that naturally occurring ginsenosides Rb1, Rb2, Re, Rg1, display no inhibitory activity against testosterone 6β-hydroxylation in rat liver microsomes. The results are consistent with Henderson’s observation with cDNA-expressed human CYP3A4.30) The intestinal bacterial metabolite, C-K, of the 20(S)-protopanaxadiol family does not exhibit any inhibitory effects. In contrast, different effects on testosterone 6β-hydroxylation were observed for 20(S)-protopanaxatriol derivatives. Rg2 weakly inhibits the activity of testosterone 6β-hydroxylation in the competitive type, with Ki of 86.4±0.8 μM. Another 20(S)-protopanaxatriol derivative, Pt, also exhibits strongly competitive inhibitory activity, with Ki of 1.7±0.1 μM. Moreover, the intestinal bacterial metabolite of 20(S)-protopanaxatriol ginsenosides, Ppt, was found to have strongly competitive inhibitory activity against testosterone 6β-hydroxylation, with Ki of 3.2±0.2 μM.

In the process of assigning the kinetic and pharmacologic properties of compounds, Ki values were widely used as one of indicators. Compounds can be divided into three groups according to their Ki values: potent inhibitors (Ki <1 μM), intermediate inhibitors (Ki =1—10 μM), and poor inhibitors (Ki >10 μM).30) The potent and intermediate inhibitors of CYPs should be carefully used in medicine practices. Significant inhibition is uncommon for compounds with values of Ki greater than about 75—100 μM because sufficiently high levels are not clinically achieved.29) In addition, after the oral administration of ginseng total saponin (1 g/kg) to rats, Ppt was detected about 0.8 μM in blood at 6 h and 1.5 μM at 24 h. The intestinal absorption of Ppt is time-dependently enhanced.31) Thus, our results indicate that Pt and Ppt, other than Rg2, might have strong potential for in vivo inhibitory effects against CYP3A.

The structural chemical difference in ginsenosides might influence their effects on CYP3A activity. We show that the 20(S)-protopanaxadiol family, differing from the 20(S)-protopanaxatriol family by lacking one hydroxyl group at C-6, exhibits no inhibitory activity against testosterone 6β-hydroxylation. Ppt structurally differs from Rg2 by the two less sugar moieties at position C-6 (Fig. 1), but exhibits much more potent inhibition than Rg2. Although differing at position C-20, Ppt and Pt display almost similar inhibitory activity against testosterone 6β-hydroxylation, with Ki of the same order of magnitude. From our above results, it can be inferred that different substitutional groups at position C-6 of ginsenosides or their derivatives might play an important role in the inhibition potential for CYP3A-mediated DDI, and further study for building a ginsenoside-CYP3A QSAR (quantitative structure—activity relationship) model is needed.

This finding suggests that ginseng products may have the potential for significant ginsenoside–drug interactions after oral administration. But to further illuminate the effect of ginsenosides or intestinal bacterial metabolites on human CYP3A, additional study must be made.

In summary, evaluation of the effects of intestinal bacterial metabolites of ginsenosides on metabolism enzymes may provide much more valuable information to predict the potential for ginseng–prescription drug interactions. In this study, utilizing the probe reaction of CYP3A, testosterone 6β-hydroxylation, the effects of derivatives of 20(S)-protopanaxadiol and 20(S)-protopanaxatriol families on CYP3A activity in rat liver microsomes were evaluated. From our results, the structural chemical differences in ginsenosides might influence the effects of ginsenosides on this activity. 20(S)-protopanaxadiol derivatives exhibit no inhibitory effects, whereas Pt and Ppt, 20(S)-protopanaxatriol derivatives, exhibit potent inhibition of an enzyme-kinetically competitive type against CYP3A activity in rat liver microsomes. This finding offers a hint that the gingseng-derived products might possess the potential for significant ginseng–drug interactions.

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