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Modulatory Effects of Korean Red Ginseng Extract (*Panax ginseng* C.A. Meyer) on Cytochrome P450 after Oral Administration to Mice for 14 Days

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Ginseng is one of the most commonly used herbal medicines and health foods. Korean red ginseng (KRG; *Panax ginseng* C.A. Meyer) extract is known to have potential therapeutic activities, such as anti-viral effects, the amelioration of food allergies, anti-oxidant effects, and obesity reduction. Nevertheless, no reports have been issued the modulatory effects of KRG extract on the activity of cytochrome P450 (CYP). In the present study, we investigated the modulatory effect of KRG extract *in vitro* and *in vivo* by using pooled human liver microsomes and male ICR mice. When human liver microsomes were incubated with KRG extract at 0.01-10 mg/ml, CYP1A2, 2B6, 2C19, 2D6, and 3A were not significantly inhibited by KRG extract, although CYP2B6 was slightly inhibited. Mice were orally administered KRG extract at 50, 250, or 500 mg/kg daily for 3, 7, or 14 days. However, the activities of CYPs in mouse livers were not significantly different from those of vehicle-treated controls. In conclusion, no significant ginseng-drug interaction was observed. KRG extract did not significantly modulate the activities of CYPs *in vitro* or *in vivo*.

Key words : Cytochrome P450, korean red ginseng extract, herb-drug interaction

Introduction

Ginseng is one of the most popular used herbal medicines worldwide. Generally, ginseng itself or natural medicines containing ginseng components are believed to have various therapeutic effects, such as, tonic, immune system enhancement, and physical stamina and appetite stimulating effects. Korean red ginseng (KRG) extract are prepared by steaming and drying fresh ginseng. During this process, the chemical constituents may be transformed, and this is of pharmacologic importance. Recently KRG extract have been reported to have various pharmacological effects, such as, anti-viral, food allergy preventing, anti-oxidant, and anti-obesitic effects [7,9,15,16]. Furthermore, KRG extract has been reported to be an effective remedy for influenza-like illnesses and atopic dermatitis [3,14].

Although the co-administration of drugs with KRG extract may give rise to ginseng-drug interactions, ginseng-drug interactions have not been tested. In herbal medicine, herb-drug interactions are an important research consideration. Of the many reasons for herb-drug interactions, the most important is herb-drug interactions originating from cytochrome P450s (CYPs). The inhibition or induction of the activities of CYPs can lead to pharmacokinetic drug interactions. Representatively, bergamottin in grapefruit juice strongly inhibits CYP3A activity in intestine and liver [13] and hyperforin in St. John's wort extract significantly induces CYP3A in liver [12].

In previous reports, the modulatory effects of ginseng extract or components on CYP activities were investigated *in vitro*. For example, it has been reported that ginsenoside Rd weakly inhibits activities of CYP3A and 2D6 in cDNA expressed CYP enzyme and that standardized ginseng extract reduce the effects of CYP1 family on the activities of human recombinant CYP1A1, 1A2, and 1B1 [2,6]. In one study, eight ginsenosides and their aglycones were found to potently induce CYP1A1 expression, and furthermore, ginsenoside Rf showed a weak effect on CYP3A promoter activation in HepG2 cells [5,10].

Although the regulatory effects of ginseng extract or active components on the activities of CYPs *in vitro* have been reported, no investigation has been conducted on the modulatory effects of KRG extract *in vitro* and *in vivo*. Moreover, the modulatory effects of KRG extract on metabolic enzymes after orally administration to animals or man have not been

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studied. In the present study, we investigated the modulatory effect of KRG extract *in vitro* and *in vivo* using pooled human liver microsomes (HLMs) and male ICR mice in order to study the potential herb-drug interaction. Using cocktail probes for CYP1A, 2B, 2C, 2D, 2E and 3A, the activities of the six major CYPs involved in drug metabolism in human were evaluated after incubating pooled HLMs with KRG extract and in microsomal protein from mice treated with KRG extract orally.

Materials and Methods

Reagents and Samples

KRG extract was purchased from the Korea Ginseng Corporation (Daejeon, Korea). Pooled HLMs were purchased from BD Gentest (Woburn, MA). Glucose 6-phosphate, β-$NADP^+$ and glucose 6-phosphate dehydrogenase were obtained from Sigma Chemical Co. (St. Louis, MO). All other chemicals used were of analytical grade and used as received.

Animal treatment and preparation of liver S9 fractions

Specific pathogen-free male ICR mice were obtained from Orient Bio Inc., (Seongnam, Korea). Animals were received at 4 weeks old and acclimated for at least 2 weeks. Animal quarters were strictly maintained at 23±3°C and 40-60% relative humidity. A 12 hr light/dark cycle was used at an intensity of 150-300 Lux. KRG extract in distilled water at 50, 250, or 500 mg/kg was treated to mice orally for 3, 7, or 14 consecutive days. Twenty-four hours after last dosing, all animals were subjected to necropsy. Livers were removed and homogenized with four volumes of ice-cold 0.1 M potassium phosphate buffer (pH 7.4). The liver S9 fractions isolated by differential centrifugation at 9,000 g were stored at -80°C until required. Protein contents were determined using bovine serum albumin as a standard, as previously described [11]. All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted by the Society of Toxicology (Reston, VA) in 1989.

Enzyme inhibition experiments in pooled human liver microsomes

To determine liver microsomal activities, the probe reactions used were: phenacetin *O*-deethylation for CYP1A2, bupropion 1′-hydroxylation for CYP2B6, omeprazole 5-hydroxylation for CYP2C19, dextromethorphan *O*-demethylation for CYP2D6, chlorzoxazone 6-hydroxylation for CYP2E1, and midazolam 1′-hydroxylation for CYP3A. The cocktail probes consisted with 80 μM phenacetin for CYP1A2, 50 μM bupropion for CYP2B6, 20 μM omeprazole for CYP2C19, 5 μM dextromethorphan for CYP2D6, and 2.5 μM midazolam for CYP3A. Probe substrates were incubated with 0.2 mg of HLM in a final incubation volume of 0.2 ml contained 0.1 M potassium phosphate buffer (pH 7.4), KRG extract, and a NADPH-generating system (NGS) containing 0.1 M glucose 6-phosphate, 10 mg/ml β-$NADP^+$, and 1.0 U/ml glucose-6-phosphate dehydrogenase. The mixture was incubated for 60 min at 37°C after a 5 min-preincubation without the substrate mixture. For identification of inhibition patterns of CYP by KRG extract, the mixture including pooled HLM, NGS and KRG extract was incubated without pre-incubation for 5 min. After incubation, the reaction was stopped by adding 100 μl acetonitrile containing on 0.1% formic acid with internal standard solution (10 μg/ml terfenadine in methanol). Samples were mixed and centrifuged at 16,000 g for 5 min, and 10 μl aliquots were analyzed by LC/MS/MS.

Monooxygenase activities in mice treated with KRG extract

Liver S9 fractions were incubated with cocktail probes with 6 types of CYP substrates, and NGS in 0.1 M potassium phosphate buffer (pH 7.4). After incubation for 60 min at 37°C, the reaction was stopped by adding 100 μl acetonitrile with 0.1% formic acid containing an internal standard solution (10 μg/ml terfenadine in methanol). Sample were mixed and centrifuged at 16,000 g for 5 min, and 10 μl aliquots were analyzed by LC/MS/MS.

Hepatotoxicity Parameters

Liver homogenate protein levels were determined as described by Lowry et al. (1951) [11], using bovine serum albumin as a standard. Lipid peroxides were determined by thiobarbituric acid reaction, as previously described [13], and liver GSH levels were determined using Ellman's method [1].

Instrumentation

The activities of CYP in incubated samples were determined using an AccelaTM LC system coupled to a TSQ

Table 1. IC_{50} values for the inhibition of CYP family members in pooled human liver microsomes by KRG extract

CYP isoforms	Substrate reaction probes	IC_{50} (mg/ml)	
		Without preincubation	With preincubation
CYP1A2	Phenacetin *O*-deethylation	17.7	> 50
CYP2B6	Bupropion 1′-hydroxylation	13.7	8.1
CYP2C19	Omeprazole 5-hydroxylation	> 50	34.2
CYP2D6	Dextromethorphan *O*-demethylation	> 50	> 50
CYP2E1	Chlorzoxazone 6-hydroxylation	> 50	> 50
CYP3A	Midazolam 1′-hydroxylation	> 50	> 50

To determine the presence of inactivation by KRG extract, pooled HLMs (0.2 mg) were pre-incubated with KRG extract at 0.01 to 10 mg/ml in 0.1 M potassium phosphate buffer (pH 7.4) for 15 min in the presence of NGS. CYP substrates were then added and incubated for 60 min at 37°C.

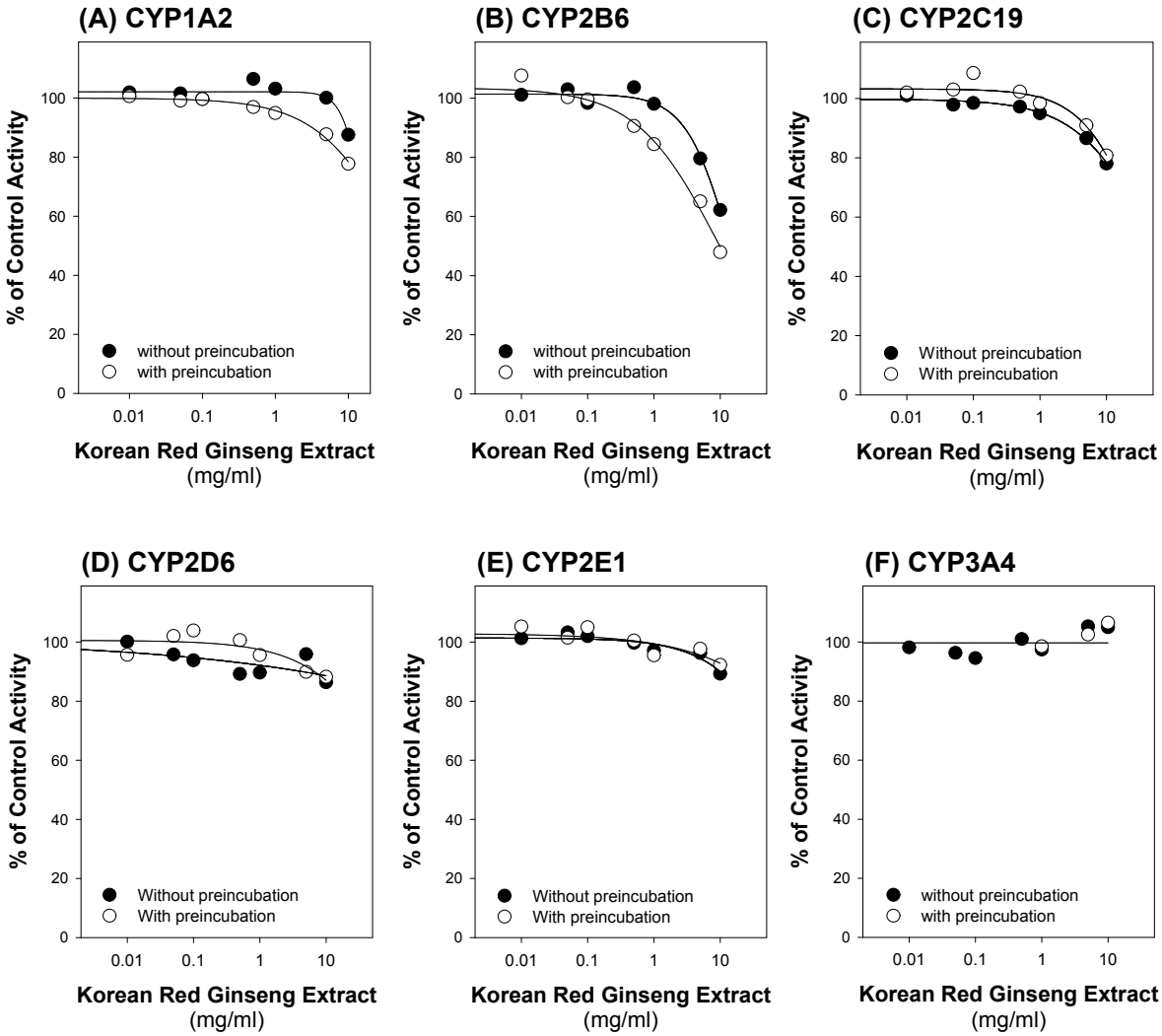

Fig. 1. Inhibition of CYP family members by KRG extract at 0 to 10 mg/ml in pooled human liver microsomes. To determine the inhibition effect of KRG extract on the activities of CYPs, the probe reaction used were: phenacetin *O*-deethylation for CYP1A2, bupropion 1′-hydroxylation for CYP2B6, omeprazole 5-hydroxylation for CYP2C19, dextromethorphan *O*-demethylation for CYP2D6, chlorzoxazone 6-hydroxylation for CYP2E1 and midazolam 1′-hydroxylation for CYP3A. Values are the means of two determinations and are expressed as percentages of control activity.

Table 2. Effects of KRG extract on liver weights in vehicle and experimental male ICR mice

Dose (mg/kg)	Weight ratio (Liver/Body)		
	3 days	7 days	14 days
VH	0.060±0.001	0.059±0.001	0.051±0.001
50	0.061±0.002	0.061±0.001	0.053±0.001
250	0.069±0.004	0.059±0.002	0.054±0.001
500	0.072±0.003*	0.063±0.002	0.054±0.001

Male ICR were treated orally with 50, 250, or 500 mg/kg of KRG extract daily for 3, 7, or 14 days. Animals were subjected to necropsy 24 hour after last treatments. Values are the means±SEs of five animals. The asterisks indicate values significantly different from the vehicle control. VH, vehicle treated animals.

Vantage triple quadrupole mass spectrometer (Thermo Fisher Scientific Inc., USA) equipped with a HESI-II Spray source. Samples (20 µl) were injected into a chromatographic system and separated on an Inertsil® ODS-3 column, 5 µm (2.1×150 mm, GL science) with a guard column C18 (4 mm, 3.0 mm i.d., Phenomenex, USA). The mobile phase consisted of 0.1% formic acid (A) and acetonitrile (B). The initial composition was increased to 90% solvent (B) over 11 min. A gradient program was used for HPLC separation at a flow rate of 230 µl/min. Electrospray ionization was performed at a spray voltage of 4,000 kV in positive mode. Vaporizer and capillary temperature were at 150 and 300°C, respectively. Nitrogen was used as the sheath and as the auxiliary gas, with the optimum values at 45 and 15 (arbitrary units), respectively.

Statistics

Mean values±standard errors (SEs) were determined for each treatment group in given experiments. Dunnett's t-test was used to determine statistical significance. Statistical significance was accepted for p values of <0.05, which are indicated in the text as asterisks. Calculation of IC_{50} values (the concentration of the inhibitor causing 50% inhibition of the original enzyme activity) was based on the curves of mean enzyme activity versus inhibitor concentration using SigmaPlot (version 10.0, Systat Software, Inc.)

Results

Inhibitory effects of KRG extract on monooxygenase activities in pooled human liver microsomes

To study the potential inhibitory effects of KRG extract on individual CYP enzymes, probe reaction assays were conducted using cocktail for CYP1A2, 2B6, 2C19, 2D6, 2E1 and 3A, which are the major CYP family members involved in human drug metabolism (Fig. 1). As shown in Table 1, IC_{50} values were determined for each CYP, and these were used to estimate inhibitory potencies. Although incubation with 0.01-10 mg/ml of extract for 60 min slightly inhibited CYP2B6-catalyzed bupropion 1'-hydroxylation with an IC_{50} at 13.7 mg/ml, other CYPs were not significantly inhibited

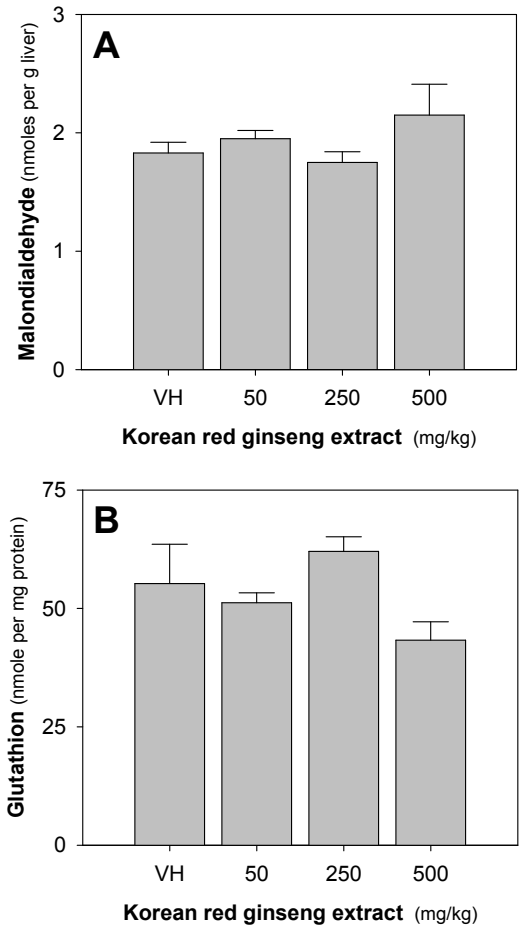

Fig. 2. Effect of KRG extract on malondialdehyde (A) and GSH (B) contents in mouse liver after oral administration. Five male ICR mice were treated orally with 50, 250, or 500 mg/kg daily for 14 days. Animals were subjected to necropsy 24 hours after last treatments. Values are the means±SEs of five animals.

by KRG extract.

Hepatotoxicity of KRG extract

To investigate the toxic effects of KRG extract, changes in liver weights and GSH and malondialdehyde contents were determined after daily treatment for 3, 7, or 14 days with 0, 50, 250 or 500 mg/kg of extract daily. As shown in Table 2, the liver weights were not changed, and GSH and malondialdehyde contents were not decreased by treatment for 14 days daily dose (Fig. 2). Additionally, we determined the activities of serum ALT and AST in animals orally treated with extract for 3, 7, or 14 days. No significant hepatotoxicity was observed versus vehicle treated controls (data not shown).

Modulatory effects of KRG extract on monooxygenase activities in mouse liver

To investigate ginseng-drug interactions *in vivo*, mice

Table 3. Effects of KRG extract on CYP activities after oral administration to mice for 3 days

Activity (pmol/min/mg protein)		Dose (mg/kg)			
		VH	50	250	500
CYP1A	Phenacetin *O*-deethylation	204.4±21.7	206.1±19.3	241.3±19.0	173.6±9.9
CYP2B	Bupropion 1′-hydroxylation	110.6±14.2	110.7±18.0	127.7±16.7	146.7±16.1
CYP2C	Omeprazole 5-hydroxylation	158.2±32.4	171.3±33.4	192.5±19.5	175.5±12.2
CYP2D	Dextromethorphan *O*-demethylation	19.2±1.2	21.7±1.2	21.1±1.3	28.2±8.6
CYP2E	Chlorzoxazone 6-hydroxylation	1066.9±92.4	1219.7±68.2	1230.8±93.8	1036.2±40.3
CYP3A	Midazolam 1′-hydroxylation	5.6±0.8	6.4±0.9	6.4±0.3	6.1±0.8
	Erythromycin *N*-demethylation	63.9±2.9	70.1±4.3	67.6±3.6	63.1±4.6

Male ICR were treated orally with 50, 250, or 500 mg/kg of KRG extract daily for 3 days, respectively. Animals were subjected to necropsy 24 hours after last treatments. Values are means±SEs for five animals. VH, vehicle treated animals.

Table 4. Effects of KRG extract on CYP activities after oral administration to mice for 7 days

Activity (pmol/min/mg protein)		Dose (mg/kg)			
		VH	50	250	500
CYP1A	Phenacetin *O*-deethylation	139.4±28.2	108.7±10.7	146.5±17.5	126.9±13.7
CYP2B	Bupropion 1′-hydroxylation	71.1±15.8	53.0±7.3	45.9±7.8	47.7±4.9
CYP2C	Omeprazole 5-hydroxylation	198.4±10.4	207.9±29.2	176.8±13.9	213.4±14.0
CYP2D	Dextromethorphan *O*-demethylation	31.6±5.3	23.7±5.3	25.8±4.5	24.8±2.6
CYP2E	Chlorzoxazone 6-hydroxylation	969.1±118.7	765.2±88.3	807.5±93.4	809.6±63.4
CYP3A	Midazolam 1′-hydroxylation	9.8±0.5	8.6±1.8	7.4±0.6	10.0±1.1
	Erythromycin *N*-demethylation	70.7±1.4	67.5±2.0	48.9±3.8*	63.8±8.2

Male ICR were treated orally with 50, 250, or 500 mg/kg of KRG extract daily for 7 days. Animals were subjected to necropsy 24 hours after last treatments. Values are means±SEs of five animals. The asterisks indicate values significantly different from the vehicle control. VH, vehicle treated animals.

Table 5. Effects of KRG extract on CYP activities after oral administration to mice for 14 days

Activity (pmol/min/mg protein)		Dose (mg/kg)			
		VH	50	250	500
CYP1A	Phenacetin *O*-deethylation	146.7±33.9	145.9±15.0	143.1±21.0	125.0±11.6
CYP2B	Bupropion 1′-hydroxylation	43.5±13.3	47.5±4.8	58.9±8.3	29.5±3.1
CYP2C	Omeprazole 5-hydroxylation	147.1±40.6	167.6±12.3	134.7±14.1	138.3±11.3
CYP2D	Dextromethorphan *O*-demethylation	27.3±5.3	26.3±1.4	30.3±2.0	22.5±2.3
CYP2E	Chlorzoxazone 6-hydroxylation	721.2±167.3	738.7±62.7	713.3±48.6	652.8±27.2
CYP3A	Midazolam 1′-hydroxylation	7.7±1.8	7.6±0.3	8.1±0.6	7.0±0.6
	Erythromycin *N*-demethylation	41.5±5.3	52.8±8.1	42.0±3.8	46.7±2.7

Male ICR were treated orally with 50, 250, or 500 mg/kg of KRG extract daily for 14 days. Animals were subjected to necropsy 24 hours after last treatments. Values are means±SEs of five animals. VH, vehicle treated animals.

were treated orally with extract in distilled water at 50, 250, or 500 mg/kg for 3, 7, or 14 consecutive days. The daily recommended dosage of extract in man is 50 mg/kg. Using microsomal fractionation, the modulatory effects of KRG extract on monooxygenase activities were determined by incubation with cocktail probe substrates, namely, phenacetin for CYP1A2, bupropion for CYP2B6, omeprazole for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, and midazolam and erythromycin for CYP3A (Tables 3-5). KRG extract were not found to have any effect on CYP activities.

Discussion

Herb-drug interactions are considerable interest to scientists developing natural medicines, prescribing doctors, and to patients. Ginseng is taken as a health supplement either as extract or as a component of a supplement. However, if people take herbal medicines or health foods over the long term, drug interactions may occur due to modulations of the activities of metabolic enzymes.

To evaluate the modulatory effects of KRG extract, we tested their inhibitory effects on 6 types of CYP using HLMs *in vitro*. In previous studies, the ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rf and Rg_1 were found to inhibit the catalytic activities of CYP1A1, CYP1A2 and CYP1B1 at a concentration of 50 μg/ml in human recombinant CYPs [2], but the modulatory effects of KRG extract on CYP activities were not investigated in HLMs. In the present study, we tested the modulatory effects of KRG extract instead of single KRG components in HLMs, because it was difficult to real reactions between ginsenoside components and specific CYPs under biologic conditions.

For the *in vivo* study, we orally administrated KRG extract to mice daily for 3, 7, or 14 days at dosages of 50, 250, or 500 mg/kg; the daily recommended dose in man is 50 mg/kg. In the present study, we orally treated mice at 10 times these recommended dosages. Nevertheless, CYP activities in mouse liver showed no notable changes.

The major pharmacological components of ginseng are ginsenosides and their aglycones, which are known to have modulatory effects on the activities of CYPs. Thus, the quantities of these principals in extract and their bioavailabilities are likely to influence ginseng-drug interactions [2,6]. The 14 ginsenosides (Rg_1, Re, Rf, Rh_1, Rg_2, Rb_1, Rc, Rb_2, Rb_3, Rd, Rg_3, Rk1, Rg_5, and Rh2) in KRG extract were present at 66 to 76 mg/g of extract [8]. Furthermore, ginsenosides have very low oral bioavailabilities. For example, the bioavailability of the major ginsenoside Rb1 P.O. is only 4.35% when *Panax notoginsengs* saponins (PNS) are administered at 600 mg/kg to rats [18], and the bioavailability of Rg1 is only 3.29% at a dose of 1,500 mg/kg P.O. of PNS in rat [4]. Moreover, the absolute bioavailability of Rd in dogs is only 0.26%, though Rd has an inhibitory effect on CYP3A and 2D6 *in vitro* [17]. Therefore, although ginsenosides and ginseng extract modulate CYP activity *in vitro*, no modulatory

effects was observed *in vivo* due to the low oral bioavailabilities of ginsenosides.

In conclusion, KRG extract were not found to modulate the activities of CYPs, which suggests that KRG extract exhibit no significant pharmacokinetic herb-drug interactions with prescribed drugs metabolized by the six major CYP families. However, further human pharmacokinetics studies should be conducted to confirm the safety of KRG extract in those that take it regularly for long periods of time.

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초록 : 마우스에 홍삼추출물의 14일간 경구 투여에 따른 약물대사효소 조절능 평가

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인삼 및 인삼 유래 물질들은 가장 대표적인 건강기능식품이며, 홍삼추출물(*Panax ginseng* C.A. Meyer)의 경우 항바이러스, 알레르기 감소, 항산화, 비만억제 등의 효과를 나타낸다고 알려져 있다. 대표적 건강기능식품임에도 불구하고 약물상호작용을 일으키는 대사효소(Cytochrome P450, CYP)에 대한 홍삼추출물의 영향은 보고되지 않았다. 본 연구에서는 사람의 간 마이크로좀 분획과 마우스 모델을 기반으로 홍삼엑기스의 약물대사 조절능을 평가하였다. 사람의 간 마이크로좀에서는 CYP2B6에 대한 미약한 억제 효과를 나타내었을 뿐, 타 대사효소 CYP1A2, 2B6, 2C19, 2D6와 3A에 대한 억제효과는 검출되지 않았다. 홍삼엑기스를 마우스에 50, 250, or 500 mg/kg의 농도로 3, 7, 14일간 하루 1회 경구 투여 후 간을 적출하여 대사효소의 활성 변화를 측정하였지만, 유의적인 변화는 관찰되지 않았다. 결과적으로 홍삼엑기스의 유의적인 약물대사효소에 대한 활성 조절능이 없는 것으로 판단되고, 홍삼엑기스 복용에 따른 홍삼-약물상호작용의 가능성은 없을 것으로 추정된다.