

EFFECTS OF GINSENOSE RD AND *PANAX GINSENG* EXTRACT ON CYP1A, CYP2B, CYP2C, CYP2E1, AND CYP3A ACTIVITIES IN C57BL/6JNARL MICE

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The roots of *Panax ginseng* has been widely used in foods and the prescriptions of traditional Chinese medical care, especially in Asia. Alteration of liver microsomal cytochrome P450 activity is one of the primary factors causing herb-drug interaction. However, administration of a daily dose up to 50 mg ginsenoside Rd/kg to male C57BL/6JNarl mice for 7 consecutive days did not affect liver microsomal 7-ethoxyresorufin O-deethylation, pentoxyresorufin O-dealkylation, tolbutamide hydroxylation, nitrosodimethylamine N-demethylation, and nifedipine oxidation activities, which were marker activities of Cyp1a, Cyp2b, Cyp2c, Cyp2e1, and Cyp3a, respectively. Treatment with 50 mg/kg of ethanol extract of *P. ginseng* did not affect these activities either. These results indicate no evidence for the alteration of P450 activities by either ginsenoside Rd or *P. ginseng* extract under the treatment regimen in this study.

Key words: ginsenoside Rd, *Panax ginseng*, liver, cytochrome P450, mice

Introduction

Alteration of cytochrome P450 (P450) activities is one of the main factors causing drug-drug or herb-drug interactions.¹ Microsomal P450-dependent monooxygenase makes a main contribution to drug metabolism. The reconstituted system of a functional monooxygenase requires a member of P450 hemo-proteins, NADPH-P450 reductase, and phospholipids.² In humans, CYP1A2, CYP2C, CYP2E1, and

CYP3A4 are the main P450 isoforms and constitute about 13%, 18%, 7%, and 29% of total hepatic P450, respectively.³ These P450 isoforms are involved in the oxidation of numerous drugs including acetaminophen, diclofenac, cyclosporin A, and felodipine. CYP1A2 is essentially the only CYP1A member in most human liver samples and untreated mouse liver. 7-Ethoxyresorufin has been commonly used as a marker substrate of CYP1A. Although the content of CYP2B6 in human liver is relatively low (< 1%),

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CYP2B6 catalyzes the oxidation of important drugs, such as propofol.^{3,4} CYP2C9 was generally measured as the most abundant CYP2C member in human liver. Tolbutamide hydroxylation is the marker reaction catalyzed by human CYP2C9.⁵ Nitroso-compounds occur in many foodstuffs special in sea-foods and have carcinogenic effects in experimental animals. The demethylation of N-nitrosodimethylamine (NDM) is mainly performed by CYP2E1, which is an ethanol inducible form in rodents.⁶ CYP3A4 is the most abundant hepatic P450 isoform and catalyzes the oxidation of about 50% of drugs in the market.^{3,5} Nifedipine, a calcium channel blocker can be used as a marker substrate of human CYP3A4.⁷ Due to the broad substrate specificity of P450, these marker substrates can be used as chemical probes for P450 enzymes.

The roots of *Panax ginseng* (ginseng) has been extensively used in foods and the prescriptions of traditional Chinese medical care worldwide, especially in Asia. Previous report of Lin *et al.* (2009) indicated that the 50% methanol eluate collected from H-20 column chromatography of the ethanol extract of ginseng prevented serum deprivation-induced apoptosis in a rat pheochromocytoma cell line, PC12.⁸ More than 30 ginsenosides have been identified in ginseng. Ginsenoside Rd is one of the main ginsenosides and constitutes 2-6% of ginseng powder.⁹ Ginsenoside Rd protects the cell insult resulting from transient focal ischemia in rats (50 mg/kg ginsenoside Rd-treatment intraperitoneally 30 minutes before transient middle cerebral artery occlusion) and irradiation-induced apoptosis in intestinal cells (20 μ M for 24 hours).^{10,11} However, there was no report showing the *in vivo* effect of ginsenoside Rd on P450s. C57BL/6J mice have been widely used as an animal model for cancer

research and showed good responsibility to P450 inducers.¹² Thus, oral effects of Rd and the ethanol extract of *P. ginseng* on P450-dependent monooxygenase were studied in male C57BL/6J mice using the marker substrates described above for determining changes of respective P450 isoforms.

Materials and Methods

I. Chemicals

The isolation of ginsenoside Rd and preparation of ethanol extract from *Panax ginseng* was performed by Dr. Lin using the method as described before.⁸ Dextromethorphan, 7-ethoxyresorufin glucose-6-phosphate, glucose-6-phosphate dehydrogenase, NADPH, and nifedipine were purchased from Sigma-Aldrich (St. Louis, MO, U.S.A.). Methanol and dichloromethane were purchased from Merck KGaA (Darmstadt, Germany).

II. Animal treatment

Male C57BL/6JNarl mice (5 weeks old, 17-21 g) were purchased from National Laboratory Animal Center, Taipei. All experimental protocols involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the National Research Institute of Chinese Medicine. Before experimentation, mice were allowed a one-week acclimation period at the animal quarters with air conditioning, free access to laboratory rodent chow (no. 5P14; PMI Feeds Inc., Richmond, IN, U.S.A.) and water. Lee *et al.* (1987) reported that oral-treatment of rats with 10-30 mg/kg ginseng extract increased aminopyrine N-demethylation activity in a dose-dependent manner.¹³ According to the ratio of body surface area¹⁴, mice were treated with ginsen-

oside Rd and *P. ginseng* extract at a daily dose up to 50 mg/kg for 7 days. Ginsenoside Rd and *P. ginseng* extract were suspended in corn oil using teflon pestle and glass homogenizer and administered to mice by gavage. Control group received the same amount of corn oil.

III. Microsomal preparation and enzyme assays

Washed microsomes were prepared by differential centrifugation at 4°C following the method of Alvares and Mannering (1970).¹⁵ P450 content was determined using the spectrophotometric method.¹⁶ NADPH-P450 reductase activity was determined using cytochrome *c* as a substrate following the method of Phillips and Langdon (1962).¹⁷ 7-Ethoxyresorufin O-deethylation and 7-pentoxoresorufin O-dealkylation activities were determined by measuring the fluorescence of resorufin.^{18,19} Nitrosodimethylamine N-demethylation activity was determined by measuring the formaldehyde formation using Nash's reagent.²⁰ Tolbutamide hydroxylation and nifedipine oxidation activities were determined following the methods of Yamazaki *et al* (1998) and Guengerich *et al.* (1986), respectively.^{7,21} Microsomal protein concentrations were determined by the method of Lowry *et al.* (1951).²²

IV. Data analyses

The statistical significance of differences between control and treated groups was evaluated by the Student's t-test. The difference between > 2 sets of data in the study of mice treated with various doses of ginsenoside Rd were analyzed by one-way analysis of variance followed by Dunnett's test for multiple comparisons (SPSS version 10.0, SPSS Inc.,

Chicago, IL, U.S.A.). A *p* value < 0.05 was considered as statistically significant.

Results

I. Effects of ginsenoside Rd on hepatic cytochrome P450-dependent monooxygenase activities in mice

Administration of a daily dose of 50 mg Rd/kg to mice for 7 consecutive days did not affect body and liver weights and microsomal protein content (Table 1). However, liver to body weight ratio was slightly reduced by 12%. Treatment with ginsenoside Rd at the dosage up to 50 mg/kg did not affect mouse hepatic P450 content. Ginsenoside Rd did not affect liver microsomal cytochrome *c* reduction activity of NADPH-P450 reductase. Ginsenoside Rd did not affect 7-ethoxyresorufin O-deethylation, 7-pentoxoresorufin O-dealkylation, tolbutamide hydroxylation, nitrosodimethylamine N-demethylation, and nifedipine oxidation activities, which were the marker activities of Cyp1a2, Cyp2b, Cyp2c, Cyp2e1, and Cyp3a, respectively (Fig. 1).

II. Effects of the ethanol extract of *Panax ginseng* on hepatic cytochrome P450-dependent monooxygenase in mice

Treatment of mice with 50 mg/kg *P. ginseng* extract did not affect mouse body and liver weights, liver weight to body weight ratio and microsomal protein content (Table 1). This treatment did not alter liver microsomal NADPH-P450 reductase, 7-ethoxyresorufin O-deethylation, 7-pentoxoresorufin O-dealkylation, tolbutamide hydroxylation, nitrosodimethylamine N-demethylation, and nifedipine oxidation activities (Table 2).

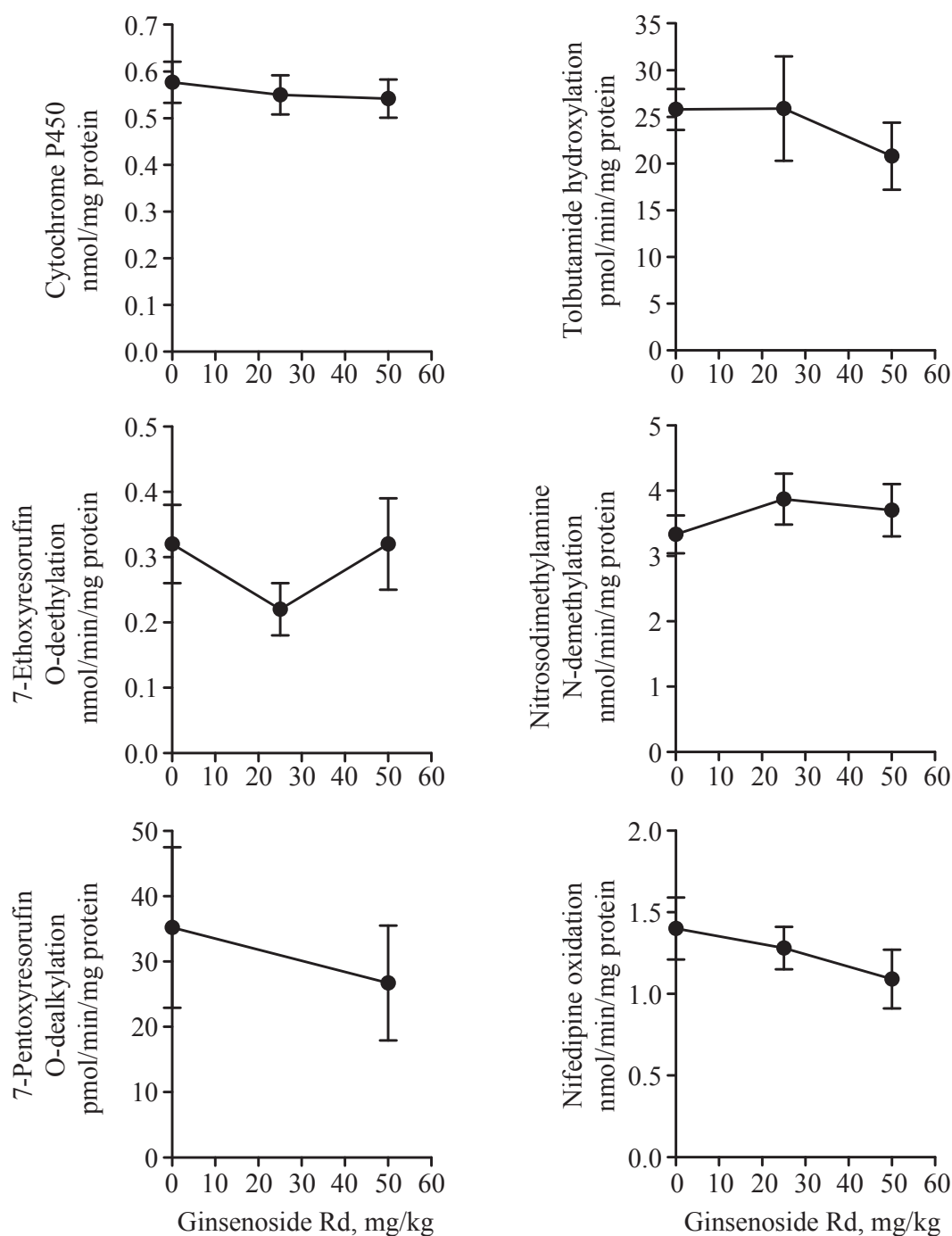


Fig. 1. Effects of ginsenoside Rd on cytochrome P450 content and activities in mouse liver microsomes. Mice were treated with ginsenoside Rd at 25 or 50 mg/kg/day for one week. Control mice received the same volume of corn oil. Data represent the mean \pm SEM of 5 or 6 mice.

Discussion

Effects of *P. ginseng* extract on the expression

and activities of some cytochrome P450 isoforms have been reported and results were inconsistent in different study systems.²³⁻²⁹ *In vitro*, in a recomb-

Table 1. Effects of ginsenoside Rd and *P. ginseng* extract on hepatic cytochrome P450-dependent monooxygenase components in mice.

Determination	Control	Ginsenoside Rd	<i>P. ginseng</i> extract
Body weight (g)	19.2 ± 0.6	19.6 ± 0.1	20.0 ± 0.4
Liver weight (g)	0.94 ± 0.04	0.85 ± 0.06	1.00 ± 0.02
Liver weight/body weight (g/g)	0.049 ± 0.001	0.044 ± 0.001*	0.049 ± 0.001
Microsomal protein (mg/g liver)	16.7 ± 0.7	15.6 ± 1.0	17.0 ± 1.6
Cytochrome P450 (nmol/mg protein)	0.58 ± 0.04	0.54 ± 0.04	0.58 ± 0.02
NADPH-Cytochrome <i>c</i> reductase (nmol/min/mg protein)	189 ± 6	182 ± 5	193 ± 17

Mice were treated with ginsenoside Rd and *P. ginseng* extract at 50 mg/kg daily for 7 days. □Data represent the mean ± SEM of 6, 5 and 6 mice of control, ginsenoside Rd and *P. ginseng* extract-treated groups, respectively. *Asterisk represent values significantly different from the control values, $p < 0.05$.

Table 2. Effects of the ethanol extract of *P. ginseng* on hepatic cytochrome P450-dependent monooxygenase activities in mice.

Assay	Control	<i>P. ginseng</i> extract
7-Ethoxyresorufin O-deethylation nmol/min/mg protein	0.32 ± 0.05	0.31 ± 0.03
7-Pentoxoresorufin O-dealkylation pmol/min/mg protein	35.2 ± 12.3	33.8 ± 8.0
Tolbutamide hydroxylation pmol/min/mg protein	20.9 ± 2.6	25.4 ± 3.0
Nitrosodimethylamine N-demethylation nmol/min/mg protein	3.33 ± 0.29	3.91 ± 0.38
Nifedipine oxidation nmol/min/mg protein	1.40 ± 0.19	1.61 ± 0.11

Data represent the mean ± SEM of 6 mice. Mice were treated with 50 mg/kg/day ginseng extract for 7 days.

nant human P450 system, ginseng extract inhibited CYP1A2 with a K_i of 0.91 ± 0.08 mg/ml.²⁵ *In vivo*, Lee *et al.* (1987) reported that oral-treatment of rats with 10-30 mg/kg ginseng extract caused a dose-dependent increase (18-24%) of aminopyrine N-demethylation activity without affecting benzo(a)pyrene hydroxylation activity.¹³ CYP2B1 and CYP3A23 had main contribution to aminopyrine N-demethylation and CYP1A had greater benzo(a)pyrene hydroxylation activity. However, oral administration of daily doses of 30 and 100 mg/kg ginseng extract to rats did not alter the mRNA levels of CYP1A2, CYP2B1, and CYP3A23 after 3 days.²⁶ In guinea pigs, intraperitoneal treatment with 100 mg/kg ginseng extract daily

for 14 days resulted in a 50% decrease of hepatic 7-ethoxycoumarin O-deethylation activity without affecting benzphetamine N-demethylation activity.²⁷ This treatment did not change P450 content and NADPH-P450 reductase activity. However, our mouse studies revealed that oral administration of 50 mg/kg ginseng extract, which equivalents to 35 mg/kg in rats, to mice did not affect Cyp1a, Cyp2b, Cyp2c, Cyp2e1, and Cyp3a activities.

In human studies, in 12 young adults with an age around 25 years old, ingestion of ginseng extract at 1.5 g/day for 28 days did not affect serum ratios of paraxanthine to caffeine and 1-hydroxymidazolam to midazolam, which were metabolic markers of

CYP1A2 and CYP3A4, respectively.²⁸ Ginseng extract did not affect CYP2D6 and CYP2E1 metabolic ratios either. Anderson *et al.* (2003) reported that ingestion of 100 mg ginseng extract daily for 14 days did not alter the urinary ratio of 6-hydroxycortisol to cortisol in 10 Caucasians and 10 Asians.²⁹ However, participants taking 200 mg ginseng product for 18 days caused a 29% increase of the C_{\max} of nifedipine, which was mainly metabolized by CYP3A4.²⁴ Malati *et al.* reported that administration of 1 g/day ginseng product for 28 days reduced the $AUC_{0-\infty}$, half life, and C_{\max} in 12 participants.³⁰ The difference in human response in different studies could be attributed to differences in ginseng extracts, differential treatment regimens, small group of participants, genetic variations, and environmental factors. In these human studies, participants took 100 mg-1.5 g/day ginseng extract, which are equivalent to the dose of 15-225 mg ginseng extract/kg in mice. Thus, the dose used in our studies was within the range of human equivalent dose in mice. The chronic effect of higher dose (> 50 – 250 mg/kg) of ginseng extract on P450 activities needs further investigation.

In vitro, the ginsenoside Rd inhibited human liver microsomal tolbutamide hydroxylation and testosterone 6 β -hydroxylation activities, which were marker activities of CYP2C9 and CYP3A4, respectively.³¹ Ginsenoside Rd inhibited human liver microsomal oxidation activities toward mephenytoin and bufuralol, which were marker substrates of CYP2C19 and CYP2D6, respectively. The IC_{50} values for the inhibition of mephenytoin and bufuralol oxidation activities were 46 and 57 μ M, respectively.³² In recombinant human P450 systems, compared to ginsenosides Rb1, Rb2, Rc, Re, Rf and Rg, ginsenoside Rd caused the most potent inhibitory effects of

CYP2C9, CYP2C19, CYP2D6, and CYP3A4 activities with IC_{50} values of 58~154 μ M.³³ Ginsenoside Rd at 50 μ g/ml moderately decreased human CYP1A1, CYP1A2, and CYP1B1 activities by 20~50%.²⁵ These reports suggested that Rd caused a weak to moderate inhibitory effects on some P450 activities. In contrast, in HepG2 cells, Hao *et al.* (2011) reported that exposure to 50 μ M ginsenoside Rd for 6 hours stimulated the mRNA expression of CYP1A2 and CYP3A4.³⁴ Our report is the first study to show the effect of ginsenoside Rd on P450 activities *in vivo*. However, our results showed that Cyp1a2, Cyp2b, Cyp2c, Cyp2e1, and Cyp3a activities were not affected by ginsenoside Rd or *P. ginseng* extract. Surprisingly, liver to body weight ratio was reduced. The cause for the decreased liver to body weight ratio was not clear.

All of these reports are hardly comparable due to different treatment regimens, preparation methods of ginseng extracts, and species difference. Possible interference of pharmacological efficacy of drugs by taking ginseng has been reported in humans.³⁵ Ginseng may increase the risk of bleeding when it was used concurrently with anticoagulants or non-steroid anti-inflammation drugs. Ingestion of ginseng may reduce the efficacy of diuretics, antihypertensive agents, and antidepressants. It was recommended for patients not to use ginseng 2 weeks before surgery. These results suggested that the risk of drug interaction with ginseng may depend on individual drug substrate and pharmacodynamic interaction should be noticed.

Acknowledgments

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人參皂苷 Rd 及人參萃取物對 C57BL/6JNarl 鼯鼠 Cyp1a, Cyp2b, Cyp2c, Cyp2e1 與 Cyp3a 活性之影響

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人參(根)被廣泛地使用於食物及傳統中藥治療，尤其是在亞洲。改變肝微粒體細胞色素 P450 活性是造成草藥-藥物交互作用之主要原因之一。然而，對雄性 C57BL/6JNarl 鼯鼠，每天口服投與劑量高至 50 毫克/公斤的人參皂苷 Rd，連續處理 7 天，不影響鼠肝微粒體 7-ethoxyresorufin O-去乙基、pentoxyresorufin O-去烷基、tolbutamide 氫氧化、nitrosodimethylamine N-去甲基、nifedipine 氧化活性，這些活性分別為 Cyp1a2、Cyp2b、Cyp2c、Cyp2e1、Cyp3a 的指標活性。口服投與 50 毫克/公斤的人參乙醇萃取物，連續處理 7 天對鼠肝微粒體的這些活性亦無影響。這些結果缺乏證據顯示在所測定的條件下，人參皂苷 Rd 或人參萃取物可以影響細胞色素 P450 活性。

關鍵字：人參皂苷 Rd、人參、肝、細胞色素 P450、鼯鼠

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