IN VITRO EFFECT OF STANDARDIZED GINSENG EXTRACTS AND INDIVIDUAL GINSENOSIDES ON THE CATALYTIC ACTIVITY OF HUMAN CYP1A1, CYP1A2, AND CYP1B1

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(Received October 25, 2001; accepted December 18, 2001)

This article is available online at http://dmd.aspetjournals.org

ABSTRACT:
Ginseng extract has been reported to decrease the incidence of 7,12-dimethylbenz[a]anthracene (DMBA)-initiated tumorigenesis in mice. A potential mechanism for this effect by ginseng is inhibition of DMBA-bioactivating cytochrome P450 (P450) enzymes. In the present in vitro study, we examined the effect of a standardized Panax ginseng (or Asian ginseng) extract (G115), a standardized Panax quinquefolius (or North American ginseng) extract (NAGE), and individual ginsenosides (Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1) on CYP1 catalytic activities, as assessed by 7-ethoxyresorufin O-dealkylation. G115 and NAGE decreased human recombinant CYP1A1, CYP1A2, and CYP1B1 activities in a concentration-dependent manner. Except for the competitive inhibition of CYP1A1 by G115, the mode of inhibition was the mixed-type in the other cases. A striking finding was that NAGE was 45-fold more potent than G115 in inhibiting CYP1A2. Compared with G115, NAGE also preferentially inhibited 7-ethoxyresorufin O-dealkylation activity in human liver microsomes. Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1, either individually or as a mixture and at the levels reflecting those found in an inhibitory concentration (100 μg/ml) of NAGE or G115, did not influence CYP1 activities. However, at a higher ginsenoside concentration (50 μg/ml), Rb1, Rb2, Rc, Rd, and Rf inhibited these activities. Overall, our in vitro findings indicate that standardized NAGE and G115 extracts, which were not treated with calf serum or subjected to acid hydrolysis, inhibited CYP1 catalytic activity in an enzyme-selective and extract-specific manner, but the effects were not due to Rb1, Rb2, Rc, Rd, Re, Rf, or Rg1.

Ginseng is one of the most commonly used herbal products by American consumers (Eliason et al., 1997; Harnack et al., 2001), and the annual sales of ginseng in the United States are more than $300 million (Gillis, 1997). Ginseng refers to the roots of species of the genus Panax. There are several species of ginseng (Soldati, 2000), including Panax ginseng C. A. Meyer (or Asian ginseng), which is mainly from Korea and Eastern China, and Panax quinquefolius L. (or North American ginseng), which is primarily from Wisconsin and British Columbia, Canada. To date, approximately 200 substances have been isolated and characterized from P. ginseng (Soldati, 2000). The characteristic markers of both species are the ginsenosides (Attele et al., 1999), which are steroidal saponins (Attele et al., 1999). Ginseng is used as a general body tonic, and it is touted to counteract fatigue, boost the immune system, improve physical stamina, and stimulate the appetite (Elias and Masline, 1995). The mechanism of action of ginseng is not known, but it is thought to have effects on learning, memory and behavior, cardiovascular function perhaps through mediation by nitric oxide, neuroendocrine function, carbohydrate and lipid metabolism, and immune function (Liu and Xiao, 1992).

The oral administration of red ginseng extracts, which were produced by steam treatment of the roots of P. ginseng, was reported to decrease the incidence of 7,12-dimethylbenz[a]anthracene (DMBA)-initiated tumorigenesis of the lung (Yun et al., 1983) and skin (Xiaoguang et al., 1998) in mice. DMBA is a polycyclic aromatic hydrocarbon that requires bioactivation to produce carcinogenicity. This metabolic activation is catalyzed principally by enzymes in the cytochrome P450 (P450) family, such as CYP1A1, CYP1A2, and CYP1B1 (Shou et al., 1996; Savas et al., 1997). Therefore, a potential mechanism by which ginseng confers protection against DMBA-initiated tumorigenesis is by inhibiting the catalytic activity of DMBA-bioactivating CYP1 enzymes. In addition to catalyzing toxicant bioactivation, CYP1 enzymes also metabolize clinically useful therapeutic agents (Rendic and Di Carlo, 1997; Rochat et al., 2001). Therefore, it is important to examine the interaction between ginseng and P450 enzymes not only because this herbal medicine may confer chemoprotection in chemical carcinogenesis but also because the concomitant ingestion of ginseng and conventional drugs may result in herb-drug interaction.

In the present study, we investigated the in vitro effect of a standardized P. ginseng (Asian ginseng) extract (G115), a standardized P. quinquefolius (North American ginseng) extract (NAGE), and

1 Abbreviations used are: DMBA, 7,12-dimethylbenz[a]anthracene; P450, cytochrome P450; G115, Panax ginseng (Asian ginseng) extract; NAGE, Panax quinquefolius (North American) ginseng extract; HPLC, high-performance liquid chromatography.
individual ginsenosides (Rb1, Rb2, Re, Rd, Re, Rf, Rg1, and Rg2) on the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1. Our results indicate that ginseng inhibits CYP1 activity in an enzyme-selective and extract-specific manner. Moreover, the observed inhibition by NAGE and G115 was not due to any of the seven individual ginsenosides that were examined.

Materials and Methods

Chemicals and Reagents. Standardized G115 extract (4% total ginsenosides w/w; batch 1254/485) and standardized NAGE extracts (10% total ginsenosides w/w; lot no. AGSP110220) were gifts from Pharmaton S.A. (Lugano, Switzerland) and Canadian Phytopharmaceuticals Corp. (Richmond, BC, Canada), respectively. G115 contained the individual ginsenosides Rb1, Rb2, Re, Rd, Re, Rf, Rg1, and Rg2, whereas NAGE contained Rb1, Rb2, Re, Rd, Re, Rf, and Rg1. Shown in Fig. 1 is the content of these individual ginsenosides in G115 and NAGE, as quantified by HPLC by the suppliers. Purified individual ginsenosides Rb1 (batch 21), Rb2 (batch 17), Re (batch 4), Rd (batch 10), Re (batch 9), Rf (batch 9), and Rg1 (batch 23) were purchased from INDOPINE Chemical Co., Inc. (Somerville, NJ). According to the manufacturer, the purity of these batches of Rb1, Rb2, Re, Rd, Re, Rf, and Rg1 was 99.3, 95.9, 98.9, 98.4, 100, 97.6, and 100%, respectively, as assessed by HPLC. Individual human liver microsomes (catalog no. H023, H030, H056, and H089), microsomes from baculovirus-infected insect cell coexpressing NADPH-cytochrome P450 reductase and human CYP1A1 (catalog no. P211), CYP1A2 (catalog no. P205), or CYP1B1 (catalog no. P220), and the corresponding control insect cell microsomes (catalog no. P201) were purchased from GENTEST (Woburn, MA). NADPH and 7-ethoxyresorufin were bought from Sigma Chemical Co. (St. Louis, MO) and authentic resorufin metabolite from Molecular Probes, Inc. (Eugene, OR).

7-Ethoxyresorufin O-Dealkylation Assay. 7-Ethoxyresorufin O-dealkylation activity was determined by a modification (Chang et al., 2001) of a continuous spectrophotometric assay (Burke and Mayer, 1974). Briefly, each standard 2-ml incubation contained 100 mM potassium phosphate buffer, pH 7.4, 5 mM MgCl2, 1.5 mM EDTA, 0.2 μM 7-ethoxyresorufin (unless indicated otherwise), human recombinant P450 enzyme (1 pmol of CYP1A1, 3 pmol of CYP1A2, or 2.5 pmol of CYP1B1) or human liver microsomes (75 pmol of total microsomal P450), and 0.25 mM NADPH. Reaction was performed at 37°C and initiated by the addition of NADPH. Fluorescence was recorded every 30 s for 3 min using a Shimadzu model RF-540 spectrophotometer (Kyoto, Japan). The excitation wavelength was set at 530 nm (5-nm slit width), and the emission wavelength was set at 582 nm (5-nm slit width). Calibration curves were constructed by determining the fluorescence in incubations containing known amounts of the authentic resorufin metabolite. Samples containing the authentic standard were processed in the same manner as the unknown samples but in the presence of heat-inactivated human liver microsomes or control insect cell microsomes.

Enzyme Inhibition Experiments. To assess the potential enzyme inhibitory effect of ginseng extract or the individual ginsenosides on the catalytic activity of CYP1A1, CYP1A2, and CYP1B1, the 7-ethoxyresorufin O-dealkylation assay was conducted in the presence of varying concentrations of the extract or the individual ginsenoside, as indicated in each figure legend. The individual ginsenosides were dissolved in methanol, and the final concentration of the solvent in each incubation mixture was 0.02 or 0.05%, v/v. At these concentrations, methanol did not affect the catalytic activity. To characterize the enzyme kinetics of CYP1A1, CYP1A2, and CYP1B1 in the presence of a ginseng extract, experiments were conducted using multiple concentrations of the extract and multiple concentrations of 7-ethoxyresorufin, as indicated in each figure legend.

Enzyme Kinetic Analysis. The apparent \( K_i \) and \( V_{\text{max}} \) values were determined by nonlinear regression analysis of the enzyme activity-substrate concentration data using the Michaelis-Menten model (Enzyme Kinetics Module software program, version 1.1; SPSS Science, Chicago, IL). The apparent \( K_i \) values were determined by fitting the enzyme activity-substrate concentration data at various inhibitor concentrations to the equations for competitive inhibition (eq. 1), noncompetitive inhibition (eq. 2), and mixed inhibition (eq. 3) using the Enzyme Kinetics Module software program.

\[
V = \frac{V_{\text{max}}[S]}{[S] + K_i(1 + [I]/K_i)} \quad (1)
\]

\[
V = \frac{V_{\text{max}}[S]}{[S] + K_i(1 + [I]/K_i)} \quad (2)
\]

\[
V = \frac{V_{\text{max}}[S]}{(K_i(1 + ([I]/K_i)) + ([S](1 + ([I]/(K_i \alpha)))))} \quad (3)
\]

\( V \) is the initial rate of product formation, \( V_{\text{max}} \) is the maximal rate of product formation, \( K_i \) is the Michaelis constant, \( S \) is the substrate concentration, \( I \) is the inhibitor concentration, \( K_i \) is the equilibrium dissociation constant for the enzyme-inhibitor complex, and \( \alpha \) is the substrate-inhibitor interaction constant (Webb, 1963). The mode of inhibition was determined on the basis of visual inspection of the Dixon and Lineweaver-Burk plots and various statistics to evaluate the goodness of fit, such as the Akaike information criterion, the size of the sum of squares of residuals, and the standard error and 95% confidence interval of the parameter estimates (Enzyme Kinetics Module software program, version 1.1).

Statistics. The significance of the difference between the group means was assessed by one- or two-way analysis of variance and, if applicable, was followed by the Student Newman-Keuls multiple range test. The level of significance was set a priori at \( p < 0.05 \).

Results

Concentration-Dependent Inhibition of Human Recombinant CYP1A1, CYP1A2, and CYP1B1 by Ginseng Extracts. To investigate whether the ginseng extracts G115 and NAGE affect the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1, the 7-ethoxyresorufin O-dealkylation assay was conducted with the corresponding recombinant enzyme and varying concentrations of G115 and NAGE. As shown in Fig. 2, A–C, both extracts decreased CYP1A1, CYP1A2, and CYP1B1 catalytic activities in a concentration-dependent manner. In the case of CYP1A1 and CYP1B1, the concentration-response curves were similar for the inhibition of each of these enzymes by G115 and NAGE. However, the curve for the inhibition of CYP1A2 by NAGE was shifted to the left when compared with that by G115, indicating that NAGE was more potent in the inhibition of this enzyme.

Kinetic Analysis of the Inhibition of CYP1 Enzymes by Ginseng Extracts. To further characterize the inhibition of CYP1A1, CYP1A2, and CYP1B1 catalytic activities by G115 and NAGE, enzyme kinetic experiments were performed, and the experimental
data were fitted to the equations for competitive (eq. 1), noncompetitive (eq. 2), and mixed inhibition (eq. 3). Based on Lineweaver-Burk plots (Figs. 3, A–C, and 4, A–C), and various statistics (e.g., Akaike information criterion) to evaluate the goodness of curve fitting, the inhibition of CYP1A1 by G115 was found to be competitive, whereas in all the other cases, the inhibition was of a mixed-type (Table 1). Analysis of the apparent $K_i$ values indicated that G115 exhibited selective inhibition of CYP1 enzymes. As shown in Table 1, these values were similar for the inhibition of CYP1A1 and CYP1B1 by G115. However, the apparent $K_i$ for CYP1A2 was 18- and 9-fold greater than that for CYP1A1 and CYP1B1, respectively. By comparison, the apparent $K_i$ values for the inhibition of CYP1A1, CYP1A2, and CYP1B1 by NAGE were in the same order of magnitude. A striking finding was the 45-fold difference in the apparent $K_i$ for the inhibition of CYP1A2 by NAGE (20 ± 5 μg/ml, mean ± S.E.M.) and G115 (906 ± 78 μg/ml). Overall, the inhibitory effect of G115 and NAGE on CYP1 catalytic activity was enzyme-selective and extract-specific.

**Comparative Effect of G115 and NAGE on Human Hepatic Microsomal 7-Ethoxyresorufin O-Dealkylation Activity.** 7-Ethoxyresorufin O-dealkylation is catalyzed mainly by CYP1A2 in human hepatic microsomes (Murray et al., 1993). Therefore, we investigated the effect of G115 and NAGE on 7-ethoxyresorufin O-dealkylation activity in a panel of four individual human hepatic microsome samples. As shown in Fig. 5, G115, at a concentration of 60 μg/ml, did not affect hepatic microsomal 7-ethoxyresorufin O-dealkylation activity. In contrast, the same concentration of NAGE decreased the enzyme activity by 37 to 60%. Therefore, similar to the finding with recombinant CYP1A2 enzyme (Fig. 2B), there was preferential inhibition of hepatic microsomal 7-ethoxyresorufin O-dealkylation activity by NAGE when compared with G115.
TABLE 1
Enzyme kinetic analysis of CYP1A1, CYP1A2, and CYP1B1 inhibition by ginseng extracts

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>Enzyme Activity</th>
<th>Apparent K_i (µM)</th>
<th>Mode of Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td></td>
<td>50 ± 2*</td>
<td>Competitive</td>
</tr>
<tr>
<td>CYP1A2</td>
<td></td>
<td>906 ± 78</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP1B1</td>
<td></td>
<td>98 ± 9*</td>
<td>Mixed</td>
</tr>
<tr>
<td>NAGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td></td>
<td>61 ± 4*</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP1A2</td>
<td></td>
<td>20 ± 5*</td>
<td>Mixed</td>
</tr>
<tr>
<td>CYP1B1</td>
<td></td>
<td>44 ± 3*</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

*Significantly different from the apparent K_i for the inhibition of CYP1A2 by GI15, p < 0.05.

TABLE 2
Effect of individual ginsenosides on CYP1A2 catalytic activity

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>Enzyme Activity</th>
<th>nmol/min/nmol P450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>4.8 ± 0.1</td>
</tr>
<tr>
<td>Rb1</td>
<td></td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>Rb2</td>
<td></td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>Rc</td>
<td></td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>Rd</td>
<td></td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>Re</td>
<td></td>
<td>5.1 ± 0.2</td>
</tr>
<tr>
<td>Rg1</td>
<td></td>
<td>5.2 ± 0.3</td>
</tr>
</tbody>
</table>

Effect of Individual Ginsenosides on CYP1A1, CYP1A2, and CYP1B1 Catalytic Activities. To determine which ginsenoside is responsible for the inhibition of CYP1 enzyme activities by GI15, we assessed the effect of Rb1 (1.07 µg/ml), Rb2 (0.66 µg/ml), Rb4 (0.67 µg/ml), Rb6 (0.46 µg/ml), Re (0.56 µg/ml), Rf (0.14 µg/ml), and Rg1 (0.44 µg/ml) at a concentration equivalent to that found in an inhibitory concentration (100 µg/ml) of GI15. These concentrations of the individual ginsenosides reflect those found in an inhibitory concentration (100 µg/ml) of NAGE (Fig. 2B). Results are expressed as mean ± S.E.M. for three independent experiments.

Effect of Individual Ginsenosides on CYP1A1, CYP1A2, and CYP1B1 Catalytic Activities. The observed inhibition of CYP1A1, CYP1A2, and CYP1B1 enzyme activities by NAGE and GI15 (Fig. 2, A–C; Table 1) may be the result of additive or synergistic effects of individual ginsenosides. Therefore, we determined whether a mixture of ginsenosides in which the concentration of each of these compounds is the same as that found in a 100-µg/ml solution of our standardized NAGE (designated as mixture A) or GI15 (designated mixture B) would inhibit CYP1 enzyme activity. Mixture A contained Rb1 (4.56 µg/ml), Rb2 (0.31 µg/ml), Rb4 (1.09 µg/ml), Rb6 (1.43 µg/ml), Re (2.36 µg/ml), Rf (0.24 µg/ml), and Rg1 (0.44 µg/ml). As shown in Fig. 7, mixture A did not decrease CYP1A1, CYP1A2, or CYP1B1 enzyme activity, whereas NAGE (100 µg/ml) reduced these activities, consistent with the concentration-response data shown in Fig. 2, A to C. Similar to the result obtained with mixture A, mixture B also did not affect CYP1 enzyme activity (data not shown).

Discussion

Based on the in vitro experimental conditions used in the present study, the standardized P. ginseng extract GI15 was found to result in a selective decrease in the catalytic activity of human CYP1 enzymes. As assessed by the apparent K_i values, the potency of inhibition of CYP1A1 and CYP1B1 by GI15 was an order of magnitude greater than that for CYP1A2. Another difference in the effects of GI15 on CYP1 catalytic activities is the mode of inhibition. Whereas GI15 competitively inhibited CYP1A1, mixed inhibition occurred with CYP1A2 and CYP1B1. The GI15 extract powder used in the present study was a preparation that was standardized to 4% w/w ginsenosides (Fig. 1). However, the observed inhibitory effects by GI15 were not due to Rb1, Rb2, Rb4, Rb6, Rf, or Rg1. This conclusion is based on the finding that the inclusion of these ginsenosides in the enzyme assays, either individually or as a mixture and at the same levels as those found in an inhibitory concentration (100 µg/ml) of GI15, did not decrease CYP1A1, CYP1A2, or CYP1B1 catalytic activity. Al-
though we used a standardized extract, it was still a mixture of many chemical constituents. At least 31 individual ginsenosides have been isolated from ginseng, but Rb1, Rb2, Rc, Rd, Re, and Rg1 account for >90% of the total content (Li et al., 2000). Most of the ginseng species contain other chemical entities, including polysaccharides, peptides, fatty acids, and polyphenolic compounds (Attele et al., 1999). As shown in a previous in vitro study, polyphenolic compounds, such as tannic acid, are capable of inhibiting P450-mediated enzyme activities (Das et al., 1987). In the present study, the ginseng extracts were not treated with calf serum to remove the tannins that are normally present in plant extracts (Cardellina et al., 1999). Therefore, the observed enzyme inhibitory effects by G115 may be due to a ginsenoside(s) other than Rb1, Rb2, Rc, Rd, Re, Rf, or Rg1, or perhaps are the result of a nonginsenoside compound, such as tannins

7-Ethoxyresorufin O-dealkylation assay was conducted with human recombinant CYP1A1, CYP1A2, or CYP1B1, and in the presence of NAGE (100 μg/ml) or a mixture of individual ginsenosides (denoted as mixture A) containing Rb1 (4.56 μg/ml), Rb2 (0.31 μg/ml), Rc (1.09 μg/ml), Rd (1.43 μg/ml), Re (2.36 μg/ml), and Rg1 (0.24 μg/ml). These ginsenosides are known to be present in NAGE, and their concentrations reflect those found in an inhibitory concentration (100 μg/ml) of our standardized NAGE sample (Fig. 1 and Fig. 2, A–C). Control incubations contained the vehicle (0.02% methanol, v/v). Results are expressed as mean ± S.E.M. of the percentage of control activity for three independent experiments. *, significantly different from the control, p < 0.05. Control enzyme activity (mean ± S.E.M.) for CYP1A1, CYP1A2, and CYP1B1 was 68 ± 1, 4.6 ± 0.2, and 17 ± 0.5 nmol/min/nmol of P450, respectively.

In contrast to the enzyme-selective inhibition of CYP1A1 and CYP1B1 by G115, no preferential effect was apparent with standardized NAGE. Rather, NAGE inhibited CYP1A1, CYP1A2, and CYP1B1 with relatively similar potency. Thus, the enzyme-selectivity in CYP1A1 and CYP1B1 inhibition that occurred with G115 was extract-specific. A striking finding is the 45-fold lower apparent K_i value for the inhibition of human recombinant CYP1A2 by NAGE when compared with that by G115. The preferential effect of NAGE on recombinant CYP1A2 was also found with human liver microsomal 7-ethoxyresorufin O-dealkylation activity, which is commonly used as an enzyme-selective catalytic monitor for hepatic CYP1A2 (Murray et al., 1993). The NAGE extract powder used in the present study was standardized to 10% w/w ginsenosides (Fig. 1). Similar to the findings with G115, the observed inhibitory effects by NAGE were not due to any of these compounds because these ginsenosides, when present in the enzyme assays either individually or as a mixture and at the same levels as those found in an inhibitory concentration (100 μg/ml) of NAGE, had no effect on CYP1A1, CYP1A2, or CYP1B1 catalytic activity.

Previous chemical analysis has shown that NAGE differs from G115 by the absence of the ginsenoside Rf (Chan et al., 2000; Li et al., 2000) and presence of a greater abundance of Rb1 than Rb2 (Ma et al., 1996). These characteristics were found in our NAGE preparation (Fig. 1) that was obtained from a commercial supplier. Another chemical difference between G115 and NAGE is that 24-(R)-pseudo-ginsenoside F11, which is an oocitol type triterpene, is found in NAGE but not in G115 (Chan et al., 2000; Li et al., 2000). However, the amount of 24-(R)-pseudoginsenoside F11 in our NAGE prepara-
In vivo biological activities of ginseng extracts. Interestingly, previous in vivo studies have reported that a crude saponin fraction of ginseng root (Eleutherococcus senticosus) (Meden et al., 1984), when administered as single or multiple i.p. doses, increased the duration of sleeping time in mice treated with hexobarbital. These data suggest P450 enzyme inhibition by the ginseng preparations used in those studies (Takagi et al., 1972; Meden et al., 1984) because hexobarbital is metabolized by P450 enzymes (Ryan and Levin, 1990). In another study, the oral administration of a single dose (30 mg/kg) of P. ginseng extract to rats was reported to have multiple effects on hepatic P450-mediated enzyme activities (Lee et al., 1987). These effects were a decrease in aryl hydrocarbon hydroxylase activity in the S9 fraction, an increase in aryl hydrocarbon hydroxylase activity in the S9 fraction, and an increase in aryl hydrocarbon hydroxylase activity in the S9 fraction.

In summary, the novel findings from the present in vitro study are: 1) both G115 and NAGE inhibited the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1; 2) the effects were enzyme-selective and extract-specific because NAGE was 45-fold more potent than G115 in inhibiting CYP1A2; 3) the effects by G115 and NAGE were not due to the individual ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, or Rg1, as assessed individually or as a mixture; and 4) at a concentration (i.e., 50 μg/ml) that is greater than that found in our standardized G115 and NAGE samples, some of these individual ginsenosides (e.g., Rb1, Rb2, Rc, Rd, and Rf) were effective CYP1 inhibitors.

Acknowledgments. We thank Pharmaton SA (Lugano, Switzerland) for providing us with the standardized P. ginseng extract G1115 and Canadian Phytopharmaceuticals Corp. (Richmond, British Columbia, Canada) for the supply of the standardized North American ginseng extract.

References


