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Influence of *Panax ginseng* on the Steady State Pharmacokinetic Profile of Lopinavir/Ritonavir (LPV/r) in Healthy Volunteers

Mónica M. Calderón[1,4], **Cheryl L. Chairez**[2], **Lori A. Gordon**[1], **Raul M. Alfaro**[1], **Joseph A. Kovacs**[3], and **Scott R. Penzak**[1,5]

[1]Clinical Research Center, Clinical Center Pharmacy Department, National Institutes of Health, Bethesda, Maryland [2]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [3]Clinical Research Center, Department of Critical Care Medicine, National Institutes of Health, Bethesda, Maryland

Abstract

Study Objective—*Panax ginseng* has been shown in pre-clinical studies to modulate cytochrome P450 (CYP) enzymes involved in the metabolism of HIV protease inhibitors. Therefore, the purpose of this study was to determine the influence of *Panax ginseng* on the pharmacokinetics of the HIV protease inhibitor combination lopinavir/ritonavir (LPV/r) in healthy volunteers.

Design—Single sequence, open-label, single-center pharmacokinetic investigation.

Setting—Government healthcare facility.

Subjects—Twelve healthy human volunteers.

Measurements and Main Results—Thirteen healthy volunteers received LPV/r (400/100 mg) twice daily for 29.5 days. On day 15 of LPV/r administration, serial blood samples were collected over 12 hrs for determination of lopinavir and ritonavir concentrations. On study day 16, subjects began taking *Panax ginseng* 500 mg twice daily, which they continued for 2 weeks in combination with LPV/r. On day 30 of LPV/r administration, serial blood samples were again collected over 12 hrs for determination of lopinavir and ritonavir concentrations. Lopinavir and ritonavir pharmacokinetic parameter values were determined using noncompartmental methods and compared pre- and post-ginseng administration using a student's t-test, where $P < 0.05$ was accepted as statistically significant.

Address for correspondence: Scott R. Penzak, UNT System College of Pharmacy, Department of Pharmacotherapy, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, Phone: 817-735-0362, Fax: 817-735-2603, scott.penzak@unthsc.edu.

[4]Current affiliation for Dr. Calderón: Office of Safety and Epidemiology, U.S. Food and Drug Administration, Silver Spring, Maryland

[5]Current affiliation for Dr. Penzak: University of North Texas System College of Pharmacy, Department of Pharmacotherapy, Fort Worth, Texas

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Conclusion—Neither lopinavir nor ritonavir steady-state pharmacokinetics were altered by two weeks of *Panax ginseng* administration to healthy human volunteers. Thus, a clinically significant interaction between *Panax ginseng* and LPV/r is unlikely to occur in HIV-infected patients who choose to take these agents concurrently. It is also unlikely that Panax ginseng will interact with other ritonavir-boosted protease inhibitor combinations, although confirmatory data are necessary.

Keywords

Panax ginseng; Lopinavir-ritonavir; Pharmacokinetics; Complementary and Alternative Medicine; Drug Interaction; Cytochrome P450; HIV; HIV Protease Inhibitor; Antiretrovirals

The widespread availability of combined antiretroviral therapy (cART) has led to a marked decline in mortality in individuals with HIV infection. As such, HIV is now regarded by many as a chronic condition in many areas of the world.[1] However, HIV-infected patients continue to be at risk for drug-drug interactions because of multiple medications often needed for prophylaxis and treatment of opportunistic infections, symptomatic relief of medication-related side effects, and treatment of chronic medical conditions unrelated to HIV.[2,3] In addition, HIV-infected patients frequently self-medicate with complementary and alternative medications (CAMs), which increases their risk of clinically significant drug interactions.[4–7]

A number of CAMs have the potential to modulate cytochrome P450 (CYP) isoforms, including CYP3A4/5, which is responsible for metabolizing approximately one third of medications that undergo CYP-mediated metabolism, including most HIV protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs).[4,8] Drug interactions between CAMs and PIs/NNRTIs may significantly increase or reduce the systemic exposure of concomitantly administered antiretroviral agents.[4] Indeed, St. John's wort and garlic significantly reduce the systemic exposure of several unboosted PIs in healthy human volunteers.[9,10] Other herbal preparations, such as *Gingko biloba* and *Echinacea purpurea*, induce CYP3A in healthy volunteers but do not interact with the boosted PI combination lopinavir-ritonavir (LPV/r).[11,12]

Panax ginseng (*Araliaceae* family) is one the most popular herbal dietary supplements in the United States, accounting for millions of dollars in yearly sales.[13,14] Individuals use *Panax ginseng* in attempts to improve vitality, immune function, cognitive function, and overall well-being.[15] In addition to a small number of studies in healthy human volunteers, several preclinical studies have been conducted in *in vitro* cellular systems and animal models to assess the modulatory effects of *P. ginseng* on CYP activity; however, these investigations have yielded conflicting results.[16–21] Recently, we reported a 34% reduction in the exposure of the CYP3A probe midazolam when it was administered as a single 8 mg dose before and after *P. ginseng* (standardized to 5% ginsenosides) 500 mg twice daily for 28 days to healthy volunteers.[22] These data suggest that *P. ginseng* induces CYP3A and may therefore reduce plasma concentrations of medications metabolized by this pathway, including HIV protease inhibitors. The objective of the current study was to determine the influence of *P. ginseng* on the steady-state pharmacokinetics (PK) of lopinavir/ritonavir in healthy volunteers.

Methods

Subjects

Healthy male and female volunteers between the ages of 18 and 50 were eligible to participate in this study. Each study candidate underwent an evaluation that included a medical history, physical examination, and laboratory analysis (serum electrolytes, liver function tests, cholesterol and triglycerides) to rule-out medical conditions that could place them at risk or potentially affect study results. Eligible subjects were required to have a negative HIV ELISA test and had not taken any medications (including prescription and non-prescription drugs, herbal supplements and oral contraceptives) within 30 days of study participation. Additional exclusion criteria included current or recent (within 6 weeks) tobacco use, drug or alcohol abuse, history of intolerance to any of the study medications, and persistent diarrhea. Acetaminophen, ibuprofen, and loperamide were allowed as needed to treat side effects associated with the study drugs; however, subjects were prohibited from taking these medications on pharmacokinetic sampling days. Subjects were instructed to refrain from ingesting fruit juices, including grapefruit juice, throughout the study period. Pregnant or breastfeeding females were excluded, and females of child-bearing potential were required to use a non-hormonal method of contraception throughout the study.

Informed consent was obtained from all subjects, and clinical research was conducted in accordance with guidelines for human experimentation as specified by the US Department of Health and Human Services. The study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board and was conducted at the Clinical Research Center at the National Institutes of Health (Bethesda, Maryland).

Study Design and Methods

This was a single-sequence, open-label evaluation of the effect of a 14-day course of orally administered *P. ginseng* on the steady-state pharmacokinetics of lopinavir and ritonavir in healthy volunteers. Subjects received lopinavir/ritonavir 400mg/100mg (two tablets of Kaletra [lopinavir 200mg-ritonavir 50mg/tablet]; Abbott, North Chicago, IL, USA) twice daily with meals for a total of 29.5 days. All subjects were instructed to take the lopinavir/ritonavir doses with breakfast and dinner at approximately the same time each day (± 1 hr). On day 15 of lopinavir/ritonavir administration, subjects received their morning dose with food in clinic, followed by blood sample collection to determine lopinavir and ritonavir steady-state concentrations (phase 1). Blood samples were collected immediately before and 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after the dose. The next morning, subjects began taking *P. ginseng* 500 mg twice daily (standardized to 5% ginsenosides; Vitamer Laboratories, Irvine, California); lopinavir/ritonavir was continued at the same dosing schedule. Total daily doses of *P. ginseng* typically range between 400 to 3000 mg (in 2–3 divided doses) depending on the formulation being used and the purported indication.[23] The 500-mg twice-daily dose was selected because it fell within the 400 to 3000-mg range and was consistent with the manufacturer's instructions. Subjects were instructed to take their *P. ginseng* doses on an empty stomach with 8 ounces of water separated by approximately 8 hrs (± 1 hr). Coadministration of lopinavir/ritonavir and *P. ginseng* continued for 2 weeks, after which subjects returned to clinic on study day 30 of lopinavir/ritonavir administration for repeat

lopinavir/ritonavir pharmacokinetic sampling (phase 2), as previously described. Adherence was assessed by self-report and examination of diary cards and pill counts at scheduled study visits.

Analytical Methods

Lopinavir and ritonavir plasma concentrations were determined by high performance liquid chromatography (HPLC) with liquid–liquid extraction using a method previously developed and validated in our laboratory.[11] The HPLC system consisted of a Waters 2795 Alliance HT separations module, and a 2996 photodiode array detector set at λ =215 nm (Waters Corp., Milford, MA, USA). The HPLC system and the assay parameters were controlled using the Empower chromatography manager software (Waters Corp., Milford, MA, USA). Lopinavir, ritonavir, and internal standard A86093 [(5S,8S,10S,11S)-9-hydroxy-2-cyclopropyl-5-(1-methyethyl)-1[2-(1-methylethyl)-4-thiazoly]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolymethyl ester] were isolated from human plasma by liquid-liquid extraction using Ethyl Acetate/Hexane/Iso-Amyl Alcohol [70:30:1]. Plasma samples were reconstituted with mobile phase and injected onto an Xterra™ MS C_{18}, 5 μm, 4.6 × 150 mm reverse-phase analytical column (Waters Corp., Milford, MA, USA), and eluted isocratically at 1.0 mL/min (T=25°C). The mobile phase consisted of acetonitrile and 10 mM ammonium acetate buffer (48:52, v/v) at pH 4.72.

Calibration curves for lopinavir and ritonavir were linear from 0.050 μg/mL to 15.0 μg/mL ($R^2 \geq 0.997$). Percent errors, as a measure of accuracy, were < 10%, and the respective inter- and intra-assay coefficients of variation (CV) for lopinavir were 4.07–9.08% and 3.16–9.36%, and those for ritonavir were 5.70–10.74% and 2.91–10.59%, respectively, at four different concentrations. The limit of quantitation was 0.050 μg/mL and the limit of detection was 0.030 μg/mL. During the validation, short-term stability of the drugs in plasma and repeated freezing and thawing of plasma were evaluated. The overall recovery of lopinavir, ritonavir and A86093 (internal standard) using the liquid–liquid extraction method were > 90%.

Panax ginseng Formulation

Chinese *Panax ginseng* 500 mg capsules (Vitamer Laboratories, Irvine, CA; lot # 115007) were used in this investigation. The formulation was standardized to 5% ginsenosides and certified by the Natural Products Association, a non–profit USA organization dedicated to the quality of manufacturing of natural supplements, in accordance with Good Manufacturing Practices (GMP). In addition, the product conformed to the dosage and mode of administration as established by the German Commission E monograph, containing *P. ginseng* powder from the whole root. After purchase from a commercial source, we did not perform further content analysis on the *P. ginseng* formulation nor did we assess serum concentrations of ginsenosides in our study population. However, the identical Vitamer product used in this study (Chinese *Panax ginseng* 500 mg capsules) was used previously in a study conducted by Gurley et al. In their study, the Vitamer *Panax ginseng* product underwent independent assessment for ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, and Rg at the National Center for Natural Products Research (University of Mississippi, University, MS, USA) using a proprietary gradient HPLC method.[24] All ginsenosides were detected in that

analysis, with Rb1 and Rb2 comprising the highest amounts (7.39 and 6.8 mg/capsule, respectively). In total, each capsule contained 22.4 mg ginsenosides. Previously conducted studies suggest that a number of ginsenosides and their deglycosylated metabolites are involved in CYP3A modulation, although a direct relationship between ginsenosides and CYP modulation has not been identified.[25,26] It is also possible that additional phytochemicals present in *P. ginseng* may contribute to CYP modulation. In a previously conducted study that used *P. ginseng* from the same lot number as the current investigation, we observed a statistically significant increase in CYP3A activity in healthy volunteers using oral midazolam as a CYP3A probe substrate.[22]

Pharmacokinetic Analysis

Plasma concentrations of lopinavir and ritonavir were analyzed by non-compartmental methods using WinNonlin pharmacokinetic software (version 5.0; Pharsight Corporation, Mountain View, CA). The maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and minimum concentration (C_{min}) were obtained by direct inspection of the plasma concentration-time profiles. The elimination rate constant (λ_Z) was determined by calculating the absolute value of the slope of the log-linear regression using at least 3 points on the plasma concentration-time plot. Area under the plasma concentration-time curve over the course of a dosing interval at steady state (AUC_{0-12}) was determined using the log-linear trapezoidal rule. Apparent oral steady state clearance was obtained by dividing the dose by AUC_{0-12}.

Statistical analysis

A difference in lopinavir AUC of at least 38% was considered to be clinically relevant for the purpose of establishing sample size. A standard deviation of 40 was assumed for a mean of 100 based on previously reported data.[11] With $\alpha = 0.05$, it was determined that a total of 12 subjects would provide 85 % power to detect a 38% difference in lopinavir AUC_{0-12} before and after *P. ginseng* administration.

Results are reported as geometric means and geometric mean ratios (GMR) ± 90% confidence intervals (CI). Pharmacokinetic parameter values for lopinavir and ritonavir at baseline (phase 1) and following *P. ginseng* administration (phase 2) were compared using a two-tailed, paired, Student's *t* test except for T_{max}, which was analyzed using the Wilcoxon Signed Rank test. Because subjects served as their own controls, a paired Student's t-test was used, and pre- and post-test measurements consisted of normally distributed parametric data. A *P* value < 0.05 was considered statistically significant for all analyses. SYSTAT Software (version 11, Richmond, CA) was used for sample size calculation and inferential statistics; Microsoft Excel was used to generate descriptive statistical data.

Results

Subjects

Fifteen individuals were screened, and 12 (8 males) completed the entire protocol. One subject withdrew because of noncompliance with protocol procedures and two subjects withdrew because of adverse events (described in detail below). The median (range) age,

weight, and BMI were 32 (23–42) years, 73 (51–114) kg, and 24.3 (20.6–43.7) kg/m^2, respectively for the 12 subjects who completed the protocol. Thesubjects were White/Hispanic (n=5), White/non-Hispanic (n=4), Black/non-Hispanic (n=2), or Asian/non-Hispanic (n=1). All reported excellent adherence to *P. ginseng* and lopinavir/ritonavir, and none missed more than 2 doses of study drug. Notably, neither of the missed doses occurred within 7 days of pharmacokinetic sampling days.

Lopinavir and ritonavir

Neither lopinavir nor ritonavir pharmacokinetic parameter values changed significantly after 14 days of *P. ginseng* coadministration (Table 1; Figures 1 and 2). The GMRs (90% CI) for lopinavir $AUC_{0\text{-}12}$ and C_{max} (post-ginseng/pre-ginseng) were 0.95 (0.85, 1.05) and 0.94 (0.84, 1.04), respectively. The GMRs (90% CI) for ritonavir $AUC_{0\text{-}12}$ and C_{max} (post-ginseng/pre-ginseng) were 0.95 (0.80, 1.09) and 0.92 (0.70, 1.14), respectively.

Safety

Adverse events included abdominal pain, headache, nausea, and diarrhea; the majority of which were grade 1 and consistent with the toxicity profile of lopinavir/ritonavir. Two adverse events resulted in study withdrawal. One subject was withdrawn from the study on day 11 of lopinavir-ritonavir dosing after experiencing a grade 2 pruritic rash, which was categorized as being “probably” related to lopinavir-ritonavir administration. Another subject was withdrawn from the study after experiencing grade 2 costochondritis that was not felt to be study-related.

Discussion

Fifteen million people in the United States report using herbal supplements or high-dose vitamins according to a nation-wide survey of CAM use.[5] Patients with HIV infection represent a significant subset of this population.[6] Many herbal products interact with prescription medications because they modulate CYP enzymes, particularly CYP3A4/5, and drug transport proteins, such as P-glycoprotein (P-gp).[27] To date, the herb associated with the greatest number of drug interactions is St. John’s wort. As a strong inducer of CYP3A and P-gp, St. John’s wort significantly decreases the systemic exposure of a variety of coadministered medications, often reducing AUC values by > 50%.[28] To a lesser magnitude, other herbal preparations induce the metabolism of coadministered medications. We previously observed reductions in midazolam AUC with Ginkgo biloba, *Echinacea purpurea*, and *P. ginseng* of 34%, 27%, and 34%, respectively, when each herbal preparation was administered for 28 days.[11,12,22] While these reductions in midazolam exposure are consistent with mild CYP3A induction, even mild-moderate reductions in drug exposure for medications with narrow therapeutic indices may be clinically relevant. To this end, we chose to study the influence of *P. ginseng* on the pharmacokinetics of the HIV protease inhibitor combination, lopinavir/ritonavir.

Despite our earlier observation of increased CYP3A activity with *P. ginseng* administration to healthy volunteers, we did not observe significant changes in lopinavir or ritonavir pharmacokinetics using the same *P. ginseng* formulation (Table 1).[22] The lack of an

observed effect of *P. ginseng* on lopinavir pharmacokinetics is likely due to CYP3A inhibition by ritonavir, which nullified the induction effects of *P. ginseng* on lopinavir metabolism via CYP3A. Indeed, low-dose ritonavir has been shown to attenuate CYP3A induction associated with other enzyme inducers, such as rifabutin and efavirenz, and the CYP3A-inducing herbal preparations *G. biloba* and *E. purpurea*.[11,12,29,30] These data suggest that *P. ginseng*, like *G. biloba* and *E. purpurea*, is unlikely to reduce the plasma concentrations of ritonavir-boosted protease inhibitors.

Despite the strong circumstantial evidence that ritonavir attenuated the CYP3A-mediated induction of lopinavir in the current study, another possibility is that the *P. ginseng* formulation we used contained insufficient quantities of ginsenosides to sufficiently induce CYP3A activity. While ginsenoside content was not confirmed by independent phytochemical analysis in this study, ginsenoside content was assessed by an independent organization (National Product Association) and found to be consistent with the quantity indicated on the manufacturer's label. Moreover, in a previous investigation that used the identical Vitamer product used in the current study (Chinese, Panax ginseng 500 mg capsules) an independent assessment for ginsenoside content found appropriate amounts of ginsenosides as described in the Methods section above.[24]

Further evidence supporting the CYP3A-inducing capabilities of the *P. ginseng* formulation used in the current investigation, is that in a previous study we observed a 34% reduction in midazolam exposure after 28 days of *P. ginseng* 500 mg twice daily using the same formulation, lot number, and dose as the current investigation.[22] One difference between the studies however, is that subjects received *P. ginseng* for 28 days in the midazolam phenotyping investigation compared to 14 days in the current study with lopinavir/ritonavir. While it is possible we may have observed different pharmacokinetic results for lopinavir had we administered *P. ginseng* for an additional 14 days, we believe this scenario to be unlikely, considering that some degree of enzymatic induction should have been apparent after 2 weeks of dosing. Indeed, even if 14 days was insufficient for maximal CYP3A induction to occur with *P. ginseng*, we would have at least expected to observe a trend toward decreased lopinavir exposure during this period, yet this was clearly not the case (LPV $AUC_{0\text{-}12}$ GMR (90% CI) [post-ginseng/pre-ginseng] = 0.95 (0.85–1.05).

Given the ability of *P. ginseng* to induce CYP3A in the absence of a potent CYP3A inhibitor such as ritonavir, antiretroviral medications that are CYP3A substrates yet not consistently coadministered with ritonavir (i.e. atazanavir, maraviroc, rilpivirine, and fosamprenavir) may undergo clinically relevant reductions in systemic exposure when taken along with *P. ginseng*.[22] In addition to CYP3A, *P. ginseng* has been tested for its influence on additional CYP enzymes including CYP2D6, CYP2E1, and CYP1A2; however, it has not been shown to alter the activity of any of these isoforms.[19] To date, *P. ginseng* has not been thoroughly studied in humans for its influence on uridine diphosphate glucuronosyl transferase enzymes (UGT). This may be of importance because *P. ginseng* induces CYP3A, which is under transcriptional control by the orphan nuclear receptor Pregnane X Receptor (PXR), and PXR is also involved in regulating the transcription of several UGT enzymes including UGT1A1, UGT1A6, UGT1A3, and UGT1A4.[31] It is therefore possible that *P. ginseng* may modulate the metabolism of drugs that are UGT substrates; these include the HIV integrase inhibitors

dolutegravir and raltegravir, as well as numerous non-HIV medications.[32–34] Despite the theoretical possibility of interactions between *P. ginseng* and UGT substrates, pharmacokinetic studies in humans are necessary to determine whether such interactions occur.

Preclinical evidence also suggests that *P. ginseng* may alter the pharmacokinetics of coadministered medications, including HIV protease inhibitors, which are well-described P-gp substrates, secondary to modulation of transport proteins such as P-gp.[35] Two weeks of orally administered *P. ginseng* (150 mg/kg/day) resulted in an approximate 50% reduction in the systemic exposure of the P-gp substrate fexofenadine in rats, and induction of brain endothelium P-gp.[36] In contrast, we previously reported that 28 days of *P. ginseng* 500 mg twice daily for 28 days did not alter the pharmacokinetic profile of fexofenadine in healthy human volunteers.[22] However, the influence of *P. ginseng* on drug distribution into sanctuary sites (i.e the brain) in humans cannot be ruled out and requires further investigation.

In conclusion, *P. ginseng* did not alter the steady-state plasma concentrations of either lopinavir or ritonavir. It is also unlikely that *P. ginseng* will alter the plasma concentrations of other ritonavir-boosted protease inhibitor combinations, although pharmacokinetic data are needed to confirm this assumption. Nonetheless, in the absence of a potent CYP3A inhibitor like ritonavir, it is plausible that *P. ginseng* may decrease the exposure of other CYP3A substrates that are not coadministered with a potent CYP3A inhibitor. Future studies are necessary to determine the influence of *P. ginseng* on the pharmacokinetics of the HIV integrase inhibitors and other UGT substrate medications.

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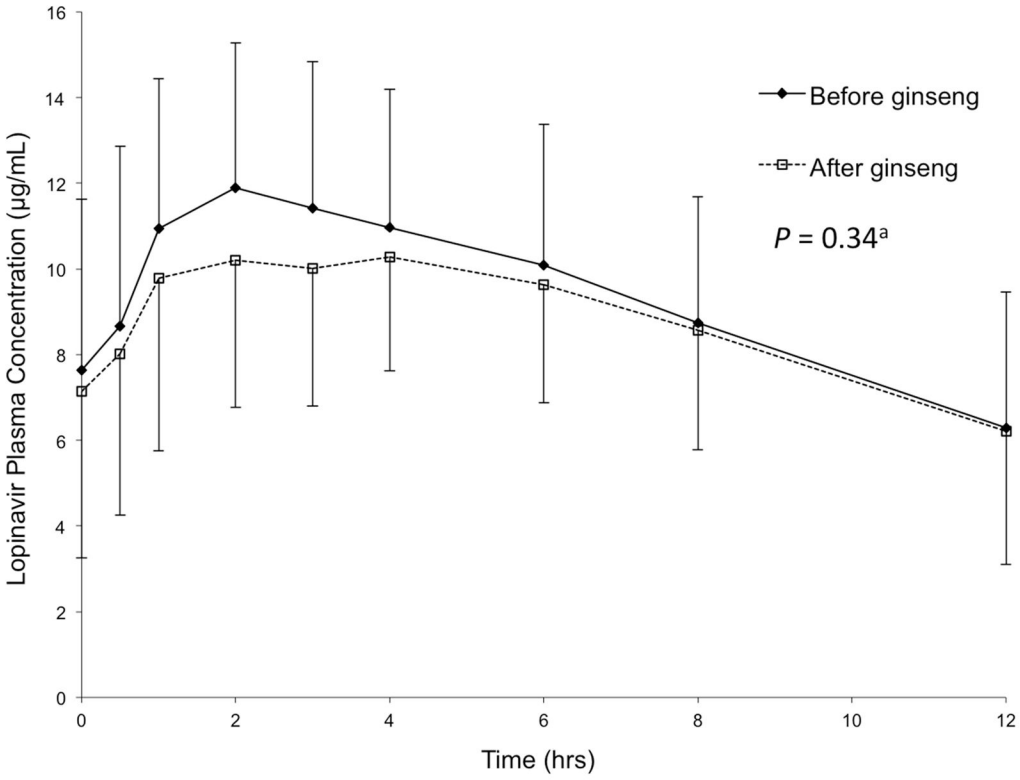

Figure 1.

Lopinavir Concentration vs. Time Curves (± SD) Before and After 14 Days of *Panax Ginseng* Administration

[a] *P* value is for lopinavir $AUC_{0\text{-}12}$ measurements before, and after 14 days of *Panax ginseng* administration using a 2-tailed Students paired t test.

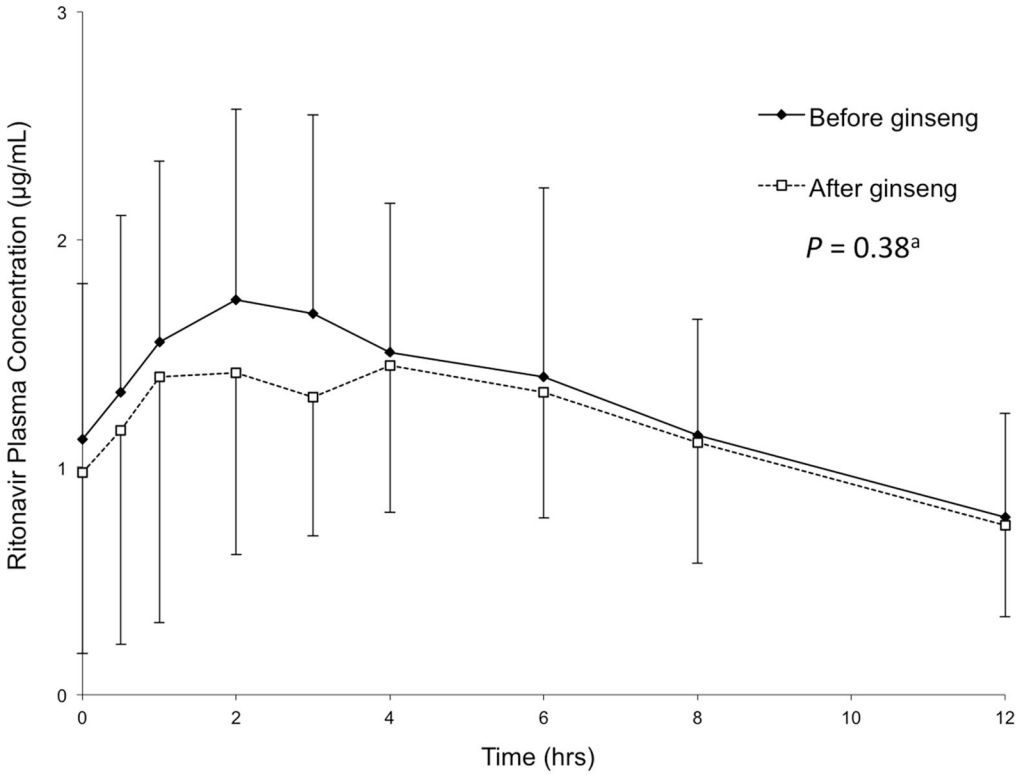

Figure 2.

Ritonavir Concentration vs. Time Curves (± SD) Before and After 14 Days of *Panax Ginseng* Administration

[a] *P* value is for ritonavir $AUC_{0\text{-}12}$ measurements before, and after 14 days of *Panax ginseng* administration using a 2-tailed Students paired t test.

Table 1

Lopinavir and ritonavir pharmacokinetic parameter values before- and after 14 days of *Panax ginseng* administration (N= 12 healthy volunteers).

	Geometric Mean Values (90% CI)[a]		Geometric Mean Ratios (90% CI)[a]	P[b]
Lopinavir	**Pre-ginseng**	**Post-ginseng**	**Post-ginseng/Pre-ginseng**	
AUC_{0-12} (μg·hr/mL)	108 (92–125)	103 (88–117)	0.95 (0.85–1.05)	0.34
C_{max} (μg/mL)	12.3 (10.8–13.8)	11.5 (10.1–12.9)	0.94 (0.84–1.04)	0.35
T_{max} (hr)	2.4 (1.7–3.2)	2.5 (1.7–3.4)	1.05 (0.62–1.48)	0.55
T ½ (hr)	8.4 (6.5–10.2)	10.0 (6.8–13.2)	1.19 (0.92–1.46)	0.06
Cl/F_{ss} (L/hr)	3.70 (3.19–4.20)	3.89 (3.47–4.32)	1.05 (0.94–1.17)	0.55
Ritonavir				
AUC_{0-12} (μg·hr/mL)	13.9 (10.5–17.2)	13.10 (10.09–16.13)	0.95 (0.80–1.09)	0.38
C_{max} (μg/mL)	1.81 (1.40–2.22)	1.66 (1.24–2.09)	0.92 (0.70–1.14)	0.50
T_{max} (hr)	2.37 (1.58–3.17)	2.70 (2.01–3.38)	1.14 (0.20–2.08)	0.67
T ½ (hr)	7.55 (6.23–8.86)	7.71 (5.45–9.97)	1.02 (0.60–1.44)	0.58
Cl/F_{ss} (L/hr)	7.22 (5.23–9.20)	7.63 (6.32–8.93)	1.06 (0.89–1.23)	0.99

[a] CI, confidence interval.

[b] The Student's paired, two-tailed T-test was used for statistical comparisons except for Tmax, for which the Wilcoxon Signed Rank test was used.