

Brief Communication: American Ginseng Reduces Warfarin's Effect in Healthy Patients

A Randomized, Controlled Trial

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Background: People using prescription medication often concurrently take herbal supplements. In a case report, the anticoagulant effect of warfarin decreased after patients consumed ginseng.

Objective: To evaluate the interactions between American ginseng and warfarin.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: General Clinical Research Center, University of Chicago, Chicago, Illinois.

Participants: 20 healthy patients.

Intervention: In this 4-week study, 20 patients received warfarin for 3 days during weeks 1 and 4. Beginning in week 2, patients were assigned to receive either American ginseng or placebo.

Measurements: International normalized ratio (INR) and plasma warfarin level.

Results: The peak INR statistically significantly decreased after 2 weeks of ginseng administration compared with placebo (difference between ginseng and placebo, -0.19 [95% CI, -0.36 to -0.07]; $P = 0.0012$). The INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC were also statistically significantly reduced in the ginseng group as compared with the placebo group. Peak INR and peak plasma warfarin level were positively correlated.

Limitations: The study sample consisted of young, healthy volunteers in a research setting rather than patients taking therapeutic doses of warfarin.

Conclusions: American ginseng reduces warfarin's anticoagulant effect. When prescribing warfarin, physicians should ask patients about ginseng use.

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The beneficial effects of several commonly used botanicals have been documented (1), but data on the safety of these herbs are limited. At least 16% of people using prescription medication concurrently take herbal supplements. An estimated 15 million Americans are at risk for herb–drug interactions (2).

Advocated for almost every purpose, including maintaining general health, combating fatigue, and improving immune function (3), ginseng is one of the best-selling herbs in the United States (4). Herbs such as ginseng may interact with medications that have a narrow therapeutic index, such as warfarin, a commonly used oral anticoagulant (5, 6). A widely cited case report showed a substantial decrease in the anticoagulant effect of warfarin after ginseng consumption in a patient who was previously maintained with stable warfarin therapy (7). We conducted a randomized, double-blind, placebo-controlled trial to evaluate the potential interactions between American ginseng and warfarin.

METHODS

Patients

Nine men and 11 nonpregnant women (who were paid \$250 after trial completion) were enrolled in this study. Patients were screened with a medical history, physical examination, 12-lead resting electrocardiography, complete blood and platelet counts, international normalized

ratio (INR) (the prothrombin time test–control ratio) (8), blood chemistry tests, and urinalysis. Patients agreed to abstain from tobacco products for at least 2 weeks before and during the study, abstain from alcohol and other medications during the study, and limit caffeine-containing products for 48 hours before and during the study.

Protocol

The institutional review board approved this 4-week study conducted at the University of Chicago Medical Center, Chicago, Illinois. All patients provided written, informed consent. Patients received oral warfarin, 5 mg daily, for the first 3 consecutive days during week 1. Beginning in week 2, patients were randomly assigned to receive either oral American ginseng, 1.0 g, or placebo, twice daily, for 3 consecutive weeks. During week 4, all patients again received oral warfarin, 5 mg daily, for the first 3 consecutive days (**Appendix Figure**, available at www.annals.org).

Ginseng or placebo assignment was determined by a table of random numbers with blocks of 8 (4 ginseng and 4 placebo assignments per block), from which sealed, opaque envelopes were prepared and opened sequentially as patients were enrolled in the study. A biostatistician who did not acquire data prepared the assignments. Patients and investigators were blinded to the treatment groups.

Patients were instructed to eat a balanced diet to maintain a consistent amount of vitamin K and to avoid drastic

Context

Consuming ginseng, a commonly used herbal dietary supplement, has been associated with a decrease in warfarin's anticoagulant effect in at least 1 case report.

Contribution

Healthy volunteers took warfarin with and without concurrently taking ginseng. Ginseng consumption lowered the international normalized ratio and decreased plasma warfarin levels.

Cautions

Patients and physicians should be aware that ginseng is among many substances that can interfere with warfarin's anticoagulant effect.

—The Editors

changes in dietary habits. The daily intake of vitamin K-containing foods was recorded 1 week before the study to obtain the baseline value and to adjust the diet if vitamin K intake was high. Patients recorded their daily diet throughout the study period, completed a written weekly questionnaire, and were asked to report any adverse events.

Blood samples were obtained at the same time (± 0.5 hour) on days 1, 3, 4, 5, and 7 of weeks 1 and 4 to measure INR and plasma warfarin levels (detection limit, $0.1 \mu\text{g}/\text{mL}$).

Study Drugs

Warfarin (3-(α -acetylbenzyl)-4-hydroxycoumarin or Coumadin, DuPont Pharmaceuticals, Wilmington, Delaware) is a racemic mixture composed of equal amounts of 2 optical isomers. In our laboratory, we ground the root of American ginseng (*Panax quinquefolius*, Wisconsin Ginseng Board, Wausau, Wisconsin) from 1 lot into a fine powder and placed 0.5 g in nontransparent capsules. Using a high-performance liquid chromatography method, we found that the total ginsenoside content was 5.19%. The constituent split was as follows: ginsenoside Rb₁, 1.93%; Rb₂, 0.20%; Rc, 0.61%; Rd, 0.42%; Re, 1.68%; and Rg₁, 0.35%. We prepared identical placebo capsules that contained cornstarch powder.

Statistical Analysis

The primary end point of this study was the change in peak INR (week 4 – week 1). Additional analysis end points were change in INR area under the curve (AUC) (week 4 – week 1), defined as the area under the INR versus time curve; change in peak plasma warfarin level; change in warfarin AUC (week 4 – week 1), defined as the area under the plasma warfarin level versus time curve; and weekly vitamin K intake. The AUC was calculated on the basis of the trapezoidal rule by using measurements for days 1 through 7. We compared changes in peak INR, INR AUC, peak plasma warfarin level, and warfarin AUC

between the ginseng and placebo groups by using the Wilcoxon rank-sum test. We calculated the difference in median changes between the 2 groups and corresponding 95% CIs according to the method described by Hollander and Wolfe (9), which is based on consideration of all pairwise differences between the 2 sets of observations. We calculated the Spearman rank correlation coefficients to examine the correlation between the change in peak INR and change in peak plasma warfarin levels. Repeated-measures analysis of variance (ANOVA) models were used to test differences in vitamin K intake between the groups and over time. A *P* value less than 0.05 was considered statistically significant. Stata, version 8 (Stata Corp., College Station, Texas), and Minitab, version 13 (Minitab, Inc., State College, Pennsylvania), were used for statistical analysis.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

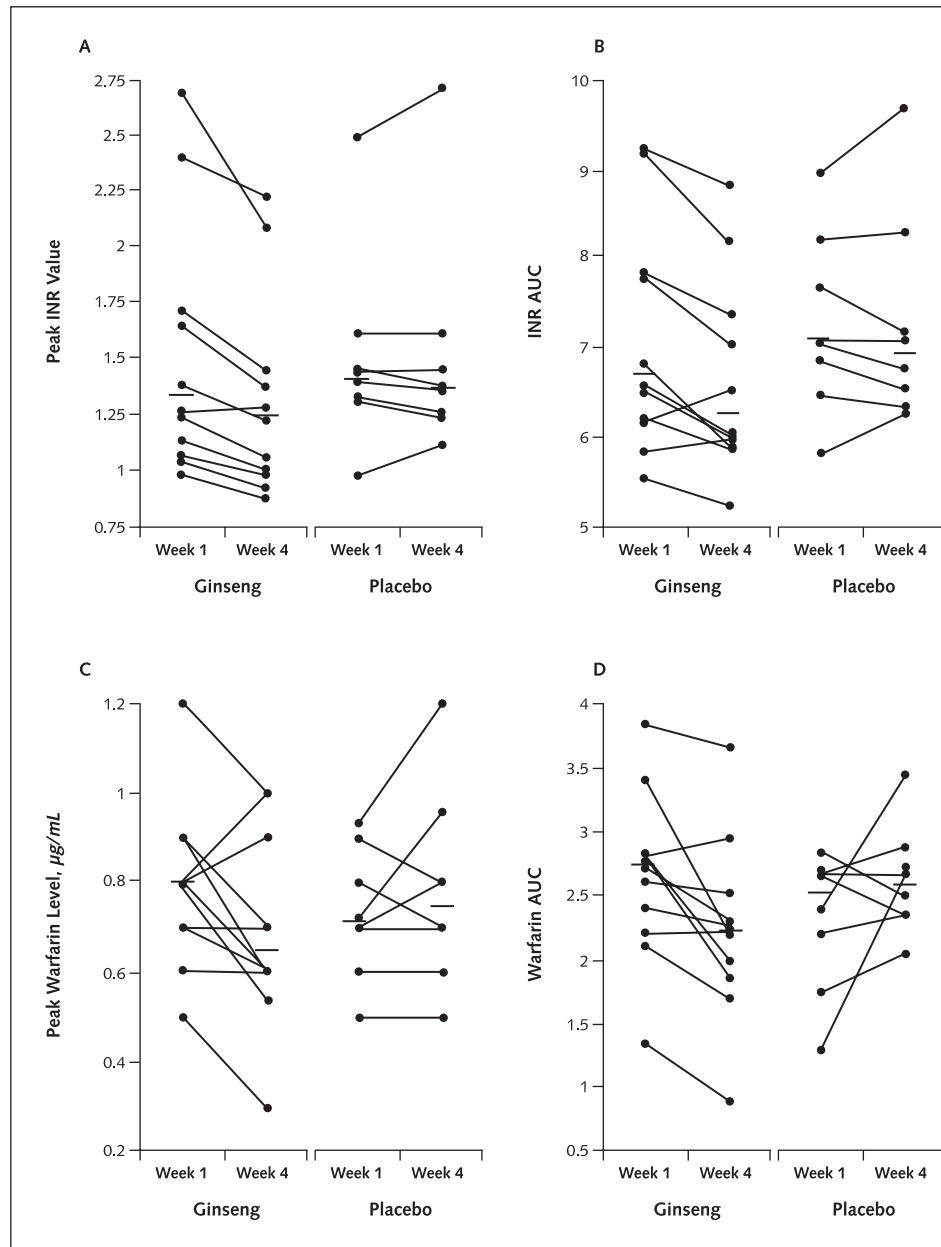
Data from all 20 patients (12 patients in the ginseng group and 8 patients in the placebo group) were used in the analysis. For the 6 men and 6 women in the ginseng group (7 patients were white, 3 patients were black, 1 patient was Hispanic, and 1 patient was Asian), the mean age and body weight (\pm SD) were 30.2 ± 7.2 years and 69.2 ± 20.6 kg, respectively. For the 3 men and 5 women in the placebo group (3 patients were white, 2 patients were black, 2 patients were Hispanic, and 1 patient was Asian), the mean age and body weight (\pm SD) were 24.3 ± 4.0 years and 62.0 ± 9.1 kg, respectively (**Appendix Table**, available at www.annals.org).

In both groups, INR generally reached peak levels on day 4 after 3 consecutive days of warfarin administration. The **Figure** shows changes in individual peak INR, INR AUC, peak plasma warfarin level, and warfarin AUC from weeks 1 to 4. The modest reduction in INR magnitude in the ginseng group was statistically significant compared with the change in the placebo group (*P* = 0.0012). Changes in INR AUC, peak plasma warfarin level, and warfarin AUC were also statistically significantly greater in the ginseng group. The **Table** summarizes results for the primary and secondary end points.

For both peak warfarin level and AUC, the changes in the placebo group were not statistically significant and therefore probably reflected random variation in the small sample size. The Spearman rank correlation coefficient between changes in peak INR values and changes in peak warfarin levels was 0.72 (*P* < 0.001).

One patient (patient 18) in the ginseng group had a high baseline INR (1.32) on day 1 compared with that in the other patients (mean INR [\pm SD], 0.94 ± 0.04). For this patient, peak INR after warfarin administration on day

Figure. Changes in individual peak international normalized ratio (INR), INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC in weeks 1 and 4 in American ginseng or placebo groups.



Short horizontal bars represent median values. Values for patient 18, which are off scale, are not plotted. **A.** Peak INR values before and after 2 weeks of treatment with ginseng or placebo. The reduction in peak INR was significantly greater after ginseng administration than after placebo administration ($P = 0.0012$). **B.** The INR AUC in patients from days 1 to 7 before and after treatment with ginseng or placebo. The AUC was significantly decreased after 2 weeks of ginseng treatment compared with placebo treatment ($P = 0.025$). **C.** Peak plasma warfarin levels before and after 2 weeks of treatment with ginseng or placebo. The reduction in peak warfarin level was significantly greater after ginseng administration than after placebo administration ($P = 0.026$). **D.** Warfarin AUC in patients from days 1 to 7 before and after treatment with ginseng or placebo. The AUC was significantly decreased after 2 weeks of ginseng treatment compared with placebo treatment ($P = 0.0069$).

4 was 5.16. After ginseng administration, the peak INR was 2.75 and the corresponding AUC decreased from 17.46 to 11.1. The patient's peak plasma warfarin level also decreased from 1.6 $\mu\text{g}/\text{mL}$ during week 1 to 0.9 $\mu\text{g}/\text{mL}$ in week 4. If this patient is excluded from the analysis, the results remain statistically significant. No un-

usual medical or drug history or diet was noted for this patient.

For weeks 1, 2, 3, and 4, average daily vitamin K intake ($\pm\text{SD}$) for the ginseng group was 32.3 ± 5.2 $\mu\text{g}/\text{d}$, 42.6 ± 7.6 $\mu\text{g}/\text{d}$, 41.9 ± 8.6 $\mu\text{g}/\text{d}$, and 34.0 ± 5.5 $\mu\text{g}/\text{d}$, respectively. The average daily vitamin K intake ($\pm\text{SD}$) for

Table. Changes in Peak International Normalized Ratio, International Normalized Ratio Area under the Curve, Peak Plasma Warfarin Level, and Warfarin Area under the Curve between Weeks 1 and 4 in American Ginseng and Placebo Groups*

Variable	Changes from Weeks 1 to 4†		Ginseng vs. Placebo	
	Ginseng Group (n = 12)	Placebo Group (n = 8)	Estimated Difference in Medians (95% CI)	P Value‡
Peak INR	-0.16 (-2.41/0.02)	-0.02 (-0.07/0.22)	-0.19 (-0.36 to -0.07)	0.0012
INR AUC	-0.46 (-6.36/0.36)	-0.09 (-0.51/0.72)	-0.43 (-1.00 to -0.09)	0.025
Peak plasma warfarin level, $\mu\text{g/mL}$	-0.20 (-0.70/0.20)	0.00 (-0.10/0.27)	-0.20 (-0.35 to 0.00)	0.026
Warfarin AUC, $\mu\text{g/mL per d}$	-0.40 (-1.20/0.20)	0.18 (-0.35/1.40)	-0.64 (-1.25 to -0.13)	0.0069

* AUC = area under the curve; INR = international normalized ratio.

† Median and range (min/max).

‡ Wilcoxon rank-sum test.

the placebo group for weeks 1, 2, 3, and 4 was 36.4 ± 11.2 $\mu\text{g/d}$, 32.0 ± 8.4 $\mu\text{g/d}$, 39.5 ± 8.7 $\mu\text{g/d}$, and 38.6 ± 11.4 $\mu\text{g/d}$, respectively. Vitamin K intake did not statistically significantly differ between the 2 groups ($P > 0.2$) or over time ($P > 0.2$). No adverse effects of clinical importance occurred in this study.

DISCUSSION

Among the several different species of ginseng, the major active components are ginsenosides, which are a diverse group of steroidal saponins (3). Ginseng may promote bleeding in surgical patients (6). Ginsenosides prolonged both thrombin time and activated partial thromboplastin time in rats (10) and inhibited platelet aggregation in vitro in human platelets (11). In our healthy patients, however, ginseng reduced the anticoagulant effect of warfarin. We selected the commonly consumed American ginseng and a dose at the high end of the recommended range (12).

Warfarin indirectly interferes with blood clotting by depressing the hepatic synthesis of vitamin K–dependent coagulation factors. The attenuation of warfarin's effect was probably not due to vitamin K since biochemical analysis did not detect vitamin K in ginseng (13, 14). In this study, vitamin K intake was closely monitored to exclude a vitamin K effect. External factors, such as diet, alcohol, and cigarette smoke, can induce or inhibit hepatic enzymes (15). The randomized, blinded design of this study attempted to exclude these factors as confounders.

Warfarin is a racemic mixture of S- and R-enantiomers. Both enantiomers are eliminated extensively through the hepatic P450 enzyme system (16). A previous case report demonstrated a decrease in the anticoagulant effect of warfarin with administration of a ginseng-containing product for 2 weeks (7). In rats, however, no statistically significant interaction was demonstrated between ginseng and warfarin over 5 consecutive days (13), perhaps an insufficient time for inducing hepatic drug–metabolizing enzyme activities. Similarly, after 4 to 8 days of administration of St. John's wort, the hepatic enzyme system in humans did not change. After 2 weeks, the AUC of other tested medications was statistically significantly reduced (17). In our trial, after ginseng consumption for 2 weeks,

warfarin's anticoagulant activity was statistically significantly reduced, suggesting that more than 1 week is required to induce hepatic enzyme activities. Steroids can induce hepatic enzymes (18). Ginsenosides may enhance enzyme functions. Whether ginseng interferes with other hepatically metabolized drugs remains to be evaluated.

Our study group consisted of young, healthy adults, whereas patients who take warfarin are often older with clinically significant health problems. Metabolism of both ginseng and warfarin may differ between our study group and actual patients.

Because of the narrow therapeutic index of warfarin, keeping its anticoagulant effect in a target range is crucial. The use of warfarin, however, is complicated by potential drug–drug or drug–herb interactions (19, 20). Our data suggest that American ginseng reduces the anticoagulant effect of warfarin. Thus, when prescribing warfarin for patients, physicians should ask them about their use of ginseng.

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