Published in final edited form as:
Curr Drug Metab. 2011 November 1; 12(9): 818–822.

Metabolism of Ginseng and its Interactions with Drugs

Lian-Wen Qi, **Chong-Zhi Wang**, **Guang-Jian Du**, **Zhi-Yu Zhang**, **Tyler Calway**, and **Chun-Su Yuan***
Tang Center for Herbal Medicine Research and Department of Anesthesia & Critical Care, The Pritzker School of Medicine, University of Chicago, 5841 South Maryland Avenue, MC 4028, Chicago, Illinois 60637, U.S.A

Abstract

Ginseng is an herbal medicine used worldwide. It is reported to have a wide range of pharmacological activities because of a diversified group of steroidal saponins called ginsenosides. Compared to extensive pharmacological studies of ginseng, the pharmacokinetics, especially the metabolism of this herb, has received less attention. In this article we review the known pharmacokinetic data on ginseng. Understanding ginseng's pharmacokinetics may reduce the potential for interactions in patients who use both ginseng and prescription medications. In addition, bioavailability after taking ginseng orally is low, and the metabolites of ginsenosides produced by gut microbiota may be biologically active. One ginseng metabolite, Compound K, and its potential for cancer chemoprevention is also discussed. An active ginseng metabolite may differ in distribution and clearance from its parent compound, and the parent compound and its metabolite may be bioactive by similar or different mechanisms. Thus, further investigation of ginseng metabolites is needed for predicting the therapeutic outcome with ginseng.

Keywords

Asian ginseng; *Panax ginseng*; American ginseng; *Panax quinquefolius*; ginsenosides; absorption; metabolism; metabolite; Compound K; herb-drug interaction

INTRODUCTION

Ginseng, one of the most popular herbal medicines, has been used for thousands of years in many oriental countries. In the last twenty years, ginseng has also been in demand in the United States and Europe as a dietary supplement. Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are the two most recognized ginseng herbs worldwide.

Ginseng is reported to have a wide range of pharmacological activities: stress reduction and homeostasis, immunomodulation, anti-fatigue, anti-aging, anti-diabetic, and anti-cancer effects [1–5]. In both Asian ginseng and American ginseng, a diversified group of steroidal saponins called ginsenosides are the major active components [2, 5, 6]. Recent advances in biomedical research and chemical analysis have improved our knowledge of the ginsenosides. However, their pharmacokinetics has received less attention. Understanding

*Address correspondence to this author at the Tang Center for Herbal Medicine Research and Department of Anesthesia & Critical Care, The Pritzker School of Medicine, University of Chicago, 5841 South Maryland Avenue, MC 4028, Chicago, Illinois 60637, USA; Tel.: (773) 702-1916; Fax: (773) 834-0601; cyuan@uchicago.edu.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

the pharmacokinetics of ginseng has clinical significance if ginsenosides have the potential to interact with prescription drugs.

Like many other herbal medicines, ginseng is nearly always taken orally. In this form its bioavailability is low because of incomplete absorption. The conversion of ginsenosides to their metabolites by intestinal bacteria has been reported. Some of the metabolites, such as Compound K, have shown cancer chemopreventive effects [7–9]. In this article, we review the pharmacokinetics, especially the metabolism, of major ginsenosides found in ginseng. Since ginseng is also metabolized by gut microbiota, we will discuss ginseng metabolites in potential therapeutics. Finally, the studies that have found interactions between ginseng and other drugs will be presented in relation to clinical importance.

PHARMACOKINETICS AND METABOLISM OF GINSENOSIDES

The pharmacokinetics of different ginseng saponin compounds has been studied in both animals and humans [1–3]. In order to obtain detectable plasma levels of the compounds, the administered test compound doses were often at the high end of the pharmacological dose range. Yet the pharmacokinetic profile of ginseng has been incompletely understood because of the many diversified and heterogeneous chemical structures of different ginsenosides.

The absorption rate of ginseng saponins is low after oral administration, and doses of test compounds must be high to detect levels in plasma. Extensive metabolism in the gastrointestinal tract [10, 11], poor membrane permeability [12], and low solubility of deglycosylated products [13] limit intestinal absorption of ginseng saponins. The bioavailability of the protopanaxadiol (PPD) group of saponins (ginsenosides Ra3, Rb1, Rd, Rg3, and Rh2) [12, 14–17] and of the protopanaxatriol (PPT) group of saponins (ginsenosides Rg1, Re, Rh1, and R1) [14, 18–20] was less than 5%. PPT saponins have better bioavailability than PPD saponins [14, 21], perhaps because PPD saponins degrade faster than PPT saponins. High oral doses may saturate metabolism and increase bioavailability [21, 22]. Changing the pharmaceutical formulation may also improve bioavailability. For instance, micronized Rh2 has doubled its bioavailability [13].

The time for saponins to reach maximum concentration (T_{max}) in plasma was generally less than 2 hr, indicating that saponins are rapidly absorbed and readily distributed in the tissues [23, 24]. In rabbits, the elimination half-lives ($T_{1/2}$) of Rg1, Re and Rb2 were between 0.8 hr and 7.4 hr [25]. In humans, the $T_{1/2}$ of the tested saponins was generally less than 24 hr [10, 26].

Tissue disposition showed that liver and bile clear ginseng saponins from circulation [22, 23, 27]. Hepatic cytochrome P450 catalyzed ginsenoside metabolism, and it has been described that CYP3A4 catalyzed metabolism by oxygenation the hepatic disposition of ginsenosides [28]. Attachment of more sugar moieties in the PPD ginsenosides Ra3, Rb1, Rc and Rd blocked their access to biliary transporters and slowed biliary excretion [12]. Most ginsenosides and their deglycosylated products were excreted by the biliary system through active transport [12]. Time curves of ginseng saponins exhibited distinct multiple peaks after oral administration, indicating the involvement of enterohepatic recirculation [22]. Approximately 0.2%–1.2% of ginsenosides were excreted in human urine [29].

SAPONIN METABOLISM BY GUT MICROBIOTA

After oral administration, ginseng is metabolized extensively by intestinal bacteria [12, 26, 30]. Studies of the degradation and metabolism of ginseng saponins have been conducted using enzymes or intestinal bacteria [32, 33]. Among the metabolic pathways are

deglycosylation reactions by intestinal bacteria via stepwise cleavage of the sugar moieties [10, 12, 26]. In the PPD group, Rb1 and Rd are metabolized to Compound K [34, 35]. Rg3 and Rg5 are biotransformed to Rh2 and Rh3, respectively [36, 37]. In the PPT group, Rg1 and Re are converted to Rh1 and F1 [10, 38, 39]. After oral ingestion, ginsenoside metabolites are absorbed from the gut into systemic circulation [12, 26, 30]. In our ongoing studies in human volunteers, ginsenoside Rb1 and Compound K reached the systemic circulation after oral administration of American ginseng (unpublished data).

Because of competitive absorption and metabolism, administration of a single ginsenoside or of a ginseng extract may have different results. The metabolic profile of a ginsenoside also can vary with method of administration. For instance, after intravenous injection of Rd, Rb1 is the dominant metabolite; after oral administration of Rd, Rg3 is dominant[35].

As an active ginseng saponin metabolite, Compound K exerts cancer chemoprevention activity. This metabolite induced apoptosis in several tumor cell lines. Compound K inhibited the growth of human leukemia cells by induction of apoptosis via cytochrome c-mediated activation of caspase-3 protease and the caspase-8-dependent pathway [7, 40]. It also arrested the G1 phase of the cell cycle [41]. In human astroglial cells, Compound K suppressed tumor necrosis factor-alpha-induced activation of the NFkappaB and JNK pathways and inhibited matrix metalloproteinase-9 [42, 43]. In HepG2 cells, Compound K induced apoptosis via the Fas/Fas ligand death receptor pathway and mitochondria-mediated pathway [44, 45]. *In vivo* experiments with mouse skin, Compound K inhibited tumor and COX-2 expression [46].

We used two human colorectal cancer cell lines HCT-116 and SW-480 to compare the chemopreventive effects of ginsenoside Rb1 and Compound K. The two cell lines differ in the expression of the tumor suppressor gene, p53. HCT-116 is a wild-type for p53 and SW-480 is mutant. Compound K showed significant antiproliferative effects on the colorectal cancer cells at 30 μM; Rb1 did not inhibit activity at 100 μM. To elucidate the mechanisms mediating the anti-proliferative effects in colon cancer cells, we examined alterations in cell cycle and apoptosis. Compound K inhibited G1 progression and increased apoptosis in both cell lines. At 40 μM, HCT-116 showed late apoptosis; SW-480 showed early apoptosis (unpublished data).

POTENTIAL GINSENG-DRUG INTERACTIONS

An herbal medicine such as ginseng has many different constituents, each of which exerts a distinct pharmacological activity. With its complex pharmacodynamics and pharmacokinetics, ginseng may place patients who take it concurrently with prescription medications at potential risk for ginseng-drug interactions.

Despite the public enthusiasm for herbal medicines, scientific knowledge of herbal-drug interaction is incomplete and often confusing for health care professionals and patients. Recommendations to avoid herbal-drug interaction are often based on *in vitro* observations, animal studies, and case reports. However, data from clinical studies, especially controlled clinical trials, are often unavailable.

When Yu et al. compared the effect of American ginseng and Asian ginseng extracts on gene expression of the hepatic P450 enzyme in adult rats and primary cultures or rat hepatocytes, there was no evidence of the induction of CYP2B1, CYP3A23, or CYP1A2 cultures of rat [47]. In another study ginseng had no effect on a number of CYP isoforms, including CYP3A4, CYP1A2, CYP2E1 and CYP2D6 [48, 49]. However, in elderly humans, CYP2D was slightly inhibited [49].

Liu et al. evaluated the ginseng influence on hepatic P450 activities using both naturally occurring ginsenosides and their degradation products in gut lumen with human liver microsomes and cDNA-expressed CYP3A4. The naturally occurring ginsenosides exhibited no or weak inhibition against human CYP3A4, CYP2D6, CYP2C9, CYP2A6, or CYP1A2 activities. Intestinal metabolites inhibited P450-mediated metabolism. Compound K, protopanaxadiol (PPD), and protopanaxatriol (PPT) inhibited CYP2C9 activity moderately; PPD and PPT also strongly inhibited CYP3A4 activity. These data suggest that after oral administration, naturally occurring ginsenosides may influence hepatic P450 activity *in vivo* via ginseng's intestinal metabolites [50].

Andrade et al. evaluated the pharmacokinetic effects of American ginseng in healthy volunteers taking the HIV protease inhibitor indinavir. Indinavir decreased insulin sensitivity, but this decrease was unaltered by co-administration of American ginseng. American ginseng did not significantly affect indinavir pharmacokinetics [51].

Herb-drug interaction is particularly important when a drug has a narrow therapeutic index and keeping the drug effect in a target range is crucial. Herbs such as ginseng may interact with warfarin, an oral anticoagulant with a narrow therapeutic window [52, 53]. A widely cited case report showed a substantial decrease in the anticoagulant effect of warfarin after ginseng consumption in a patient whose warfarin therapy had been stable previously [52, 53].

In a randomized, double-blind, placebo-controlled trial to evaluate the potential interactions between American ginseng and warfarin, 20 health subjects participated in a 4-week study [54]. During weeks 1 and 4, subjects received warfarin for 3 days. Beginning in week 2, patients received either American ginseng or placebo. The international normalized ratio (INR) and plasma warfarin levels were measured. Peak INR decreased significantly after 2 weeks of ginseng administration compared with 2 weeks of placebo. There was also a statistically significant reduction in INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC in the ginseng group compared with the placebo group. Steroids can induce hepatic enzyme activities [55]. Ginsenosides may also enhance enzyme functions. Whether ginseng interferes with other hepatically metabolized drugs remains to be evaluated.

The reduction of warfarin's anticoagulant effect by American ginseng was not supported in studies using another ginseng species. Neither Asian [56] nor Korean red ginseng [57] significantly interacted with warfarin. Because warfarin is often used following orthopedic or vascular procedures, the potential for drug interaction is more than theoretical in nature and deserves further evaluation.

The effect of ginseng on coagulation pathways has raised concerns. Ginsenosides inhibited platelet aggregation *in vitro* [58] and in rats they prolonged both thrombin time and activated partial thromboplastin time [59]. One study suggested that the antiplatelet activity of panaxynol, a constituent of ginseng, might be irreversible in humans [60]. Recently, Lee et al. evaluated ginsenosides Rg6, F4, Rk3, Rh4, Rs3, Rs4, and Rs5 isolated from processed ginseng for their effects on platelet aggregation. The degree of inhibitory activity on platelet aggregation varied [61, 62]. Because platelet inhibition by ginseng may be irreversible, it is prudent for surgical patients to discontinue ginseng use at least one week before surgery [63].

COMMENTARY

Pharmacokinetics deals with the process by which a drug is absorbed, the magnitudes of the desired response as a function of the drug concentration at the site of action, the drug

metabolism, and its elimination from the body. Drug plasma concentrations over time are often obtained with the assumption that they are the concentrations at the site of action. Like other herbal medicines, ginseng harbors many different components, such as ginsenosides, polysaccharides, and peptides. Several dozen ginsenosides have been identified in the ginseng plant. Although nearly all of them belong to a family of steroids, some of their pharmacokinetic parameters vary by species. To connect the pharmacokinetics of one ginsenoside to its pharmacodynamic activity is of limited usefulness because when ginseng root is ingested, one ginsenoside may also alter the pharmacokinetics of another ginsenoside. Further complicating the study results of ginseng is that the potency of the plant products is often measured by total ginsenoside content, which varies from lot to lot. Cultivation conditions such as soil, temperature, moisture, length of cultivation, and harvest season can change total ginsenoside content, or ginsenoside percentages, thus altering ginseng kinetics [64, 65].

Conventionally, the metabolism of a new compound in humans is studied *in vivo* using radiotracer techniques for absorption and disposition. Ideally, the metabolism of a new compound is evaluated *in vitro* before clinical studies. In some studies, hepatic P450 has catalyzed ginsenoside metabolism in hepatocytes. Yet when ginseng root is studied *in vivo*, pharmacokinetic interaction of ginsenosides may exist.

Many prescription drugs have one or more metabolites that may have their own biological effects. Taken orally, the bioavailability of ginseng is low, and many of the parent ginsenosides are converted to metabolites by gut microbiota. Some of these metabolites, such as Compound K, possess significantly stronger cancer chemoprevention activity than the parent compounds. Pharmacologically, the parent compound and its metabolites may act by similar mechanisms, different mechanisms, or even by antagonism. Pharmacokinetically, the active metabolites of ginseng differ in distribution and clearance from that of the parent compound. Further studies are needed before the pharmacokinetic information of ginseng's metabolites can be used to predict therapeutic outcome in humans.

Acknowledgments

We thank Sally Kozlik for editing the manuscript. This work was supported in part by NIH grants P01 AT004418 and K01 AT005362.

REFERENCES

1. Qi LW, Wang CZ, Yuan CS. Isolation and analysis of ginseng: advances and challenges. Nat. Prod. Rep. 2011; 28(3):467–495. [PubMed: 21258738]
2. Christensen LP. Ginsenosides chemistry, biosynthesis, analysis and potential health effects. Adv. Food Nutr. Res. 2009; 55:1–99. [PubMed: 18772102]
3. Yun TK. Panax ginseng--a non-organ-specific cancer preventive? Lancet Oncol. 2001; 2(1):49–55. [PubMed: 11905620]
4. Qi LW, Wang CZ, Yuan CS. Ginsenosides from American ginseng: Chemical and pharmacological diversity. Phytochemistry. 2011; 72:689–699. [PubMed: 21396670]
5. Qi LW, Wang CZ, Yuan CS. American ginseng: Potential structure–function relationship in cancer chemoprevention. Biochem. Pharmacol. 2010; 80(7):947–954. [PubMed: 20599804]
6. Fuzzati N. Analysis methods of ginsenosides. J. Chromatogr. B. 2004; 812(1–2):119–133.
7. Cho SH, Chung KS, Choi JH, Kim DH, Lee KT. Compound K, a metabolite of ginseng saponin, induces apoptosis via caspase-8-dependent pathway in HL-60 human leukemia cells. BMC Cancer. 2009; 9:449–461. [PubMed: 20017956]
8. Chae S, Kang KA, Chang WY, Kim MJ, Lee SJ, Lee YS, Kim HS, Kim DH, Hyun JW. Effect of compound K, a metabolite of ginseng saponin, combined with gamma-ray radiation in human lung

cancer cells in vitro and in vivo. J. Agric. Food Chem. 2009; 57(13):5777–5782. [PubMed: 19526988]

9. Kim DY, Yuan HD, Chung IK, Chung SH. Compound K, intestinal metabolite of ginsenoside, attenuates hepatic lipid accumulation via AMPK activation in human hepatoma cells. J. Agric. Food Chem. 2009; 57(4):1532–1537. [PubMed: 19182950]
10. Tawab MA, Bahr U, Karas M, Wurglics M, Schubert-Zsilavecz M. Drug Metab. Dispos. 2003; 31(8):1065–1071. [PubMed: 12867496]
11. Cai ZW, Qian TX, Wong RNS, Jiang ZH. Liquid chromatography–electrospray ionization mass spectrometry for metabolism and pharmacokinetic studies of ginsenoside Rg3. Anal. Chim. Acta. 2003; 492(1–2):283–293.
12. Liu HF, Yang JL, Du FF, Gao XM, Ma XT, Huang YH, Xu F, Niu W, Wang FQ, Mao Y, Sun Y, Lu T, Liu CX, Zhang BL, Li C. Absorption and disposition of ginsenosides after oral administration of Panax notoginseng extract to rats. Drug Metab. Dispos. 2009; 37(12):2290–2298. [PubMed: 19786509]
13. Gu Y, Wang GJ, Sun JG, Jia YW, Wang W, Xu MJ, Lv T, Zheng YT, Sai Y. Pharmacokinetic characterization of ginsenoside Rh2, an anticancer nutrient from ginseng, in rats and dogs. Food Chem. Toxicol. 2009; 47(9):2257–2268. [PubMed: 19524010]
14. Li XY, Wang GJ, Sun HG, Hao HP, Xiong YQ, Yan B, Zheng YT, Sheng LS. Pharmacokinetic and absolute bioavailability study of total panax notoginsenoside, a typical multiple constituent traditional chinese medicine (TCM) in rats. Biol. Pharm. Bull. 2007; 30(5):847–851. [PubMed: 17473424]
15. Wang W, Wang GJ, Xie HT, Sun JG, Zhao S, Jiang XL, Li H, Lv H, Xu MJ, Wang R. Determination of ginsenoside Rd in dog plasma by liquid chromatography-mass spectrometry after solid-phase extraction and its application in dog pharmacokinetics studies. J. Chromatogr. B. 2007; 852(1–2):8–14.
16. Xie HT, Wang GJ, Sun JG, Tucker I, Zhao XC, Xie YY, Li H, Jiang XL, Wang R, Xu MJ, Wang W. High performance liquid chromatographic-mass spectrometric determination of ginsenoside Rg3 and its metabolites in rat plasma using solid-phase extraction for pharmacokinetic studies. J. Chromatogr. B. 2005; 818(2):167–173.
17. Qian T, Cai Z, Wong RN, Jiang ZH. Liquid chromatography/mass spectrometric analysis of rat samples for in vivo metabolism and pharmacokinetic studies of ginsenoside Rh2. Rapid Commun. Mass Spectrom. 2005; 19(23):3549–3554. [PubMed: 16261639]
18. Sun J, Wang G, Haitang X, Hao L, Guoyu P, Tucker I. Simultaneous rapid quantification of ginsenoside Rg1 and its secondary glycoside Rh1 and aglycone protopanaxatriol in rat plasma by liquid chromatography-mass spectrometry after solid-phase extraction. J. Pharm. Biomed. Anal. 2005; 38(1):126–132. [PubMed: 15907630]
19. Joo KM, Lee JH, Jeon HY, Park CW, Hong DK, Jeong HJ, Lee SJ, Lee SY, Lim KM. Pharmacokinetic study of ginsenoside Re with pure ginsenoside Re and ginseng berry extracts in mouse using ultra performance liquid chromatography/mass spectrometric method. J. Pharm. Biomed. Anal. 2010; 51(1):278–283. [PubMed: 19729261]
20. Lai L, Hao HP, Liu YT, Zheng CN, Wang Q, Wang GJ, Chen XJ. Characterization of Pharmacokinetic Profiles and Metabolic Pathways of 20(S)- Ginsenoside Rh1 in vivo and in vitro. Planta Med. 2009; 75(8):797–802. [PubMed: 19266426]
21. Xu QF, Fang XL, Chen DF. Pharmacokinetics and bioavailability of ginsenoside Rb-1 and Rg (1) from Panax notoginseng in rats. J. Ethnopharmacol. 2003; 84(2–3):187–192. [PubMed: 12648814]
22. Paek IP, Moon Y, Kim J, Ji HY, Kim SA, Sohn DH, Kim JB, Lee HS. Pharmacokinetics of a ginseng saponin metabolite compound K in rats. Biopharm. Drug Dispos. 2006; 27(1):39–45. [PubMed: 16302287]
23. Li L, Sheng YX, Zhang JL, Wang SS, Guo DA. High-performance liquid chromatographic assay for the active saponins from Panax notoginseng in rat tissues. Biomed. Chromatogr. 2006; 20(4): 327–335. [PubMed: 16138297]
24. Gui FJ, Yang XW, Li LY, Tian JM. Simultaneous enantiomer determination of 20 (R)- and 20 (S)-ginsenoside-Rg (2) in rat plasma after intravenous administration using HPLC method. J. Chromatogr. B. 2007; 850(1–2):1–6.

25. Chen SE, Sawchuk RJ, Staba EJ. American ginseng. III. Pharmacokinetics of ginsenosides in the rabbit. Eur. J. Drug Metab. Pharmacokinet. 1980; 5(3):161–168. [PubMed: 7202434]
26. Hasegawa H. Proof of the mysterious efficacy of ginseng: Basic and clinical trials: Metabolic activation of ginsenoside: Deglycosylation by intestinal bacteria and esterification with fatty acid. J. Pharmacol. Sci. 2004; 95(2):153–157. [PubMed: 15215638]
27. Lee PS, Song TW, Sung JH, Moon DC, Song S, Chung YB. Pharmacokinetic characteristics and hepatic distribution of IH-901, a novel intestinal metabolite of ginseng saponin, in rats. Planta Med. 2006; 72(3):204–210. [PubMed: 16534723]
28. Hao H, Lai L, Zheng C, Wang Q, Yu G, Zhou X, Wu L, Gong P, Wang G. Microsomal cytochrome p450-mediated metabolism of protopanaxatriol ginsenosides: metabolite profile, reaction phenotyping, and structure-metabolism relationship. Drug Metab. Dispos. 2010; 38(10): 1731–1739. [PubMed: 20639434]
29. Cui JF, Bjorkhem I, Eneroth P. Gas chromatographic-mass spectrometric determination of 20(S)-protopanaxadiol and 20(S)-protopanaxatriol for study on human urinary excretion of ginsenosides after ingestion of ginseng preparations. J. Chromatogr. B. 1997; 689(2):349–355.
30. Lee J, Lee E, Kim D, Lee J, Yoo J, Koh B. Studies on absorption, distribution and metabolism of ginseng in humans after oral administration. J. Ethnopharmacol. 2009; 122(1):143–148. [PubMed: 19146939]
31. Hasegawa H, Sung JH, Matsumiya S, Uchiyama M. Main Ginseng saponin metabolites formed by intestinal bacteria. Planta Med. 1996; 62(5):453–457. [PubMed: 8923812]
32. Kong H, Wang M, Venema K, Maathuis A, van der Heijden R, van der Greef J, Xu G, Hankemeier T. Bioconversion of red ginseng saponins in the gastro-intestinal tract in vitro model studied by high-performance liquid chromatography-high resolution Fourier transform ion cyclotron resonance mass spectrometry. J. Chromatogr. A. 2009; 1216(11):2195–2203. [PubMed: 19041979]
33. Ruan JQ, Leong WI, Yan R, Wang YT. Characterization of metabolism and in vitro permeability study of notoginsenoside R1 from Radix notoginseng. J. Agric. Food Chem. 2010; 58(9):5770–5776. [PubMed: 20405945]
34. Qiang TX, Jiang ZH, Cai ZW. High-performance liquid chromatography coupled with tandem mass spectrometry applied for metabolic study of ginsenoside Rb, on rat. Anal. Biochem. 2006; 352(1):87–96. [PubMed: 16564485]
35. Yang L, Deng YH, Xu SJ, Zeng X. In vivo pharmacokinetic and metabolism studies of ginsenoside Rd. J. Chromatogr. B. 2007; 854(1–2):77–84.
36. Bae EA, Han MJ, Choo MK, Park SY, Kim DH. Metabolism of 20(S)- and 20(R)- ginsenoside R-g3 by human intestinal bacteria and its relation to in vitro biological activities. Biol. Pharm. Bull. 2002; 25(1):58–63. [PubMed: 11824558]
37. Shin YW, Bae EA, Kim DH. Inhibitory effect of ginsenoside Rg5 and its metabolite ginsenoside Rh3 in an oxazolone-induced mouse chronic dermatitis model. Arch. Pharm. Res. 2006; 29(8): 685–690. [PubMed: 16964764]
38. Wang Y, Wang BX, Liu TH, Minami M, Nagata T, Ikejima T. Metabolism of ginsenoside Rg (1) by intestinal bacteria II. Immunological activity of ginsenoside Rg (1) and Rh-1. Acta Pharmacol. Sin. 2000; 21(9):792–796. [PubMed: 11501159]
39. Yang L, Xu SJ, Liu CJ, Su ZJ. In vivo metabolism study of ginsenoside Re in rat using high-performance liquid chromatography coupled with tandem mass spectrometry. Anal. Bioanal. Chem. 2009; 395(5):1441–1451. [PubMed: 19774367]
40. Lee SJ, Ko WG, Kim JH, Sung JH, Lee SJ, Moon CK, Lee BH. Induction of apoptosis by a novel intestinal metabolite of ginseng saponin via cytochrome c-mediated activation of caspase-3 protease. Biochem. Pharmacol. 2000; 60(5):677–685. [PubMed: 10927026]
41. Kang KA, Kim YW, Kim SU, Chae S, Koh YS, Kim HS, Choo MK, Kim DH, Hyun JW. G1 phase arrest of the cell cycle by a ginseng metabolite, compound K, in U937 human monocytic leukamia cells. Arch. Pharm. Res. 2005; 28(6):685–690. [PubMed: 16042078]
42. Jung SH, Woo MS, Kim SY, Kim WK, Hyun JW, Kim EJ, Kim DH, Kim HS. Ginseng saponin metabolite suppresses phorbol ester-induced matrix metalloproteinase-9 expression through

inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathways in human astroglioma cells. Int. J. Cancer. 2006; 118(2):490–497. [PubMed: 16049964]

43. Choi K, Kim M, Ryu J, Choi C. Ginsenosides compound K and Rh-2 inhibit tumor necrosis factor-alpha-induced activation of the NF-kappa B and JNK pathways in human astroglial cells. Neurosci. Lett. 2007; 421(1):37–41. [PubMed: 17548155]
44. Oh SH, Lee BH. A ginseng saponin metabolite-induced apoptosis in HepG2 cells involves a mitochondria-mediated pathway and its downstream caspase-8 activation and Bid cleavage. Toxicol. Appl. Pharm. 2004; 194(3):221–229.
45. Oh SH, Yin HQ, Lee BH. Role of the Fas/Fas ligand death receptor pathway in ginseng saponin metabolite-induced apoptosis in HepG2 cells. Arch. Pharm. Res. 2004; 27(4):402–406. [PubMed: 15180305]
46. Surh YJ, Lee JY, Choi KJ, Ko SR. Effects of selected ginsenosides on phorbol ester-induced expression of cyclooxygenase-2 and activation of NF-kappa B and ERK1/2 in mouse skin. Ann. Ny. Acad. Sci. 2002; 973:396–401. [PubMed: 12485900]
47. Yu CT, Chen J, Teng XW, Tong V, Chang TKH. Lack of evidence for induction of CYP2B1, CYP3A23, and CYP1A2 gene expression by Panax ginseng and Panax quinquefolius extracts in adult rats and primary cultures of rat hepatocytes. Drug Metab. Dispos. 2005; 33(1):19–22. [PubMed: 15466162]
48. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CYW. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin. Pharmacol. Ther. 2002; 72(3):276–287. [PubMed: 12235448]
49. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui YY, Ang CYW. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly - St John's wort, garlic oil, Panax ginseng and Ginkgo biloba. Drug Aging. 2005; 22(6):525–539.
50. Liu Y, Zhang JW, Li W, Ma H, Sun J, Deng MC, Yang L. Ginsenoside metabolites, rather than naturally occurring ginsenosides, lead to inhibition of human cytochrome P450 enzymes. Toxicol. Sci. 2006; 91(2):356–364. [PubMed: 16547074]
51. Andrade ASA, Hendrix C, Parsons TL, Caballero B, Yuan CS, Flexner CW, Dobs AS, Brown TT. Pharmacokinetic and metabolic effects of American ginseng (Panax quinquefolius) in healthy volunteers receiving the HIV protease inhibitor indinavir. BMC Complement. Altern. Med. 2008; 8(50):1–10. [PubMed: 18173849]
52. Zhu M, Chan KW, Ng LS, Chang Q, Chang S, Li RC. Possible influences of ginseng on the pharmacokinetics and pharmacodynamics of warfarin in rats. J. Pharm. Pharmacol. 1999; 51(2): 175–180. [PubMed: 10217316]
53. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am. J. Health Syst. Pharm. 1997; 54(6):692–693. [PubMed: 9075501]
54. Yuan CS, Wei G, Dey L, Karrison T, Nahlik L, Maleckar S, Kasza K, Ang-Lee M, Moss J. Brief communication: American ginseng reduces warfarin's effect in healthy patients: A randomized, controlled trial. Ann. Int. Med. 2004; 141:23–27. [PubMed: 15238367]
55. Pascussi JM, Gerbal-Chaloin S, Fabre JM, Maurel P, Vilarem MJ. Dexamethasone enhances constitutive androstane receptor expression in human hepatocytes: Consequences on cytochrome P450 gene regulation. Mol. Pharmacol. 2000; 58(6):1441–1450. [PubMed: 11093784]
56. Lee SH, Ahn YM, Ahn YM, Doo HK, Lee BC. Interaction between warfarin and Panax ginseng in ischemic stroke patients. J. Altern. Complement. Med. 2008; 14(6):715–721. [PubMed: 18637764]
57. Lee YH, Lee BK, Choi YJ, Yoon IK, Chang BC, Gwak HS. Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. Int. J. Cardiol. 2010; 145(2):275–276. [PubMed: 19913311]
58. Kuo SC, Teng CM, Lee JC, Ko FN, Chen SC, Wu TS. Antiplatelet components in Panax-Ginseng. Planta Med. 1990; 56(2):164–167. [PubMed: 2353062]
59. Park HJ, Lee JH, Song YB, Park KH. Effects of dietary supplementation of lipophilic fraction from Panax ginseng on cGMP and cAMP in rat platelets and on blood coagulation. Biol. Pharm. Bull. 1996; 19(11):1434–1439. [PubMed: 8951159]

60. Teng CM, Kuo SC, Ko FN, Lee JC, Lee LG, Chen SC, Huang TF. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. Biochim. Biophys. Acta. 1989; 990(3):315–320. [PubMed: 2923911]

61. Lee JG, Lee YY, Kim SY, Pyo JS, Yun-Choi HS, Park JH. Platelet antiaggregating activity of ginsenosides isolated from processed ginseng. Pharmazie. 2009; 64(9):602–604. [PubMed: 19827304]

62. Lee JG, Lee YY, Wu B, Kim SY, Lee YJ, Yun-Choi HS, Park JH. Inhibitory activity of ginsenosides isolated from processed ginseng on platelet aggregation. Pharmazie. 2010; 65(7): 520–522. [PubMed: 20662322]

63. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA. 2001; 286(2): 208–216. [PubMed: 11448284]

64. Lim W, Mudge KW, Vermeylen F. Effects of population, age, cultivation methods on ginsenoside content of wild American ginseng (Panax quinquefolium). J. Agric. Food Chem. 2005; 53(22): 8498–8505. [PubMed: 16248544]

65. Lin WN, Lu HY, Lee MS, Yang SY, Chen HJ, Chang YS, Chang WT. Evaluation of the cultivation age of dried ginseng radix and its commercial products by using (1)H-NMR fingerprint analysis. Am. J. Chin. Med. 2010; 38(1):205–218. [PubMed: 20128055]