ARTICLE

# Interactions between Warfarin and Herbal Products, Minerals, and Vitamins: A Pharmacist's Guide

*Sunita Bond Stenton, Tammy J. Bungard, and Margaret L. Ackman*

## ABSTRACT

**Objective:** To prepare for pharmacists a reference regarding herbal products, minerals, and vitamins with either theoretical or documented interactions with warfarin.

**Methods:** The databases of MEDLINE, EMBASE, and PubMed (for the period January 1966 to June 2000) were searched with the medical subject heading (MeSH) "warfarin" combined with "drug interactions", "herbal medicine", and "megavitamin therapy."

**Results:** The following herbal products have been reported to increase, through various mechanisms, the risk of bleeding when used concomitantly with warfarin: cinchona (quinine), danshen, devil's claw, dong quai, garlic, ginkgo, ginseng, and papaya (papain). Coenzyme $Q_{10}$, ginseng, green tea, St John's wort, and vitamin K decrease the international normalized ratio by a variety of mechanisms. Products with theoretical interactions for which there is no clinical evidence include bromelain, cayenne, echinacea, feverfew, flaxseed, and ginger. Herbal products containing coumarin, coumarin derivatives, and *p*-coumaric acid, which may potentiate warfarin's anticoagulant action, are identified in the article. Minerals and vitamins that interact with warfarin are discussed, including iron, magnesium, zinc, and vitamins C, E, and K.

**Conclusions:** Data from case reports, animal studies, and *in vitro* and *in vivo* studies serve as information sources for interactions among herbal products, minerals, megavitamins, and warfarin. Limited information is available concerning the onset and extent of an increase or decrease in the international normalized ratio. As such, pharmacists must be diligent and informed about the potential for such interactions and must be ready to serve as proactive patient advocates.

**Key words:** alternative medicine, anticoagulants, dietary supplements, drug interactions, enzymes, megavitamins, vitamins, warfarin

**Can J Hosp Pharm 2001;54:186–92**

## RÉSUMÉ

**Objectif :** Préparer à l'intention des pharmaciens un ouvrage de référence sur les produits à base de plantes médicinales, les minéraux et les vitamines et leurs interactions, théoriques ou documentées, avec la warfarine.

**Méthodes :** Des recherches dans les bases de données MEDLINE, EMBASE et PubMed (pour la période allant de janvier 1966 à juin 2000) ont été effectuées à partir du mot pivot (MeSH) «warfarin» et 1) «drug interactions», 2) «herbal medicine» et 3) «megavitamin therapy».

**Résultats :** Des rapports indiquent que les produits à base de plantes médicinales suivants augmentent, par divers mécanismes, le risque de saignement lorsqu'ils sont utilisés en concomitance avec de la warfarine : quinine, Dangshen, griffe du diable, Don Quai, ail, *Ginkgo biloba*, ginseng, papaïne. Quant aux produits suivants : coenzyme Q10, ginseng, thé vert, vitamine K, millepertuis commun, ils diminuent, aussi par divers mécanismes, le rapport international normalisé. Les produits pour lesquels on a identifié des interactions théoriques mais non prouvées cliniquement sont les suivants : broméline, cayenne, échinacée, grande camomille, graine de lin and gingembre. Les herbes contenant de la coumarine, des coumariniques et de l'acide *p*-coumarinique, lesquels peuvent potentialiser l'action anticoagulante de la warfarine, sont identifiés dans l'article. Les minéraux et vitamines qui interagissent avec la warfarine y sont également traités, notamment le fer, le magnésium, le zinc et les vitamines C, E et K.

**Conclusions :** Des données issues de rapports de cas, d'études chez les animaux et d'études *in vitro* et *in vivo* sont les sources d'information sur les interactions entre la warfarine et les produits à base de plantes médicinales, les minéraux et les mégavitamines. L'information sur le début et l'ampleur de l'augmentation ou de la diminution du rapport international normalisé est toutefois limitée. Par conséquent, les pharmaciens doivent faire preuve de vigilance, être informés à propos de ces interactions potentielles et être prêts à défendre proactivement les intérêts du patient.

**Mots clés :** médecine douce, anticoagulants, suppléments alimentaires, interactions médicamenteuses, enzymes, mégavitamines, vitamines, warfarine

## INTRODUCTION

Herbal products represent an area of considerable growth among alternative medicine practices. Estimates indicate that one-third of all Americans use herbal products.[1] Between 1990 and 1997 in the United States, the use of herbal products increased by 380%, and megavitamin use increased by 130%.[2] Surveys of Canadians indicate that the proportion of the population using herbal remedies doubled, to 30%, between 1996 and 1998.[3] In addition, 60% or more of those using alternative therapies do not disclose this use to their health care providers.[2,4]

Both herbal and vitamin products are available to consumers without consultation with a health care professional, but limited data are available concerning their safety, efficacy, and potential for interaction with prescription drugs. Recent surveys show that 18% of adults in the United States use prescription drugs concurrently with herbal or vitamin products, which places an estimated 15 million patients at risk of potential interactions.[5] Complementary therapies are generally used to supplement conventional medical care,[2] and people using herbal remedies are more likely than the general population to be using conventional nonprescription or prescription drugs (or both).[3] In spite of this extensive concurrent use of traditional and alternative medicines, documentation regarding interactions between drugs and herbal medicines is sparse, and many health care professionals rely on anecdotes or case reports to guide therapeutic decisions.[5,6]

The potential for serious interactions of herbal products and megavitamins with conventional drugs is greater for drugs with a narrow therapeutic window. Specific patient populations, such as those taking warfarin, should be monitored very closely. Warfarin is commonly used to treat several disease states, including atrial fibrillation, pulmonary embolism, and deep vein thrombosis. More food and drug interactions have been reported in association with warfarin than for any other prescription medication,[1] and 6 of the 10 most popular herbal remedies in Canada have been mentioned in case reports as interacting with or having the potential to interact with warfarin.[3] Therefore, pharmacists must be aware of these interactions if they are to properly counsel and monitor patients receiving anticoagulation therapy to diminish the risk of bleeding or thrombosis.

The purpose of this article is to serve as a reference for pharmacists regarding herbal products, minerals, and vitamins associated with theoretical or documented interactions with warfarin. Both potential and documented interactions of warfarin with herbal products, minerals, and megavitamins are discussed. The information presented here is intended to serve as a resource for the pharmacist, as clinical judgement regarding thromboembolic and hemorrhagic risk is always necessary for each individual patient.

## METHODS

Relevant articles for a literature review were identified by searching MEDLINE (January 1966 to June 2000), with the medical subject heading (MeSH) "warfarin" combined with "drug interactions", "herbal medicine", and "megavitamin therapy", and EMBASE (January 1994 to June 2000) and PubMed with the same terms, as well as bulletins, updates, and personal or colleagues' files on the subject. The reference lists of identified articles were also examined for additional articles.

For the purposes of this paper, herbal products were defined as medicinal agents obtained from plants. Herbs were considered a subset of alternative or complementary therapies, which encompass treatments such as acupuncture, massage, and relaxation techniques.

None of the interactions reported, either potential or actual, have been documented in well-designed trials. Instead, case reports, animal studies, and *in vitro* and *in vivo* studies serve as the information sources for interactions of warfarin with herbal products, minerals and megavitamins. The mechanism of interaction is indicated when known.

## RESULTS

A variety of herbal products that have been reported to interact (Table 1)[5,7–68] and that could theoretically interact (Table 2)[7,26,28,34–37,40,43,68–76] with warfarin were identified. There are several mechanisms for these interactions, and some herbal products have multiple pathways. Evidence for the interactions, categorized as theoretical or documented by case reports, is provided in the tables. For all interactions listed, the extent of the increase or decrease in the international normalized ratio (INR) and time of onset are generally not quantified, as this information was either not available or poorly defined. The lack of this type of information is problematic because the risk of bleeding increases exponentially once the INR exceeds 4 or 5, as does the occurrence of thromboembolic events once the INR falls below 2 or 2.5, depending on the indication for therapy.[77]

The following mechanisms result in increased INR: decreased elimination of warfarin; decreased platelet aggregation; decreased levels of thromboxane, prostaglandin, or phospholipase $A_2$; decreased formation of cyclooxygenase; inhibition of platelet-activating factor, conversion of fibrin to fibrinogen, and cytochrome (CYP) P450 2C9 liver enzymes; and high

**Table 1. Documented Interactions between Warfarin and Herbal Products**

| Herbal Product | Common Use | Interaction* |
|---|---|---|
| Cinchona (*Cinchona* spp.), source of quinine[7,8] | Recovery and support after surgery, treatment of tinnitus | Potentiated anticoagulant action of warfarin |
| Coenzyme Q10, also known as ubiquinone[7,9–12] | Treatment of coronary artery disease, cardioprotective agent | Reduced INR (compound is structurally similar to vitamin K) |
| Danshen (*Salvia miltiorrhiza*), also known as tan seng[7,13–26] | Treatment of coronary artery disease, postsurgical supplement (taken as an oral supplement and contained in some Chinese cigarettes) | Increased INR and prolonged PT/PTT (i.e., altered pharmacokinetics) by reducing elimination of warfarin; reduced platelet aggregation and TXA formation |
| Devil's claw (*Harpagophytum procumbens*)[7,15,27,28] | Anti-inflammatory and analgesic agent | Increased action of warfarin (by unknown mechanism); caused purpura |
| Dong quai (*Angelica sinensis*) [5,29–35] | Treatment of symptoms of premenstrual syndrome, menstrual cramping | Active ingredient (ferulic acid) inhibits PAF; herb contains coumarins; increased risk of bleeding because of reduced platelet aggregation; increased INR, leading to widespread bruising |
| Garlic (*Allium sativum*), fresh or commercially pressed, in large amounts[7,15,18,26,34–42] | Antiatherosclerotic agent, antihypertensive agent, treatment of infection, hypolipidemic agent | Increased risk of bleeding by reducing platelet aggregation; increased INR and reduced TXA production; reports of bleeding (postoperative bleeding and spontaneous spinal epidural hematoma reported with garlic alone); may increase hypoprothrombinemia |
| Ginkgo (*Ginkgo biloba*) [5,7,9–11,15,25,26,43–50] | Treatment of dementia, treatment of disturbances of the cerebral and peripheral circulation | Increased risk of bleeding by reducing platelet aggregation; ginkolides and terpenoids inhibit PAF; intracerebral hemorrhage reported in patients taking ASA with or without warfarin |
| Ginseng[5,7,18,26,34–37,43,51–59] | Treatment of stress, prevention of cancer, enhancement of physical endurance | Altered INR (both increase and decrease have been reported) by unknown mechanism; may increase risk of bleeding by reducing platelet aggregation; may inhibit PAF and conversion of fibrin to fibrinogen; may induce CYP P450 3A4 liver enzymes (and thereby increase warfarin metabolism) |
| Green tea and herbal teas (made with tonka beans, melilot, or woodruff)[26,60–64] | Antioxidant; also consumed as nonmedicinal beverages | Reduced INR because of high vitamin K content; teas contain natural coumarins |
| Papaya (*Carica papaya*), source of papain[7,15,65] | Digestive aid | Increased INR |
| St John's wort (*Hypericum perforatum*)[66–68] | Antidepressive agent | Reduced INR by inducing CYP P450 3A4 (and thereby increasing warfarin metabolism) |

INR = international normalized ratio, PT = prothrombin time, PTT = partial thromboplastin time, TXA = thromboxane, PAF = platelet-activating factor, ASA = acetylsalicylic acid, CYP = cytochrome.
*Interactions based on case reports.

natural coumarin content. In contrast, a reduction in INR may be caused by induction of CYP P450 2C9 liver enzymes, high vitamin K content, or structural similarity to vitamin K. Other CYP P450 isozymes metabolize warfarin; however, this occurs to a much lesser extent (for example, CYP P450 1A2, 3A4, and 2C19 metabolize the R-isomer of warfarin, which is much less potent than the S-isomer). Products affecting these isozymes have the ability to affect INR, although the interaction is thought to be of smaller impact than those affecting the CYP P450 2C9 component.

Many herbal preparations contain natural coumarins (Table 3). Coumarins and their derivatives probably potentiate warfarin's action and increase INR, although the degree of the increase is unknown.[28]

Common minerals and vitamins that have the potential to interact with warfarin are listed in Table 4.[7,40,78–83] Zinc, iron, and magnesium are suspected to bind warfarin, thereby decreasing its absorption. As such, administration of warfarin should be separated from intake of these minerals by a period of 2 h. Vitamin K decreases the INR through an antagonist effect on warfarin and is used as an antidote for warfarin overdose. Warfarin, by inhibiting vitamin K epoxide reductase, prevents the reduction of vitamin K.[82] Reduced vitamin K is necessary for the carboxylation of factors II, VII, IX, and X. The anticoagulant effect of warfarin can be overcome by low doses of vitamin K because the oxidized form of the vitamin can be reduced through a different warfarin-resistant vitamin K reductase system that is operative at high tissue

**Table 2. Theoretical Interactions between Warfarin and Herbal Products***

| Herbal Product | Common Use | Theoretical Interaction* |
|---|---|---|
| Bromelain, a proteolytic enzyme found in pineapple[7,69] | Anti-inflammatory agent, digestive aid | May potentiate anticoagulant action of warfarin |
| Cayenne (*Capsicum* spp.)[28] | Anti-inflammatory agent, appetite stimulant, digestive aid, circulation aid | May potentiate anticoagulant action and antiplatelet effect of warfarin |
| Echinacea[26,36,43] | Prevention and treatment of colds, healing of wounds | May increase INR by decreasing elimination of warfarin; may inhibit CYP P450 3A4 liver enzymes (thereby decreasing warfarin metabolism) |
| Feverfew (*Tanacetum parthenium*)[26,28,34–37,43,70–75] | Migraine prophylaxis, treatment of rheumatoid arthritis | May increase risk of bleeding by preventing platelet aggregation; reduces production of PG and TXA, inhibits phospholipase $A_2$ and cyclooxygenase |
| Flaxseed (*Linum usitatissimum*), a source of mucilage[28] | Fibre supplement, source of omega oils | May reduce absorption of warfarin |
| Ginger (*Zingiber officinale*)[7,26,40,68,76] | Prevention and treatment of motion sickness | May increase risk of bleeding by reducing platelet aggregation |

INR= international normalized ratio, CYP = cytochrome, PG = prostaglandin, TXA = thromboxane.
*Theoretical interactions based on *in vitro* studies without clinical evidence.

**Table 3. Herbs and Herbal Products Containing Coumarin, Coumarin Derivatives, or *p*-Coumaric Acid[28]**

| Constituent* | Herb or Herbal Product |
|---|---|
| Coumarin | Angelica root, licorice root, melilot, sweet clover, sweet woodruff, tonka bean |
| Coumarin derivatives | Angelica root, arnica flower, celery, chamomile, danshen, dong quai, eleuthero (Siberian ginseng) root, fenugreek, feverfew, garlic, ginkgo, ginseng, horse chestnut, licorice root, lovage root, passion flower herb, red clover, sweet clover, sweet woodruff |
| *p*-Coumaric acid | Sweet clover |

*All of these constituents can potentiate warfarin's anticoagulant action.

concentrations of vitamin $K_1$. Therefore, increased levels of vitamin K antagonize warfarin's anticoagulant action. All vitamin K intake (such as through green leafy vegetables) should be closely monitored, and daily intake should be consistent. Patients taking warfarin who also take a multivitamin should either use one that does not contain vitamin K or be consistent in the use of multivitamins containing vitamin K.

Vitamin C and E are of concern only at megavitamin doses (greater than 10 times the daily recommended intake).

## DISCUSSION

The use of herbal products, as well as other alternative therapies such as megavitamin therapy, is steadily increasing. There is concern about the safety of these alternative therapies, especially within certain patient populations, for whom the risk of adverse events is increased. One such population comprises patients taking warfarin. If there is a potential for serious drug–herb interactions, it is within this category, and as such it is generally recommended that patients taking warfarin not self-treat with herbal supplements, since interactions may result in fatal hemorrhagic or thromboembolic sequelae. Additional research is needed to determine the role of herbal products and megavitamin therapy in health care. Randomized, controlled clinical trials would best evaluate the efficacy, tolerability, and safety of herbal products, as well as their potential drug interactions and comparative efficacy with conventional therapy.[2]

Although information regarding contraindications and interactions between herbal products and prescription or over-the-counter products is generally provided by physicians and pharmacists, a survey found that users of natural products get most of their information from family and friends, health books, and other health care reference materials available to the general public.[3] Furthermore, patients are less likely to voluntarily report adverse reactions resulting from use of a herbal product than they are to report adverse events resulting from consumption of prescription drugs.[4]

Pharmacists must take the initiative in creating opportunities to discuss herbal products with patients. All medication histories should include questions about the use of herbal and other alternative therapies.[36,60] To encourage patients to discuss alternative therapies, inquiries should be made in an open and nonjudgemental manner, similar to that used when inquiring about conventional nonprescription products.[2] In this type of environment, consumers may be willing to seek

**Table 4. Interactions between Warfarin and Minerals or Vitamins**

| Mineral or Vitamin | Daily Recommended Intake | Common Use | Interaction | Evidence of Interaction |
|---|---|---|---|---|
| Iron, magnesium, zinc | 18 mg, 400 mg, 15 mg, respectively | Various | Reduces warfarin absorption (by binding) | Theoretical* (recommend that administration of minerals be separated from warfarin administration by 2 h)[78,79] |
| Vitamin C† | 60 mg | Antioxidant | Reduces anticoagulant effect of warfarin | Theoretical* [7,79] |
| Vitamin E† | 30 IU | Antioxidant, cardioprotective agent | Increases anticoagulant effect of warfarin; may inhibit oxidation of reduced vitamin K; antiplatelet effect | Theoretical* [40,79–81] |
| Vitamin K | Women 19–24 years old: 60 µg<br>Women ≥25 years: 65 µg<br>Men 19–24 years: 70 µg<br>Men ≥25 years: 80 µg | Antidote for excessive anticoagulation (in therapeutic doses) | Reduces INR | Observational studies[7,79,82,83] |

IU = international units, INR = international normalized ratio.
*Theoretical interaction based on *in vitro* studies with no clinical evidence.
†At megavitamin doses (i.e., more than 10 times daily recommended intake).

information from a pharmacist as they take charge of their health to a greater extent.[36]

Up-to-date and accurate information concerning contraindications and interactions with herbal products is found in primary literature sources such as journals and bulletins, which are readily available to pharmacists. As such, a tremendous opportunity exists for pharmacists to sharpen their expertise and stay current in the area of interactions and contraindications involving herbal products, prescription drugs, and over-the-counter drugs. In doing so, pharmacists will be in a position to provide accurate information to patients.

Nonetheless, the literature has a variety of limitations that impede the ability of pharmacists to make informed clinical decisions about herb–drug interactions. The availability of scientific evidence on interactions between warfarin and herbal products comes largely from *in vitro* data, animal studies, and individual case reports. Results from *in vitro* and animal studies cannot generally be extrapolated to predict responses in humans. While case reports provide some indication of adverse events resulting from an interaction, they often do not allow adequate characterization of the prevalence or extent of risk, nor do they represent conclusive cause-and-effect relationships between specific herbs and warfarin. Case report findings can also be influenced by patient-specific factors such as concurrent medications, coexisting diseases, and lifestyle. These reports generally do not provide information about onset or severity of the potential interactions, which further complicates the difficulty associated with making recommendations to patients. Case reports that do document the onset and extent of the interaction with warfarin are limited in that INR testing is typically not performed (so a clear time association cannot be determined), or the patient's baseline INR is not reported, which prevents further definition of the extent of the interaction. These limitations are compounded by the lack of manufacturing regulations regarding the purity and potency of herbal products.

Potential interactions between warfarin and herbal products cannot be predicted with certainty, because the pharmacokinetic and pharmacodynamic properties of herbal products are inadequately understood. In addition, there is a distinct lack of reliable information regarding the safety and efficacy of most herbal products. As such, the tables and information presented in this article are not comprehensive and will evolve with further studies and reports.

Pharmacists must be vigilant in detecting and reporting suspected serious adverse events and interactions between herbal products, megavitamins, and conventional drug therapy. Provincial poison control centres are listed in the *Compendium of Pharmaceuticals and Specialties*. Once contacted, these agencies pass relevant information on to Health Canada's Health Products and Food Branch, which then shares information with the World Health Organization. By reporting all suspected adverse events and interactions, pharmacists assist in the effort to ensure that drug and herbal therapy remains safe.

The use of herbal products will likely continue, and it is the pharmacist's responsibility to provide accurate information about the risks associated with using herbal products in conjunction with warfarin. As the role of the pharmacist evolves, we must optimize efficacy and safety outcomes related to anticoagulation therapy. As

such, pharmacists must assess patients, identify their use of herbal medicines, and recognize and report potential adverse effects and interactions. They must take the time to ask patients in an open and nonjudgemental way about their use of herbal and megavitamin therapies, so that this information can be used to make informed and complete recommendations to the patient.

## References


1. Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health Syst Pharm* 2000;57:1221-7.
2. Miller LG, Hume A, Harris IM, Jackson EA, Kanmaz TJ, Cauffield JS, et al. White paper on herbal products. American College of Clinical Pharmacy. *Pharmacotherapy* 2000;20:877-91.
3. Sibbald B. New federal office will spend millions to regulate herbal remedies, vitamins. *CMAJ* 1999;160:1355-7.
4. Klepser TB, Doucette WR, Horton MR, Buys LM, Ernst ME, Ford JK, et al. Assessment of patients' perceptions and beliefs regarding herbal therapies. *Pharmacotherapy* 2000;20:83-7.
5. Smolinske SC. Dietary supplement–drug interactions. *J Am Med Womens Assoc* 1999;54(4):191-2,195.
6. Levy S. What they're asking you about herbs—and what you can tell them. *Drug Top* 2000;[17 Jan]:42-4.
7. Harris JE. Interaction of dietary factors with oral anticoagulants: review and applications. *J Am Diet Assoc* 1995;95:580-4.
8. Anticoagulants—quinine derivatives. In: Tatro D, editor. *Drug interaction facts*. St Louis (MO): Facts and Comparisons; 1993.
9. Spigset O. Reduced effect of warfarin caused by ubidecarenone [letter]. *Lancet* 1994;344:1372-3.
10. Pepping J. Coenzyme Q10. *Am J Health Syst Pharm* 1999;56:519-21.
11. Morton RA. Ubiquinones, plastoquinones and vitamins K. *Biol Rev Camb Philos Soc* 1971;46:47-96.
12. Combs AB, Porter TH, Folkers K. Anticoagulant activity of a naphthoquinone analog of vitamin K and an inhibitor of coenzyme Q10-enzyme systems. *Res Commun Chem Pathol Pharmacol* 1976;13(1):109-14.
13. Yu CM, Chan JC, Sanderson JE. Chinese herbs and warfarin potentiation by "danshen." *J Intern Med* 1997;241:337-9.
14. Tam LS, Chan TY, Leung WK, Critchley JA. Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil [letter]. *Aust N Z J Med* 1995;25:258.
15. Fugh-Berman A. Herb–drug interactions. *Lancet* 2000;355:134-8.
16. Cheng TO. Interaction of herbal medicine with Coumadin [letter]. *J Emerg Med* 2000;18(1):122.
17. Cheng TO. Warfarin danshen interaction [letter]. *Ann Thorac Surg* 1999;67:894.
18. Cheng TO. Herbal interactions with cardiac drugs [letter]. *Arch Intern Med* 2000;160:870-1.
19. Izzat MB, Yim AP, El-Zufari MH. A taste of Chinese medicine! *Ann Thorac Surg* 1998;66:941-2.
20. Li CP, Yung KH, Chiu KW. Hypotensive action of *Salvia miltiorrhiza* cell culture extract. *Am J Chin Med* 1990;18:157-66.
21. Lei XL, Chiou GC. Cardiovascular pharmacology of *Panax notoginseng* (Burk) F.H. Chen and *Salvia miltiorrhiza*. *Am J Chin Med* 1986;14:145-52.
22. Wang Z, Roberts JM, Grant PG, Colman RW, Schreiber AD. The effect of a medicinal Chinese herb on platelet function. *Thromb Haemost* 1982;48:301-6.
23. Lo AC, Chan K, Yeung JH, Woo KS. The effects of danshen (*Salvia miltiorrhiza*) on pharmacokinetics and pharmacodynamics of warfarin in rats. *Eur J Drug Metab Pharmacokinet* 1992;17(4):257-62.
24. Chan K, Lo AC, Yeung JH, Woo KS. The effects of danshen (*Salvia miltiorrhiza*) on warfarin pharmacodynamics and pharmacokinetics of warfarin enantiomers in rats. *J Pharm Pharmacol* 1995;47:402-6.
25. Chan TY. Drug interactions as a cause of overanticoagulation and bleedings in Chinese patients receiving warfarin. *Int J Clin Pharmacol Ther* 1998;36:403-5.
26. de Lemos M, Sunderji R. Herbal interactions with warfarin. *Drug Ther Newsl* 1999;6(2):6-7.
27. Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case. *Neurosurgery* 1990;26:880-2.
28. Blumenthal M, Gruenwald J, Hall T, Riggins C, Rister R, editors. *The complete German Commission E monographs: medicinal plants for human use*. Austin (TX): American Botanical Council; 1998.
29. Page RL 2nd, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999;19:870-6.
30. Israel D, Youngkin EQ. Herbal therapies for perimenopausal and menopausal complaints. *Pharmacotherapy* 1997;17:970-84.
31. Zhu DP. Dong quai. *Am J Chin Med* 1987;15(3-4):117-25.
32. Lo AC, Chan K, Yeung JH, Woo KS. Danggui (*Angelica sinensis*) affects the pharmacodynamics but not the pharmacokinetics of warfarin in rabbits. *Eur J Drug Metab Pharmacokinet* 1995;20(1):55-60.
33. Hebel SK, editor. *The review of natural products*. St Louis (MO): Facts and Comparisons; 1999. p. 1-2.
34. Bauer G. Alternative measures. *Pharm Pract* 1999;15(6):39-43.
35. Martin JE. Help on herbals. *Pharm Pract* 1999;15(6):45-57.
36. Boullata JI, Nace AM. Safety issues with herbal medicine. *Pharmacotherapy* 2000;20:257-69.
37. Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. *Am J Health Syst Pharm* 1999;56:125-38.
38. Ariga T, Oshiba S, Tamada T. Platelet aggregation inhibitor in garlic [letter]. *Lancet* 1981;1:150-1.
39. Bordia A. Effect of garlic on human platelet aggregation in vitro. *Atherosclerosis* 1978;30:355-60.
40. Carruthers-Czyzewski P. Heart failure in the older adult. *Can Pharm J* 1999;132(10):32-6.
41. Gadkari JV, Joshi VD. Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects. *J Postgrad Med* 1991;37:128-31.
42. Burnham BE. Garlic as a possible risk for postoperative bleeding [letter]. *Plast Reconstr Surg* 1995;95(1):213-3.
43. O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. *Arch Fam Med* 1998;7:523-36.
44. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract [letter]. *N Engl J Med* 1997;336:1108.
45. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology* 1996;46:1775-6.
46. Gilbert GJ. *Ginkgo biloba* [letter]. *Neurology* 1997;48:1137.
47. Matthews MK Jr. Association of *Ginkgo biloba* with intracerebral hemorrhage [letter]. *Neurology* 1998;50:1933-4.

48. Vale S. Subarachnoid haemorrhage associated with *Ginkgo biloba* [letter]. *Lancet* 1998;352:36.
49. Skogh M. Extracts of *Ginkgo biloba* and bleeding or haemorrhage [letter]. *Lancet* 1998;352:1145-6.
50. Kleijnen J, Knipschild P. *Ginkgo biloba. Lancet* 1992;340:1136-9.
51. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health Syst Pharm* 1997;54:692-3.
52. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug–herb interactions. *Arch Intern Med* 1998;158:2200-11.
53. Cui J, Garle M, Eneroth P, Bjorkhem I. What do commercial ginseng preparations contain? [letter]. *Lancet* 1994;344:134.
54. Ng TB, Li WW, Yeung HW. Effects of ginsenosides, lectins and *Momordica charantia* insulin-like peptide on corticosterone production by isolated rat adrenal cells. *J Ethnopharmacol* 1987;21(1):21-9.
55. Konno C, Murakami M, Oshima Y, Hikino H. Isolation and hypoglycemic activity of panaxans Q, R, S, T and U, glycans of *Panax ginseng* roots. *J Ethnopharmacol* 1985;14(1):69-74.
56. Singh VK, Agarwal SS, Gupta BM. Immunomodulatory activity of *Panax ginseng* extract. *Planta Med* 1984;50:462-5.
57. 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;51:175-80.
58. Lui J, Staba EJ. The ginsenosides of various ginseng plants and selected products. *J Nat Prod* 1989;43:34-6.
59. Cupp MJ. Herbal remedies: adverse effects and drug interactions. *Am Fam Physician* 1999;59:1239-45.
60. Rivera JO, Kalpana MV. Hidden problems with herbal remedies. *Pharmacotherapy* 2000;20:874-6.
61. Taylor JR, Wilt VM. Probable antagonism of warfarin by green tea. *Ann Pharmacother* 1999;33:426-8.
62. Mukhtar H, Ahmad N. Green tea in chemoprevention of cancer. *Toxicol Sci* 1999;52(2 Suppl):111-7.
63. Booth SL, Sadowski JA, Pennington JAT. Phylloquinone (vitamin $K_1$) content of foods in the US Food and Drug Administration's total diet study. *J Agric Food Chem* 1995;43:1574-9.
64. Booth SL, Sadowski JA, Pennington JAT. Vitamin $K_1$ (phylloquinone) content of foods: a provisional table. *J Food Compos Anal* 1993;6:109-20.
65. Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study (1991–1995). *Drug Saf* 1997;17:342-56.
66. Ernst E. Second thoughts about safety of St John's wort. *Lancet* 1999;354:2014-6.
67. Yue QY, Bergquist C, Gerden B. Safety of St John's wort (*Hypericum perforatum*) [letter]. *Lancet* 2000;355:576-7.
68. Anderson LA, Newall CA, Phillipson JD. *Herbal medicines: a guide for health-care professionals.* London: Pharmaceutical Press; 1990.
69. Metzig C, Grabowska E, Eckert K, Rehse K, Maurer HR. Bromelain proteases reduce human platelet aggregation in vitro, adhesion to bovine endothelial cells and thrombus formation in rat vessels in vivo. *In Vivo* 1999;13:7-12.
70. Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988;2:189-92.
71. Knight DW. Feverfew: chemistry and biological activity. *Nat Prod Rep* 1995;12:271-6.
72. Heptinstall S, Groenewegen WA, Spangenberg P, Loesche W. Extracts of feverfew may inhibit platelet behaviour via neutralization of sulphydryl groups. *J Pharm Pharmacol* 1987;39:459-65.
73. Loesche W, Mazurov AV, Voyno-Yasenetskaya TA, Groenewegen WA, Heptinstall S, Repin VS. Feverfew—an antithrombotic drug? *Folia Haematol Int Mag Klin Morphol Blutforsch* 1988;115:181-4.
74. Groenewegen WA, Heptinstall S. A comparison of the effects of an extract of feverfew and parthenolide, a component of feverfew, on human platelet activity in-vitro. *J Pharm Pharmacol* 1990;42:553-7.
75. Heptinstall S, Awang DV, Dawson BA, Kindack D, Knight DW, May J. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 1992;44:391-5.
76. Backon J. Ginger: inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry. *Med Hypotheses* 1986;20:271-8.
77. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996;335:540-6.
78. Holt GA. *Food and drug interactions.* Chicago (IL): Precept Press; 1998.
79. Gray J, editor. *Therapeutic choices.* 2nd ed. Ottawa (ON): Canadian Pharmacists Association; 1998.
80. Corrigan JJ Jr, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974;230:1300-1.
81. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* 1996;77:545-6.
82. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;114 (5 Suppl):445S-469S.
83. Weibert RT, Le DT, Kayser SR, Rapaport SI. Correction of excessive anticoagulation with low-dose oral vitamin K1. *Ann Intern Med* 1997;126:959-62.

**Sunita Bond Stenton** was, at the time of writing, a pharmacy student at the University of Alberta, Edmonton, Alberta. She is currently a resident at the Royal Columbian Hospital, New Westminster, British Columbia.

**Tammy J. Bungard**, PharmD, is with the Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta.

**Margaret L. Ackman**, PharmD, is with Regional Pharmacy Services, Capital Health, and the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta.

**Address correspondence to:**
Dr Tammy J. Bungard
213 Heritage Medical Research Centre
University of Alberta
Edmonton AB
T6G 2S2

**e-mail:** tammy.bungard@ualberta.ca