Potential interactions between alternative therapies and warfarin

AMY M. HECK, BETH A. DEWITT, AND ANITA L. LUKES

Abstract: Potential and documented interactions between alternative therapy agents and warfarin are discussed. An estimated one third of adults in the United States use alternative therapies, including herbs. A major safety concern is potential interactions of alternative medicine products with prescription medications. This issue is especially important with respect to drugs with narrow therapeutic indexes, such as warfarin. Herbal products that may potentially increase the risk of bleeding or potentiate the effects of warfarin therapy include angelica root, arnica flower, anise, asafoetida, bogbean, borage seed oil, bromelain, capiscum, celery, chamomile, clove, fenugreek, feverfew, garlic, ginger, ginkgo, horse chestnut, licorice root, lovage root, meadowsweet, onion, parsley, passionflower herb, poplar, quassia, red clover, rue, sweet clover, turmeric, and willow bark. Products that have been associated with documented reports of potential interactions with warfarin include coenzyme Q10, danshen, devil’s claw, dong quai, ginseng, green tea, papain, and vitamin E. Interpretation of the available information on herb–warfarin interactions is difficult because nearly all of it is based on in vitro data, animal studies, or individual case reports. More study is needed to confirm and assess the clinical significance of these potential interactions.

There is evidence that a wide range of alternative therapy products have the potential to interact with warfarin. Pharmacists and other health care professionals should question all patients about use of alternative therapies and report documented interactions to FDA’s MedWatch program.

Index terms: Alternative medicine; Angelica sinensis; Anticoagulants; Dietary supplements; Drug interactions; Enzymes; Ginseng; Papain; Plants; Salvia miltiorrhiza; Teas; Ubidecarenone; Vitamin E; Vitamins; Warfarin

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Alternative medicine therapies have become increasingly popular, and it has been estimated that one third of all Americans use herbal products. In 1997, herbal medicine sales increased nearly 59%, reaching an estimated total of $3.24 billion. Despite widespread use of alternative therapies, scientific data about their safety and efficacy are lacking in most cases. This makes it very difficult for pharmacists to advise patients appropriately about safe concomitant use of alternative therapies and prescription medications. New information about therapeutic efficacy, adverse effects, and potential drug interactions of alternative therapies is frequently reported in the medical literature. Therefore, it is important for pharmacists to have current knowledge in order to remain a reliable source of drug information for patients and other health care professionals.

One particular safety concern is potential interactions of alternative medicine products with prescription medications. This issue is especially important with respect to drugs with narrow therapeutic indexes, such as warfarin. More food and drug interactions have been reported for warfarin than for any other prescription medication. Multiple pathways exist for interference with warfarin, and interactions may lead to either hemorrhage or thrombotic episodes by increasing or reducing this agent’s effect. Therefore, close monitoring of therapy and knowledge of potential interactions of herbs with warfarin are extremely important.

This article discusses potential
and documented herb–warfarin interactions.

Potential interactions of herbs with warfarin

Several herbs may have the potential to interfere with warfarin therapy. However, because information about the pharmacologic activity, therapeutic efficacy, and adverse effects of most alternative medicine products is limited, the clinical significance of potential warfarin–herb interactions is unknown. Herbs that have been identified as having the theoretical potential to interfere with warfarin therapy are listed in Table 1.5–11 Further study is needed to confirm these potential interactions and assess their clinical significance.

**Herbs with coumarin, salicylate, or antiplatelet properties.** Several natural products contain substances that have coumarin, salicylate, or antiplatelet properties. Therefore, a theoretical risk for potentiation of the pharmacologic activity of warfarin exists when these herbs are taken with warfarin. Herbs thought to contain coumarin or coumarin derivatives include angelica root, arnica flower, anise, asafoetida, celery, chamomile, fenugreek, horse chestnut, licorice root, lovage root, parsley, passionflower herb, quassia, red clover, and rue.5–9 Meadowsweet, poplar, and willow bark contain high concentrations of salicylates, while bromelain, clove, onion, and turmeric have been reported to exhibit antiplatelet activity.5,5 Borage seed oil contains γ-linoleic acid, which may increase coagulation time.10 Bogbean has been noted to demonstrate hemolytic activity,9 and capsicum has been reported to cause hypocoagulability.11 There have been no documented case reports of an interaction of warfarin with any of these herbs. However, patients taking any products containing these herbs concurrently with medications that have anticoagulant effects, such as warfarin, should be closely monitored for signs or symptoms of bleeding.

Sweet clover also contains coumarin derivatives and therefore poses an increased risk of bleeding if given with warfarin.5 There have been no reports of an interaction between sweet clover and warfarin or hemorrhagic disease in humans. However, several cases of severe hemorrhage and death have been reported in cattle.12,13 Patients taking both sweet clover and an anticoagulant should be closely monitored for signs and symptoms of bleeding.

**Garlic.** Garlic (Allium sativum) is thought to provide several cardiovascular benefits, such as blood pressure lowering, serum lipid lowering, and antithrombotic activity.6,14 Garlic oil has been reported to interrupt thromboxane synthesis, thereby inhibiting platelet function.22 One author reported that in vitro platelet aggregation decreased within five days when blood samples from six healthy adults were mixed with essential garlic oil.23 An elderly man developed a spontaneous epidural hematoma after he ingested approximately 2000 mg of garlic daily (equivalent to about four cloves) for an undetermined period.24 The man denied use of aspirin, nonsteroidal anti-inflammatory drugs, and any other medications that may precipitate a bleeding event.

There have been no reports of potentiation of warfarin’s activity with concomitant administration of garlic, but the available information suggests that a serious interaction is possible.

### Table 1.

**Potential and Documented Interactions of Herbs with Warfarin**

<table>
<thead>
<tr>
<th>Potential Increase in Risk of Bleeding</th>
<th>Potential Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelica root</td>
<td>Ginkgo</td>
</tr>
<tr>
<td>Arnica flower</td>
<td>Horse chestnut</td>
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<tr>
<td>Anise</td>
<td>Licorice root</td>
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<tr>
<td>Asafoetida</td>
<td>Lovage root</td>
</tr>
<tr>
<td>Bogbean</td>
<td>Meadowsweet</td>
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<tr>
<td>Borage seed oil</td>
<td>Onion</td>
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<tr>
<td>Bromelain</td>
<td>Parsley</td>
</tr>
<tr>
<td>Capsicum</td>
<td>Passionflower herb</td>
</tr>
<tr>
<td>Celery</td>
<td>Poplar</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Quassia</td>
</tr>
<tr>
<td>Clove</td>
<td>Red clover</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Rue</td>
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<tr>
<td>Feverfew</td>
<td>Sweet clover</td>
</tr>
<tr>
<td>Garlic</td>
<td>Turmeric</td>
</tr>
<tr>
<td>Ginger</td>
<td>Willow bark</td>
</tr>
</tbody>
</table>

**Documented Reports of Possible Increase in Warfarin’s Effects**

- Danshen
- Devil’s claw
- Dong quai
- Papain
- Vitamin E

**Documented Reports of Possible Decrease in Warfarin’s Effects**

- Coenzyme Q10
- Ginseng
- Green tea

*Excessive amounts are necessary for this interaction to occur.*
sible. Patients taking warfarin should be advised to avoid garlic supplements. However, they should also be aware that regular ingestion of food products containing small amounts of garlic should not pose a problem. If excessive garlic consumption and warfarin use occur concomitantly, the patient’s INR should be closely monitored.

Ginger. Ginger (Zingiber officinale), promoted for use in motion sickness and arthritis, has been reported to reduce platelet aggregation through the inhibition of thromboxane synthetase. Ginger supplements, containing amounts of ginger much greater than regularly found in food products, may lead to an increased risk of bleeding when taken with warfarin. Therefore, patients taking warfarin and ginger supplements concurrently should have their INR checked regularly and be advised to watch for symptoms of bleeding.

Ginkgo. Ginkgo (Ginkgo biloba) is a common herbal product available in the United States and advertised to improve cognitive function. Ginkgolide B, one component of ginkgo, inhibits platelet-activating factor by displacing it from its receptor-binding site, resulting in reduced platelet aggregation. Several cases of bleeding thought to be secondary to ginkgo ingestion have been reported. A 70-year-old man ingested 40 mg of concentrated ginkgo extract twice daily for one week. He complained of blurred vision and was diagnosed with a spontaneous hyphema. He was also taking 325 mg of aspirin daily. A second report involved a 33-year-old woman who complained of diffuse headaches and was later diagnosed with bilateral subdural hematomas. The patient’s medication list included occasional acetaminophen use, a brief trial of ergotamine–caffeine tablets, and 60 mg of ginkgo twice daily for two years. Yet another report described a 72-year-old woman diagnosed with a left frontal subdural hematoma after taking 50 mg of ginkgo three times daily for at least six months.

Currently, there are no reports of bleeding associated with concomitant administration of warfarin and ginkgo. However, it is recommended that patients taking warfarin, or any other anticoagulant, not take ginkgo-containing products because of an increase in the risk of serious bleeding.

Documented reports of possible herb–warfarin interactions

Herbal products that have been associated with published case reports of possible interactions with warfarin include danshen, devil’s claw, dong quai, green tea, ginseng, and papain. Dietary supplements such as coenzyme Q10 and vitamin E have also been reported to adversely affect warfarin therapy. It should be noted that the following information is derived primarily from individual case reports; further study is needed to identify the exact mechanism, time of onset, severity, and appropriate management of these potential interactions.

Coenzyme Q10. Coenzyme Q10 (also known as ubiquinone or ubidecarenone) is a provitamin found in the mitochondria of plant and animal cells. It is involved in electron transport and may act as a free-radical scavenger, an antioxidant, or a membrane stabilizer. Coenzyme Q10 supplementation is primarily promoted to treat a variety of cardiovascular disorders, including heart failure, hypertension, stable angina, and ventricular arrhythmias. Many patients with these conditions may also be prescribed warfarin.

Coenzyme Q10 is structurally related to menaquinone (vitamin K) and may have procoagulant effects. The vitamin K–like effects of coenzyme Q10 have been demonstrated in vitro and in four case reports describing possible warfarin and coenzyme Q10 interactions. In Denmark, a 72-year-old woman had a decreased response to warfarin while she was taking coenzyme Q10. Appropriate anticoagulation was achieved only when she stopped taking the product. A 68-year-old man who had a history of several episodes of pulmonary and cerebrovascular emboli and whose condition had been stabilized with warfarin (INR, 2–3) for six years had a reduction in his INR to 1.31 after consuming 30 mg of coenzyme Q10 daily for two weeks. The other case reports involved (1) a 72-year-old man with pulmonary embolism and repeated low INR measurements (1.46 and 1.27) while taking warfarin and undetermined doses of coenzyme Q10 and (2) a 70-year-old woman with thromboembolic disease stabilized on warfarin (INR, 2–3) for several months who had a reduction in her INR to 1.46 within two weeks of starting coenzyme Q10. In each of these patients the INR, which had been stable and therapeutic, fell below the therapeutic range during coenzyme Q10 use and subsequently returned to the therapeutic range after the provitamin was discontinued.

Until more is known about the effect of the combination of coenzyme Q10 and warfarin, patients should be advised to avoid the combination because of the possible risk of thrombotic complications. If warfarin and coenzyme Q10 are used concomitantly, the patient’s INR should be monitored periodically within the first two weeks.

Danshen. Although not commonly used in the United States, danshen (the root of Salvia miltiorrhiza), also known as tan seng, is a very popular herb recommended in the Chinese community for various cardiovascular diseases. The pharmacologic effects of danshen have been described primarily in vitro and in animals and include hypotensive effects, positive inotropic effects, coronary artery vasodilation, and inhibition of platelet aggregation. Pharmacokinetic and pharmacodynamic studies in rats indicate that danshen root extracts increase the absorption rate, area under the plasma concentration-versus-
time curve, and maximum concentration of warfarin, as well as reduce the elimination half-life.40,41

There have been several case reports of a warfarin–danshen interaction.42–45 A 62-year-old man who had been receiving 5 mg of warfarin daily after a mitral valve replacement and who had had a stable INR for several weeks was admitted to a Hong Kong hospital with pleural and pericardial effusion; his hemoglobin concentration was 7.6 mg/dL and his INR was >8.4.41 The man reported consuming a danshen extract daily for two weeks before his admission. The INR of a 48-year-old woman taking warfarin 4 mg/day increased to 5.6 after she consumed danshen every other day for about one month.42 A 66-year-old man who had been receiving warfarin 2–2.5 mg/day for nearly a year and had an INR stabilized at 2.0 was hospitalized for bleeding from a gastric carcinoma; the associated INR was 5.5.43 He reported consuming danshen three and five days before admission and using a Chinese medicated topical oil containing methyl salicylate. Both this man and the 48-year-old woman in the previous example achieved a therapeutic INR after discontinuing danshen.

The available evidence contraindicates concurrent use of danshen and warfarin.

**Devil’s claw.** Devil’s claw (Harpagophytum procumbens) is an expensive herbal product that has been promoted for use as an analgesic in the treatment of arthritis, gout, and myalgia.3,8 Although information about the pharmacologic effects of devil’s claw is limited, one case of purpura was reported in a patient receiving warfarin and devil’s claw.44 This case was uncovered during a toxicology review conducted between 1991 and 1995 by the National Poisons Information Service, which provides emergency information for poisonings throughout the United Kingdom. However, key details of this case, including the patient’s medical conditions, other medications, and the doses and duration of warfarin and devil’s claw ingestion, were not reported. Until more is known about this possible interaction, patients taking warfarin should be advised to avoid devil’s claw.

**Dong quai.** Dong quai (Angelica sinesis) is a Chinese herbal supplement promoted in the United States for use in the treatment of menopausal complaints and menstrual disorders.46 Dong quai contains at least six coumarin derivatives; these substances are believed to promote vasodilation and uterine stimulation and to have anti-inflammatory, antipyretic, antispasmodic, immunosuppressant, and estrogen-like effects.46 Dong quai may also exert an antithrombotic effect by inhibiting platelet activation and aggregation.47 On the basis of the known pharmacologic effects of dong quai and a small pharmacokinetic study in rabbits that suggested the potential for increased prothrombin times when this herb is administered with warfarin, a potentially dangerous interaction was theorized.48 A recent case report supports this idea. A 46-year-old woman who had been taking warfarin 5 mg/day for nearly two years and had an INR stabilized at 2–3 experienced a sudden increase in her INR to 4.9.49 The patient denied any changes in her medication regimen, diet, alcohol consumption, or other lifestyle factors that may affect her INR—except for the recent addition of dong quai 565 mg once or twice daily during the preceding four weeks for the management of menopausal symptoms (her “herbalist” had recommended this). The patient was instructed to discontinue dong quai, and within four weeks her INR declined to the therapeutic range. In view of this information, patients receiving warfarin should be advised to avoid dong quai.

**Ginseng.** Three ginseng species—American ginseng (Panax quinquefolius), Oriental ginseng (Panax ginseng), and Siberian ginseng (Eleutherococcus senticosus)—have been promoted as enhancing energy, reducing the effects of stress, and improving mood, among several other claims.46,47 The active components of ginseng are known as ginsenosides, more than 20 of which have been identified. The pharmacologic activity of each ginsenoside appears to vary depending on where the plant grew and the extraction techniques used.50 Also, data suggest that the ginsenoside composition varies widely among commercially available ginseng products.51 This variability makes it difficult to evaluate the safety and efficacy of ginseng products. Although the exact pharmacologic actions of ginsenosides in humans are not fully understood, studies in vitro and in animals suggest that these substances may increase adrenal hormone synthesis, decrease blood glucose concentrations, and promote immunomodulation.52–54

One published case report suggests that Oriental ginseng (Ginsana) may antagonize the anticoagulant effects of warfarin.55 The INR of a 47-year-old man who had been receiving warfarin for nine months (7.5 mg every Tuesday and 5 mg on all other days) to prevent thrombotic complications associated with a mechanical heart valve was stabilized at 3.0–4.0. The patient began taking Oriental ginseng, and within two weeks his INR fell to 1.5. The patient denied any other changes in his medication regimen (including other nonprescription or herbal products), diet, alcohol consumption, or other lifestyle factors that may have affected his response to warfarin. The patient’s INR returned to therapeutic level (3.3) two weeks after he stopped using ginseng.

The possible mechanism for this interaction has not been identified, and it is not known which ginsenoside or ginsenosides may be responsible. A 1999 pharmacokinetic study in rats did not reveal a significant interaction between warfarin and pure ginseng extract.56 Nevertheless, because of the potential seriousness of thrombotic complications resulting from a subtherapeutic INR, patients...
receiving warfarin should avoid ginseng until more is known.

**Green tea.** Green tea (Camellia sinensis), also known as Chinese tea, is a popular beverage purported to prevent various cancers, treat gastrointestinal disorders, and enhance cognition.\(^{58,59}\) However, large amounts of green tea leaves have been found to contain substantial amounts of vitamin K, brewed green tea is generally not considered a significant source of the vitamin.\(^{58,59}\) Although dried green tea leaves have been found to contain vitamin K, brewed green tea may potentially antagonize the effects of warfarin. The INR of a 44-year-old warfarin recipient with a mechanical heart valve decreased substantially when he started consuming large amounts of brewed green tea.\(^{60}\) The patient reported to the outpatient clinic with an INR of 1.37; his INR 22 days prior to this visit had been 3.79. The patient was unable to be reached until his return visit to the clinic one month later, at which time his INR was 1.14. In an interview, the patient disclosed that he had begun drinking 0.5–1 gallon of brewed green tea daily approximately one week before the INR measurement of 1.37. There were no other identifiable causes of the dramatic decrease in the INR, including changes in the patient’s medications, dietary intake, medication compliance, or medical conditions.

A significant drop in the INR would not generally be expected to result from usual consumption of moderate amounts of brewed green tea. It is probably not necessary to advise patients receiving warfarin therapy to avoid green tea. However, patients should be advised that large quantities of green tea might decrease the effectiveness of warfarin.

**Papain.** Papain is a mixture of proteolytic enzymes found in extract of papaya, the fruit of the papaya tree (Carica papaya).\(^{61}\) It is taken orally in the belief that it reduces edema, inflammation, herpes zoster symptoms, diarrhea, and psoriasis symptoms.\(^{62}\) The pharmacologic mechanisms by which papain may affect coagulation are not known. However, one case of an interaction between warfarin and papain was identified in the 1991–95 toxicology review conducted throughout the United Kingdom by the National Poisons Information Service.\(^{64}\) A patient who had maintained a therapeutic INR while receiving warfarin began taking papaya extract containing papain as a weight-loss aid. The patient was admitted for cardiac surgery with an INR of 7.4. After withdrawal of both papaya extract and warfarin, the patient’s INR decreased to 2.0. The details of the case have not been published, however.

Patients receiving warfarin should be advised to avoid papain supplementation until further information about this potential interaction becomes available.

**Vitamin E.** Vitamin E has received much publicity as one of several antioxidants that may be useful in treating a variety of disorders, including cardiovascular diseases. Vitamin E may inhibit the oxidation of reduced vitamin K.\(^{61}\) Vitamin K oxidation is necessary for carboxylation of vitamin K-dependent clotting factors, which must occur for these clotting factors to be fully functional. Conflicting information exists about the effect of vitamin E on prothrombin time.

A 55-year-old man taking warfarin and 1200 units of vitamin E daily developed ecchymoses and hematuria, and his prothrombin time increased. After a two-month period of stable clinical and hematologic status without concomitant vitamin E intake, the patient was rechallenged with vitamin E 800 units/day. Again, multiple ecchymoses appeared on his extremities. His prothrombin time began to increase at four weeks and continued to increase over the next two weeks. Within a week after the patient stopped taking vitamin E, his prothrombin time returned to the value reported before he had begun the vitamin.\(^{62}\)

Studies in animals and humans consuming adequate vitamin K and not receiving vitamin E have found no effect of vitamin E on coagulation. However, vitamin K-deficient animals have demonstrated bleeding diatheses associated with vitamin E.\(^{63,64}\) A study in 12 patients undergoing warfarin treatment who received 100 or 400 units of vitamin E daily for one month found that neither dose induced a clinical bleeding state.\(^{64}\) Kim and White\(^{65}\) conducted a randomized, double-blind study in which four patients received 1200 units of vitamin E daily, three patients received 800 units/day, and four received placebo, all for four weeks.\(^{65}\) During the study’s second phase, which was single-blind and not randomized, six subjects were told they would receive placebo or vitamin E, but all were given vitamin E 1200 units/day for an additional four weeks. The INR did not increase to a level necessitating warfarin dosage adjustments in either treatment group. Although these studies indicated no interaction between vitamin E and warfarin, both were small and limited to only one month.

Vitamin E up to 400 units/day does not appear to affect prothrombin time in patients receiving warfarin. Although higher dosages appeared to be safe in the study by Kim and White,\(^{65}\) some conflicting information suggests the potential for certain patients to be adversely affected by the combination of vitamin E and warfarin. The characteristics of those patients have not been determined. Therefore, patients receiving warfarin who are beginning vitamin E therapy, particularly dosages greater than 400 units/day, should have INR measurements conducted once to two weeks after starting vitamin E. This should be followed by INR monitoring every two to four weeks during the first two months of combination therapy. Increased prothrombin times induced by combined vitamin E and warfarin therapy may be managed by discontinuing vitamin E, and, if necessary, by administering vi-
tamin K.

Limitations of the literature

Several limitations exist for health care professionals attempting to use this information to make clinical decisions. Nearly all available information on potential drug interactions between warfarin and herbal products is based on in vitro data, animal studies, or individual case reports. Definitive cause-and-effect relationships have not been proven. The findings to date may be confounded by several patient-specific variables, including the presence of other concomitant medications, diseases, and lifestyle factors. Information from in vitro or animal studies may not always predict responses in humans. In addition, the available reports provide only limited information about the onset or severity of the potential interactions, which further limits the development of sound recommendations for managing patients. These problems are further complicated by the lack of information about the safety and therapeutic efficacy of most herbal products and the lack of regulations governing the purity and potency of herbal products during manufacturing. Because the pharmacokinetic and pharmacodynamic properties of most herbal products are poorly understood, potential interactions with warfarin cannot be predicted with any confidence. Therefore, the list presented in this review cannot be considered all-inclusive, and continued vigilance and reporting of potential interactions are needed.

Discussion

Increases in alternative medicine use in the United States have made information about potential drug and herb interactions very important, especially for medications with a narrow therapeutic index, such as warfarin. More information is needed about the severity, onset, and therapeutic management of these potential interactions.

Because nearly 70% of patients who use alternative therapies do not inform their health care providers about these products, pharmacists and other health care professionals should question all patients about their use of alternative therapies. Health care professionals should remain vigilant for potential interactions between alternative therapies and prescription medications, especially medications with a narrow therapeutic index, and should report suspected interactions to FDA’s MedWatch program. FDA recently established the Special Nutritional Adverse Event Monitoring System, a searchable database including information about suspected adverse events associated with dietary supplements or nutritional products. This database includes reports that have been submitted to MedWatch and can be accessed via the Internet (http://vm.cfsan.fda.gov/~dms/aems.html). Continued efforts by health care professionals to recognize and report suspected interactions between prescription medications and herbal and other alternative therapies should ultimately increase knowledge and awareness of interactions and improve the quality of patient care.

Conclusion

There is evidence that a wide range of herbal products have the potential to interact with warfarin. Pharmacists and other health care professionals should question all patients about use of alternatives and report documented interactions to FDA’s MedWatch program.

References
