Review Article

Herbal remedies and anticoagulant therapy

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Summary

Herbal remedies, considered to be both safe and effective by most consumers, may interact with conventional drugs. Warfarin, a vitamin K antagonist originally derived from the sweet clover plant, has a narrow therapeutic window which can be monitored using prothrombin international normalized ratios (PT-INR). Many herbs can increase the risk for bleeding when combined with warfarin, either by augmenting the anticoagulant effects of the drug (with increased PT-INR levels) or through intrinsic anti-platelet properties (without altering PT-INR levels). The increased risk for bleeding among such patients may be difficult to predict, especially when formulas which contain many herbs are used. Further research into herb-drug interactions is warranted, as are guidelines for the use of herbal remedies by patients on chronic anticoagulation therapy.

Keywords

Herbs, warfarin, anticoagulation, antiplatelet, bleeding

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Use of herbal remedies by patients on anticoagulant therapy

Herbal remedies are considered by most consumers to be both safe and effective, and their use is on the rise (1). Nearly one in six adults in the United States taking prescription drugs is concomitantly using at least one herbal remedy (2), while less than 40% of patients will disclose the use of herbal and other alternative therapies to their regular physicians or emergency room staff (1, 3). Although herbal medicines are thought to cause fewer adverse and toxic effects than conventional drugs due to the lower concentration of active components, the use of certain herbs may result in severe, even lethal, side effects (4). Legislation requiring licensing for herbal remedies has been implemented in only a few countries such as Germany, France, Sweden and Australia, while in the U.S. the Dietary Supplement Health and Education Act of 1994 eliminated the requirement that these products be reviewed by the Food and Drug Administration (FDA).

Warfarin, a drug originally derived from the sweet clover plant, interrupts the vitamin K–dependent posttranslational modification of coagulation proteins II, VII, IX and X via inhibition of vitamin K epoxide reductase. Dosage of the drug is adjusted according to target prothrombin international normalized ratios (PT-INR), which varies according to the indication for treatment. Few patients on chronic anticoagulant therapy have completely stable PT INR values, due, in part, to interactions with certain drugs and foods (5), and the annual incidence of minor and major bleeding is 24 and 7 episodes per hundred patients, respectively (6).

Herbal remedies can potentially increase the risk of spontaneous bleeding, as well as augment the anti-coagulant effects of warfarin (Table 1). This interaction is a result of a combination of factors, such as intrinsic anticoagulant and anti-platelet properties of the herbs, as well as effects on the pharmacokinetics of warfarin (Fig. 1). It is therefore imperative that physicians be aware of the use of such remedies by their patients and advise them accordingly.

Anticoagulant effects of herbs

The narrow therapeutic window of anticoagulant therapy can be maintained in most cases by close monitoring of PT-INR values. However, any sudden change in drug compliance or diet can lead to dangerous bleeding or clotting in these patients. Many herbs can augment the effects of warfarin (24, 25) (Table 2), through one or more mechanisms. More than 1300 naturally occurring coumarins have been identified. Coumarins are ubiquitous in green plants and structurally similar to warfarin, though not necessarily with anticoagulant effects. The compound dicoumarol (a 4-hydroxycoumarin) is formed from coumarin through the

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Table 1: Case reports of coagulation complications due to herbs.

Herb	Age / Gender	Dosage	Complication
Garlic	32/F	na	prolonged postoperative bleeding (7)
	87/M	2g/d	spontaneous epidural hematoma (8)
	72/M	na	postoperative bleeding (9)
Ginkgo Biloba	70/M	80mg/d	spontaneous hyphema (10)
	33/F	120mg/d	spontaneous subdural hematoma (11)
	72/F	150mg/d	spontaneous subdural hematoma (12)
	78/F	na	intracerebral hemorrhage (13)
	61/M	160mg/d	subarachnoid hemorrhage (14)
Quilinggao	61/M	1 can/d *	mucosal bleeding (15)
Herbal tea	25/F	na	menometrorrhagia (16)
Ginseng	47/M	3 capsules/d *	reduced response to warfarin (17)
	44/F	Face cream	vaginal bleeding d/t use of cream (18)
	72/F	200mg	vaginal bleeding (19)
Danshen	48/F	na *	increased response to warfarin (20)
	66/M	na *	bleeding gastric carcinoma (21)
	62/M	na *	pleural hemorrhage (22)
Devil's claw	na	na	Purpura (23)

* patient on chronic anticoagulation therapy with warfarin

actions of fungi and molds, and its anticoagulant effect is equivalent to other pharmaceutical anticoagulants that antagonize vitamin K (26).

Some herbs have been found to alter the pharmacokinetics of warfarin. The Chinese herb Danshen (*salvia miltiorrhiza*) is commonly used in China for the treatment of cardiovascular and cerebrovascular disease (28, 29). Danshen has been found to significantly increase plasma concentrations of warfarin in rats by increasing absorption rates as well as decreasing clearance and apparent volume distribution of both the R- and S- enantiomers of the drug (30, 31). Some herbs have other, non-specific anticoagulant effects, such as the non-coumarin herb skullcap (*scutellaria baicalensis georgi*), found to have anti-HIV activity (32), which inhibits coagulation via the flavones baicalin and oroxylin (33). The herb *geum japonicum*, used as a diuretic and astringent, contains seven known tannins which inhibit key serine proteinases of thrombin and factor Xa and significantly inhibit fibrinogen hydrolysis (34).

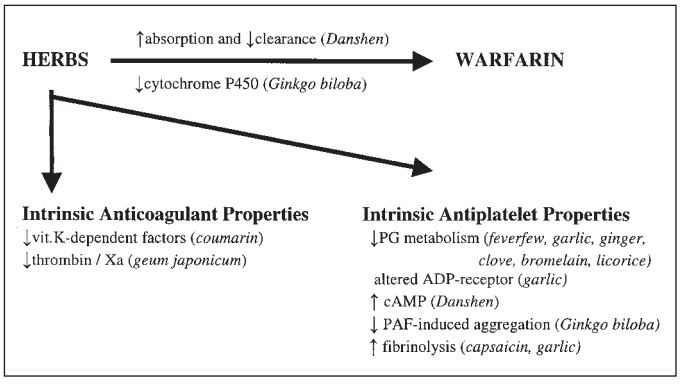

Figure 1: Anticoagulant and antiplatelet properties of herbs.

Antiplatelet effects of herbs

Patients on chronic anticoagulation treatment with therapeutic PT-INR values may still be at increased risk for bleeding if given antiplatelet medications as well. Some herbs, such as wintergreen leaf, sweet birch bark and willow bark, contain methyl sa-

Table 2: Herbs which may potentiate anticoagulant effects of warfarin (based on: Norred [24] and Heck [25]).

Agrimony	Garlic	Pau d'arco
Angelica	Geum japonicum	Pineapple (bromelain)
Anise	Ginger	Poplar
Arnica	Ginkgo biloba	Prickly ash
Asasoetida	Ginseng	Red clover
Bogbean	Green tea	Red pepper (casaicin)
Borage seed	Horse chestnut	Reishi
Celery	Licorice	Rue
Chamomille	Lovage root	Skullcap
Clove	Magnolia bark	Sweet clover
Cordyalis yanhuso	Meadowsweet	Turmeric
Danshen	Onion	Uassia
Devil's claw	Papain	Willow bark
Fenugreek	Parsley	Wintergreen leaf
Feverfew	Passionflower	

licylate, while others may have significant antiplatelet activity that may even surpass that of aspirin and indomethacin (35). Garlic preparations are taken by many patients because of their antilipid and anti-platelet effects, significant factors in the prevention of thrombus formation (36–38). The allicin derivative of garlic root has been shown to enhance fibrinolytic activity and inhibit platelet aggregation in patients with coronary artery disease (39–41), either via a dose-dependent alteration in the production of arachidonic acid metabolites (i.e. inhibition of thromboxane formation in platelets (40, 42, 43) or by altering physiochemical properties (i.e. the ADP-receptor) of the platelet membrane (44–46).

Other herbs may also affect platelet function through inhibition of prostaglandin metabolism. Ginger, used by pregnant women for the relief of nausea and vomiting (47, 48), reduces the production of PG-endoperoxides and thromboxane through either inhibition of platelet cyclooxygenase (COX) (49) or as a result of the anti-oxidant components in the herb which suppress the lipid peroxide essential for COX activity (50, 51). Feverfew, an herb used to treat migraine headaches (52–54), suppresses up to 88% of prostaglandin production without inhibiting COX (55–59), while clove – a common kitchen spice and important source of dietary antioxidants (60), contains two antiplatelet components (eugenol and acetyl eugenol) which inhibit platelet thromboxane formation and increase formation of 12-HPETE, both of which are more potent than aspirin in their antiplatelet effects (61). Bromelain, a derivative of pineapple with immunomodulatory effects (62), also inhibits platelet prostaglandin synthesis (63), while the coumarin-containing herb licorice (with the 3-arylcoumarin derivative GU-7 [64]) inhibits COX, lipoxygenase and peroxidase activity in platelets (65).

Some herbs affect platelet function through other mechanisms. In addition to is anticoagulant effect, the Chinese herb Danshen inhibits platelet aggregation and release via increasing intracellular cyclic AMP (66). Ginseng, a popular herb comprising 15–20% of the total annual sales of botanical products in the United States (67) (whose real benefits are still controversial [68]), inhibits platelet aggregation induced by thrombin or collagen in the rat model (69). Ginkgo biloba, use by Chinese doctors for centuries for the treatment of "chest complaints", has been shown in clinical studies to be superior to placebo for intermittent claudication (70) and (questionably) beneficial for dementia as well (71, 72). The increased risk for bleeding in patients using this herb is thought to be due to a dose-dependent inhibition of PAF-induced platelet aggregation (73). Red pepper (capsaicin), an herb used to alleviate diabetic neuropathy (74), inhibits both platelet aggregation and release (75), as well enhancing fibrinolytic activity (76).

Herbal formulas

Herbal formulas are an important aspect of traditional Chinese medicine, and are termed "Fang Ji" (written / prepared recipes). Each herb in a formula is selected according to its individual traits as well as the interaction with the other herbs. Together, the herbal formula is believed to harmonize the body's energies and heal disease (77). Today many standard formulas can be purchased over-the–counter in pharmacies and health food stores, with the quantity and quality of the contents receiving minimal mention, if at all. It is therefore difficult to predict the effects of these formulas on anticoagulant therapy, further increasing the risk for complications.

The herbal formula Kangen Karyu (KGK) is used to reduce blood viscosity and improve microcirculation. KGK contains 6 known herbs (peony root, cnidium root, safflower root, saussure root and Danshen), and has been found to significantly enhance bleeding time (78) as well as suppress the metabolism and elimination of warfarin (79). KGK may also augment the antithrombotic effects of ticlopidine, potentially increasing the risk of developing thrombotic thrombocytopenic purpura, a severe adverse effect of this drug (80). Another commonly used formula, the Bak Foong Pill (BFP), also known as Bai Feng Wan, is an over-the-counter traditional Chinese medicine with 26 ingredient herbs used for treating dysmenorrhea, irregular menstrual cycle and bleeding. BFP inhibits platelet aggregation, while 17 of its components have been found to significantly prolong thrombin time, 11 prothrombin time and 8 activated partial thromboplastin times (81).

Discussion

Patients on chronic anticoagulant therapy have unlimited access to hundreds of herbs which, with increasing likelihood, they will eventually purchase and use. Much research is still required to understand both the *in vitro* and, more importantly, *in vivo* effects of herbs on the pharmacodynamics of medications such as warfarin. For example, Ginkgo biloba extract was found to strongly inhibit the major human cytochrome P450 enzymes CYP2C9, CYP1A2, CYP2E1 and CYP3A4 (82), as well as competitively inhibiting the metabolism of the oral anti-diabetic agent tolbutamide by the enzyme (S)-warfarin 7-hydroxylase in rat liver microsomes (83). However, a randomized, double-blinded study found that 100mg/day of Gingko biloba (over a period of 4 weeks) had no significant effect on PT INR levels in patients treated with warfarin (84). It is possible that the bleeding diathesis associated with this herb is most likely attributable to its effects on platelet aggregation alone and not on warfarin metabolism.

One of the major obstacles to understanding herb-drug interactions is the inconsistencies in the quantity and quality of the various preparations of the herbs. Herbal preparations and formulas may contain either large or, conversely, insignificant amounts of active components. In one study of 50 commercially produced ginseng preparations, 6 products contained no specific ginsenosides whatsoever, while the remaining 44 had levels ranging from 1.9% to 9.0% (85). Garlic preparations may also have varied amounts of active metabolites, depending on the mode of preparation (chopped, crushed, cooked, distilled or homogenized in oil) (43).

The National Center for Complementary and Alternative Medicine (NCCAM) fact sheet warns consumers that one cannot assume that because an herbal supplement is 'natural' it is safe or without harmful effects. The NCCAM goes on to recommend that anyone using an herbal supplement should "do so under the guidance of a medical professional who has been properly trained in herbal medicine" (86). At the same time, physicians are

Table 3: Questions to ask before using an herbal remedy with warfarin.

1. Is the patient compliant, and have PT-INR been maintained at therapeutic levels during the past 3 months?
2. Have there been any incidents of serious bleeding in the past? Have these events occurred even when PT-INR levels were in the therapeutic range?
3. Is there evidence that the herb or herbal formula to be used has been shown to be of benefit for the desired indication?
4. What is the dosage of the herb or herbal formula to be used? Will this dosage be increased over time? How long will the herbal treatment last?
5. Are there any other herbal remedies being used as well (such as teas or creams)?

being encouraged to try and accept even those "therapies for which scientific support is anecdotal, equivocal or preliminary…We as a profession must address the challenge of discussing alternative therapies with our patients and put a end to the 'don't ask, don't tell' approach that characterizes communication in this area" (87).

The first step in preventing unwanted complications of drug-herb interactions is for the physician to initiate discussion and learn of current or planned use of herbal remedies. A list of questions (Table 3) may help evaluate the risk-benefit ratio of the combination, and more frequent testing for PT-INR and physical examinations for signs of platelet-related bleeding should help reduce complications once herbal treatment is initiated. Unfortunately, research in the field of herbal medicine is not considered 'economical' (88), and it is therefore helpful that organizations such as the NCCAM are funding such studies. These studies should examine both the clinical benefits and mechanisms of actions (such as effects on the hepatic cytochrome system) of herbal remedies, and should be conducted among all age groups. It is also of utmost importance to study the interaction between herbal and conventional therapies, especially for medications such as warfarin whose therapeutic window is so narrow. Patients should be allowed to benefit from the 'best of both worlds' without increasing the risk of iatrogenic complications, both 'chemical' and 'natural'.

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