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Warfarin and its interactions with foods, herbs and other dietary supplements

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Despite its complex pharmacokinetic and pharmacodynamic profile, warfarin is still one of the most widely used oral anticoagulant agents. Attaining optimal anticoagulation with this agent is clinically challenging in view of its many food and drug interactions. Inappropriate anticoagulation control can expose patients to an increased risk of bleeding or thromboembolic complications, due to over and underanticoagulation, respectively. Fluctuations in dietary vitamin K intake can have a significant effect on the degree of anticoagulation in patients treated with warfarin. In addition, the explosion in use of various dietary supplements and herbal products can lead to undesired outcomes on anticoagulant levels. The aim of this review is to discuss the scope and the potential clinical impact of the most commonly reported food, dietary supplement and herbal interactions with warfarin therapy. Practical steps for patients and providers to minimise these interactions are highlighted.

Keywords: anticoagulation, dietary supplement, drug interaction, food interaction, herb, vitamin, warfarin

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1. Introduction

Anticoagulation is the mainstay of therapy for the prevention of thromboembolic complications in patients with atrial fibrillation, prosthetic heart valves, venous thromboembolism and coronary artery disease. For long-term chronic management, oral anticoagulation is preferred over the intravenous or subcutaneous routes due to patient convenience and cost [1]. Warfarin has been in clinical use for over six decades and it is still one of the most widely used oral anticoagulant agents. The drug is a racemic mixture of *S*- and *R*-enantiomers, with the *S*-enantiomer being 2 – 5 times more active than the *R*-enantiomer. Warfarin exerts its effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K_1 epoxide). Vitamin K is an essential cofactor for the postribosomal synthesis of the vitamin K dependent clotting factors II, VII, IX and X, which require γ-carboxylation for their procoagulant activity, as do the anticoagulant proteins C and S, as well as protein Z. Treatment with warfarin results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced anticoagulant activity. The anticoagulant effect of warfarin can be reversed by the intake of vitamin K_1 (phytonadione) [1-3].

Warfarin is metabolised in the liver by the cytochrome P450 (CYP) system to inactive hydroxylated metabolites (major pathway) and by reductases to reduced metabolites (warfarin alcohols) with little anticoagulant activity. The CYP isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4. The 2C8/9 isozyme is primarily responsible for the metabolism of the *S*-enantiomer to 7-hydroxywarfarin and 6-hydroxywarfarin (major pathway), whereas the 3A4 isozyme is primarily responsible for the metabolism of the *R*-enantiomer to

10-hydroxywarfarin and 4′-hydroxywarfarin (minor pathway). Warfarin has a narrow therapeutic index. A patient's international normalised ratio (INR) should be monitored frequently to maintain values within the desired therapeutic INR range [1-3]. Dosing of warfarin is highly variable among patients and must be individualised. Average doses are around 5 mg/day, but may be as low as 0.5 mg/day in some patients, or up to 50 mg/day in others. Factors such as age, gender, ethnicity, indication for anticoagulation, vitamin K intake, body weight, albumin level and interacting medication(s) can all contribute to this variability [1,3]. More recently, single nucleotide polymorphisms in CYP 2C9 [4-5] and vitamin K epoxide reductase (VKOR) [6] have been shown to correlate with the dose of warfarin required for effective anticoagulation.

There are numerous mechanisms by which warfarin interacts with other medications. Absorption of warfarin may be inhibited by drugs that affect the bioavailability of warfarin, such as colestyramine or sucralfate. Due to its high protein binding, warfarin also interacts with medications that are highly protein-bound (e.g., salsalate, sulfasalazine). Displacement of either drug can occur and, although it is usually transient, may cause significant temporary increases in INR requiring dose reduction and close monitoring. Warfarin is inhibited by medications that induce cytochrome P450 liver enzymes (e.g., as rifampin, carbamazepine) and enhanced by medications that inhibit CYP liver enzymes (e.g., metronidazole, cimetidine). Because CYP 2C9 is the most important isoenzyme in the metabolism of *S*-warfarin, potent inhibitors or inducers of this enzyme result in significant effects on warfarin. Pharmacodynamic interactions may occur with medications that affect platelet function and aggregation, causing increased risk of bleeding (e.g., aspirin, clopidogrel, NSAIDs). Warfarin also interacts with many foods, vitamins, and herbal supplements via some of these same mechanisms [7].

Complementary and alternative medications (CAMs) are defined by the National Center for Complementary and Alternative Medicine as practices and products that are not currently considered to be part of conventional medicine. Examples include relaxation techniques, herbal medicines, energy healing, hypnosis and acupuncture. The 1994 Dietary Supplement Health and Education Act (DSHEA) allows herbal products to be marketed as dietary supplements in the US [8]. Manufacturers of herbal products can market these products without submitting safety or efficacy data to the FDA. Although these products can not claim to diagnose, cure, treat or prevent specific diseases, manufacturers are allowed to include statements about the effects of the supplement on the structure or function of the body or on the improvement in well-being that the product would produce. Statements regarding interactions with prescription and over-the-counter medications or adverse effects are not required to be included on the product label. This leaves the patient and healthcare professional with limited information to decide which products are safe and effective.

The use of CAMs in patients taking anticoagulants is more common than the healthcare provider may know. One study found that 17% of patients reported using herbal products, and that 70% reported that no practitioner in the clinic had discussed the use of herbal products with them [9]. Another study found that 26.9% of patients were taking some form of CAM [10]. Stys *et al.* conducted a study to evaluate the use of herbal and nutritional supplements in cardiovascular patients [11]. Of 187 patients enrolled, 106 (57%) used supplements. Vitamins were used by 94%, herbals were used by 37%, and naturoceuticals (fish oils, glucosamine, melatonin) were used by 51%. The most commonly used herbal supplements included garlic, gingko, psyllium and saw palmetto. Patients who use supplements generally believe that they can help with a wide range of diseases and that they are relatively safe [12]. Compounding this problem, another study found that 92.2% of the patients who admitted taking herbal medicines while receiving warfarin had not mentioned this use to a conventional healthcare provider [13].

Clinically significant drug interactions can occur when an interacting drug, food or herbal supplement is added during warfarin therapy, discontinued during warfarin treatment, or used intermittently during warfarin treatment. These situations represent significant risk for the development of interactions and need careful attention in order to avoid any adverse outcomes. Education of healthcare professionals and consumers as to the potential risks associated with the use of herbal and nutritional supplements in patients taking warfarin therapy should be a priority. The aim of this review is to discuss the scope and the potential clinical impact of the most commonly reported food, dietary supplement and herbal interactions with warfarin therapy.

2. Interactions of warfarin and dietary vitamin K

Vitamin K, a fat-soluble vitamin, serves as a cofactor for the production of clotting factors II, VII, IX, X, proteins C, S and Z. It has also been reported to aid in bone and cartilage metabolism [14,15]. The primary sources of vitamin K-containing foods are dark green vegetables and oils. Other sources of vitamin K, often overlooked, include processed foods and fast foods because of the oils used in production of these items [16]. There are three forms of vitamin K which include phylloquinone (vitamin K_1), menaquinone (vitamin K_2) and dihydrophylloquinone. Vitamin K_1 is the primary dietary source of vitamin K, whereas vitamin K_2 and dihydrophylloquinone do not contribute to dietary stores of vitamin K in the body [14,17]. The adequate intake of vitamin K as recommended by the National Academy of Science for woman and men is 90 and 120 µg/day, respectively. Older adults are more likely to eat vegetables than younger adults and, therefore, have higher vitamin K intake. It is estimated that intake of vitamin K among adults < 45 years of age is between 60 and 110 µg/day. Adults > 55 years of age have a vitamin K consumption ranging from 80 to 210 µg/day [18]. Foods rich in vitamin K,

Table 1. Weekly requirements of vegetables based on age and gender.

	Dark green vegetables	Orange vegetables	Dry beans and peas	Starchy vegetables	Other vegetables
Females 19 – 50 years old	3 cups	2 cups	3 cups	3 cups	6.5 cups
Females ≥ 51 years old	2 cups	1.5 cups	2.5 cups	2.5 cups	5.5 cups
Men 19 – 50 years old	3 cups	2 cups	3 cups	6 cups	7 cups
Men ≥ 51 years old	3 cups	2 cups	3 cups	3 cups	6.5 cups

Adapted from The USDA food pyramid, Center for Nutrition Policy and Promotion [204].

as well as unusual sources of vitamin K, will be discussed in detail below as potential sources of warfarin interactions.

In 2005, the United States Department of Agriculture (USDA) revised the food pyramid to make specific recommendations about each food group which consequently results in an increase in dietary vitamin K. The main sources of vitamin K are found in the vegetable group, specifically dark green vegetables, which are known to interact with warfarin. A decrease in INR is observed when consumption of vitamin K foods becomes in excess of a patient's usual intake. The revised food pyramid makes specific recommendations about the amount of dark green vegetables an individual requires based on age (Table 1). Also of significance is the category of 'other vegetables'. This group includes foods such as brussel sprouts and cabbage, which are high in vitamin K and can be overlooked by clinicians because they are not categorised under dark green vegetables. The recommended intake is in the range of 5 – 7 cups/week based on age and gender in this group.

As these dietary recommendations are implemented, patients taking warfarin may begin consuming more vitamin K than usual. In a study by Franco *et al*., changes in vitamin K intake played a major, independent role in INR fluctuations noted in patients taking vitamin K antagonists [19]. Two additional studies found that patients with unstable control of INR had poor and variable intake of vitamin K, and INR was reduced by 0.2 for every 100 µg of vitamin K consumed. The authors of both studies recommend daily supplementation of vitamin K to allow for better INR control [20,21]. To ensure a stable warfarin regimen, it is important to keep track of the quantity of rich vitamin K foods eaten on a weekly basis, thus, if a patient increases vitamin K intake, warfarin doses can be adjusted accordingly. Education should focus on keeping a consistent amount of vitamin K from week to week. Table 2 provides a list of various vegetables and their vitamin K content.

Many factors such as soil, climate and growing conditions can affect the amount of vitamin K in vegetables. Ferland and Sadowski performed high-performance liquid chromatography (HPLC) analyses on five different vitamin K-rich vegetables grown in two different regions, Montreal, Canada and Boston, MA. The vitamin K content of Montreal vegetables was significantly higher than vegetables grown in Boston. The amount of vitamin K also increased with maturation of the plant [22]. This information puts into perspective that the amount of vitamin K can vary among similar vegetables reported in various sources. It is important to point out that the clinical significance of this finding has not been studied.

Oils are not only a significant source of vitamin K, but may also increase the absorption of vitamin K in foods. Oils that are highest in vitamin K content include rapeseed (canola), soybean, and olive oil. Olive oil can have as much as 60 µg of vitamin K per 100 g [17]. It is not likely that 100 g of olive oil, equivalent to about 7 tablespoons, is eaten in a meal but rather the intake may occur over the course of the day or week. Because vitamin K is a fat-soluble vitamin, the bioavailability is maximised in meals containing > 35 g of fat [23]. For this reason, large consumption of these oils should be recognised as potential food interactions with warfarin. Table 3 lists the amount of vitamin K found in commonly used oils.

Like the dark green vegetables, many factors can also affect the vitamin K content found in oils such as heating and exposure to light. Heating oil for 20 minutes can result in a 7% loss of vitamin K content. Fluorescent light and sunlight exposure has also been reported to decrease vitamin K in canola oil by 46 and 87%, respectively, over the course of 2 days [22]. Storing oils in amber bottles resulted in minimal loss of vitamin K.

Oil in processed and fast foods is often an unnoticed source of vitamin K and is of concern when these foods are consumed in large quantities. The amount of vitamin K was determined in 109 fast foods and 23 snack foods. One chicken sandwich was reported to contain almost 24 µg of vitamin K per 100 g. Hamburgers also contained about 23 µg of vitamin K per 100 g. Although potatoes are not high in vitamin K, french fries can have as much as 17 µg in 100 g, depending on the type of oil used in cooking. Processed foods such as cheeto-type chips and potato chips can have as much as 41 µg and 24 µg of vitamin K in 100 g, respectively [16]. Again, these amounts are not large, but when consumed in great quantities, can potentially decrease INR. Table 4 gives a list of various processed and fast foods and their vitamin K content.

Table 2. Vitamin K content of selected vegetables.

Description	Common measure	Vitamin K (μg) per measure
Asparagus, frozen, cooked	1 cup	144
Beans, green, cooked	1 cup	20
Beet greens, cooked	1 cup	697
Broccoli, cooked	1 cup	220
Brussels sprouts, cooked	1 cup	219
Cabbage, cooked	1 cup	73
Collards, cooked	1 cup	836
Collards, frozen, cooked	1 cup	1060
Cucumber with peel	1 large	49
Dandelion greens, cooked	1 cup	203
Endive, raw	1 cup	116
Kale, cooked	1 cup	1062
Kale, frozen, cooked	1 cup	1147
Lettuce, butterhead	2 medium leaves	15
Lettuce, iceberg	1 cup	13.3
Mustard greens, cooked	1 cup	419
Okra, frozen, cooked	1 cup	88
Onions, spring or scallions	1 cup	207
Parsley, raw	10 sprigs	164
Peas, green, frozen, cooked	1 cup	38
Rhubarb, frozen	1 cup	71
Soybeans, cooked	1 cup	33
Spinach, canned	1 cup	988
Spinach, raw	1 cup	145
Turnip greens, cooked	1 cup	529
Turnip greens, frozen, cooked	1 cup	851

Adapted from US Department of Agriculture, Agricultural Research Service, 2004. National Nutrient Database for Standard Reference, Release 17. Vitamin K content (μg) of selected foods per common measure [205]. Note: Content of vitamin K is representative of the samples studies, variations can occur among the same vegetables depending on soil, climate and maturation of the plant.

Olestra, a fat substitute available in many snack foods in the US, can decrease the absorption of fat-soluble vitamins, including vitamin K. To prevent depletion of vitamin K in the body, manufacturers have supplemented olestra with 3.3 μg of vitamin K per 1 g of olestra [201]. A study of 40 patients evaluating the effects of olestra on INR compared with placebo over a 2-week period did not find a significant difference in INR fluctuations [24]. The sample size as well as the length of the trial are considerable limitations in this case, but the results bring to light the need for additional studies to report actual amounts of vitamin K absorbed from olestra containing products.

Fruits are not a significant source of vitamin K, but two case reports of avocado (8 μg of vitamin K/100 g) consumption altering the INR exist. A decrease in INR was observed when 100 g of avocado were consumed daily and when 400 g were consumed over 2 days in two patients with previously stable INR [25]. One proposed mechanism is that avocado induces liver enzymes and, therefore, individuals require larger doses of warfarin [26]. The authors also hypothesised that avocado may decrease absorption of warfarin from the gut much like colestyramine does. It is important to note that one avocado has

Table 3. Vitamin K content in commonly used oils.

Type of oil	Vitamin K (μg/100g)*
Peanut	0.65
Corn	2.91
Safflower	9.13
Walnut	15
Sesame	15.5
Olive	55.5
Canola	141
Soybean	193

Adapted from reference [14].
*100 g of oil is equivalent to ~ 7 tablespoons.

Table 4. Average vitamin K content found in fast foods and various processed foods oils.

Food	Vitamin K (μg/100g)
Hamburger with cheese (2 – 4 oz)	6.0
Hamburger with sauce (> 4 oz)	19.3
Chicken sandwich	15.1
Fish sandwich	13.7
French fries	11.2
Taco with beef	16.0
Cheeto-type chips	36.1
Potato chips	22.0
Olestra potato chips	347
Tortilla chips	20.9
Olestra tortilla chips	180

Adapted from reference [16].

Table 5. Nutritional supplements and vitamin K content per 8 oz.

Product	Vitamin K (μg)
Advera	24
Boost	30
Carnation Instant Breakfast	20
Ensure	25
Glucerna	14
Glucerna shake	20
Isocal	31
Jevity 1 cal	15
Nepro	20
Osmolite 1 cal	15
Slim Fast shake	20

Table 6. Vitamin K content in energy bars and supplemental bars.

Product	Weight (g)	Vitamin K content (μg)
Balance bar	50	20
Clif bar	68	20
Glucerna Meal bar	58	28
Luna bar	48	8
MetRx bar	85	0
Pria bar	28	12
Pria Complete Nutrition bar	45	12
Power Bar	65	0
Slim Fast Breakfast bar	44	20
Slim Fast Meal Options bar	56	20

~ 30 g of fat which can increase the bioavailability of vitamin K when other foods are eaten concomitantly.

Nutritional supplements can also contain considerable amounts of vitamin K [14]. Supplements are given when nutritional status is compromised, but are often substituted for missed meals or when dietary intake is inadequate. Although an 8 oz can of Ensure contains 25 μg of vitamin K, well under the recommended intake, it is an extra source of vitamin K and can decrease INR if a significant amount is consumed. It is important to specifically ask patients on warfarin if they drink any supplements throughout the week. Education should focus on keeping the supplement intake consistent throughout the week. If a patient's nutritional status is not compromised, avoiding these supplements is preferred. Table 5 gives a list of various nutritional supplements and their vitamin K content. Energy bars and shakes can also be added sources of vitamin K in a diet. Many of these energy bars or shakes often replace meals or are consumed as snacks in between meals. They can be potential causes for INR fluctuations in an otherwise stable patient. Again, consistency in intake of these products should be the focus when educating patients on warfarin. Table 6 lists popular diet and energy bars and their respective vitamin K contents.

High protein diets such as Atkins or South Beach diet have been reported to decrease INR. Two case reports of patients with stable INR required higher warfarin doses when starting these diets [27]. The mechanism is thought to be that high protein diets contribute to increased albumin stores resulting in added warfarin binding and ultimately increased warfarin dose requirements. Greater quantities of fat are also consumed on the Atkins diet, which can enhance the absorption of vitamin K. Because high protein diets limit carbohydrates, more vegetables are consumed, resulting in an increase in vitamin K intake and ultimately alter warfarin dose requirements.

Ethnic foods can also be considerable sources of vitamin K. Sushi has been reported in the literature to decrease INR because of its seaweed content. A patient on a stable warfarin dose had a drop in INR after consuming 12 pieces of sushi in 1 day and an unknown amount a few days later [28]. The type of seaweed used in sushi is known as asakusa-nori. The same authors measured the vitamin K content of the asakusa-nori consumed as well as another brand and found 18.8 μg/100 g and 11.4 μg/100 g, respectively. They estimated the patient had about 45 μg of vitamin K from 12 pieces of sushi. The vitamin K content of many ethnic foods are unknown, but generally, the greener the vegetable the more likely it is a rich source of vitamin K. Table 7 gives a list of unusual foods and their vitamin K content.

An overlooked source of vitamin K is chewing tobacco. One gram of tobacco can have up to 50 μg of vitamin K. One case report describes an increase in INR in a stable patient when smokeless tobacco was discontinued [29]. The mechanism of action is thought to be due to the lipid soluble nature of vitamin K and the potential for accumulation in the body over several years of tobacco use leading to warfarin resistance. A can of tobacco contains 34 g of product, making it a large source of vitamin K if a patient uses a substantial amount of smokeless tobacco.

Liver has long been a debatable source of vitamin K. As most production of clotting factors occurs in the liver, it is assumed that animal liver would contain sizeable amounts of vitamin K and in the past has been reported to have a high amount. This was because of the use of chick bioassays which were based on clotting times and offered better qualitative analysis rather than quantitative [18]. Currently, the use of HPLC provides a more accurate analysis of vitamin K content in foods than in the past. With the new HPLC analysis, liver has been reported to contain ~ 5 μg of vitamin K per 100 g, making it a less likely source for interaction with warfarin.

Table 7. Ethnic and other foods and vitamin K content.

Food	Common measure	Vitamin K (µg)
Algae – purple laver	3.5 oz	1385
Algae – Konbu	100 g	66
Algae – Hijiki	100 g	327
Asatsuki, leaf	100 g	190
Ashitaba, leaf	100 g	590
Bok – Choy	1 cup	58
Komatsuna	100 g	280
Noodles, spinach enriched	1 cup	162
Pistachio	3.5 oz	70

Adapted from reference 14 and from US Department of Agriculture, Agricultural Research Service. 2004. National Nutrient Database for Standard Reference, Release 17. Vitamin K content (µg) of selected foods per common measure [205].

When a patient begins warfarin therapy, baseline education should include information on vitamin K-rich sources. A chart or booklet identifying foods high in vitamin K can be a helpful reference for the patient. Asking a patient to recall what types of foods or nutritional supplements they have eaten may help uncover foods high in vitamin K. Guidelines about consumption of vitamin K foods should be offered, educating the patient on importance of a consistent intake of vitamin K foods. Counselling patients on avoidance of vitamin K foods is not recommended as this may prevent intake of other essential vitamins and minerals found in dark green vegetables, rather, if patients have a difficult time remembering how many servings of vitamin K foods were eaten, keeping a food diary may be useful. To increase compliance with keeping a consistent amount of vitamin K consumption throughout the week, select 2 or 3 days that allow the patient to eat 1 – 2 servings of vitamin K-containing foods. Reinforcing baseline education, as well as offering information on risks involved with INR fluctuations at subsequent visits, increases adherence to a consistent and stable vitamin K diet allowing for improved maintenance of therapeutic anticoagulation in patients taking warfarin [15,19].

3. Interactions of warfarin and other dietary supplements, herbs and vitamins

3.1 Interactions that have an effect on INR

Limited information about the pharmacokinetics, pharmacodynamics and true ingredients in various herbal and dietary supplements lead to sometimes theoretical 'speculation' as the bases for many of the interactions with warfarin. Case reports and small cohort studies, make up the bulk of the data regarding the nature of the interactions between warfarin and various supplements. In addition to vitamin K-based mechanisms, there are many other possible mechanisms by which dietary supplements and herbs can interact with warfarin.

Box 1. Dietary supplements that may decrease the absorption of warfarin.

- Agar
- Algin
- Aloe
- Barley
- Blond psyllium
- Butternut
- Carrageenan
- Cascara
- Castor
- Coffee Charcoal
- European Buckthorn
- Iceland Moss
- Glucomannan
- Jalap
- Karaya Gum
- Larch Arabinogalactan
- Marshmallow
- Mexican Scammony Root
- Quince
- Rhubarb
- Rice Bran
- Slippery Elm
- Tragacanth

Adapted from [75].

Theoretically, the anticoagulant effect of warfarin can be reduced by a decrease in its absorption. Supplements and herbal medications that may decrease absorption of warfarin are listed in Box 1. However, no case reports of this mechanism have been reported to date in the literature [7].

Enzyme inhibition or induction is another potential mechanism leading to many of warfarin's drug interactions (Table 8). Inhibition of the enzymes that metabolise warfarin into inactive metabolites can lead to decreased clearance of warfarin and potentiation of its anticoagulant effect. In contrast, induction of the enzymes that metabolise warfarin can lead to an increased clearance and a decrease in anticoagulant effect [1,7].

3.1.1 Alcohol

Alcohol inhibits the metabolism of warfarin when consumed excessively and acutely thereby potentiating its anticoagulant effect [30]. However, chronic consumption results in CYP enzyme induction and a decreased INR. Alcohol is metabolised through CYP 2E1, and less so by 3A4 and 1A2. With minor consumption, CYP 2E1 is not a predominant route, but increases almost 10-fold with heavy consumption [31]. Alcohol has also been shown to alter the degree of protein binding thereby increasing the free concentration of warfarin. One study estimated that the increase in the free concentration of warfarin could range from 3 to 34% [32]. Any

Table 8. Warfarin–dietary supplements interactions involving cytochrome P450 metabolism.

Dietary supplement	Mechanism
Bergamottin (component of grapefruit juice)	2C9 inhibitor
Bishop's weed (Bergapten)	3A4 inhibitor
Bitter Orange	3A4 inhibitor
Cat's Claw	3A4 inhibitor
Chrysin	1A2 inhibitor
Cranberry	2C9 inhibitor
Devil's Claw	2C9 inhibitor
dehydroepiandrosterone	3A4 inhibitor
Diindolymethane	1A2 inducer
Echinacea	3A4 inhibitor
Eucalyptus	3A4, 2C9, 2C19, 1A2 inhibitor
Feverfew	1A2, 2C9, 2C19, 3A4 inhibitor
Fo-Ti	1A2, 2C9, 2C19, 3A4 inhibitor
Garlic	2C9, 2C19, 3A4 inhibitor
Ginseng	CYP P450 inducer
Goldenseal	3A4 inhibitor
Guggul	3A4 inducer
Grape	1A2 inducer
Grapefruit juice	1A2, 2A6, 3A4 inhibitor
Indole-3-carbinol	1A2 inducer
Ipriflavone	2C9, 1A2 inhibitor
Kava	1A2, 2C9, 2C19, 2D6, 3A4 inhibitor
Licorice	3A4 inhibitor
Lime	3A4 inhibitor
Limonene	2C9, 2C19 substrate and 2C9 inducer
Lycium (Chinese wolfberry)	2C9 inhibitor
Milk Thistle	2C9, 3A4 inhibitor
Peppermint	1A2, 2C9, 2C19, 3A4 inhibitor
Red Clover	1A2, 2C9, 2C19, 3A4 inhibitor
Resveratrol	1A, 2E1 3A4 inhibitor
St. John's wort	1A2, 2C9, 3A4 inducer
Sulforaphane	1A2 inhibitor
Valerian	3A4 inhibitor
Wild Cherry	3A4 inhibitor

amount of alcohol increases the risk of haemorrhagic stroke and fall which could result in a major bleeding event. Even a low amount of alcohol, half a can of beer every other day was reported to increase the INR to 8.0 in a 58-year-old man on long-term anticoagulation with warfarin [33]. Patients should be counselled to limit their alcohol consumption to < 2 alcoholic beverages per day, if at all, to minimise this potential for an increase in INR. Habitual, chronic drinkers should be encouraged to moderate their drinking and also to maintain a regular pattern of drinking to allow for avoidance of fluctuations in INR. Ideally, the goal should be avoidance of large amounts of alcohol on a chronic basis in order to avoid the associated problems, such as higher warfarin dose requirements, noncompliance with medications, poor food intake, falls, loss of consciousness and a high risk of bleeding.

3.1.2 Bishop's Weed

Bishop's Weed, also known as *Ammi majus*, is used orally for digestive disorders, asthma, angina, kidney stones and as a diuretic. This product is known to contain several coumarin derivatives, including psoralen, bergapten, xanthotoxin, isopimpinellin, imperatorin and their precursor umbelliferone [34]. One of the constituents, bergapten, also has antiplatelet effects. Theoretically, Bishop's Weed might inhibit elimination and increase blood levels of drugs metabolised by CYP 3A4 isoenzymes [35]. The bergapten constituent of Bishop's Weed is the same constituent as in bitter orange, which inhibits CYP 3A4. There are no published human case reports of an interaction with warfarin, and caution with using this product in combination with warfarin is warranted.

3.1.3 Grapefruit juice

Grapefruit juice is a well-known inhibitor of CYP liver enzymes, primarily 3A4, 1A2 and 2A6 [36]. There are two proposed theories for an interaction with grapefruit juice and warfarin. The first is that accumulation of the *R*-enantiomer of warfarin via inhibition of its metabolism (3A4) could result in a clinically significant increase in INR [37]. This theory involves the flavanoid component of grapefruit juice, naringenin, which exerts an inhibitory effect on CYP 3A4. A second theory involves another ingredient, bergamottin (furocoumarine) which inhibits CYP 2C9 (the primary isozyme responsible for the metabolism of the *S*-enantiomer) [36].

However, there is evidence that only the CYP enzymes in the gastrointestinal wall are inhibited by grapefruit juice [38,39]. In which case, only drugs with high first pass metabolism would be affected. Warfarin does not undergo first pass metabolism, so its metabolism is not likely to be inhibited by this mechanism. Additionally, a study of 10 men found no significant changes in prothrombin time (PT) or INR with ingestion of 1.5 litres (50 oz) of frozen grapefruit juice from concentrate per day for 8 days [36]. These authors comment that it is unknown whether or not grapefruit juice prepared from fresh fruit would have had a different effect than their prepared frozen grapefruit juice, because it is unclear if the flavonoids in grapefruit juice are stable when frozen. One case of a man who began to drink 50 oz of grapefruit juice per day attributes a greater than twofold increase in INR to grapefruit juice [37], but smaller quantities do not appear to create a problem. Although there is little evidence of an interaction between

grapefruit juice and warfarin, the magnitude of a possible interaction warrants caution in patients taking warfarin.

3.1.4 Cranberry juice

There are three published case reports describing a potential cranberry juice/warfarin drug interaction [40-42]. The first case involved a male patient in his seventies who suffered a fatal gastrointestinal and pericardial haemorrhage after presenting to the hospital with an INR > 50 [40]. The patient had been drinking cranberry juice for six weeks preceding the incident, developed a chest infection for which he received cephalexin, and had a severely reduced appetite of primarily cranberry juice. A second report consisted of a 69-year-old male patient taking warfarin for atrial fibrillation and prosthetic mitral valve replacement [41]. He was admitted preoperatively for warfarin discontinuation prior to an elective bladder surgery, with an unexpectedly elevated admit INR of 12 which required held warfarin doses and vitamin K administration. Warfarin was reinitiated postoperatively several days later and resulted in an INR of 11 followed by episodes of frank haematuria into his catheter and bleeding from the anastomosis site. It was discovered that the patient had been drinking 2 l/day of cranberry juice for 2 weeks prior to surgery to prevent recurrent urinary tract infections. Three days after ceasing intake of cranberry juice, his INR stabilised at 3, and the patient fully recovered. A third case report describes an elderly male with hypertension and atrial fibrillation who had fluctuations in INR (between 1 and 10) suspected to be a result of cranberry juice intake [42].

Including the cases aforementioned, at least 12 occurrences of an interaction between cranberry juice and warfarin have been reported [202]. The UK's Committee on Safety of Medicines (CSM) states that they have received a total of 12 reports as of October 2004. The CSM briefly describes that eight cases involved an increase in INR with or without bleeding, three cases were characterised by an unstable INR, and the INR decreased in one case. Based on their review of the cases, CSM has advised that patients taking warfarin should avoid consumption of cranberry juice and cranberry capsules/concentrates if possible. If the patient has a medical necessity for cranberry juice, they should be closely monitored during concurrent use.

Several mechanisms of the interaction between cranberry juice and warfarin have been postulated. One potential mechanism involves salicylic acid, a common constituent of cranberries, and an antiplatelet effect that can increase bleeding risk [43]. A possible explanation for the INR increase may stem from the increased concentration of salicylic acid, which is highly protein bound, causing a displacement of warfarin from albumin binding sites. Salicylic acid is 50 – 80% bound to plasma proteins, and salicylate exhibits high protein binding (90%) at low/therapeutic serum concentrations, whereas toxic levels are associated with a lower percentage of protein binding (76%) and higher free levels [44]. Therefore, the salicylic acid content in cranberry juice leads to low serum levels of salicylic acid and a high percentage of protein binding. Another possible explanation for the increase in INR seen in warfarin patients who drink cranberry juice involves the presence of flavonoids in cranberry extract, causing an effect on the CYP system, similar to those mentioned with grapefruit juice. However, a recent randomised five-way crossover study of healthy volunteers given single doses of flurbiprofen (as a surrogate index of CYP 2C9 activity) after receiving 8 oz of cranberry juice failed to show a significant reduction in flurbiprofen clearance or elimination half-life, suggesting that a pharmacokinetic interaction with warfarin was unlikely [45]. Although the exact mechanism for a cranberry–warfarin interaction is not well understood, these case reports substantiate the likelihood that a clinically significant interaction can occur when patients taking warfarin drink large amounts of cranberry juice for prolonged periods of time. Therefore, patients receiving anticoagulation therapy with warfarin should be informed to reduce or eliminate concomitant ingestion of cranberry juice until more data become available.

3.1.5 Chinese wolfberry

Lycium barbarum L., (family *Solanaceae*) also known as Chinese wolfberry, is a common Chinese herb. There is one case report of an increased INR in a patient stabilised on warfarin whose INR increased to 4.1 after drinking a concentrated Chinese herbal tea containing *Lycium barbarum* L. fruits (3 – 4 glasses daily) [46]. One dose of warfarin was held and the tea was discontinued with subsequent return of INR control. Lycium was found to have only weak inhibition of *S*-warfarin metabolism by CYP 2C9, suggesting that other factors beyond the CYP system may be responsible for the interaction, such as an anticoagulant effect of the herb itself.

3.1.6 Curbicin (containing saw palmetto, pumpkin and vitamin E)

There is a report of two cases of an increased INR associated with the use of curbicin [47]. The first involved an elderly patient taking curbicin three tablets daily for a year who was admitted to the hospital after feeling badly from a cold with an INR of 2.1 despite a normal albumin and no anticoagulation treatment. His INR improved to 1.3 while he was being treated with vitamin K, but did not normalise until curbicin was discontinued 1 week later. The second involved a patient on warfarin and simvastatin with INRs stable around 2.4. He started taking curbicin five tablets daily for micturition difficulties. After 6 days of treatment, his INR increased to 3.4. Curbicin was discontinued and the INR returned to previous levels 1 week later. The authors believed the effects on the INR were related to the vitamin E component, which was 30 – 50 mg/day, a dose used for treating vitamin E deficiency.

3.1.7 Vitamin E

Vitamin E may inhibit the oxidation of reduced vitamin K. There is conflicting information about the effects of

vitamin E on the INR. A case report of a 55-year-old man taking warfarin and 1200 units/day of vitamin E states he developed bruising and haematuria and had an increased INR. After having stable clinical and haematological status and no vitamin E, he was rechallenged two months later with 800 units/day, with more bruising occurring. His PT began to increase at four weeks and continued to increase over the next two weeks. His PT returned to previous values within a week after the patient stopped the vitamin E [48]. One small study in 12 patients suggested that doses of 400 international units/day were not enough to increase the INR [49]. Another small, randomised, placebo-controlled, double-blind protocol did not find that high doses of 800 IU or 1200 IU/day for 1 month caused any significant effects on the INR [50]. The ADMIT trial (Arterial Disease Multiple Intervention Trial) showed that antioxidant therapy (consisting of 800 units vitamin E plus 1000 mg vitamin C and 25 mg β-carotene) had a significant reduction of von Willebrand factor (202 ± 52% in the placebo group versus 194 ± 69% in the antioxidant group, mean ± SD, $p = 0.04$), but not on fibrinogen, prothrombin fragment 1.2, plasminogen activator inhibitor-1, or Factor VII clotting activity [51]. Until more data is available, patients should be advised to avoid high doses of vitamin K, greater than 400 – 800 units/day, to minimise the potential effect on the INR.

3.1.8 Garlic

Orally, garlic *(Allium sativum*) is used for many reasons, some of which include hypertension, hyperlipidaemia, preventing coronary heart disease, preventing age-related vascular changes and atherosclerosis. The applicable part of garlic is the bulb. *In vitro* evidence suggests that garlic might inhibit several CYP enzymes including CYP 2C9, CYP 2C19 and CYP 3A4 [52]. However, researchers suspect that garlic supplements containing allicin induce the CYP 3A4 isoenzyme and can produce clinically significant decreases in levels of drugs metabolised by this enzyme [53]. Garlic's effect on platelet function is well known, and can possibly increase the risk of bleeding. Consumption of dietary garlic has caused platelet dysfunction, prolonged bleeding time, postoperative bleeding, and spinal epidural haematoma in patients not taking anticoagulants [54,55]. Two anecdotal cases were briefly described in which the INR approximately doubled in patients stabilised on warfarin when they took garlic products. The strength, duration of exposure, INR values and outcomes were not reported [56]. In contrast, a recent randomised, double-blind trial in 48 patients comparing aged garlic extract 5 ml given twice daily for 12 weeks with placebo, showed no evidence of increased haemorrhage in either group and concluded that aged garlic extract may be safely used in patients on warfarin therapy [57]. Although the evidence supporting an increased INR in warfarin patients taking garlic is weak, the larger concern appears to be its effect on platelet function.

3.1.9 Ginger

Ginger (*Zingiber officinale*) is reported to have antiplatelet effects. There is a single case report of a 76-year-old woman on warfarin for atrial fibrillation who presented with haematuria and gingival bleeding and an INR of 7.0 [58]. She was found to be eating pieces of ginger root and drinking tea made from ginger powder as a natural remedy for an upset stomach. She required i.v. vitamin K for reversal of her INR. The authors suggested that the mechanism behind the increase in INR was due to an interaction between ginger and warfarin involving either intestinal or hepatic CYP system. This mechanism has not been described elsewhere.

3.1.10 Ginkgo

Ginkgo biloba (ginkgo) is one of the most common herbal supplements touted for its memory-enhancing and cognition-improving effects. There have been several case reports suggesting that spontaneous bleeding may occur during ginkgo use that may be related to its adverse effects on platelets. Two cases of subdural haematoma and one case of subarachnoid haemorrhage were reported in three patients taking ginkgo without concomitant warfarin or antiplatelet therapy [59-61]. Another report discusses the development of hyphema in a 70-year-old man taking ginkgo plus aspirin 325 mg/day [62]. One additional case reports that a 78-year-old woman stabilised on warfarin developed intracerebral haemorrhage 2 months after starting ginkgo [63].

In addition to its antiplatelet effects, it has been suggested that ginkgo has effects on the CYP system in animals [64,65]. However, a randomised double-blind placebo-controlled crossover clinical trial in 24 out-patients on stable, long-term warfarin treatment showed no increase in INR from ginkgo or coenzyme Q10 [66]. Moreover, a recent publication of two open-label, crossover pharmacokinetic studies of healthy adults using tolbutamide and diclofenac as probes for CYP 2C9 substrates showed *in vitro* inhibition of CYP 2C9, but no interaction between gingkgo biloba extract and CYP 2C9 probe substrates *in vivo* [67]. Additionally, a randomised, double-blind, two-way crossover trial of healthy volunteers given a standardised gingkgo biloba leaf preparation or matching placebo in patients who also received single doses of flurbiprofen, a probe substrate for CYP 2C9, showed no effect of ginkgo on the kinetics or dynamics of warfarin [68]. Although it does not appear that there is a pharmacokinetic interaction involving the cytochrome P450 enzyme system, the possibility of increased risk of bleeding due to antiplatelet effects is still of concern and it should be advised that patients on warfarin avoid concomitant use of ginkgo.

3.1.11 Mango

Mango (*Mangifera indica*) has been associated with an increased INR in 13 patients, with a rechallenge in 2 patients showing similar results [69]. Patients were consuming 1 – 6 mangos per day for 2 days to 1 month before the INR was tested. INR values decreased in all 13 patients after

discontinuing mango ingestion. The mechanism for this interaction has been theorised to be related to the high amount of vitamin A in mangos. Human studies have shown that vitamin A (retinol) inhibits CYP 2C19 enzymes [70]. Until further clinical trials are completed, it is prudent to advise warfarin patients to limit their intake of mangos, or alternatively, keep a consistent weekly intake, to minimise INR fluctuations.

3.1.12 Ethylenediamine tetraccetic acid

Chelation therapy has been used for treating patients after heavy metal poisonings. The active constituents ethylenediamine tetraccetic acid (EDTA) and dimercaptopropane sulfonate bind and remove minerals and metals from the body, such as arsenic, copper, lead, nickel and mercury. There is one case report of chelation therapy causing a drop in the INR of a patient from 2.6 to 1.6 one day after receiving the treatment [71]. The mechanism of this interaction is unclear. One would expect the INR to increase because EDTA inhibits coagulation by binding to calcium ions that are required for normal blood coagulation, and there are reports of prolonged PTs [72]. One possible explanation suggested by the authors, was that high dose (7 g) of vitamin C in the chelation therapy may have contributed to the decrease in INR. The issue of whether or not vitamin C interacts with warfarin is controversial. Oral administration of vitamin C is thought to decrease warfarin absorption. In this case, however, the vitamin C was given intravenously and, therefore, would not likely be the explanation. Reduction of warfarin absorption by high vitamin C content is the theoretical mechanism for which acerola and Cherokee Rosehip are thought to reduce the INR, although there are no human case reports for either of these products [203].

3.1.13 Ginseng

Ginseng is a generic term for three separate ginseng species: American ginseng (*Panax quinquefolius*), Oriental ginseng (*Panax ginseng*) and Siberian ginseng (*Eleutherococcus senticosus*). Ginseng may promote bleeding in surgical patients [73]. Ginsenosides prolong both thrombin time and activated partial PT in rats [74] and inhibited platelet aggregation *in vitro* in human platelets [75,76]. Ginsenosides are considered the major pharmacologically active constituents, and ~ 12 have been identified. One of these types, ginsenoside Rd produced weak inhibitory activity against the surrogate substrates for CYP 3A4 and CYP 2D6 and even weaker inhibitory activity against the surrogate substrates for CYP 2C19 and CYP 2C9, whereas ginsenoside Re and Rf increased the activity of CYP 2C9 and CYP 3A4 [77].

One case has been reported of a decreased effect of warfarin in a patient receiving Oriental ginseng (Ginsana). The patient was on warfarin for a mechanical heart valve with INR stabilised at 3.0 – 4.0. The INR fell to 1.5 within 2 weeks after starting ginseng. The INR returned to 3.3 two weeks after stopping the ginseng [78]. One study did not find any effects of ginseng on the pharmacokinetics or pharmacodynamics of warfarin [79]. More recently, however, a randomised, double-blind, placebo-controlled trial in 20 healthy volunteers showed peak INR decreased significantly after 2 weeks of ginseng administration compared with placebo (-0.19 [95% CI: -0.36 to -0.07]; p = 0.0012). The INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC were also statistically significantly reduced in the ginseng group as compared with the placebo group. Peak INR and peak plasma warfarin level were positively correlated [80]. These authors suggest that greater than one week is required to induce hepatic enzyme activities. The effect of ginseng on CYP isoenzymes in humans needs further study. It has been recommended by some to either refrain from taking ginseng with warfarin or regularly monitor the INR in patients taking concomitant warfarin [81].

3.1.14 St. John's wort

Concomitant use of St. John's wort and warfarin may decrease the therapeutic effects of warfarin by decreasing the INR. St. John's wort induces CYP 2C9 and 1A2, but to a lesser extent than CYP 3A4 [82]. In healthy volunteers, St. John's wort increases the clearance of both *S*- and *R*-warfarin. This suggests it might induce CYP 1A2 and CYP 3A4, which metabolise *R*-warfarin and CYP 2C9, which metabolises *S*-warfarin [79]. In addition, warfarin physically interacts with hypericin and pseudohypericin, active constituents of St. John's wort. When the dried extract is mixed with warfarin in an aqueous medium, up to 30% of warfarin is bound to particles, reducing its absorption [83]. Taking warfarin at the same time as St. John's wort might reduce its bioavailability. There have been numerous case reports of this interaction, all of which resulted in unstable INR, with a decrease in INR being the most commonly observed effect [82]. Stopping the St. John's wort would be preferred, or if that is not possible due to patient preference, then careful monitoring of the INR is suggested.

3.1.15 Green tea

Conflicting reports exist about the amount of vitamin K in green tea. It has been reported that green tea contains high amounts of vitamin K [84]. It is true that the dried leaf of *Camellia sinansis*, the plant from which green tea is derived, is rich in vitamin K, reported to contain as much as 1428 µg/100 g of leaves. However, brewed tea only contains about 0.03 µg of vitamin K per 100 g of brewed tea, or 7 µg/cup [85].

Although the antagonism of warfarin by green tea has been associated with the vitamin K content, green tea has also been reported to have an antiplatelet effect which would augment the effects of warfarin [203]. The compounds catechin and caffeine, found in green tea, may inhibit the release of arachidonic acid from platelets, thereby inhibiting thromboxane production and clot formation.

One case report of a significant drop in INR occurred in a 44-year-old man on warfarin for stroke prevention from a

St. Jude's mechanical heart valve in the aortic position [86]. His first INR after transferring his care to another clinic 14 months after starting warfarin was 3.7. His goal INR was 2.5 – 3.5. At that time he was counseled to keep vitamin K consistent in his diet, and no dose change was made, continuing at 7.5 mg daily. His next INR 22 days later was 1.37. He could not be reached for follow-up, and presented the next month with an INR of 1.14. Upon questioning it was discovered that he had begun drinking 0.5 – 1 gallon of green tea each day about 1 week prior to the first low INR. No other cause for the decreased INR could be found and he was instructed to continue his usual dose of warfarin, discontinue the green tea and return for an INR check in 1 week. This result was 2.55 and remained therapeutic with no adverse sequelae.

In lieu of the rarity of reports and the massive quantity of green tea that appears to be necessary to cause an effect on anticoagulation, patients who drink moderate amounts of green tea are not at an increased risk for thrombosis and need not be counselled to avoid it.

In addition to the interactions discussed above, several other dietary substances, such as glucosamine-chondroitin, papaya, coenzyme Q10 and soy, have been reported to interfere with warfarin and affect the INR by mechanisms that are not yet fully elucidated.

3.1.16 *Glucosamine and chondroitin*

There is concern that high-dose chondroitin sulfate (2400 mg/day) combined with high-dose glucosamine (3000 mg/day) may enhance the effects of warfarin. There is one case report of a warfarin patient taking six capsules daily of Cosamin DS, each containing 500 mg glucosamine hydrochloride and 400 mg sodium chondroitin sulfate, and manganese ascorbate [87]. The patient's INR before starting Cosamin DS was 2.58, whereas the INR four weeks after the start of the product was 4.52. The patient required a dose reduction of his warfarin from 47.5 mg/week to 40 to get a therapeutic INR 2 weeks later. There is no known reason to expect a pharmacokinetic interaction in this case. However, because glucosamine is a chemical component of heparin [88], and chondroitin is a minor component of danaparoid [89], it has been postulated that high-dose glucosamine and chondroitin may have an additive pharmacodynamic effect on coagulation [90]. Until further evidence supports or refutes this potential drug interaction, it is prudent to closely monitor the INR in patients on this combination.

3.1.17 *Papaya*

Papain is a mixture of enzymes found in the extract of papaya, the fruit of the papaya tree (*Carica papaya*). There is one case report of an interaction between warfarin and papaya in a patient using papaya extract containing papain as a weight-loss aid. The patient was admitted for cardiac surgery with an INR of 7.4, which decreased to 2.0 after withdrawal of both warfarin and the papaya extract [91]. Although the data supporting an interaction between warfarin and papaya is weak, it has been suggested that use of papaya is contraindicated in patients taking warfarin because it may cause gastrointestinal mucous membrane damage and bleeding [92]. It may also increase the INR, but this effect has only been reported in a single case with papaya extract, not with the fruit [91-93].

3.1.18 *Coenzyme Q10*

Coenzyme Q10 is used for a variety of disorders. Also known as ubiquinone, or ubidecarenone, coenzyme Q10 is chemically similar to menaquinone and may have vitamin K-like procoagulant effects. Concomitant use of coenzyme Q10 might reduce the anticoagulation effects of warfarin. Four cases of decreased warfarin efficacy thought to be due to coenzyme Q10 have been reported [94,95]. In each case, the INR fell below range and then returned to therapeutic range after coenzyme Q10 was discontinued. However, there is some preliminary clinical research that suggests coenzyme Q10 might not significantly decrease the effects of warfarin in patients that have a stable INR [66,96]. Close monitoring of patients taking warfarin and coenzyme Q10 is indicated as dose adjustment of warfarin may be necessary.

3.1.19 *Soy*

Soy protein is derived from soybeans containing the isoflavones genistein and daidzein, which are thought to have pharmacological activity to prevent cardiovascular disease [97]. One case report in a 70-year-old white man on warfarin for atrial fibrillation for 7 months noted a decreased INR after drinking 480 ml (two 8 oz glasses) per day of soy milk [98]. His INR 10 days prior to starting the soy was 2.5 and 5 days after starting the soy milk, his INR was 2.3. He continued taking his usual warfarin dose of 3 mg/day. After 4 weeks of drinking the soy milk, his INR dropped to 1.6 and could not be explained by any other variations. He stopped drinking the soy milk, continued his usual warfarin 3 mg /day, and returned 1 week later with an INR of 1.9, and his INRs in the next 2 months remained within therapeutic range on warfarin 3 mg/day.

The mechanism for an interaction with soy and warfarin is uncertain. Although soybeans are found to have high amounts of vitamin K, soy protein in the form of soy milk contains only trace amounts of vitamin K and would not be expected to alter warfarin metabolism [99]. Theoretical mechanisms include changes in warfarin absorption or metabolism resulting from alterations in the P-glycoprotein efflux system or organic anion-transporting polypeptides [98]. Soy may also inhibit platelet aggregation [100]. Although the evidence does not suggest that soy milk should be avoided in patients taking warfarin, it may be prudent to monitor INR closely whenever initiation or discontinuation of soy protein occurs. In addition, patients on warfarin should be educated to maintain consistency of dietary intake of soy.

Box 2. Dietary supplements containing coumarin derivatives.

- Alfalfa
- Angelica root
- Aniseed
- Arnica
- Artemesia
- Asa foetica (asafoetida)
- Bishop's weed
- Bogbean
- Buchu
- Capsicum
- Cassia
- Celery seed
- Chamomile
- Danshen (*salvia miltiorrhiza*)
- Dandelion
- Dong quai (Danggui, *Angelica sinensis*)
- Fenugreek
- Horse chestnut
- Horseradish
- Licorice root
- Lovage root
- Meadowsweet
- Melilot
- Nettle
- Parsley
- Passion flower
- Prickly ash
- Quassia
- Red clover
- Rue
- Sweet clover
- Sweet woodruff
- Tonka beans
- Wild carrot
- Wild lettuce

Adapted from references [93,116].

3.2 Interactions with supplements that contain coumarin derivatives

Many supplements and herbal products have been found to contain coumarin derivatives, thereby enhancing the anticoagulant effect of warfarin. Below is a description of these interactions that have been substantiated by published case reports. Several other herbal products have been shown to contain coumarin derivatives, although no actual case reports have been reported to date. These products are listed in Box 2.

3.2.1 *Danshen*

Danshen (the root of *Salvia miltiorrhiza*), also known as tan seng, is used for various cardiovascular diseases. Danshen may increase the rate of absorption and decrease the rate of elimination of warfarin in rats [101], and has been shown to display antiplatelet effects [102]. Danshen is taken by mouth, often in tea, but has also been incorporated into some Chinese cigarettes [103]. There have been several case reports of elevation in INR with concomitant use of danshen and warfarin, occurring as early as 3 – 5 days after starting danshen [104-107].

In one case, a 62-year-old man with mitral valve replacement developed a right pleural and pericardial effusion, a drop in Hgb to 7.6 g/dl, and INR > 8.4 on his correct and previously therapeutic dose of warfarin 2 weeks after starting an herbal tea containing danshen. The patient required 6 units fresh frozen plasma with 7 units of packed red blood cells to bring INR back down to 2.0, as well as a pleural drain to remove the collected blood within the effusions. After two weeks, warfarin was gradually reintroduced and the patient required a similar warfarin dose to stabilise his INR [105]. Another case involved a 66-year-old man stabilised with an INR around 2.0 on warfarin 2 – 2.5 mg/day for over a year who started consuming danshen 3 and 5 days before admission and using a Chinese medicated topical oil containing methyl salicylate. He was hospitalised for bleeding from a gastric carcinoma with an associated INR of 5.5 [106]. A 48-year-old housewife taking warfarin 4 mg/day for atrial fibrillation had an INR that increased to 5.6 after consuming danshen every other day for about one month. Her corresponding Hgb was 5.3. Warfarin was stopped and fresh frozen plasma was given, with eventual correction of the INR. Clinically there was no obvious source of bleeding and her anaemia was attributed to occult gastrointestinal loss [107]. Based on these case reports, caution is warranted and avoidance of concomitant use of warfarin and danshen should be recommended.

3.2.2 *Dong quai*

Dong quai (*Angelica sinensis*) also known as tang-kuei, dang gui, and Chinese angelica, is a Chinese herbal supplement for use in menopausal and menstrual disorders. The applicable part of dong quai is the root. Dong quai root has several coumarin constituents including osthole, psoralen, and bergapten [203,93]. A study in rabbits showed an increase in PT, but no changes in the pharmacokinetic parameters of warfarin [108], suggesting active anticoagulant components other than warfarin were present. Additionally, ferulic acid from the root's oil and osthole have been shown to inhibit platelet aggregation [109].

In one case, a 46-year-old woman on warfarin for a history of stroke and atrial fibrillation had her INR increase to 4.9 after taking 4 weeks of dong quai 565 mg once or twice daily. The INR normalised 4 weeks after discontinuation of dong quai with no adverse bleeding outcomes [110]. Another case with limited details reported that a patient taking warfarin for 10 years for a mitral valve replacement started dong guai for menopausal symptoms, and subsequently developed an INR of 10 and had widespread bruising [111]. These cases suggest that dong guai should be avoided in patients taking warfarin, both due to the increased INR that may occur, as well as the effects on platelet function.

3.2.3 *Fenugreek*

Orally, fenugreek is used for treatment of diabetes, loss of appetite, heartburn, constipation, atherosclerosis, hyperlipidaemia, and for promoting lactation. There is a case of an increased INR in a patient taking boldo and fenugreek that recurred upon rechallenge [112]. Fenugreek contains coumarin derivatives that might have additive effects with warfarin causing an increase in the INR. Some fenugreek constituents have antiplatelet effects, although these might not be present in concentrations that are clinically significant.

3.2.4 *Devil's Claw*

Devil's Claw (*Harpagophytum procumbens*) has been promoted for the use as an analgesic in the treatment of gout, arthritis and myalgias. There is limited evidence about the pharmacological or pharmacokinetic effects of Devil's Claw; however, there is one case report of purpura reported. The patient's medical history, other medications, doses and duration of warfarin, and doses and duration of Devil's Claw were not reported [91]. There is preliminary evidence that Devil's Claw may inhibit CYP 2C9, 2C19 and 3A4 [113]. Until better evidence about this product's metabolism and drug interaction capabilities are known, combination of this product with warfarin should be used with caution, if at all.

3.2.5 *PC-SPES*

PC-SPES is a mixture of eight herbal drugs, namely *Dendrathema morofolium* (chrysanthemum), *Isatis indigotica* (dyer's woad), *Glycyrrhiza glabra* (licorice), *Gonoderma lucidum* (reishi), *Panax pseuodginseng* (san-qui ginseng), *Rabdosia rubescens* (rubescens), *Serenoa repens* (saw palmetto), *Scutellaria bacicalensis* (Baikal skullcap) [92]. PC-SPES was found to be adulterated with indometacin, warfarin and diethylstilbestrol [114]. This product was suspended from sale by the FDA in 2003 [115].

3.3 Interactions that have an effect on platelet function and bleeding profile

Many dietary and herbal supplements have the potential to affect platelet function either through inhibition of aggregation or by having an antiplatelet activity. Table 9 summarises the supplements that are reported to affect platelet function and describes the proposed mechanism for the interaction. The anticipated effect of these interactions is an increased risk for bleeding or bruising. Combination products that contain more than one of the herbs on this list can further potentiate these effects. Because it is impossible to exactly quantify the effects of these herbal products on platelet function, concomitant use with warfarin should be avoided.

4. Clinical and patient care considerations

Although most of the evidence of the various interactions discussed in this review come from case reports or small cohort studies, as healthcare providers it must be remembered that just because the evidence is not currently there, it does not mean that the interaction will not occur in certain patients. In addition, despite some negative studies in healthy volunteers, actual interactions may still be possible in individual patients. As very often there is no 'typical response' to certain interactions, providers need to be aware that there will be variability in how susceptible patients are to various interactions, the magnitude of the interaction, and in the time of onset and duration of the interaction [116,117].

As many patients have the tendency not to report the use of supplements or herbal products to their traditional healthcare providers, providers need to make an effort to work closely with the patient and gather this type of information in order to allow for safe and stable anticoagulation. It is crucial that in the dialogue with the patient, the healthcare provider remains non-judgmental with regards to the patient's habits relating the use of CAM. The use of supplements in patients taking warfarin therapy needs to be routinely assessed and documented. Patients need to be educated about the risks versus the benefits of such supplements. The safest approach would be to avoid potentially interacting supplements, especially the ones that contain multiple active ingredients. However, some patients may feel strongly about taking certain products. In these cases, or whenever potential interactions are suspected or expected (i.e., when a new product is initiated or discontinued) the frequency of INR monitoring needs to be increased and warfarin doses adjusted accordingly. Concurrent use of products with an anticoagulant or antiplatelet effect should be discouraged as these agents can have an additive effect with warfarin and lead to bleeding complications. Special care needs to be undertaken in patients undergoing various surgical interventions as use of some supplements can increase the risk of bleeding. It is best that all dietary supplements and CAM are avoided and discontinued at least 1 – 2 weeks prior to surgery [118].

5. Conclusion

Clinically significant drug interactions can occur when an interacting drug, food or herbal supplement is added during warfarin therapy, discontinued during warfarin treatment, or used intermittently during warfarin treatment. These situations represent significant risk for the development of interactions and need careful attention in order to avoid any adverse outcomes. Many healthcare providers are unaware of the extent of use and the specific dietary supplements that patients on warfarin take. Education of healthcare professionals and consumers as to the potential risks associated with the use of specific herbal and nutritional supplements in patients taking warfarin therapy is crucial. Appropriate steps to avoid and to minimise these interactions need to be followed in order to allow for more stable and safer anticoagulation of patients treated with warfarin.

Table 9. Dietary supplements that can affect platelet function and anticoagulant effect.

Agent	Mechanism	Comments
Bladderwrack	Has anticoagulant effects	Increased risk of bleeding or bruising
Boldo	Constituents may have antiplatelet effects	Increased risk of bleeding or bruising
Bromelain	Decreased platelet aggregation	Increased risk of bleeding or bruising
Burdock	Decreased platelet aggregation by inhibiting platelet activation factor	Increased risk of bleeding or bruising
Caffeine	May have antiplatelet activity; not reported in humans	Increased risk of bleeding or bruising; found in black tea, green tea, guarana, mate, oolong tea
Clove	Eugenol has antiplatelet activity	Increased risk of bleeding or bruising
Cod liver oil	May inhibit platelet aggregation	Increased risk of bleeding or bruising; avoid concomitant use
Coltsfoot	May inhibit platelet aggregation	Increased risk of bleeding or bruising; avoid concomitant use
Danshen	Decreased platelet aggregation; may also have antithrombotic effects	Increased risk of bleeding or bruising; avoid concomitant use
Dong quai	May inhibit platelet aggregation	Increased risk of bleeding or bruising
Fenugreek	Constituents may have antiplatelet effects; concentration may not be clinically significant	Increased risk of bleeding or bruising
Fish Oil	Has antiplatelet effects	Increased risk of bleeding or bruising
Flax seed	Decreased platelet aggregation and increased bleeding time	Increased risk of bleeding or bruising
Gamma linolenic acid	Has anticoagulant effects	Found in borage and evening primrose oil, Increased risk of bleeding or bruising
Garlic	Has anticoagulant effects and may inhibit platelet aggregation	Increased risk of bleeding or bruising
Ginger	Inhibit thromboxane synthetase and decrease platelet aggregation	Increased risk of bleeding or bruising
Ginkgo	Decreased platelet aggregation; ginkgolide B, a component of ginkgo, is a potent inhibitor of PAF	Increased risk of bleeding or bruising
Ginseng, panax	Components may decrease platelet aggregation through PAF antagonism; not shown in humans	Increased risk of bleeding or bruising; use with caution until more is known.
Ginseng, Siberian	A component, dihydroxybenzoic acid, may inhibit platelet aggregation	Increased risk of bleeding or bruising
Melatonin	Unknown; might increase the anticoagulant or antiplatelet effect; decreased prothrombin activity observed	Increased risk of bleeding or bruising
Nattokinase	Has thrombolytic activity	Increased risk of bleeding or bruising
Onion	Decreased platelet aggregation	Increased risk of bleeding or bruising
Pantethine	Decreased platelet aggregation	Increased risk of bleeding or bruising
Policosanol	Inhibits platelet aggregation	Increased risk of bleeding or bruising
Poplar	Contains salicylates and may cause decreased platelet aggregation	Increased risk of bleeding or bruising
Resveratrol	Has antiplatelet effects	Increased risk of bleeding or bruising
Sea buckthorn	Inhibits platelet aggregation	Increased risk of bleeding or bruising
Turmeric	Decreased platelet aggregation; has antiplatelet effects	Increased risk of bleeding or bruising
Vinpocetine	Has antiplatelet effects	Increased risk of bleeding or bruising
Vitamin E	Inhibits platelet aggregation and antagonises the effects of vitamin K-dependent clotting factors	Dose-dependent and significant with doses > 800 units/day. Advise patients to avoid high doses of vitamin E; increased risk of bleeding or bruising.
Willow bark	Decreased platelet aggregation; has antiplatelet effects, but less than aspirin	Increased risk of bleeding or bruising

Adapted from [7,116,117-119,203]. PAF: Platelet-activating factor.

6. Expert opinion

After > 60 years following its release into clinical use, warfarin is still one of the most widely used oral anticoagulant agents. Although an effective anticoagulant if appropriately used, its efficacy to safety window is narrow. Attaining and maintaining appropriate warfarin anticoagulant levels are a clinical challenge. Among many factors that interfere with warfarin, its interactions with dietary vitamin K and other dietary and herbal supplements are some of the most commonly reported variables leading to fluctuations in anticoagulant control. The amount of dietary vitamin K intake needs to be kept constant and patients must be educated on the appropriate vitamin K content and serving sizes of various foods and supplements. In addition, the use of dietary supplements and herbal products in patients taking warfarin must be frequently evaluated and documented. Patients must be educated on the risks versus the benefits of various supplements. Just because something is natural or a herb, does not mean that it is also safe.

New oral anticoagulant agents such as direct thrombin inhibitors and Factor-Xa inhibitors are in development and may be less likely to exhibit the large number of drug and food interactions that warfarin does. However, dietary supplements and CAM with an anticoagulant or antiplatelet effect will still contribute to the overall bleeding risk an individual patient manifests. Therefore, patient dialogue and education about these concerns will remain very important even in the light of new drugs becoming available in the near future.

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