



## Warfarin interactions with complementary medicines, herbs and dietary supplements

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### ABSTRACT

Warfarin is a highly efficacious oral anticoagulant agent, whose use is limited by the well founded fear of bleeding. Many complementary medicines found to have potential interaction with warfarin and these interactions are marked as a cause of adverse events. The concomitant use of warfarin with drugs and herbal products leads to major safety concerns due to its narrow therapeutic window. Warfarin therapy is thought to interact with 250 different drugs. Various herbal products like cinchona, danshen, devil's claw, dong quai, garlic, ginkgo, ginseng, Coenzyme Q10, ginseng, green tea, St John's wort, vitamin K etc are thought to either increase or decrease the international normalized ratio. The purpose of this article is to serve a reference for pharmacists regarding the potential and documented interactions of warfarin with herbal products and dietary supplements associated with warfarin. In this review provide update information regarding the reported and documented interactions of warfarin.

**Keywords:** warfarin, anticoagulants, hyperlipidemia

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### INTRODUCTION

Warfarin (coumarin) is the most commonly used oral anticoagulant agent. It is highly effective in the treatment and management of deep venous thrombosis and can meliorate symptoms of patients suffering from arterial fibrillation, prosthetic heart valves, indwelling central venous catheters and myocardial infarction[1]. The drug exerts its anticoagulant activity by interfering with the hepatic conversion of the vitamin K dependent clotting factors II (prothrombin), VII, IX and X. In addition to this, warfarin also inhibits the activation of vitamin K dependent regulatory proteins C and S[2].

Fluctuations in the ingestion of vitamin K rich sources such as green, leafy vegetables and certain vegetable oils may lead to hypoprothrombinemia on interaction with warfarin and so, should require dosage adjustment [3]. Herbal drugs affect the pharmacokinetics of warfarin by decreasing its absorption from the gastrointestinal tract or by altering its metabolic clearance. Possible mechanisms which results in herbal warfarin interactions include decreased warfarin absorption, decreased platelet aggregation, and decreased serum levels of thromboxane, prostaglandin or phospholipase A2, decreased synthesis of cyclo-oxygenase, inhibition of platelet activating factor, conversion of fibrin to fibrinogen and inhibition of CYP2C9, and vitamin K and coumarin content[4].

Patients receiving warfarin therapy should require regular blood tests to measure how long your blood takes to clot, called International Normalised Ratio (INR). Vegetables like broccoli, Brussels sprouts, kale, parsley, spinach etc are rich sources of vitamin K and eating large quantities or making sudden changes in the consumption of these vegetables, may interfere in the effectiveness and safety of warfarin therapy. Changes in the use of concomitant

medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors can also interfere with the therapy, so regular monitoring of INR and dose adjustments of warfarin are frequently required [5].

#### Warfarin- ginseng interactions

Ginseng is used to enhance the body's resistance to stress and to improve mental and physical performance. The active constituent of Ginseng is ginsenosides. The ginsenosides are considered to inhibit the platelet aggregation and inhibit the conversion of fibrinogen to fibrin. Both American and Asian ginseng can antagonize the effect of warfarin [6,7].

#### Warfarin-ginger interactions

Ginger (*Zingiber officinale Roscoe*) has anti inflammatory, anti platelet and antispasmodic activity. Ginger interacts with warfarin on the basis of its inhibition on platelet aggregation *in vitro*. Large amounts of ginger cause inhibition of arachidonic acid induced platelet aggregation. Patients taking anticoagulants should be warned against consuming large amounts of ginger [6,7].

#### Warfarin- coenzyme Q10 interactions

Coenzyme Q10 (*Theobroma cacao*) is obtained from parsley, broccoli, peanuts, and grape. It is often taken orally as a supplement for treatment of cardiovascular disorders including congestive heart failure, hypertension and angina. Coenzyme Q10 is structurally similar to menaquinone (vitamin K2) that possess pro-coagulant properties. It produces a significant increase in the total clearance of both S and R warfarin. The mechanism of interaction between coenzyme Q10 and warfarin was unclear. Coenzyme Q10 may have some vitamin K like activity, which would explain the decrease in INR. Until more is known, it is reasonable to increase the frequency of INR monitoring in patients taking combined therapy of warfarin and coenzyme Q10 together [7,8].

#### Warfarin- danshen interactions

A Chinese herb, danshen (the dried root of *Salvia miltiorrhiza Bunge*) is promotes circulation and improve the blood flow. Danshen is used in the treatment of various cardiovascular, cerebrovascular diseases, including angina pectoris, hyperlipidemia, and acute ischemic stroke. The oral administration of danshen extract can alter the overall pharmacokinetics of both S- and R-warfarin and can increase the plasma concentrations of both enantiomers. Patients taking danshen in combination with warfarin therapy can increase the risk for bleeding. Therefore, patients should monitor their INR regularly to prevent the adverse events [4,5,6,7].

#### Warfarin- garlic interactions

Garlic (*Allium sativum*) is used for respiratory infection and cardiovascular disease. Garlic cloves inhibit the platelet aggregation and consumption of garlic produces a dose related inhibition of platelet aggregation and found to have antithrombotic activity. Patients using warfarin should be cautioned regarding the possible risk of increased bleeding on consumption with garlic [8,9].

#### Warfarin- dong quai interactions

Dong quai contains coumarin derivatives and can lower the prothrombin times, when administered concomitantly with warfarin. Concurrent use of dong quai with warfarin should be avoided [10].

#### Warfarin- saw palmetto interactions

Saw palmetto fruit (*Serenoa repens*) is used to treat benign prostatic hyperplasia. It is also used as an endocrine agent. *In vitro* studies show that Saw palmetto inhibits some cytochrome P450 isoenzymes, including CYP2D6, CYP2C9, and CYP3A4. The nature of the interaction may due to the presence of vitamin E rich component. Therefore, the patients receiving anticoagulation therapy should be closely monitored with concomitant administration of saw palmetto rich products [10,11].

#### Warfarin-omega fatty acid interactions

Omega fatty acids are found in fish oil supplements can potentially interact with anticoagulants. The eicosapentaenoic acid and docosahexaenoic acids, found in fish oil affect the platelet aggregation and vitamin K dependent coagulation factors. Therefore, concomitant use of omega fatty acids with warfarin, theoretically increase the risk of bleeding [12,13].

#### Warfarin- red clover interactions

Red Clover (*Trifolium pratense*) is used to reduce the symptoms of menopause. It is also used for mastalgia, premenstrual syndrome, and cancer prevention. *In vitro* studies showed that Red clover reduced the activity of CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2C19, and CYP3A4 and especially inhibited CYP2C8 and

CYP2C9. Some studies listed that Red clover have the potential to increase the risk of bleeding or potentiate the effects of the warfarin, based on the fact that Red clover inhibited CYP2C9 and contain natural coumarins [14,15].

#### Warfarin- soy interactions

*Soya (Glycine max Merr.)* is widely used in the treatment of hyperlipidemia, menopausal symptoms, and osteoporosis. *In vitro* studies showed that Soya bean products inhibited CYP3A4 and CYP2C9. Complementary and Alternative Medicine of Fermented Soya bean products contain high level of vitamin K and can decrease the activity of warfarin and related anticoagulants. Un-hydrolyzed extract of soy had little effect on CYP1A2, CYP2A6, and CYP2D6 but hydrolyzed soy extract inhibits the CYP2C9 and CYP3A4. Patients undergoing anticoagulation therapy should be warned against use of large amounts of soy products and should be closely monitored for adverse drug events [10,11,12].

#### Warfarin- green tea interactions

*Green Tea (Camellia sinensis)* contains high amounts of vitamin K, indicating the presence of vitamin K in green tea. Dried leaves of *Camellia sinensis* are also rich in vitamin K, containing as much as 1428 µg/100g of leaves. Brewed tea contains about 0.03 µg of vitamin K per 100 g of the brewed tea. The antagonism of warfarin by green tea is mainly due to the presence of vitamin K contained in the tea. Various compounds like catechin and caffeine, present in green tea can stop the arachidonic acid release from platelet and thereby inhibit blood clot formation [14]. Green tea is a potent inhibitor of thrombin stimulated platelet thromboxane formation which suggests that green tea extracts can be beneficial for the treatment of vascular disease, but it can increase the risk of bleeding when used in combinations with antiplatelet and anticoagulant drugs. The reasons for this interaction are still unclear, but patients are suggested to take attention when receiving warfarin treatment [11,13].

#### Warfarin- cannabis interactions

*Cannabis (Cannabis sativa L)* contains cannabinoids as the active constituent. It is used for the treatment of chronic conditions, including adjunct and neuropathic pain. Studies shows that the major constituents of Cannabis are induced by CYP2C9 and this can increase the metabolism of warfarin effects. However, a case report showed raised INR and bleeding in a patient who smoked Cannabis (2.5 packs/day for 35 years) while taking warfarin. Because of the existence of other factors, it is not reasonable to suggest the INR change is specifically due to cannabis-warfarin interaction [8,9,10].

#### Warfarin- G. biloba interactions

*Ginkgo (Ginkgo biloba)* contain active constituent ginkgolides have both antiplatelet and anti inflammatory properties. It is used for the treatment of cerebrovascular and peripheral vascular disorders. The effects of Ginkgo on cytochrome P450 isoenzymes were well studied and found that the flavonoids fraction of Ginkgo have more effects on cytochrome P450 iso-enzymes than the terpene lactones. And these effects disappear quickly when Ginkgo is stopped. *In vitro* and rat studies found Ginkgo have effects on CYP2C9, CYP2D6 and CYP2E1. But the effect of Ginkgo on CYP3A4 was unclear and some *in vitro* studies did not appear to be clinically relevant. Evidences are insufficient to justify advising patients taking warfarin to avoid ginkgo, but patients are suggested to monitor their INR when co-administrated ginkgo with warfarin. Ingestion of 120 mg daily of standardized G. biloba extract for 3 months non selectively inhibited cyclooxygenase-1 (COX-1) mediated thromboxane A2 and COX-2 mediated prostaglandin-12 in patients with type 2 diabetes mellitus. Ginkgolide B, a constituent in G. biloba, has been shown to decrease platelet aggregation and ginkgolide B displaces platelet-activating factor (PAF) from its binding sites, thus potentially decreasing blood coagulation [13,14,15].

#### Warfarin- vitamin C interactions

High doses of vitamin C can interact with warfarin leads to diarrhoea and reduced warfarin absorption. Lower doses of vitamin C can reduce absorption of warfarin when taken daily [15].

#### Warfarin- vitamin E interactions

Daily consumption of more than 400 IU of vitamin E and concomitant administration of warfarin can prolong the INR and increase the risk of bleeding due to interference with production of vitamin K dependent clotting factors. Vitamin E potentiates the antiplatelet activity of aspirin in collagen stimulated platelets. Supplementation with 1000 IU RRR-alpha-tocopherol daily for 12 weeks antagonize the vitamin K dependent clotting factors in men and women, not taking warfarin. The risk for interaction between warfarin and vitamin E interaction are probably higher in patients with deficiency in vitamin E [14,15,16,17].

#### Warfarin- cranberry interactions

*Cranberry (Vaccinium macrocarpon)* is commonly used for the blood and digestive disorders. It is widely used for treatment of recurrent urinary tract infections. Although, clinical study found no evidence of significant effects in

human, there were some case reports of raised INR and significant bleeding with co-administration of warfarin and Cranberry. The flavonoids that are present in the cranberries have an established effect on cytochrome P-450 (CYP) drug metabolizing enzyme system. Increased INR of prothrombin time values were reported in some patients. Deaths due to gastrointestinal and pericardial haemorrhage were also reported. Frequent INR monitoring should be done for patient taking warfarin and regular intake of Cranberry juice [7,9,10].

#### Warfarin- St John's wort interactions

St John's wort (*Hypericum perforatum*) is an herbal drug used for treatment of depression. Concomitant use of St John's wort was associated with a loss of anticoagulant activity in patients stabilized on warfarin. Although no thromboembolic episodes occurred, the decrease in anticoagulant activity was considered clinically significant. Anticoagulant activity was restored when St John's wort is terminated or the warfarin dose increased. Observations suggest that increased clearance of warfarin, possibly due to the induction of CYPs, particular CYP2C9, and 3A4 [11,14,15].

#### Warfarin- Chitosan interactions

Chitosan (*Swertia chirayita*) is used as a dietary supplement for obesity and hypercholesterolemia. Chitosan is an absorption enhancer and increases the permeability of hydrophilic drugs across the intestinal and mucosal epithelia. Report suggests that Chitosan can increase the effects of warfarin. Warfarin being a vitamin K antagonist and a reduction in vitamin K would be expected to enhance its effects [12,16,17].

#### Warfarin-Devils claw interactions

*Devil's Claw (Harpagophytum procumbens)*. Devil's claw is used as bitter tonic and for inflammatory disorders. *In vitro*, extract of Devil's claw moderately inhibited the activity of CYP2C8, CYP2C9, CYP2C19, and CYP3A4. *In vitro* studies showed that Devil's claw had the greatest effect on CYP2C9 and may increase the effects of warfarin and other coumarins [13,15].

#### Warfarin-grape fruit interactions

*Grapefruit (Citrus paradisi)* can inhibit the CYP3A4 irreversibly and cause drug interactions in a relatively low dose. Mechanism of the interaction was inferred to be that Grapefruit inhibited by CYP2C9 and CYP3A4 and therefore affected the metabolism of warfarin. Data obtained from the studies suggest that Grapefruit had the potential to interact with warfarin. On this basis, it would probably be prudent to avoid the co-administration of warfarin with grapefruit or for concurrent use should to be monitored closely [3,8,11].

#### Warfarin- Eleuthero interactions

Eleuthero (*Eleutherococcus senticosus*) has not been studied; however, it contains a constituent that inhibits the platelet aggregation. The narrow therapeutic index of warfarin and the serious consequences associated with small changes, the anticoagulation status in patients taking dietary supplements should be carefully monitored whenever they initiate or stop taking any supplement or when a new bottle of the same product is used, until the effect in the individual patient is known [4,15,17].

In contrary to the popular belief, that "natural drugs are safe", the herbal medicines can lead to a significant toxic effects, drug interaction and even morbidity or mortality. The potential interaction of warfarin and herbal products cannot be predicted with certainty, as the pharmacokinetic and pharmacodynamic properties of herbal products are understood inadequately. Majority of the population are taking conventional non prescription or prescription drugs with or without the consultation of a physician [15,17]. The extensive and concurrent use of these traditional and alternative medicines are increasing but, documentation regarding interactions between drugs and herbal medicines are scarce, and many health care professionals rely on anecdotes or case reports to make therapeutic decisions. In addition, there is a distinct lack of reliable information regarding the safety and efficacy of most herbal products. This article is not comprehensive and will evolve with further studies and reports [18].

More food and drug interactions have been reported in association with warfarin than for any other prescription medication. Although many drugs, including antibiotics, drugs affecting the central nervous system, and cardiac medications, had been reported to interact with warfarin, the quality of reports was so poor that few clinical recommendations could be made other than careful monitoring around initiating and discontinuing treatment with other medications [11,15]. The potential for serious interactions of herbal products and megavitamins with conventional drugs is greater for drugs with a narrow therapeutic window. Specific patient populations, such as those taking warfarin, should be monitored very closely [17,19]. Patients at high risk for drug interactions who also take drugs with a narrow therapeutic index should be monitored more closely for drug interactions, especially when a new drug is added or discontinued [17,19,20].

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