Pharmacokinetic and Pharmacodynamic Interactions between Food or Herbal Products and Oral Anticoagulants: Evidence Review, Practical Recommendations, and Knowledge Gaps

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Abstract

Interactions between food and oral anticoagulants (OACs), particularly vitamin K antagonists such as warfarin, are widely recognized and may also be clinically relevant for direct OACs. Pharmacokinetic and pharmacodynamic interactions with food or herbs can lead to anticoagulation potentiation, increased risk of bleeding, or reduced drug efficacy, all compromising patient safety. We conducted a systematic search for randomized controlled trials (RCTs) on PubMed for assessments of interactions between OACs and various ingestants. Since the RCT evidence was slim, we also reviewed prospective longitudinal studies, case series, and case reports to identify possible associations between foods and anticoagulation therapy. We referred to basic or translational studies that shared putative explanations for such interactions, but we failed to identify high-quality evidence in most cases. The limited evidence, small sample size of the studies, conflicting results, and possible heterogeneity in the contents of herbal products prevent a conclusive assessment of these interactions. Existing evidence suggests that (1) cranberry juice consumption (up to 240 mL/d and probably even more) with warfarin is safe; (2) use of green leafy vegetables

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with a high daily content (more than 250 μg) of vitamin K should be cautioned for patients receiving warfarin, because it may decrease warfarin efficacy. It is also advisable for patients to maintain highly constant intake of green leafy vegetables to ensure stable warfarin effectiveness; (3) ginger, even in small quantities (excluding commercial ginger-flavored beverages, which contain only negligible amounts of ginger), and mango (more than one fruit) can both potentiate warfarin effects; (4) patients taking OACs should avoid St. John's wort due to diminished anticoagulant effect; and (5) consumption of less than 240 mL of grapefruit juice daily is unlikely to interact with OACs. Future longitudinal observational cohort studies and RCTs with larger sample sizes are needed to study specific interactions between food or herbal products and OACs.

Clinically relevant interactions between food and oral anticoagulants (OACs) have considerable potential to limit patient lifestyle, medication adherence, and drug efficacy, all of which jeopardize patient safety and quality of life.[1–3] Previous reports have noted over 68 foods, herbs, and supplements that affect warfarin efficacy.[4] Considering the narrow therapeutic index of vitamin K antagonists (VKAs), interactions between these medications and food may elevate patients' risk for hemorrhagic or thrombotic events. VKAs are known to interact with various foods and herbal products, which necessitates frequent international normalized ratio (INR) monitoring. Warfarin, the most prescribed VKA, inhibits the vitamin K epoxide reductase complex 1 (VKORC1), which is essential for activating vitamin K, and ultimately reduces the synthesis of clotting factors II, VII, IX, and X, as well as proteins C and S. Patients prescribed warfarin are routinely advised to maintain a diet with consistent daily vitamin K consumption.[5] Interactions between food and direct oral anticoagulants (DOACs) are not dependent on food's vitamin K content, because these medications inhibit factor IIa or Xa independent of vitamin K. Thus, vitamin K intake does not interact with and does not need to be restricted for patients receiving DOACs.[6]

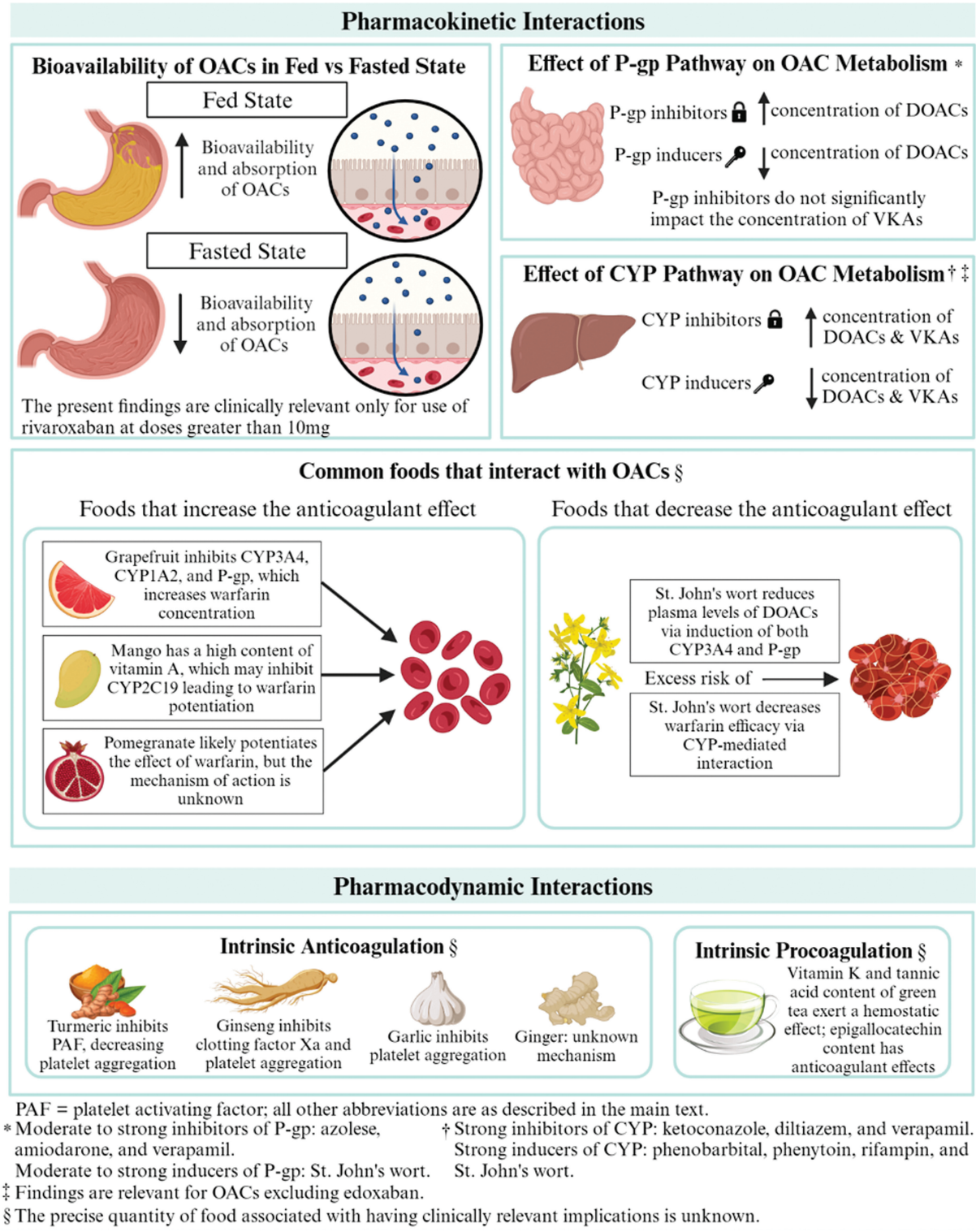
OACs interact with foods and herbal products both pharmacokinetically (i.e., can change the absorption, distribution, or elimination) and pharmacodynamically (i.e., altering their pharmacologic effect), which result in excess or reduced antithrombotic effect (►**Fig. 1**).[7,8] Food and herbal products also have the potential to affect platelet activity, thereby influencing the efficacy of anticoagulant therapy or the risk of bleeding through pharmacodynamic interactions. The present review is dedicated to discussing these potential interactions, summarizing evidence, and sharing medical practice guidance and research ideas for future studies.

Methods

We conducted a systematic search using PubMed, through October 19, 2023. For causality assessments of the interactions between food or herbal products and OACs, with the search terms of "food," "herbal product," "OACs," "DOACs," "VKA," "warfarin," "rivaroxaban," "apixaban," "edoxaban," "dabigatran," "interaction," and "randomized clinical trial," English-language randomized controlled trials (RCTs) on human subjects (without any limitation on sample size) were included, and outcomes of interest were bleeding, treatment failure (thrombotic events), measures of coagulation as assessed by laboratory parameters, and direct or indirect measures of drug levels. We also excluded uncommon foods restricted to very specific geographical regions. We planned to conduct meta-analyses of RCTs that compared the impact of different foods versus placebo on the pharmacokinetics or pharmacodynamics of OACs. We aimed to calculate the pooled results for the outcomes with at least three eligible RCTs using the fixed-effect inverse variance method. We anticipated, *a priori*, that the evidence would be limited. Therefore, we also reviewed prospective longitudinal studies (and if not available, case series or case reports), which noted potentially relevant interactions between food or herbal products and OACs to supplement RCT data while recognizing that causality could not be established. We also searched for studies related to food (RCTs, prospective/retrospective cohort studies, case series, or case reports), which reported notable intrinsic antithrombotic or prothrombotic properties, independent of prescribed anticoagulant use. We categorized the results into pharmacodynamic (covering foods with intrinsic antithrombotic or prothrombotic properties) and pharmacokinetic (discussing foods that cause changes in coagulation profile or drug concentration) interactions. The potential effects of supplements, recreational drugs, alcohol, and specific diets on anticoagulant drugs have been described elsewhere and were not the subject of this review.[9,10] Finally, we shared practical recommendations in each section. However, considering the limitations with evidence, these recommendations should supplement rather than supplant clinical judgment in individual scenarios.

Results

In total, 650 RCTs were screened. By applying the exclusion criteria and assessing for eligibility, 21 RCTs were included to evaluate the effect of certain foods or herbal products on bleeding, OAC concentration, and therapy failure (►**Fig. 2**).



PAF = platelet activating factor; all other abbreviations are as described in the main text.

* Moderate to strong inhibitors of P-gp: azolese, amiodarone, and verapamil. Moderate to strong inducers of P-gp: St. John's wort.

† Strong inhibitors of CYP: ketoconazole, diltiazem, and verapamil. Strong inducers of CYP: phenobarbital, phenytoin, rifampin, and St. John's wort.

‡ Findings are relevant for OACs excluding edoxaban.

§ The precise quantity of food associated with having clinically relevant implications is unknown.

Fig. 1 Possible mechanisms for the clinically significant interactions between oral anticoagulants (OACs) and herbs or food.

Pharmacodynamic Interactions: Foods with Possible Intrinsic Antithrombotic/Prothrombotic Properties

Foods with Antithrombotic Properties

Turmeric

Turmeric is reported to decrease platelet aggregation via inhibition of platelet-activating factor in biological assays. It is also thought to increase both prothrombin time (PT) and activated partial thromboplastin time (aPTT) through inhibition of thrombin and factor Xa by fibrin polymerization independent of antithrombin.[11,12] In a small underpowered crossover RCT in 75 participants, limited by small sample size and type II error, turmeric (500 mg), compared with not using turmeric, did not affect PT, aPTT, thrombin generation,

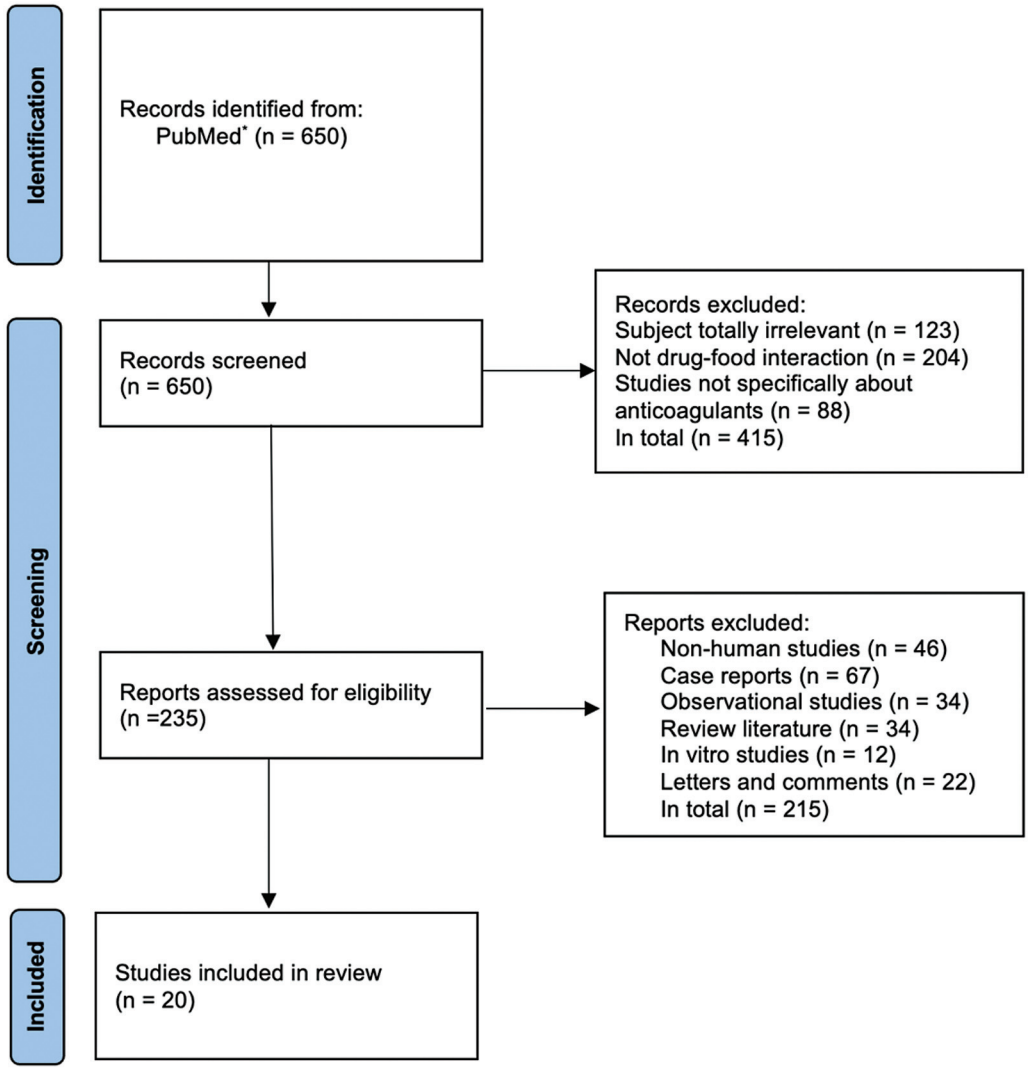


Fig. 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process. PRISMA flow chart details our systematic review of randomized clinical trials (RCTs) investigating interactions between food or herbs and oral anticoagulants. Longitudinal observational cohort studies or case reports were identified separately to explore guideline recommendations or elucidate interaction mechanisms not covered by RCTs. However, a systematic review of observational studies was not conducted. Search terms: ["Warfarin" OR "Coumadin" OR "Apixaban" OR "Rivaroxaban" OR "Dabigatran" OR "Edoxaban" OR "Vitamin k antagonist" or "DOAC" or "Direct oral anticoagulants" or "NOAC" or "Novel oral anticoagulants"] AND ["food interaction" OR "Food Drug Interactions" OR "Food-Drug Interaction" OR "Interaction, Food-Drug" OR "Interactions, Food-Drug" OR "Drug-Food Interactions" OR "Drug Food Interactions" OR "Drug-Food Interaction" OR "Interaction, Drug-Food" OR "Interactions, Drug-Food" OR "Food Interactions" OR "Food Interaction" OR "Interaction, Food" OR "Interactions, Food" OR " Fruit" OR "Fruits" OR "Herb Drug Interactions" OR "Herb-Drug Interaction" OR "Interaction, Herb-Drug" OR "Interactions, Herb-Drug" OR "Drug-Herb Interactions" OR "Drug Herb Interactions" OR "Drug-Herb Interaction" OR "Interaction, Drug-Herb" OR "Interactions, Drug-Herb" OR "Drug-Plant Interactions" OR "Drug Plant Interactions" OR "Drug-Plant Interaction" OR "Interaction, Drug-Plant" OR "Interactions, Drug-Plant" OR "Plant-Drug Interactions" OR "Interaction, Plant-Drug" OR "Interactions, Plant-Drug" OR "Plant Drug Interactions" OR "Plant-Drug Interaction" OR "Herbal Drug Interactions" OR "Drug Interaction, Herbal" OR "Drug Interactions, Herbal" OR "Herbal Drug Interaction" OR "Interaction, Herbal Drug" OR "Interactions, Herbal Drug"] AND ["Clinical trial" OR "randomized clinical trial"].

or platelet inhibition caused by aspirin.[13] The bioavailability of turmeric is likely too low when used in small quantities (as a spice) to cause a clinically relevant antithrombotic effect.[14] However, for larger quantities, RCTs are needed to establish the risk of bleeding associated with turmeric consumption.

Ginseng

Ginseng is reported to increase bleeding by inhibiting factor Xa, platelet aggregation, and thromboxane formation in biological assay studies.[15,16] The underpowered RCT described in the previous section about turmeric also investigated the antithrombotic properties of ginseng and failed to identify any clinically relevant effect on PT, aPTT, platelet function, or thrombin production.[13] A patient consuming 200 mg of ginseng daily experienced clinically relevant postoperative bleeding due to severe coagulopathy following an urgent aortic and mitral valve replacement. Bleeding persisted despite using several pools of platelets, fresh frozen plasma, cryoprecipitate, and multiple units of packed red blood cells.[17] Although RCT data are lacking, patients should exercise caution when

consuming ginseng until these findings are validated in future studies.

Garlic

Garlic inhibits platelet aggregation via cyclooxygenase inhibition, suppression of thromboxane B2 production, and reduction of leukotriene C4 and prostaglandin E2 synthesis.[18] In a systematic review of 12 RCTs that assessed the effect of garlic consumption versus placebo or control on platelet aggregation, two studies provided evidence of garlic's inhibitory effect on platelet aggregation, whereas five studies found no significant difference between the two groups. Mixed findings were also reported on the effect of garlic on fibrinogen levels: RCTs noted either no change in fibrinogen, increased fibrinogen, or significant reduction in fibrinogen. In contrast, a significant increase in PT and aPTT was reported for those receiving garlic compared with those taking placebo.[19] Garlic has also been reported to cause postoperative bleeding in a dose-dependent manner.[20,21] Large-scale prospective studies should be performed using standardized quantities of garlic to definitively determine the effect of garlic on bleeding risk and to identify the quantity that causes a clinically relevant effect. Until then, it is reasonable to consider that consuming small quantities of garlic powder (up to half a teaspoon) is unlikely to have any clinically meaningful effect on coagulation. Consumption of more than four cloves of fresh garlic daily has been cautioned perioperatively.[22]

Ginger

The postulated mechanism of ginger's intrinsic antithrombotic effect is not clear. In a placebo-controlled RCT in 20 patients with coronary artery disease, a single 10 g dose of ginger was reported to significantly inhibit platelet aggregation ($p < 0.05$, details not reported in the original study).[23] However, in a systematic review of 10 studies (eight RCTs) evaluating the effect of ginger versus placebo or control on platelet aggregation, four RCTs reported decreased platelet aggregation and the remaining four reported no significant effect. No meta-analysis was performed due to the heterogeneity of the studies. The evidence is equivocal and limited by the incongruent nature of the results.[24] Consuming 48 mg or more of oral ginger or ginger supplement daily for 1 month may increase the risk of excess bleeding in patients taking OACs.[25]

Hawthorn

Hawthorn increases bleeding risk by inhibiting platelet function.[26] In a prospective cohort study in 116 patients who underwent cardiac surgery, there was a significantly larger volume of total chest tube output in patients who reported consuming hawthorn recently versus those who did not (mean mL ± standard deviation [SD]: 1056.8 ± 896 vs. 729.7 ± 441, $p = 0.01$).[27] Although there is no RCT on the effect of hawthorn on bleeding, it is likely that consumption of brewed hawthorn tea in close proximity to invasive procedures increases the risk of excessive bleeding, considering the evidence provided by this cohort study.

Foods with Prothrombotic Properties

Green Tea

The net effect of green tea extract on bleeding is not fully understood. The vitamin K and tannic acid content of green tea exert a prohemostatic effect, whereas its epigallocatechin content reportedly has anticoagulant effects in a dose-dependent manner in mice.[28–30] In a RCT in 62 patients undergoing a tooth extraction, investigators observed shorter bleeding time in subjects treated with green tea extract-impregnated gauze (total phenolic compounds 18.67 mg/mL) versus placebo (5.87 ± 1.76 vs. 10.09 ± 3.61 minutes, $p = 0.001$). The study also reported a significantly decreased number of patients with 1-hour postprocedure oozing (6 vs. 29 patients, $p = 0.001$) in the cohort using green tea extract compared with placebo.[31] Conversely, in a comparative cohort study, PT and aPTT were compared between 100 volunteers consuming green tea (≥3 cups/day for at least 1 year) and 100 volunteers who did not drink green tea. Significantly increased PT and aPTT were reported for those who consumed green tea (mean [second] ± SD, PT: 19.88 ± 3.70 vs. 15.43 ± 0.52, $p < 0.001$, and aPTT: 34.94 ± 3.40 vs. 32.86 ± 3.20, $p < 0.002$) compared with those who did not.[32]

Given the unknown net effect of green tea on coagulation, bench research must be conducted to understand the mechanism of green tea's prothrombotic and antithrombotic effect, and the clinical impact should be assessed in future RCTs. It is unknown whether the hemostatic effect of green tea interferes with anticoagulants. However, a previously published guideline from the American College of Chest Physicians (ACCP) on OAC therapy states that an interaction between green tea and warfarin is unlikely.[33]

Pharmacokinetic Interactions and Food–Warfarin Interactions

Potentiating Interactions

Cranberry Juice

Multiple cases of increased INR due to cranberry juice consumption have been reported in patients prescribed warfarin, which may be attributed to the flavonoid content in cranberries and their suspected inhibitory effects on the cytochrome P450 (CYP) system, specifically CYP2C9, that lead to increased effect of warfarin.[34,35] An open-label randomized crossover trial in 12 healthy subjects taking warfarin reported 30% higher INR after 2 weeks of cranberry capsules taken three times daily (equivalent to 57 g fruit/day [~120 mL juice]) compared with warfarin alone (geometric mean ratio [GMR] [90% confidence interval, CI]: 1.28 [1.06–1.53]).[36]

In a crossover RCT in 10 healthy subjects drinking a 10-day course of 200 mL of cranberry juice 3 times/day versus placebo, participants did not have a significant change in maximum or total concentration of warfarin (mean difference [95% CI]: maximum concentration (C_{max}): −0.02 [−0.08 to 0.05] vs. 0.40 [−2.20 to 2.90]).[37] Similar findings were reported in a RCT in 30 patients on warfarin, for various indications, who received 240 mL of cranberry juice/day

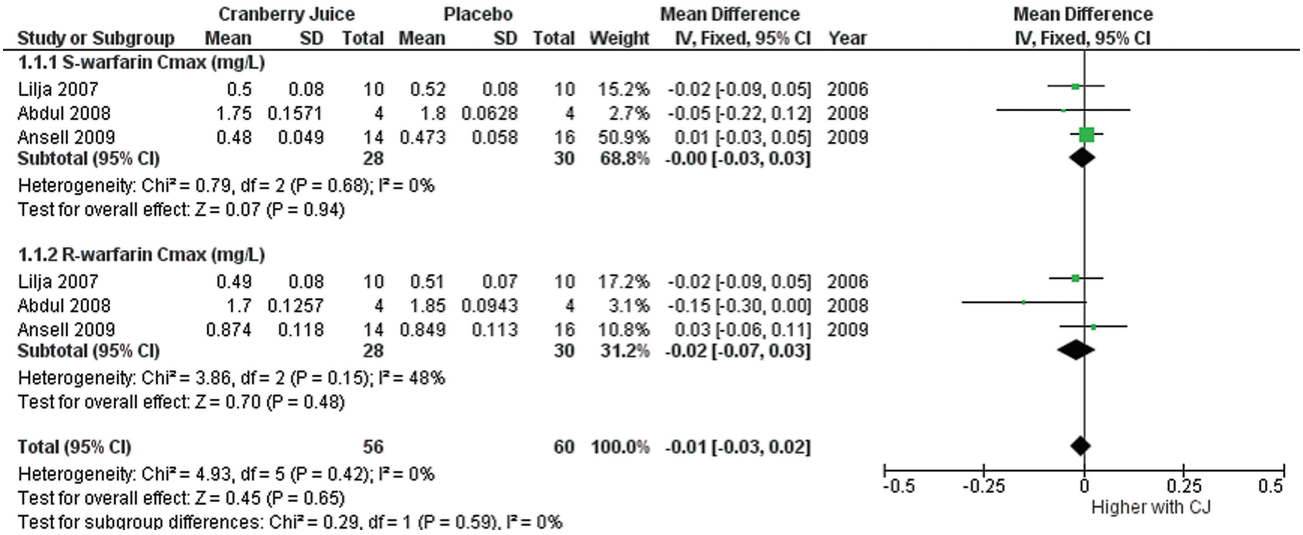


Fig. 3 Meta-analyses comparing the effect of cranberry juice consumption versus placebo on warfarin R and S concentrations in patients on warfarin due to a variety of indications. *R and S warfarin are the two enantiomeric forms of molecular warfarin structure; S warfarin is three times more potent than R warfarin. The pooled estimates are provided based on the assumption that the baseline C_{max} for S and R warfarin were similar between the participants receiving Cranberry juice and those receiving placebo. Ansell et al noted that there were no statistically significant differences in the mean values for maximum R and S warfarin levels between the Cranberry juice and placebo groups before the initiation of the intervention.[38]

versus placebo for 2 weeks [concentration difference ± standard error; −65 (±31) vs. −17 (±29)].[38] In a randomized crossover study in seven patients with atrial fibrillation (AF) on stable dose of warfarin, 250 mL of cranberry juice/day for 1 week did not affect INR (INR: 2.23 ± 0.53 vs. 2.16 ± 0.40, cranberry juice vs. placebo, respectively).[39,40] We conducted a meta-analysis comparing the effect of cranberry juice consumption (240–600 mL/d) versus placebo, on the maximum concentration of warfarin in patients prescribed warfarin for a variety of indications. As shown in ►**Fig. 3**, there was no significant difference in the maximum concentration of warfarin between groups. In response to findings from recent studies, the interaction between cranberry and warfarin has been removed from the warfarin U.S. Food and Drug Administration (FDA) label.[41,42]

Garlic

Besides the pharmacodynamic effects discussed previously, garlic has been postulated to have pharmacokinetic/pharmacodynamic interactions with warfarin by potentiating its effect. In an open-label randomized crossover study in 12 healthy patients who received a single dose of warfarin (25 mg), 2-week pretreatment with garlic (Garliplex 2 g, 3.71 mg allicin/tablet) did not affect INR compared with those who took warfarin alone (GMR [90% CI]: 1.22 [1.11–1.34]).[36] In another pilot RCT in 48 patients on warfarin for various indications, no significant effect was observed in INR in patients taking aged garlic extract (5 mL twice daily for 12 weeks; S-allyl cysteine concentration: 1.47 g/L) versus placebo (mean changes ± SD: 0.0 ± 1.20 vs. 0.20 ± 0.90, $p = 0.58$).[36,43] The University of Wisconsin's Ambulatory Consensus Care Guideline on warfarin management warns about the possible interaction between garlic and warfarin. Warfarin FDA labeling also states that coadministration with garlic may lead to bleeding, although it is unlikely to have a clinically significant impact when used in very small quantities, as a spice.[42,44]

Ginkgo

Ginkgo is listed on warfarin drug labeling as an herb with potential to interact with warfarin through its effect on the cytochrome system; however, the exact mechanism of interaction has yet to be established.[42] In an underpowered three-way, crossover, open-label RCT in 12 healthy volunteers, neither INR nor platelet aggregation were affected by ginkgo consumption (2 g of ginkgo biloba leaf, 9.6 mg of ginkgo flavonglycosides, and 2.4 mg of ginkgolides and bilobalide) with warfarin compared with warfarin alone.[45] A study conducted on records in the Veteran's Administration database reported a significantly increased risk of bleeding associated with ginkgo consumption with warfarin compared with warfarin alone (hazard ratio: 1.38; 95% CI: 1.20–1.58, $p < 0.001$).[46] Despite the uncertainties, the National Health Service (NHS) (university hospitals, Coventry, and Warwickshire) advises against ginkgo consumption in patients taking warfarin.[47]

Ginger

According to current warfarin labeling, ginger and warfarin have potential to interact, yet the mechanism of this interaction remains unknown.[42] In the same underpowered RCT mentioned in the section above, ginger consumption in patients taking warfarin did not affect INR or platelet aggregation compared with warfarin alone.[45] However, a prospective longitudinal study in 171 patients on warfarin, for a variety of indications, found a higher risk of self-reported bleeding in patients who consumed ginger compared with those who did not (odds ratio [95% CI]: 3.20 [2.42–4.24]).[48]

Seven days of 3.6 g of dry ginger powder/day did not seem to affect INR or platelet aggregation in warfarin users,[45] yet a case report recorded an instance of supratherapeutic INR with the use of 0.048 g of ginger/day for 1 month.[25] Although the ginger content in commercial ginger-flavored beverages is negligible, patients should exercise caution when consuming ginger in other forms (even gingerbread cookies) and avoid long-term daily consumption of ginger, more than 2 g/d until additional data are available. The University of Wisconsin's guide on warfarin use states that an interaction between ginger and warfarin is possible.[44]

Grapefruit

Grapefruit juice inhibits CYP3A4, 1A2, and Permeability-glycoprotein (P-gp), and therefore increases warfarin concentration in blood; consuming at least 240 mL of grapefruit juice can inhibit intestinal CYP3A4 activity for 24 to 72 hours by almost 47%.[42,49] In a small study in nine subjects receiving a stable dose of warfarin, no differences in INR were reported before or after a 1-week course of 235 mL of grapefruit juice taken three times daily.[50] These findings are limited by the small study population and the low number of reported cases of increased INR with grapefruit consumption.[51] Mechanistic studies and large RCTs are needed to determine the exact mechanism of interaction between grapefruit and warfarin and to ascertain the quantity of grapefruit/grapefruit juice required to cause a clinically meaningful interaction. Based on available data, consumption of less than 240 mL of grapefruit juice is unlikely to have a clinically relevant effect in patients receiving OACs.[52]

Mango Fruit

Retinoids, the synthetic form of vitamin A, are reported to exert an inhibitory effect on CYP2C19 in human liver microsomes. Mango fruit has a high content of vitamin A and may have a similar mechanism of action and therefore potentiate the effects of warfarin.[53] A case series of 13 patients on chronic warfarin therapy for a variety of indications reported a mean increase of 38% in INR after consuming mango fruit. This increase was reversed when patients stopped eating mango (mean: 17.7% decrease) and upon rechallenge with mango in two of the patients, both experienced high INR once again.[54] These findings are limited by the small sample size of patients and the lack of specified mango quantities. Until further data are available, the possibility of a mango–warfarin interaction should be considered in practice by warning patients about potential bleeding risk. In patients taking warfarin, limiting mango consumption to less than one fruit/day will likely enhance their ability to maintain therapeutic INR.[55] The ACCP guideline postulates that the interaction between mango and warfarin is very likely.[33]

Pomegranate

Very limited data exist about the direct effect of pomegranate on coagulation or its interaction with OACs. There are two relevant case reports on patients taking warfarin, one suggestive of subtherapeutic INR after discontinuing pomegranate juice consumption (formerly taken two to three times weekly) and another case of a large thigh hematoma and an INR of 14 after consuming 3 L of pomegranate juice over 1 week.[56,57] The findings of these two case reports affirm the need for future RCTs to investigate both the effect of pomegranate on coagulation and the potential interactions between pomegranate and OACs. The NHS advises against pomegranate juice consumption in patients taking warfarin. Based on available reports, limiting its use to 1 cup/week seems reasonable.[47]

Turmeric

The antiplatelet effect of turmeric and its inhibitory effect on CYP3A4, 2C9, and P-gp likely serve as the mechanism of interaction between warfarin and turmeric.[58] A patient (on fluindione) developed an INR of 6.6 after consuming turmeric tea for 5 days (2.5 g/d).[58] The New Zealand Medicines and Medical Devices Safety Authority has issued a warning against the coadministration of products containing curcumin–turmeric with warfarin after receiving a report of increased INR (10) in a patient who consumed turmeric while taking warfarin.[59] Future RCTs are needed to decisively inform patients taking warfarin about the risk of bleeding associated with turmeric consumption, although it is unlikely that turmeric poses such risks when used in small quantities, as a spice.

Attenuating Interactions

Warfarin inhibits VKORC1, so foods with high vitamin K content may attenuate warfarin's effects. Therefore, limiting daily intake of vitamin K to less than 250 µg and consuming a consistent daily amount of vitamin K is crucial (►**Fig. 4**).[5,60] Frequent INR monitoring is essential to adjust warfarin dosage in cases of a dramatic change in vitamin K consumption.

Ginseng

Ginseng decreases warfarin's effect by activating coagulation factors II and VII and via CYP2C9 activation; however, factor Xa inhibition was also observed in chromogenic substrate assays.[16,61] In a RCT performed on healthy subjects who were treated with 5 mg of warfarin daily, treatment with American ginseng (1 g for 2 weeks) led to decreased INR (INR_{peak} [95% CI]: −0.19 [−0.36 to −0.07]; $p = 0.001$) and warfarin level (area under the curve, AUC, µg/mL/d [95% CI]: −0.64 [−1.25 to −0.13]; $p = 0.006$) compared with placebo.[62]

In another randomized placebo-controlled, crossover trial in 20 healthy subjects who received a single 25 mg dose of warfarin, 0.5 g of ginseng versus placebo did not have a significant effect on the pharmacokinetics (C_{max}, time to maximum concentration, half-life, and clearance) or pharmacodynamics (INR and platelet aggregation) of warfarin.[63] A randomized open-label study in 25 patients with previously diagnosed ischemic stroke did not observe a significant effect on INR (control vs. ginseng difference between means [95% CI]: INR_{peak}: 0.113 [−0.202 to 0.429]) when treated with warfarin and ginseng (aqueous extracts 0.5 g) three times a day for 2 weeks compared with warfarin alone.[64] Similarly, a randomized crossover study in 25 patients with heart valve

Raw Parsley	984
Cooked Spinach	888
Cooked Collard greens	772
Cooked or raw Swiss chard	704
Cooked Turnip greens	677
Cooked Beet greens	628
Cooked Kale	551
Cooked Mustard greens	386
Cooked Brussels sprouts	289

Cooked Broccoli	220
Raw Collard greens	157
Raw Brussels sprouts	156
Raw Spinach	145
Restaurant Style Coleslaw	143
Raw Turnip greens	138
Cooked Green cabbage	118

Raw Kale	97.5
Raw Broccoli	77.5
Raw Kiwi	72.5
Raw Green cabbage	68.4
Cooked Green peas	61
Cooked Green beans	58
Cooked Okra	57.8
Raw Butter lettuce	56.3
Raw Asparagus	55.7
Raw Tuna salad with mayonnaise	48.3
Raw Romaine lettuce	48.2
Raw Avocado	42.2
Raw Blueberries	28.6

Cooked Cauliflower	24.3
Raw Artichoke	22.2
Cooked Carrots	21.2
Baked Sweet potato	14.5
Raw Tomato	13.5
Raw Green pepper	11.1
Raw Cucumber	9.6
Cooked Summer squash	7.4
Raw Banana	1.1
Raw Onion	0.6

Foods with very high vitamin K content
Foods with high vitamin K content
Foods with moderate vitamin K content
Foods with low vitamin K content

*Frozen, cooked and boiled green vegetables have higher amounts of vitamin K compared to their raw forms.

*Consistent consumption of approximately 250μg of vitamin K per day may result in clinically relevant changes to INR although reports for these quantities are varied. [60]

Fig. 4 Dietary content of vitamin K in commonly used food/herbs measured by mg of vitamin K per cup.

replacement receiving stable warfarin therapy reported no effect on INR (estimate difference in medians [95% CI], placebo vs. ginseng: −0.430 [−1.005 to 0.190]) when treated with 1 g of Korean red ginseng extract versus placebo, daily.[65] These conflicting results may be attributed to the dual effects of ginseng, which complicates our ability to predict the net effect of the ginseng–warfarin interaction. Despite the contradicting nature of these findings, the ACCP guideline states that an interaction between warfarin and ginseng is probable,[33] and thus individuals prescribed warfarin should avoid ginseng consumption. According to warfarin drug labeling, ginseng may interact with warfarin and attenuate its anticoagulant effect.

St. John's Wort (Hypericum perforatum)

St. John's wort induces the CYP450 system, which decreases warfarin efficacy.[66] A randomized crossover trial in 12 healthy subjects who received a single 25 mg dose of warfarin reported decreased INR and platelet aggregation ([90% CI]: 1.0 [0.88–1.14]) in subjects taking St. John's wort (one tablet 3 times/day for 2 weeks; each tablet contained standardized dry extract equivalent to 1 g *Hypericum perforatum* flowering herb top, 0.825 mg hypericin, and 12.5 mg hyperforin) compared with control.[63] Although this was the only existing RCT and the sample size was small, St. John's wort is well-known for its numerous drug interactions. Australia's Therapeutic Goods Administration has issued a physician and pharmacist alert for this herb's possible drug interactions, including warfarin, thus patients taking warfarin should exercise extreme caution and avoid consumption of St. John's wort entirely.[67] Comparatively, the 2023 American College of Cardiology/American Heart Association/American College of Chest Physicians/Heart Rhythm Society (ACC/AHA/ACCP/HRS) Guideline for the Diagnosis and Management of AF recommends that patients taking concomitant warfarin and St. John's wort adjust their warfarin dosage according to INR.[68]

Pharmacokinetic Interactions and Food–Direct Oral Anticoagulant Interactions

There are a limited number of RCTs and high-quality studies on the interaction between food and DOACs. The 2021 European Heart Rhythm Association (EHRA) practical guide on the use of non-VKA OACs in patients with AF recommends that patients heed caution with concomitant consumption of curcumin, *Echinacea purpurea* (discussed separately in the ►**Supplementary Material**, available in the online version

only), garlic, ginger, Ginkgo biloba, ginseng, and green tea with DOACs.[66] However, the guideline states that no pharmacokinetic or clinical data are available to support these interactions or their corresponding recommendations. Recommendations are based on expert opinion, excluding St. John's wort for which the recommendation is based on the summary of product characteristics.[66]

Besides interactions with specific foods and herbal products mentioned earlier, the bioavailability of rivaroxaban is moderated by food intake. Without gastric contents, the bioavailability of rivaroxaban (with doses >10 mg/d) is 66%, compared with 100% when taken with food. Consequently, rivaroxaban doses greater than 10 mg should be taken with food to achieve optimal bioavailability and therapeutic effect.[69] Other DOACs do not have this requirement.

Potentiating Interactions

Ginger–Cinnamon

According to a recent case report, the consumption of ginger–cinnamon tea had a significant effect on dabigatran potentiation. A patient with AF on dabigatran (110 mg twice daily) for 4 years, with no prior history of bleeding, developed severe gastrointestinal bleeding and hemorrhagic shock after consuming 200 mg/d of boiled ginger–cinnamon for 3 days. The bleeding was uncontrollable and resulted in the patient's death. The coumarin content in the cinnamon and inhibition of P-gp-mediated clearance of dabigatran likely caused the bleeding.[70] It is worth noting that the source of cinnamon is important. Cassia cinnamon, which can be found in Indonesia and Sumatra, contains up to 1% coumarin, whereas true cinnamon, which can be found in Sri Lanka and Southern India, contains only trace amounts of coumarin (about 0.004%).[71] The 2021 EHRA guideline recommends that patients on DOACs exercise caution when consuming products containing ginger.[66] Until further data emerge, caution should be exercised with use of ginger–cinnamon (Cassia cinnamon) with DOACs, including dabigatran.

Attenuating Interactions

St. John's Wort

As previously stated, St. John's wort significantly induces both CYP3A4 and P-gp. The only trial on food–rivaroxaban interactions was an open-label nonrandomized trial performed on 12 healthy subjects who received a single dose of 20 mg of rivaroxaban and a subsequent 2-week course of 450 mg of St. John's wort (hyperforin content: 0.7 mg/100 mg) taken twice daily. Rivaroxaban concentration and factor Xa inhibition were significantly affected by consumption of St. John's wort (GMR of after/before extract [90% CI]: $AUC_{0-\infty}$: 0.76 [0.70–0.82], $p < 0.001$, and factor Xa inhibition: 0.80 [0.71–0.89], $p = 0.007$, respectively).[72] Presently, the 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of AF and the 2021 EHRA practical guide on the use of non-VKA oral anticoagulants in patients with AF recommend to either avoid or exercise caution with St. John's wort use while on DOACs.[66,68]

Discussion

Management of Food–Drug Interactions

This systematic review of studies related to interactions between food and OACs was limited by the scarcity of RCT data, absence of disclosed quantities of foods/active ingredients in the available studies, and in some cases, the lack of known mechanisms of interaction. However, (1) consumption of cranberry products (up to 600 mL of cranberry juice) with warfarin is safe; (2) ginger, even in small quantities (excluding ginger-flavored beverages with negligible amount of ginger), and mango (more than one fruit a day) can both lead to excess warfarin levels; (3) foods with high vitamin K content indisputably attenuate the effects of warfarin; patients prescribed warfarin are advised against consuming high quantities (>250 µg daily) of vitamin K-rich foods and should consume consistent daily amounts of vitamin K; (4) St. John's wort should not be consumed by those taking OACs due to decreased anticoagulant effect and increased risk of thrombotic events; and (5) grapefruit juice, in quantities less than 240 mL daily, is unlikely to have any clinically relevant effect on OAC therapy.

Patient and Clinician Education

As with all drug interactions, educating patients about agents that interact with OACs is of paramount importance. Patients prescribed OACs should be advised against using herbal products without first discussing it with their physician or pharmacist. If not properly educated, patients (and even clinicians) may often overlook the interactions between food and oral drug therapies, including anticoagulants.[73] Thus, clinicians should routinely inquire about patient's use of herbal supplements, as this tends to be left out of discussion during medical visits.[74] In many cases, there may not be enough information regarding the management of said interactions; therefore, the safest course of action is moderating these ingredients.

Currently Available Decision-Making Aids

Limited resources detail practical guidance on food–OAC interactions. Warfarin's full prescribing information as well as professional organizations have shared recommendations regarding food and OAC interactions directed toward both patients and clinicians. The warfarin package insert warns about increased bleeding risk with garlic and ginkgo and warfarin attenuation with St. John's wort, and ginseng. The ACCP recommends a consistent daily intake of vitamin K-containing foods in warfarin users and avoidance of St. John's wort consumption with DOACs. The NHS also provides a pamphlet with easy-to-remember portion sizes of foods that are high in vitamin K, which should not be consumed more than 1 portion per day.[33,42,47]

The following recommendations on foods with clinically significant pharmacodynamic and pharmacokinetic interactions are in line with the data presented in this review. Consumption of turmeric in small quantities does not appear to have any clinically meaningful intrinsic antithrombotic effects. Conversely, consumption of ginseng and large

quantities of fresh garlic (4 cloves) may increase the risk of bleeding. Use of hawthorn products in proximity to invasive procedures may also increase the risk of adverse bleeding. Large quantities of garlic, ginkgo, pomegranate, or turmeric are cautioned in patients taking warfarin because they can increase the bleeding risk. Patients taking DOACs should exercise caution regarding the consumption of ginger–cinnamon (Cassia cinnamon) due to the increased risk of bleeding.

Knowledge Gaps and Data Scarcity

There are limited RCTs on the intrinsic pro-/anticoagulant effects of food and food–VKA interactions. Studies on food–DOAC interactions are even more scarce. All RCTs have small sample sizes and inconsistencies in measured outcomes, which makes meta-analyses challenging. Furthermore, most trials lack a description of the active ingredients in their respective herbal products.

Notably, there are many foods or herbal products reported to interact with warfarin; however, a limited number of studies have been conducted to evaluate these reports. Of these foods, some of which are discussed in the supplement, their mechanism of interaction with OACs is not well understood. Previous studies have suggested various foods that may lead to warfarin attenuation or potentiation, but the available evidence was not sufficiently robust for inclusion in this review. The magnitude of data scarcity on the interactions between various foods or herbal products and OACs must be addressed in future studies to ensure the safety of patients taking these medications.

Conclusion

Future studies can provide evidence on the causality of the currently reported potential interactions and elucidate the importance of said interactions. Patient education on known food–OAC interactions and the disclosure of all herbal products to medical professionals are strongly encouraged.

Conflict of Interest

Outside the submitted work, A.C. has served as a consultant for MingSight, Pfizer, Sanofi, and Synergy and has received authorship royalties from UpToDate. G.P. received funding as Research Grants (paid to his institution from BMS/Pfizer, Janssen, Alexion, Bayer, Amgen, BSC, Esperion, 1R01HL164717-01) and has Advisory Roles in BSC, Amgen, BCRI, PERC, NAMSA, BMS, Janssen, Regeneron. Outside the submitted work, B.B. is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814). B.B. was supported by the Scott Schoen and Nancy Adams IGNITE Award and is supported by the Mary Ann Tynan Research Scientist award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at the Brigham and Women's Hospital, and the Heart and Vascular Center Junior Faculty Award from the Brigham and Women's Hospital. B.B. reports that he was a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of inferior vena cava (IVC) filters. B.B. has not been involved in the litigation in 2022 to 2024 nor has he received any compensation in 2022 to 2024. B.B. reports that he is a member of the Medical Advisory Board for the North American Thrombosis Forum and serves in the Data Safety and Monitory Board of the NAIL-IT trial funded by the National Heart, Lung, and Blood Institute, and Translational Sciences. B.B. is a collaborating consultant with the International Consulting Associates and the U.S. Food and Drug Administration in a study to generate knowledge about utilization, predictors, retrieval, and safety of IVC filters. B.B. receives compensation as an Associated Editor for the New England Journal of Medicine Journal Watch Cardiology, as an Associate Editor for Thrombosis Research, and as an Executive Associate Editor for JACC, and is a Section Editor for Thrombosis and Haemostasis (no compensation).

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