

Dietary supplements and bleeding

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ABSTRACT

An estimated one-third of US adults use herbal supplements, often without reporting that use to their physicians. These supplements can potentially alter bleeding and coagulation during surgery and when used concomitantly with anticoagulants. Our objective was to provide a comprehensive review of the evidence of bleeding risks of the most popular herbal and dietary supplements. A PubMed search and review of the literature was performed. We found that garlic and hawthorn supplementation is strongly associated with surgical bleeding independent of anticoagulants. Cordyceps sinensis, echinacea, and aloe vera are loosely associated with surgical bleeding independent of anticoagulants. In patients on anticoagulants, ginkgo biloba, chondroitin-glucosamine, melatonin, turmeric, bilberry, chamomile, fenugreek, milk thistle, and peppermint are associated with bleeding risk. No evidence was found for bleeding with these supplements independent of anticoagulants. Fish oil, ginseng, and saw palmetto are not associated with bleeding. Evidence for overall bleeding risk associated with St. John's wort, ginger, ginkgo biloba, or cranberry supplementation is conflicting. In conclusion, physicians must be aware of the potential anticoagulant effects of these supplements. It is imperative to report dietary and herbal supplement usage to physicians and is best to discontinue nonessential supplement use 2 weeks prior to surgery.

KEYWORDS Anticoagulants; bleeding; dietary supplements; herbal supplements; surgical bleeding

CME

Target audience: All physicians.

Learning objectives: After completing the article, the learner should be able to

1. Review with the patient a current list of herbal supplements the patient may not have disclosed, especially before procedures and when patients are on anticoagulants.
2. Differentiate between those dietary supplements for which there is high-level evidence of a bleeding risk and those supplements that should be approached with caution due to lack of substantial literature.

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In practice, physicians must anticipate the bleeding potential of patients who are on anticoagulants. In addition, proceduralists must anticipate bleeding potential of patients to properly obtain intraoperative hemostasis and to reduce postoperative bleeding complications. Physicians are aware of when their patients are on medications that alter platelet function, which are often continued through procedures to minimize adverse cardiovascular events.¹ However, the literature is less clear on the topic of dietary and herbal supplements with regard to bleeding risk. Approximately 33% of adults in the United States use herbal supplements.² Supplements are generally considered safe, but they are not regulated as strictly as pharmaceuticals and can also lead to adverse outcomes.³ Thus, in this review, we sought to gather data on the most current popular dietary supplements and the effects they may have on bleeding.

METHODS

The search strategy is outlined in *Figure 1*. Forty-seven of the most popular herbal and dietary supplements in the United States were identified using five sources: the top 50 best-selling “herbal supplements” on Amazon.com, the US Department of Health and Human Services website,⁴ and the Mayo Clinic, Johns Hopkins, and Cleveland Clinic websites. Multiple vitamins and minerals were excluded to isolate specific supplements.

Next, a search of PubMed was conducted using the following search terms: “[supplement] AND (“bleeding” OR “clotting” OR “anticoagulant” OR “antiplatelet” OR “warfarin” OR “heparin”). All articles that these searches yielded were reviewed by title or abstract. Reference lists of relevant articles were also examined. Using these search strategies, a total of 261 articles were selected and reviewed: 63 randomized controlled trials (RCTs), 3 cohort studies, 1 case crossover study, 2 chart or database analyses, 82 case series or case reports, and 110 bench research studies. Ratings of 1 to

5 from the Center for Evidence-Based Medicine were initially used to rate each article.⁵ Of these 261 articles, the 57 most clinically relevant were chosen for direct reference in this review.^{6–63}

FINDINGS

The 47 individual supplements in this results section are divided into nine categories (*Table 1*) and are reviewed in that order.

There is convincing evidence associating garlic supplementation and hawthorn supplementation with surgical bleeding (*Table 2*). Garlic has been associated with surgical bleeding in many case reports,^{6,7} and multiple RCTs show that garlic decreases platelet aggregation. A recent systematic review concluded that, based on the aggregated evidence, garlic does predispose to surgical bleeding.⁸ Hawthorn extract consumption has been shown in a cohort study to increase the risk of bleeding during cardiac surgery.⁹

Cordyceps sinensis, echinacea, and aloe vera are loosely associated with surgical bleeding (*Table 2*). A 2018 case report described excessive surgical bleeding in a patient using Cordyceps sinensis daily as a tonic.¹⁰ Another case report described surgical bleeding associated with echinacea,¹¹ but an RCT showed no increase in bleeding or international normalized ratio (INR) increase associated with echinacea.¹² Finally, aloe vera was associated with surgical bleeding in a case report, in which a patient consuming excess aloe vera had an adverse bleeding reaction with sevoflurane.¹³

There is convincing evidence associating ginkgo biloba supplementation and chondroitin-glucosamine supplementation with bleeding in patients on warfarin (*Table 3*). A large chart review (n = 807,399) revealed that taking ginkgo biloba with warfarin is associated with increased risk for major bleeding events compared to warfarin alone.¹⁴ In addition, two case reports described chondroitin-glucosamine use associated with an increased INR in patients on warfarin.^{15,16} As of 2011, over 40 cases of glucosamine-warfarin interactions had been reported by various drug-monitoring agencies.¹⁷

While there is no higher level evidence available, case reports have associated melatonin,¹⁸ turmeric,^{19,20} bilberry,²¹ chamomile,²² fenugreek,²³ milk thistle,²⁴ and peppermint²⁵ with increased INR or bleeding in patients on warfarin (*Table 3*). Another case report described fatal gastrointestinal bleeding in a patient taking dabigatran along with cinnamon and ginger.²⁶

Many supplements are notable due to their effect on platelet aggregation in humans. Melatonin, flaxseed, and grape seed extract affect platelet aggregation activity and/or blood coagulation activity in humans in RCTs.²⁷ RCTs have additionally shown that flaxseed oil decreases platelet aggregation,²⁸ and grape seed extract increases platelet closure time in humans.²⁹

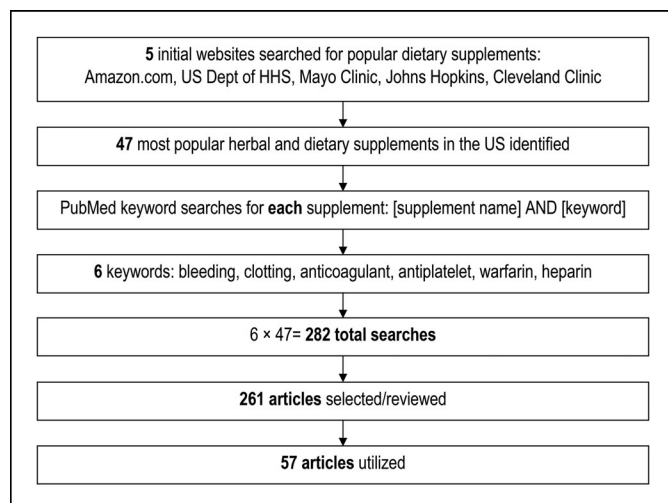


Figure 1. Search strategy.

Table 1. Categorization of the 47 identified supplements based on their association with bleeding outcomes and level of evidence to support the association

Category	Supplements included
Surgical bleeding (5)	Garlic; hawthorn; Cordyceps sinensis; echinacea; aloe vera
Anticoagulant-related bleeding (11)	Ginkgo biloba; chondroitin-glucosamine; melatonin; turmeric; bilberry; chamomile; fenugreek; milk thistle; peppermint; cinnamon; ginger
Platelet aggregation affected in humans (3)	Melatonin; flaxseed; grape seed extract
No effect on platelet aggregation (3)	Fenugreek; turmeric; spirulina
Bench research supporting bleeding potential (8)	Ashwagandha; black pepper; dandelion; evening primrose; feverfew; honey; lavender; lion's mane
No clinical association with bleeding (3)	Fish oil; ginseng; saw palmetto
Unclear evidence (4)	St. John's wort; ginger; ginkgo biloba; cranberry
Procoagulant properties (8)	Black cohosh; chlorella vulgaris; green tea; menthol; propolis; red yeast rice; honey; isoflavones
No evidence (8)	Acidophilus; apple cider vinegar; beet; elderberry; goldenseal; horny goat weed; tea tree oil; valerian

Table 2. Supplements associated with surgical bleeding (independent of anticoagulants)

Supplement	Highest-level evidence
Garlic	Review of RCTs
Hawthorn	Cohort study
Cordyceps sinensis, echinacea, aloe vera	One case report

RCT indicates randomized controlled trials.

Conversely, some supplements that are clinically linked to bleeding through low-level evidence show no effect on platelet aggregation in humans. Previously described case studies associated fenugreek and turmeric with increased INR in patients on warfarin.^{19,20,23} However, RCTs showed that fenugreek does not affect platelet aggregation,³⁰ and turmeric does not increase platelet inhibition, prothrombin time/activated partial thromboplastin time, or thrombin generation in humans.³¹ Additionally, subjective observations by those in an RCT treating patients with spirulina included multiple reports of bleeding, but the same RCT reported that thrombin clotting time and activated partial thromboplastin time were not changed.³²

Some supplements showed anticoagulant or antiplatelet properties through level 5 evidence (bench research), but we could find no clinical evidence for or against bleeding in these supplements. These supplements include ashwagandha,³³ black pepper,³⁴ dandelion,³⁵ evening primrose,³⁶ feverfew,³⁶ honey,³⁷ lavender,³⁸ and lion's mane.³⁹

Fish oil, ginseng, and saw palmetto were thought to be associated with bleeding, by bench research or low-level clinical evidence, but have since been shown in RCTs to have no

Table 3. Supplements associated with anticoagulant-related bleeding, with no evidence for bleeding independent of anticoagulants

Supplement	Highest-level evidence
Ginkgo biloba	Large-scale chart review
Chondroitin-glucosamine	Case series, government reporting bodies
Melatonin	Six case reports
Turmeric	Two case reports
Bilberry, chamomile, fenugreek, milk thistle, peppermint, cinnamon, ginger	One case report

association with bleeding. There are many case reports of fish oil associated with bleeding, and multiple RCTs have shown that fish oil has antiplatelet effects⁴⁰; however, multiple RCTs have shown that these antiplatelet effects do not translate to increased bleeding.⁴⁰ Additionally, a retrospective cohort study of 573 patients showed no interaction between fish oil and warfarin.⁴¹ Finally, a large RCT involving 25,871 participants showed no excess risks of bleeding associated with fish oil.⁴² As with fish oil, there are many case reports of the various types of ginseng associated with bleeding events and procoagulation events.^{7,43-45} However, RCTs have shown that ginseng does not affect³¹ or decreases⁴⁶ warfarin's anticoagulant effect, and a case-crossover study showed no association between ginseng and bleeding.⁴⁷ Similarly to fish oil and ginseng, many case reports have also associated saw palmetto with increased bleeding⁶; however, two RCTs showed that saw palmetto does not increase perioperative bleeding in prostate resection surgery.^{48,49}

Table 4. Approximation of overall bleeding risk for each supplement, based on the highest level of evidence for each

Bleeding risk*	Supplement
High (4)	Garlic; hawthorn; ginkgo biloba; chondroitin-glucosamine
Moderate (25)	a. Cordyceps sinensis; echinacea; aloe vera b. Melatonin; turmeric; bilberry; chamomile; fenugreek; milk thistle; peppermint; cinnamon c. Flaxseed; grape seed extract d. Ashwagandha; black pepper; dandelion; evening primrose; feverfew; honey; lavender; lion's mane e. St. John's wort; ginger; cranberry; spirulina
Low (15)	a. Acidophilus; apple cider vinegar; beet; elderberry; goldenseal; horny goat weed; tea tree oil; valerian b. Black cohosh; chlorella vulgaris; green tea; menthol; propolis; red yeast rice; isoflavones
None (3)	Fish oil; ginseng; saw palmetto

*Inclusion in the "high risk" group is supported by high-level evidence in the clinical setting; systematic reviews, cohort studies, randomized controlled trials, and large case series. Supplements in the "moderate risk" group are supported by case reports (a, b), platelet aggregation studies (c), basic science research (d), or unclear/conflicting evidence (e). Supplements in the "low risk" group have no reported bleeding risk in the literature (a) or procoagulant properties (b). Supplements in the "no risk" group have strong evidence that suggests no clinical association with bleeding. The data include both surgical bleeding and anticoagulant-related bleeding risk.

St. John's wort, ginger, ginkgo biloba, and cranberry are all heavily studied supplements, but the literature is unclear on their effect on bleeding. One RCT showed St. John's wort to have the procoagulant effect of increasing warfarin clearance.⁵⁰ In contrast, a World Health Organization database analysis showed a positive correlation between St. John's wort and hemorrhage events.⁵¹ There are many case reports of ginger associated with bleeding, often due to interaction with anticoagulants.^{6,44,45} Four RCTs reported that ginger reduces platelet aggregation, while four RCTs reported no effect of ginger on platelet aggregation.⁵² Similar to ginger, there are many case reports of ginkgo biloba associated with bleeding—mostly cerebral or orbital bleeding.^{44,45} Despite these reports, a systematic review and meta-analysis including 18 RCTs found no bleeding risk associated with ginkgo biloba.⁵³ Interestingly, as previously discussed, ginkgo biloba did increase bleeding in patients on warfarin in a large chart review.¹⁴ Finally, there are many case reports of cranberry-related bleeding, typically with patients on warfarin.^{6,36,44,45} An RCT of 12 participants showed that cranberry capsules coadministered with warfarin significantly increased INR, but did not cause major bleeding.¹² In contrast, three RCTs concluded that there is no significant interaction between cranberry juice and warfarin at 240 to 480 mL per day.^{54–56}

Many of the supplements investigated have a procoagulant effect, at varying levels of evidence. These include black cohosh,⁵⁷ chlorella vulgaris,⁵⁸ green tea,⁵⁹ menthol,⁴⁴ propolis,⁶⁰ red yeast rice,⁶¹ honey,⁶² and isoflavones.⁴⁵

The remaining supplements investigated had no evidence associating them with bleeding: acidophilus, apple cider vinegar, beet, elderberry, goldenseal, horny goat weed, tea tree oil, and valerian.

DISCUSSION

This review outlines a list of popular supplements that may be associated with bleeding, corroborated by varying

levels of evidence. These supplements alter bleeding through (1) direct antiplatelet or anticoagulant effects, and/or (2) interaction with anticoagulant drugs, often through cytochrome P450 enzymes. Notably, warfarin is metabolized by cytochrome P450 enzymes; supplements that alter these enzymes often affect the coagulation status of patients on warfarin.⁶

It is imperative that physicians have a current list of their patients' herbal supplements, especially before surgery and when patients are on drugs that affect coagulation. Though an estimated one-third of adults take herbal supplements,² many patients do not report supplements they are taking to their physicians.³ In fact, a 2002 survey showed that while 4.8% (131/2723) of patients presenting for surgery were taking herbal supplements, only two of these instances were recorded in their charts.⁶³ Due to the potential for adverse events, it is our conclusion that surgeons should encourage discontinuation of dietary supplements 2 weeks before surgery. This has been encouraged unless otherwise indicated on a case-by-case basis.⁶⁴

While some supplements have clear contraindications, the evidence associating many of the supplements discussed in this review with bleeding is sparse or conflicting. For clinical ease, we have summarized relative bleeding risk of all the supplements discussed in *Table 4*. Due to high-level evidence, garlic and hawthorn should be discontinued prior to surgery. Additionally, there is strong evidence that ginkgo biloba and chondroitin-glucosamine should not be coadministered with warfarin. Many of the other supplements discussed have associations with bleeding in the form of case studies, platelet aggregation studies, and bench research and should be discontinued prior to surgery. However, low-level evidence can be misleading; it was previously thought that fish oil should be discontinued prior to surgery, but level 1 prospective studies have now shown it can be continued.⁶⁴ Additionally, a limitation of our review is that much of the

data is from specific surgical and medical fields and may not be directly applicable to all fields. Thus, larger prospective randomized trials and large-scale chart reviews will assist in guiding further recommendations for many of these supplements.

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