



Natural supplements, herbs, vitamins and food: Do some prevent blood clots?

By Beth Waldron, MA and Stephan Moll, MD

Patients who have ended their recommended course of prescription anticoagulation treatment are understandably concerned about a clot recurrence and will ask “is there anything I can do to prevent a future clot?” Some have heard from friends or the internet that a particular herb, vitamin, or food will aid in the prevention of DVT and PE.

Since more than half of adults in the United States take a dietary supplement of some kind, it may be helpful to examine the science behind some of the most common natural supplements and foods said to prevent blood clots.[1]

Blood clotting background

To put the scientific information which follows into context, it is useful to first understand a bit about how blood clots form in the body.

- Blood clots which form in veins are different from clots which occur in arteries. Therefore, the medications which will prevent and treat them are also different.

Arteries are the blood vessels that carry blood away from the heart, to the legs and arms, the organs in the abdomen, and the brain. Blood clots which form in arteries lead to stroke, transient ischemic attack (TIA or mini-stroke), heart attack, peripheral arterial clot and gangrene, or infarcts in the internal organs (e.g. kidney, spleen, intestine).

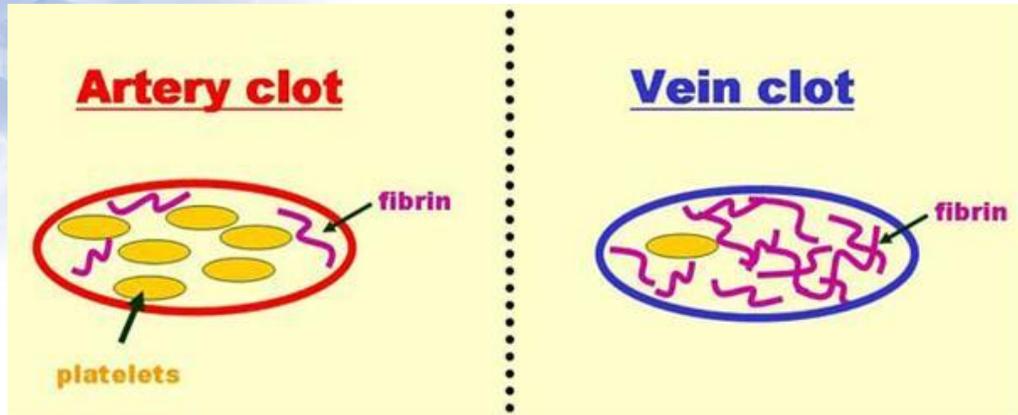
Veins are the blood vessels that carry blood back to the heart from the extremities, the abdomen, and the brain. Blood clots which form in the deep veins of the body lead to deep vein thrombosis (DVT) and pulmonary embolism (PE).

A key point in assessing the effectiveness of a natural product in preventing DVT or PE is:

- Clots which occur in arteries are composed primarily of platelets with a small amount of the clotting protein fibrin. Platelets are the little particles in our blood that help us clot. **Drugs most effective in preventing arterial clots are, therefore, ones which mostly effect platelets, making them slick and preventing them from clumping together.**
- Clots which occur in veins (DVT and PE) are composed primarily of fibrin, with only a small amount of platelets. Fibrin is a protein which crosslinks and forms a meshwork to



help us clot. **Drugs most effective in the prevention of vein clots (DVT and PE) are, therefore, ones which primarily effect fibrin, preventing it from binding together into a clot.**



The majority of herbs, vitamins and foods reviewed below derive their blood clot preventive properties from their effect on platelets, meaning they may have a greater potential role in the prevention of *arterial clots*; but they would likely have less of an impact, if any, on preventing *venous clots* (DVT and PE).

How do we know what supplements may prevent blood clots?

- Laboratory testing: Tests can be done to show if a supplement has an effect on blood clotting in the laboratory setting. For example, if supplements have an effect on blood platelets, making them slick, this can be tested in the laboratory with tests called platelet aggregation studies. Typically, human volunteers ingest the supplement and their blood is then tested in the laboratory to see whether there has been any effect on the platelets. Similarly, supplements have been shown in the laboratory to have an effect in slowing the formation of the clotting protein fibrin. And finally, some supplements have been shown to have clot dissolving (fibrinolytic) properties.
 - *An important consideration:* A demonstrable effect on blood platelets, fibrin or blood clots in laboratory testing does NOT necessarily mean that the supplement prevents blood clots in humans. The result may be a pure laboratory phenomenon. What happens in a test tube may not happen in humans.
 - Clinical trials: An appropriate study to assess the efficacy and safety of a supplement is a clinical trial, in which meaningful clinical endpoints – i.e. the development of DVT, PE, or heart attack or stroke – are investigated in people who take the supplement and compared to people who do not. Such studies have to be of rigorous design, if the results are to be considered credible, applicable, and generalizable. Very few such studies have been done.



Federal regulatory control over safety and efficacy of supplements

Among manufactured nutritional supplements containing natural and naturally derived ingredients, one should keep in mind that in the US nutritional supplements are not regulated the same way as prescription drugs. Supplements are regulated by the Food and Drug Administration (FDA), but not as food or drugs. They fall into a special category called 'dietary supplements'.

Key points are:

- Unlike prescription drugs that must be proven safe and effective for their intended use **before** marketing, there are no provisions in the law for FDA to “approve” dietary supplements for safety or effectiveness before they reach the consumer.[2] Manufacturers don’t have to seek FDA approval before putting dietary supplements on the market. The manufacturer of a dietary supplement or dietary ingredient is solely responsible for ensuring that the product is safe before it is marketed.
- The FDA does have authority to remove a supplement because of safety, but only **after** it has reached market and consumers. Once the product is marketed, the FDA must first show that a “dietary supplement is unsafe, before it can take action to restrict the product’s use or removal from the marketplace.”[3]
- The manufacturer is responsible for ensuring that any claims made about the product are “substantiated by adequate evidence to show that they are not false or misleading.”[3] However, there is no provision under any law or regulation that requires manufacturers to disclose to the FDA or consumers the information they have about the safety or purported benefits of their dietary supplement products.[3]
- The FDA has issued regulations for companies who manufacture and package dietary supplements. “These regulations focus on practices that ensure the identity, purity, quality, strength and composition of dietary supplements.”[2] However, there is no routine regulatory monitoring to insure compliance. From the FDA: “In that FDA has limited resources to analyze the composition of food products, including dietary supplements, it focuses these resources first on public health emergencies and products that may have caused injury or illness.”[3]
- In short, when purchasing dietary supplements, it is “buyer beware”. One must have a good deal of confidence in the individual manufacturer or brand of product one is purchasing that the company is reputable and holds high standards to operate with the integrity to consistently self-regulate itself.



Supplements with anti-blood clot (anti-thrombotic) properties

Definitions:

Anti-platelet = potentially most effective for arterial clot prevention

Anticoagulant = potentially most effective for venous clot prevention

Fibrinolytic = aids in dissolving clots, potentially both arterial and venous

Dietary supplement category	Possible clot prevention properties
Salicylate-containing	anti-platelet
Coumarin-containing	anticoagulant
Vitamin E	anti-platelet, anticoagulant
Vitamin D	anticoagulant
Fish oil (omega 3 fatty acid)	anti-platelet, fibrinolytic
Garlic	anti-platelet
Nattokinase	fibrinolytic
Chocolate	anti-platelet
Evening prime rose oil	anti-platelet, anticoagulant

1. Salicylate-containing foods and supplements

Salicylates are compounds found in many of the over-the-counter products and foods and include the compound acetyl-salicylic acid, the active ingredient in **aspirin**.

Since aspirin affects platelets, it has historically been viewed as an over-the-counter therapy most effective in the prevention of arterial clots. However, new research has emerged in just the past year that suggests patients who are ending standard prescribed anticoagulation (due to DVT or PE) may wish to consider aspirin to potentially decrease the risk of clot recurrence. The data are inconclusive as to whether aspirin prevents recurrent DVT or PE. It is clearly not as effective as prescription anticoagulants, but may be better than doing nothing. See this post for a more detailed description of aspirin's use to potentially prevent recurrent DVT and PE: <http://patientblog.clotconnect.org/2012/05/23/aspirin-prevents-recurrent-dvt-and-pe/>

Many foods contain salicylates, which can mimic some of the anti-platelet effects of aspirin.[4], [5] However, the amount of salicylates even if one eats a large amount of these foods is still only a fraction of the 81 mg of salicylates that a baby aspirin contains. For example, most fruits contain less than 1 mg of salicylate per kg (ie per 2.2 pounds) of fresh mass, while spices and herbs typically fall in the 20-30 mg/per kg range.[5] Clinical studies which have examined the



antithrombotic effects of aspirin have used dosages which “exceed that which can be obtained from diet alone.”[5]

Spices containing salicylates:

- Cinnamon
- Turmeric
- Curry powder
- Oregano
- Peppermint
- Cayenne
- Ginger
- Paprika
- Thyme
- Dill
- Garam masala

Foods containing salicylates:

- Most fruits, including dried fruits. (Slightly higher quantities can be found in blueberries, cranberries, grapes, cherries, strawberries, nectarine, tangerines, oranges)
- Honey
- Vinegar

Beverages containing salicylates:

- Tea, both black and green tea
- Pineapple juice
- Wine, white and red

Bleeding: Since natural salicylates have antithrombotic properties, caution may be warranted by persons taking prescription anticoagulants to avoid excessive bleeding risk.

2. Coumarin-containing plants and herbs

Coumarin is a sweet smelling, natural compound found in some plants. Coumarin has been used as both a food additive and as an ingredient in perfume because of its sweet and aromatic odor.[6] When ingested, it has anticoagulant properties and can be toxic at high doses.[7]

Coumarin has several chemical derivatives that can be found naturally or synthesized in the laboratory. The prescription anticoagulant warfarin (which goes by the brand names Coumadin and Jantoven) is a synthetic derivative of coumarin. Coumarin derivatives are vitamin K antagonists, meaning they get their anticoagulant effect by interfering with the role vitamin K plays in clot formation. Vitamin K antagonists are effective in preventing both arterial and venous clots (DVT/PE).

While some plants and supplements contain coumarin derivatives, evidence is lacking to show what specific clot preventative effect might be achieved at a specific dose.



Plants and dietary supplements containing coumarin derivatives include: [7],[8]

- Alfalfa
- Angelica root
- Aniseed
- Arnica
- Artemesia
- Asa foetica (asafetida)
- Bael fruit
- Bilberry
- Bishop's weed
- Bogbean
- Buchu
- Capsicum
- Cassia cinnamon (*Cassia cinnamon* is one of the four species of cinnamon and contains an especially high amount of coumarin. Cassia cinnamon is a less expensive variety and is the most common cinnamon sold in supermarkets in North America.)
- Celery seed
- Chamomile
- Cloudberry
- Chicory
- Danshen (salvia miltiorrhiza)
- Dandelion
- Dong quai (Danggui, Angelica sinensis)
- Fenugreek
- Horse chestnut
- Horseradish
- Lavender
- Licorice root
- Lovage root
- Meadowsweet
- Melilot
- Nettle
- Parsley
- Passion flower
- Prickly ash
- Quassia
- Red clover
- Rue
- Sweet clover
- Sweet woodruff
- Tonka beans (high levels of coumarin)
- Wild carrot
- Wild lettuce
- The essential oils: cassia oil, cinnamon bark oil, lavender oil
- Some green teas (common green tea generally has low levels of coumarin; however there are certain specialty cultivars of Japanese green tea which have been found to contain a comparatively high content of coumarin)

Bleeding: Since natural coumarins have anticoagulant properties, caution may be warranted by persons taking prescription anticoagulants to avoid excessive bleeding risk.



3. Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant properties. Vitamin E has antiplatelet and possibly also anticoagulant properties, although the mechanism is speculative.[1],[9],[10] Data suggest vitamin E inhibits platelet aggregation and antagonizes the effects of clotting factors.[8] Animal studies indicate that vitamin E supplementation has an anticoagulant effect in the presence of low vitamin K intake.[10] However, vitamin E intake has not been shown to alter coagulation times in humans, although evidence indicates that vitamin E supplementation may inhibit vitamin K and, hence, vitamin K–dependent clotting factors which contribute to clot formation.[10]

The clot preventative effect of vitamin E seen in the laboratory appears to be dose dependent. Significant inhibition of platelet aggregation in laboratory studies has been found only at very large dosages > 800 IU/day, which also carry a risk of increased bleeding and bruising.[8] Doses lower than 400IU/day have demonstrated inconsistent effects on platelets.[1]

In a large-scale, 10 year trial in women (known as the Women’s Health Study) 600 IU of vitamin E taken on alternate days was associated with a significant reduction in DVT/PE, and women with a priory history of clotting or who had a genetic clotting predisposition had a particularly strong benefit.[10] The study authors concluded that “vitamin E may be a useful treatment for prevention of a first or recurrent” DVT/PE.[10] A prospective study which included a large sample size of 129,420 men and women also found that vitamin E intake was associated with a lower risk of DVT/PE.[18]

Bleeding risk: In the Women’s Health Study, no significant difference in bleeding was seen between those taking vitamin E and those who were not. However, a more recent summary of randomized, placebo-controlled trials (meta-analysis) shows that taking vitamin E supplements slightly increases risk for bleeding in the brain.[10] The study authors, therefore, cautioned against the widespread use of daily vitamin E supplementation. Patients who are already at a higher risk for bleeding (such as those taking a prescription anticoagulant or antiplatelet drug) may wish to avoid vitamin E.

4. Vitamin D

We can get Vitamin D from foods, vitamin-fortified foods, supplements and from sunlight. Vitamin D is a nutrient most often linked to the maintenance of strong bones, but it has also been suspected to have an anticoagulant effect by changing certain proteins involved in the clotting mechanism (upregulating thrombomodulin and downregulating tissue factor).[11] However, study results are mixed as to whether vitamin D lowers DVT/PE risk.[11]



One large Swedish study, which looked at the sun exposure habits of 40,000 women over an average of 11 years, found that regular sun exposure reduced DVT/PE risk by one-third.[11] It was hypothesized that vitamin D obtained through sunlight exposure may be the reason behind the protective effect.[11],[12]

However, a notable Norwegian study found that serum levels of vitamin D were not associated with future risk for DVT/PE.[12] Supplementing vitamin D to increase blood serum levels above normal levels did not lower risk of future DVT/PE.[12] The data was inconclusive whether supplementing low levels of vitamin D (vitamin D deficiency) to bring them to higher levels would reduce DVT and PE risk.

In short, sunlight and/or vitamin D *may* play a role in DVT/PE prevention, especially if one is vitamin D deficient, but this is far from being clear.

5. Fish oil, Omega-3 fatty acids

Fish oil is an omega-3 polyunsaturated fatty acid that comes from cold water fish, such as wild salmon, tuna, herring, and anchovies. Omega-3 fatty acids affect blood clotting by decreasing platelet aggregation, which modestly prolongs bleeding time.[9],[13] Some evidence suggests that fish oil supplementation may also enhance fibrinolysis (the break-up of clots).[13],[14]

Randomized controlled clinical trials have reported beneficial effects of omega-3 fatty acids on both preventing and improving cardiovascular disease (heart attack, stroke, high blood pressure).[1],[13] A recently published study from April 2013 confirms these findings by showing that healthy older people who ate at least two servings of fatty fish a week were less likely to suffer fatal heart-rhythm changes or strokes.[15] The study followed almost 2,700 people over age 65 for 16 years and measured their blood levels of omega-3 fats.[15]

However, a 2012 meta-analysis of 20 clinical trials involving more than 68,000 people found that fish-oil supplements did not reduce the risk of heart attack, stroke or sudden death.[16] How to easily reconcile the differing results of these studies with regards to fish oil's effect on cardiovascular health is not clear.

Even less clear is whether the studies examining cardiovascular health (which reflect arterial clots) can be interpreted to have relevancy to the prevention of DVT/PE (venous clots). Studies show fish oil has fibrinolytic properties (meaning it dissolves both arterial and venous clot). [13],[14] However, no study has shown that fish oil supplementation reduces DVT/PE risk. Two large studies which examined the dietary habits of women found no association between risk of DVT/PE and the consumption of omega-3 fatty acids.[17],[18]



Bleeding: An American Heart Association scientific statement concludes that there is little evidence to suggest that an intake of less than 3 grams per day of omega-3 fatty acids would cause clinically significant bleeding.[13] However, fish oil when taken with prescription anticoagulants or anti-platelet drugs like aspirin may increase bleeding time; therefore, caution may be warranted by person taking these drugs to avoid excessive bleeding.[1]

6. Nattokinase

Nattokinase is a soybean food content, produced by the bacterium *Bacillus subtilis* (natto) during fermentation of soybeans. It is a 275 amino acid protein. It is also called “Subtilisin NAT”. [19] It is claimed to have clot-dissolving abilities, similar to plasmin. Plasmin is an important enzyme that we all have in our blood as our natural defense mechanism to dissolve unwanted blood clots. The “clot busters” used in clinical medicine (tPA=tissue plasminogen activator, streptokinase, urokinase, etc) to dissolve blood clots all work through enhancing plasmin’s action. They are sometimes used to dissolve clots causing heart attacks, strokes, pulmonary embolism or deep vein thrombosis. They have to be given intravenously, because they are not active when given orally.

Whether Nattokinase protects from clots is not known. There are some research data that indicate that orally taken Nattokinase increases the clot dissolving activities (fibrinolytic activity) of blood in animals and human volunteers and that it suppresses clot formation and enhances clot resolution in animals.[20],[21],[22],[23],[24],[25],[26] However, to our knowledge, only one clinical study has been performed to assess whether Nattokinase has any real benefit in humans in the prevention of blood clots.[27] In that study, Nattokinase or placebo was given to individuals prior to long distance (7-8 hours) flights. Of the 92 individuals in the placebo group, 7 were said to have developed a clot, all without symptoms, discovered by ultrasound; of the 94 individuals in the Nattokinase group none was found to have a clot. The main flaw of the study, limiting the usefulness of its conclusions, is, that the publication does not indicate whether this was a double-blinded study, or, at least, an investigator-blinded study. A non-blinded study has the potential for bias, limiting the validity of its findings and conclusions.

The FDA has warned that unsubstantiated and illegal claims are being published about the effectiveness of NSK-SD Nattokinase and that Nattokinase products are not “generally recognized as safe and effective” to prevent blood clots.[28],[29] Other health care professionals have also concluded that there is an absence of data at this time that Nattokinase has clinical effectiveness.[30]



7. Garlic

Three compounds in garlic (allicin, adenosine, and paraffinic sulfide) are thought to have antiplatelet properties.[1] There are few data on its effect on preventing venous clots. However, garlic supplements taken in combination with a prescription anticoagulant may play a role in increased bleeding.[1]

8. Chocolate

Chocolate (cocoa) has been said to have many health benefits and one of them is to prevent clots. Dark chocolate has been found to affect platelet aggregation, while white and milk chocolate did not show such platelet effects.[31] The platelet inhibitory effects of dark chocolate is “less profound, but similar to those seen in low dose aspirin”. [32]

It is hypothesized that the flavanols found in cocoa are responsible for chocolate’s inhibitory effect on platelets.[9] Flavanols may influence platelets through several mechanisms.[9]

In addition to dark chocolate and cocoa, flavonoids are also found in red wine, grapes and tea. How much chocolate or flavonoids would need to be consumed to potentially obtain a protective effect is unclear. Participants in studies have consumed a wide range of amounts in concentrated forms, but most often the amount of flavonoids ingested was quite large.[31],[32] However, one major study looking at casual consumption of chocolate found “relatively modest consumption of chocolate in products with highly unpredictable flavanol levels and a variety of other ingredients can still achieve an antiplatelet effect.”[33]

With regards specifically to clot prevention, one study in which participants consumed 100g (approximately 3.5 ounces) of dark chocolate containing 75% cocoa concluded “potentially eating a bar of dark chocolate may provide as much protection as taking an aspirin”.[31]

9. Evening primrose oil (Gamma linolenic acid-containing oils)

Evening primrose oil, borage oil, and black currant oil all contain an unsaturated fatty acid called gamma-linolenic acid. Patients taking warfarin are sometimes advised to not take evening primrose oil because it can increase bleeding risk, but this recommendation has been based primarily upon anecdotal case reports rather than the result of clinical studies. There are few studies examining the anticoagulant effect of these oils in humans.

One study, in rabbits, found that evening primrose oil has both anticoagulant and antiplatelet effects.[34] Evening primrose oil caused an increase in clotting time (prothrombin time [PT]



and activated partial thromboplastin time [aPTT]), at all doses. The effect of moderate doses was said by the study authors to be “almost equivalent” to that of warfarin.[32]

10. Other foods and supplements

It has also been reported other supplements (below) have clot preventative effects. However, there was very little solid data found in a review of scientific literature to suggest they should be considered ‘clot preventatives’. The majority of clot prevention claims appear to be based more upon case reports of bleeding (documented instances where a patient experienced excessive bleeding while taking one of these supplements) than on clinical study. In many of the reported instances of excessive bleeding, patients were taking both a supplement and a prescription anticoagulant or antiplatelet medication—so the impact of the supplement alone is less than clear. Here is what was found regarding laboratory study:

- ginkgo biloba = supplementation does not appear to affect coagulation or bleeding time, no impact on platelet studies except in the lab at very high doses [1, 9]
- ginseng (panax ginseng) = may affect an enzyme necessary in clot formation, no effect on platelet function [1]
- ginger = no confirmed anticoagulant properties in lab studies, possible antiplatelet properties [1,9]
- policosanol = may affect platelet aggregation [1]
- magnesium= inhibited platelet aggregation in lab study[1]
- dong quai = no studies have examined its effects on coagulation, case reports only [1]
- coenzyme Q-10 = no alteration of platelets found in lab study [1]
- glucosamine = may suppress platelet activation in humans, shown to effect platelet aggregation in guinea pigs [1]
- lyopene/tomatoes = reported to inhibit platelet aggregation [1]
- L-arginine = may inhibit platelet response [1]
- taurine = may reduce platelet aggregation [1]
- feverfew = no clinical evidence of anticoagulant activity, possible anti-platelet activity [1]
- selenium = may affect an enzyme necessary in clot formation [1]
- onion = may effect platelet aggregation [9]
- resveratrol = inhibition of platelet adhesion, platelet aggregation [9]
- B-group vitamins = no evidence supplementation prevents DVT/PE [9]



Conclusion

Most of the foods, herbs and vitamins referenced above do have a potential clot preventative effect due to their impact on platelets. Since clots which form in the veins (DVT and PE) are comprised primarily of fibrin with only small involvement of platelets, the impact of these products on the prevention of DVT and PE is likely minimal, if present at all. However, since vein clots do contain some platelets and there are few solid studies on which to base a firm conclusion, some role in the prevention of DVT and PE is possible and cannot be completely discounted.

For the patient who has finished the recommended course of prescription anticoagulant therapy and wishes to do *something* proactive to lessen future clot risk, these natural products *may* provide some measure of additional protection over doing nothing. To what extent these supplements are beneficial, if at all, is not known. There simply are not enough data available to make any solid conclusions.

To be clear: foods, herbs and vitamins are not appropriate alternatives to prescription anticoagulants. If your physician has indicated you should take a prescription anticoagulant, do not stop. If you want to try a natural product after your prescription anticoagulation therapy has ended, we strongly encourage you to do so only under the supervision of your physician who will know your medical history best.

If you are currently taking a prescription anticoagulant or anti-platelet drug, be aware that taking a natural dietary supplement with known anti-thrombotic properties in addition to your prescription *may* increase bleeding risk. It is best to discuss and disclose ALL medications—whether prescription, over the counter, herbal, and vitamin—with your healthcare professional and pharmacist who manage your anticoagulation therapy to insure there are no drug interactions.

Beth Waldron- My personal perspective as a patient:

I've had DVT and PE. I don't want to have another clot. Here is my personal thought process with regards to supplements:

- **Based on what I know, would I take a natural supplement instead of a prescription blood thinner (anticoagulant)?** No. There is absolutely no evidence to suggest any of the dietary supplements are as effective in preventing clots as prescription anticoagulants. None. A pulmonary embolism is life-threatening. If my risk of clot recurrence is considered high and I'm told I should



be anticoagulated, then I'm not going to take any chances on some unproven remedy. I'd stick with what is clinically proven to be safe and effective in the prevention of DVT/PE: prescription anticoagulants.

- **Based on what I know, would I take a natural supplement to prevent future clots after a recommended course of prescription anticoagulation has ended?** Yes. My fear of a recurrent clot is strong enough that I would desire to do something proactive over doing nothing...even if that action has weak clinical evidence....as long as a supplement isn't likely to cause an adverse effect. Worst case, I'm wasting my money; best case, it actually does have some benefit. Taking the chance that there might be some benefit, however slight, in my view would be acceptable over no benefit at all.
- **Which supplement would I take?** Based on the current evidence, I'd strongly consider taking an aspirin over supplementing with one of the natural forms of salicylates. I'd also consider vitamin E and vitamin D. However, I would not take aspirin and vitamin E together as there is evidence this might increase serious bleeding. While natural coumarins, nattokinase and evening primrose oil look good on first glance for venous clots, the limited research leaves me asking more questions than there are answers; so I'm not yet fully comfortable with these choices. All the other supplements I might consider if my goal was to improve cardiovascular health (heart attack, stroke); but I would not consider them to prevent DVT/PE.

Stephan Moll, MD- My personal perspective as a clinician:

- **Based on what I know, would I recommend a natural supplement instead of a prescription blood thinner (anticoagulant)?** No. My arguments match the ones delineated above.
- **Based on what I know, would I recommend a natural supplement to prevent future clots after a recommended course of prescription anticoagulation has ended?** In this situation I would state that it might be reasonable to take a baby aspirin (81 mg once daily) long-term, if the patient tolerates aspirin well and has no significant risk factors for bleeding. If the patient prefers not to take aspirin then I would say that taking any one of the discussed natural products is a reasonable choice. However, I would also say that the patient should not count on these products to have any benefit. Thus, good DVT prevention with drug-anticoagulants is still needed in risk situations (major surgery, immobility, possibly also with long distance travel). And the patient needs to be aware of the symptoms of DVT and PE and seek early medical attention if such symptoms occur.
- **Which supplement would I recommend?** I would not recommend any particular one. None of them has been appropriately studied to draw any solid conclusions about its effectiveness or ineffectiveness. If the patient prefers not to take aspirin, I think any one of the discussed agents is a fair choice.



Disclaimer: We intend this review for informational purposes only. It is not medical advice. We are not advocating natural alternatives over prescription anticoagulants. If you are taking a prescription anticoagulant, do not stop. If you want to try a natural product, we strongly encourage you to do so only under the supervision of your physician who will know your medical history best.

REFERENCES

- [1] Stanger MJ, Thompson LA, Young AJ, Lieberman HR. Anticoagulant activity of select dietary supplements. *Nutr Rev.* 2012 Feb;70(2):107-17.
- [2] FDA Dietary Supplements <http://www.fda.gov/food/dietarysupplements/>
- [3] FDA FAQ on Dietary Supplements http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm#FDA_role
- [4] Swain AR, Dutton SP, Truswell AS. Salicylates in foods, *Journal of the American Dietetic Association* 1985 Aug;85(8):950-60.
- [5] Garry G. Duthie and Adrian D. Wood, Natural salicylates: foods, functions and disease prevention, *Food Funct.*, 2011,2, 515-520
- [6] Ziyin Yang et al, Analysis of coumarin and its glycosidically bound precursor in Japanese green tea having sweet-herbaceous odour, *Food Chemistry*, Volume 114, Issue 1, 1 May 2009, pps 289–294
- [7] Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity, *Biomed Res Int.* 2013;2013:963248.
- [8] Nutescu EA et al, Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opin Drug Saf* 2006 5(3):433–451
- [9] Phang M, Lazarus S, Wood LG, Garg M. Semin, Diet and thrombosis risk: nutrients for prevention of thrombotic disease, *Thromb Hemost.* 2011 Apr;37(3):199-208.
- [10] Robert J. Glynn, PhD, ScD; Paul M Ridker, MD; Samuel Z. Goldhaber, MD; Robert Y.L. Zee, PhD; Julie E. Buring, ScD Effects of Random Allocation to Vitamin E Supplementation on the Occurrence of Venous Thromboembolism: Report From the Women’s Health Study, *Circulation* 2007; 116: 1497-1503
- [11] Lindqvist PG, Epstein E, Olsson H. J, Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis, *Thromb Haemost.* 2009 Apr;7(4):605-10.
- [12] Brodin E, Lerstad G, Grimnes G, Brækkan SK, Vik A, Brox J, Svartberg J, Jorde R, Hansen JB; Serum levels of vitamin D are not associated with future risk of venous thromboembolism. *The Tromsø Study; Thrombosis and Haemostasis* Feb 2013, 109 (5)
- [13] Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee; Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002 Nov 19;106(21):2747-57..
- [14] Jehangir N Din, Rachel M Archer, Scott A Hardin, Jaydeep Sarma, Karin Lyall, Andrew D Flapan, David E Newby; Effect of ω -3 fatty acid supplementation on endothelial function, endogenous fibrinolysis and platelet activation in male cigarette smokers; *Heart* 2013;99:168-174
- [15] Dariush Mozaffarian, Rozenn N. Lemaitre, Irena B. King, Xiaoling Song, Hongyan Huang, Frank M. Sacks, Eric B. Rimm, Molin Wang, David S. Siscovick; Plasma Phospholipid Long-Chain ω -3 Fatty Acids and Total and Cause-Specific Mortality in Older Adults A Cohort Study. *Annals of Internal Medicine.* 2013 Apr;158(7):515-525.



- [16] Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis. *JAMA*. 2012;308(10):1024-1033.
- [17] Pamela L. Lutsey, Lyn M. Steffen, Beth A. Virnig, Aaron R. Folsom Diet and incident venous thromboembolism: The Iowa Women's Health Study, *American Heart Journal*, Volume 157, Issue 6, Pages 1081-1087
- [18] Raphaelle Varraso, Christopher Kabrhel, Samuel Z Goldhaber, Eric B Rimm, Carlos A Camargo Jr; Prospective study of diet and venous thromboembolism in US women and men. *Am. J. Epidemiol.* (2012) 175 (2): 114-126.
- [19] Urano T et al: The profibrinolytic enzyme subtilisin NAT purified from *Bacillus subtilis* cleaves and inactivates plasminogen activator inhibitor type I. *J Biol Chem* 2001;27:24690-6.
- [20] Sumi H et al.: A novel fibrinolytic enzyme (Nattokinase) in the vegetable cheese natto: A typical and popular soybean food in the Japanese diet. *Experientia* 1987;1110-1111.
- [21] Sumi H et al.: Enhancement of the fibrinolytic activity in plasma by oral administration of Nattokinase. *Acta Haematol* 1990;84:139-143.
- [22] Fujita M et al.: Purification and characterization of a strong fibrinolytic enzyme (Nattokinase) in the vegetable cheese natto, a popular soybean fermented food in Japan. *Biochem Biophys Res Commun* 1993;30:1340-1347.
- [23] Urano T et al: The profibrinolytic enzyme subtilisin NAT purified from *Bacillus subtilis* cleaves and inactivates plasminogen activator inhibitor type I. *J Biol Chem* 2001;27:24690-6.
- [24] Suzuki Y et al.: Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. *Life Sci* 2003;73:1289-1298.
- [25] Suzuki Y et al.: Dietary supplementation of fermented soybeans suppresses intimal thickening. *Nutrition* 2003;19:261-264.
- [26] Hsia CH et al. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. *Nutr Res*. 2009 Mar;29(3):190-6
- [27] Cesarone MR et al.: Prevention of venous thrombosis in long-haul flights with Flite Tabs: The LONG-FLITE randomized, controlled trial. *Angiology* 2003;54:T1-T9.
- [28] FDA letter, 2005
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/CyberLetters/ucm058997.pdf>
- [29] FDA letter, 2011 <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm268821.htm>
- [30] Lee T et al. *Harvard Heart Letter*. Oct 2006, Vol.17, Issue 2, 7-8.
- [31] Innes AJ, Kennedy G, McLaren M, Bancroft AJ, Belch JJ. Dark chocolate inhibits platelet aggregation in healthy volunteers. *Platelets*. 2003 Aug;14(5):325-7.
- [32] Debra A. Pearson et al. Flavanols and platelet reactivity. *Clinical and Developmental Immunology*, March 2005; 12(1):1-9.
- [33] Brian Bordeaux et al. Casual chocolate consumption and inhibition of platelet function. *Prev Cardiol*. 2007 Fall;10(4):175-80.
- [34] Azra Riaz, Rafeeq Alam Khan, Shahida Parveen Ahmed. Assessment of anticoagulant effect of evening primrose oil *Pak J Pharm Sci* Oct 2009;22(4):355-9.