REVIEW

Dietary Supplements with Antiplatelet Activity: A Solution for Everyone?

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ABSTRACT

Dietary supplements can have beneficial effects on a number of risk factors for cardiovascular diseases, and interest in the use of nonpharmacologic nutraceutical-based treatments for cardiovascular disorders is growing. The aim of this review is to present the role of dietary supplements with antiplatelet activity in the prophylaxis and treatment of cardiovascular disorders. In addition, this paper describes their effects on another very important element of hemostasis—blood coagulation. However, because controlled human clinical experiments are too limited to clearly identify the antiplatelet and anticoagulant properties of dietary supplements, used alone or in combination with classical antiplatelet therapy (e.g., with aspirin), most information in this article is based on in vitro studies. Therefore, it cannot be unequivocally stated whether dietary supplements are universally safe and bring benefits to all. Some authors suggest that blood platelet count and function should be monitored in patients taking such supplements, especially before and after surgery, as well as other hemostasis parameters such as coagulation times. *Adv Nutr* 2018;9:51–57.

Keywords: supplement, blood platelet, omega fatty acid, fruit, antioxidant, coagulation

Introduction

Blood platelet activation is involved not only in hemostasis, but also in the pathophysiology of various diseases. One such group of diseases is that of cardiovascular disorders: these are the leading cause of global mortality and have a substantial economic impact. Dysregulation of blood platelet activity is linked to the progression of atherosclerosis and other diseases of the cardiovascular system, including blood clots and blockages. The modulation of platelet function involves various steps of platelet activation, particularly blood platelet aggregation. The activation of blood platelets by physiologic agonists such as thrombin, ADP, collagen, and arachidonic acid involves various pathways, e.g., eicosanoid biosynthesis, phosphoinositide hydrolysis, or the production of free radicals, which may act as secondary messengers (1–3).

Various in vitro and in vivo studies indicate that not only antiplatelet drugs, such as aspirin (acetylsalicylic acid), but also certain components of the diet and dietary supplements with antiplatelet activity may reduce blood platelet activation and may have an important influence on the prophylaxis and treatment of cardiovascular disorders, including blood clots and blockages (**Figure 1**) (4, 5). It is known that the presence of elevated levels of inflammatory factors in the blood promotes the development of various diseases, including cardiovascular disorders such as atherosclerotic lesions. Since oxidative stress triggers inflammatory disorders, the antioxidants present in fruits, vegetables, and dietary supplements are therefore believed to slow the progression of cardiovascular diseases (6).

Dietary supplements are a very commonly used modality in complementary and alternative medicine (7–9). However, the recommendations for the use of different dietary supplements are often based on case reports, small clinical experiments, and animal studies, and these supplements are often widely adopted by the public before adequate data about their efficacy and safety are provided (8, 10, 11). This mini-review paper discusses the health effects of various selected dietary supplements, particularly on blood platelet functions. It also describes their effects on another very important element of hemostasis: blood coagulation. Although this article draws mainly on in vitro studies, it does also examine the findings of some in vivo experiments on humans, rats, and mice. This review also reviews the current state of knowledge concerning certain dietary components and supplements, and derived natural products: especially those fruits and vegetables which contain bioactive compounds with antiplatelet, anti-inflammatory, and antioxidant activities (i.e., phenolic compounds and omega fatty acids). This review also describes their role in the treatment of cardiovascular diseases.

Author disclosures: BO, no conflicts of interest.

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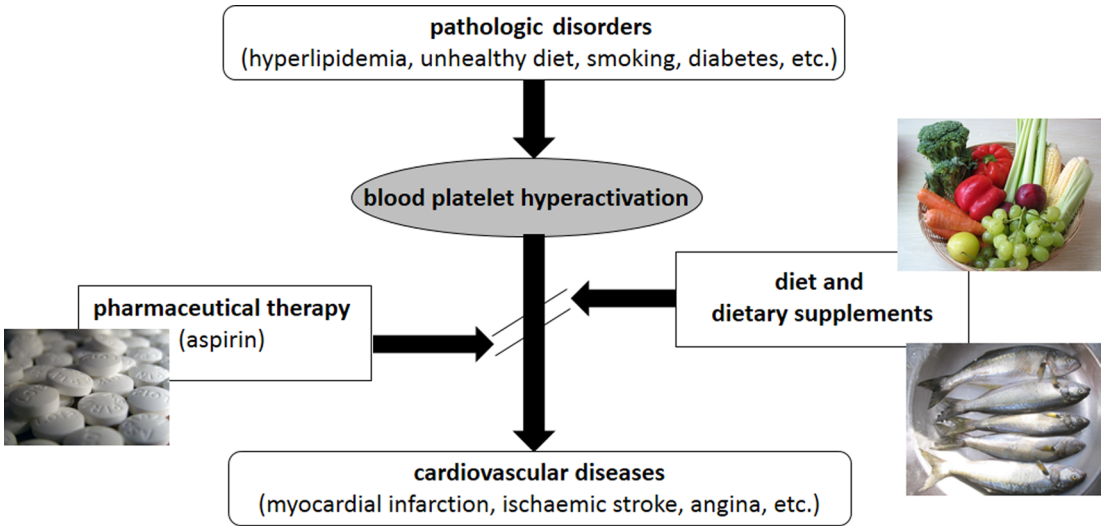

FIGURE 1 Possible alternatives for prophylaxis and treatment of cardiovascular diseases.

Characteristics of Nutraceuticals and Dietary Supplements

Nutraceuticals are used to supplement the diet with substances of natural origin that occur normally in food but in limited quantities, and which have characteristics conducive to maintaining health and the proper functioning of the body. The concept of nutraceuticals was first introduced in 1989 in the United States by Stephan DeFelice, President of the Foundation for Innovation in Medicine. The concept of "nutraceuticals" has been in common use since the 1990s to define dietary supplements or other foodstuffs in pharmaceutical form with health-promoting properties, that is, those yielding health benefits. Sometimes the term is understood to cover all foodstuffs with special health-promoting properties, regardless of their form. Nutraceuticals are also defined as foods that combine nutritional value with the characteristics of pharmaceuticals (12).

However, the difference between a medicine and a nutraceutical is a subject of debate by scientists and health authorities. Usually, it is considered that nutraceuticals should only contain doses lower than those present in typical drugs and exhibit a higher level of safety, particularly during long-term use. Five general groups of compounds are included in nutraceuticals: *1*) carotenoids, tocotrienols, and tocopherols; *2*) phenolic compounds (i.e., flavonoids, isoflavonoids, and anthocyanins), *3*) carbohydrates and their derivatives (i.e., ascorbic acid and fiber), *4*) minerals (i.e., selenium compounds), and *5*) micro-organisms (probiotics and prebiotics).

A recent study by Santini and Novellino (12) proposes a clear difference between dietary supplements and nutraceuticals. They regard dietary supplements as micronutrient-based formulations, which are often multicomponent in nature, containing dietary ingredients such as amino acids, vitamins, and minerals, which are not specifically intended to prevent or cure a health issue.

Supplements and nutraceuticals act by various mechanisms. One such mechanism is based on their antioxidant activity, which protects cellular structures against the processes of degeneration resulting from environmental pollution, the aging process, and other adverse influences on health. In addition, some nutraceuticals and dietary supplements also possess antiplatelet activity (6, 13–18). Supplements may also compensate for the needs of those with particular nutrient insufficiencies, and in this case, their basic mechanisms of action are associated with the typical molecular, biochemical, and physiological properties of their ingredients.

Blood Platelets and Dietary Supplements

Blood platelets play an important role in cardiovascular disorders, both in atherosclerosis and in the development of acute thrombotic events (6). Their significance in cardiovascular disorders is demonstrated by the beneficial effects of antiplatelet agents, i.e., aspirin and clopidogrel. Blood platelets also demonstrate increased activity in people with obesity, diabetes, and insulin resistance, particularly increased aggregation (6). However, as therapy with antiplatelet drugs is often associated with various side effects, the use of natural compounds represents an interesting alternative approach.

Recently, O'Kennedy et al. (6) found water-soluble tomato extract (Fruitflow) to be the first commercial product in Europe, now commercially available worldwide, to contain bioavailable cardioprotective compounds including an anti-angiotensin–converting enzyme and anti-inflammatory factors. Although the authors do not specify the lycopene concentration in Fruitflow, its cardioprotective action may be associated with its presence: it is well known that tomato and tomato-based products constitute the main dietary source of lycopene in Western countries, constituting >80% of lycopene intake, but apricot, pink grapefruit, watermelon, and papaya are also plentiful sources. Recent experiments indicate that lycopene has cardioprotective properties: it

exerts its antioxidant properties via the inhibition of LDL and cholesterol oxidation, which is central to the initiation of atherosclerosis. Moreover, lycopene possesses anti-inflammatory properties which counter the inflammatory component of the action of atherosclerosis (19).

O'Kennedy et al. (6) note that Fruitflow is prepared in 2 ingredient formats: Fruitflow 1 is a syrup, of which >50% w/w consists of tomato-derived carbohydrates, and ~3% w/w of known compounds with antiplatelet activity; Fruitflow 2 is a low-carbohydrate powder, of which >55% w/w consists of bioactive compounds dried to produce a tablet-grade powder. Fruitflow 1 is suitable for use in drinks and foods with high water content. The authors studied the effect of these 2 products (Fruitflow 1 and 2) on blood platelet aggregation in platelet rich-plasma from 20 donors using 4 major platelet agonists: collagen, arachidonic acid, ADP, and thrombin receptor-activated peptide (TRAP; a peptide beginning with the SFLLRN sequence Ser-Phe-Leu-Leu-Arg-Asn). The antiplatelet activity of the 2 tested products was expressed as IC_{50} values for platelet aggregation stimulated by ADP or collagen. These were found to be <1.0 for Fruitflow 1 and <0.05 for Fruitflow 2.

Importantly, Fruitflow does not directly affect blood coagulation, i.e., it does not change clotting time. However, Fruitflow differs fundamentally from typical antiplatelet drugs in the reversibility of its action. A study of 47 healthy people demonstrated that the effects of a single dose of Fruitflow were similar to a single 75-mg dose of aspirin, based on measurements of blood platelet aggregation and thromboxane A_2 biosynthesis. The European Health Claims Regulation recommends that Fruitflow should be consumed daily: 3 g for Fruitflow 1 and 150 mg for Fruitflow 2. These products must only be included in foods (i.e., yogurt drinks, fruit juice with a total volume ≤250 mL), provided as tableted or encapsulated food supplements, or powdered, to be taken with 250 mL water (6).

Other observations have shown that the consumption of berries, i.e., aronia berries (*Aronia melanocarpa*), cranberries (*Vaccinium* sect. *Oxycoccus*), sea buckthorn berries (*Hippophae rhamnoides*), and grapes (*Vitis*), as well as their various commercial derivatives, is inversely associated with cardiovascular diseases, such as atherosclerosis in elderly men (20–22). Some papers have demonstrated that supplementation with commercial products made from aronia berries (Aronox by Agropharm LTP, Poland, both no. 020/2007k) has cardioprotective properties. This dietary supplement inhibited blood platelet aggregation stimulated by ADP, decreased total cholesterol and LDL cholesterol concentrations, and reduced clot formation in patients with metabolic syndrome when administered at 100 mg 3 times/d (17). In addition, Aronox was found to modify hemostasis in in vitro experiments. Inhibition of platelet aggregation was observed in a model of hyperhomocysteinemia, and in platelets isolated from healthy subjects (14, 16).

Various experiments showed that not only fresh berries, but also berry products (i.e., Aronox) possess high concentrations of phenolic compounds (23, 24), which demonstrate antiplatelet activity, as well as anti-inflammatory and antioxidant properties in vivo and in vitro. These properties are very important for their cardioprotective activity, i.e., aronia berry extract has the capacity not only to reduce blood platelet aggregation, but also to lower blood pressure and decrease inflammation in atherosclerosis (25–27). It is interesting that Aronox inhibited in vitro reactive oxygen species production in platelets isolated from healthy subjects, but also in platelets from patients with invasive breast cancer, both before and after surgery and after phase I of chemotherapy (15). Daskalova et al. (28) report that aronia berry juice sold commercially in 250-mL glass bottles (Vitanea Ltd., Plovdiv, Bulgaria) demonstrates anti-atherogenic and cardioprotective properties in aging rats. In addition, there are no data associating Aronox, berry juices, or other berry products with toxic effects. More details about the multifunctionality of berries toward blood platelets and the role of berry phenolics in cardiovascular disorders are described in a review by Olas (21).

Moreover, other studies note that grape seed extract, supplied by Bionorica (Germany), has antiplatelet and antioxidative properties: it inhibited different steps of platelet activation, including platelet adhesion and aggregation in vitro. This extract is rich in phenolics, consisting of a mixture of ~95% oligomeric phenolic compounds (29).

The berry phenolic compounds that have the greatest beneficial impact on cardiovascular disorders and blood platelet functions may well be anthocyanidins, procyanidins, flavonols, and phenolic acids (21, 22). The richest known natural source of anthocyanidins (representing water-soluble flavonoids)—in this case delphinidins—is the maqui berry (*Aristotelia chilensis*) from which another commercial supplement, Delphinol, is produced. Watson and Schonlau (18) report that Delphinol, standardized to 25% delphinidin, with anthocyanins, phenolic acids, flavonols, and flavanols (30), has anti-inflammatory and antioxidant properties; in addition, studies by Yang et al. (31) based on platelet-rich human blood plasma, gel-filtered human plasma, or the platelet agonists ADP and TRAP, suggest that it may lower blood platelet aggregation and contribute to thrombosis prevention. They also report that delphinidin glucoside does not affect bleeding time when applied intravenously to mice at concentrations of 0.5, 5, and 50 μM, possibly indicating an absence of side effects. Another study, by Brunswick Laboratories (Southborough, MA, USA) (32), indicates that Delphinol is a good scavenger of various reactive oxygen species and reactive nitrogen species, i.e., peroxynitrite, single oxygen and peroxyl radicals. The standardized aqueous maqui berry extract Delphinol is distributed worldwide by the company Maqui New Life, based in Santiago, Chile and Cham, Switzerland (18).

However, it is important to note that fresh berries and their products, including dietary supplements, exhibit more effective antiplatelet action than do the pure compounds (21).

Another interesting product with antiplatelet and antioxidative properties is the extract of the bark of *Yucca schidigera*, which contains various phenolic compounds, including resveratrol (3,4′,5-trihydroxystilbene). It was found to inhibit

platelet adhesion and secretion, and reduced the oxidative stress measured by various biomarkers in blood platelets in vitro. This product has a generally-recognized-as-safe label, and is approved by the United States FDA to be used as a food additive (29, 33, 34).

In the United States, Applephenon, a phenolic compound extract from Granny Smith apples recognized as safe by the FDA, may not possess antiplatelet properties, but it does reduce serum cholesterol concentration. Nagasako-Akazome et al. (13) observe that a maximum administrated dose of 1500 mg/d reduces total cholesterol by ~5% and LDL cholesterol by ~8%, but also increases HDL cholesterol by ~5%. Santini and Novellino (12) found that AppleMets, a commercial product containing the Annurca phenolic compound extract, was also found to reduce hypercholesterolemia in healthy people during a clinical study. Their results showed that administering two 400-mg capsules/d with 2 main daily meals reduces total cholesterol by ~25% and LDL cholesterol by ~40%, while increasing HDL cholesterol by ~50%. Moreover, as the product does not cause any chemical, hematological, or urinary effects, it is safe for use in humans (12).

A considerable body of research has demonstrated that garlic and its bioactive compounds are effective in reducing cardiovascular disorders by normalizing pathological states such as high blood pressure, abnormal blood platelet aggregation, and high concentrations of oxidized LDL cholesterol (35–42). However, there is no clear information in the literature about the influence of commercial garlic supplements on hemostasis, including the inhibition of platelet aggregation and changes in coagulation.

Numerous epidemiologic studies and clinical trials have demonstrated the health benefits of various omega-3 PUFAs as dietary lipids and also as different commercial products, the key advantage being a reduced risk of coronary heart diseases. PUFAs act mainly by changing gene expression via influencing the activity of a number of key nuclear transcription factors that inhibit or activate the expression of specific genes. The European Food Safety Agency recommends a daily intake of 250 mg/d of EPA and DHA for adults (43). However, the quality of fish oil depends on the species of fish, the season, and the location of fishing sites (44). There are several different reviews available on the effects of PUFAs such as EPA and DHA on the risk factors for cardiovascular disorders, e.g., the oxidative modification of LDL, elevated plasma lipid concentrations, and blood platelet aggregation. McEwen et al. (45) suggest that patients with cardiovascular diseases should receive a higher dose of PUFAs than should healthy subjects.

Elsewhere, Browning et al. (46) examine the short-, medium-, and long-term incorporation of selected PUFAs (EPA and DHA) into blood platelets. The subjects were provided with identical amounts of EPA and DHA, equivalent to 2 oily fish servings/wk (or 6.54 g/wk EPA and DHA), either intermittently (i.e., 1 portion 2 times/wk) or continuously (i.e., divided into daily amounts). Sixty-five subjects completed the study. It was found that EPA and DHA enrichment of blood platelets is greater when provided as a continuous daily supply compared with the same amounts in biweekly "portions" of oily fish. These findings may have implications on the associated health benefits demonstrated in experiments based on continuous supplementation, and suggest that the same dose of DHA and EPA may have a lesser impact on DHA and EPA status when obtained by sporadic oily fish consumption (46).

Haimeur et al. (47) compared the effects of 2 PUFA-rich food supplements on risk factors for cardiovascular disease. They used freeze-dried *Odontella aurita* and fish oil, and observed that both the microalga and the fish oil significantly reduced serum lipid concentrations and ADP- and collagen-stimulated blood platelet aggregation in rats.

Vericel et al. (48) found a low intake of DHA of 400 mg/d for 2 wk to have a beneficial effect on blood platelet functions and to play a favorable role in reducing oxidative stress in type 2 diabetic patients. They measured blood platelet aggregation induced by collagen, as well as production of thromboxane B_2 and F_2-isoprostanes. The study group comprised 11 postmenopausal women with type 2 diabetes. Other studies on blood platelets have also shown that docosapentaenoic acid reduces platelet aggregation (49).

Bachmair et al. (50) demonstrated that supplementation with a 9c,11t-rich conjugated linoleic acid (9c,11t-CLA) shows no clear inhibitory action on blood platelet function in healthy subjects at low and moderate cardiovascular risk. In this study, 43 healthy adults received 4 g/d of 9c,11t-CLA enriched oil (CLA80:20). On the other hand, Reiner et al. (51) indicate that dietary alpha-linolenic acid did not protect against venous thrombosis in mice.

Blood Coagulation and Dietary Supplements

Wang et al. (8) suggest that dietary supplements contain various pharmacologically active agents, which may affect not only blood platelet function, but also blood coagulation. The modulation of platelet function and coagulation may act by various mechanisms, i.e., direct effects, pharmacokinetic and pharmacodynamic interactions (8). They describe the effects of the most commonly used natural products on blood platelet functions and coagulation: 11 herbal medicines including garlic, Echinacea, ginger, green tea, and ginkgo, as well as 5 dietary supplements—vitamins, fish oil, coenzyme Q10, glucosamine, and chondroitin sulfate. Their findings indicate that garlic, gingko, green tea, and fish oil may increase the risk of bleeding. Other in vivo experiments demonstrated that PUFAs decreased blood platelet aggregation, but did not influence bleeding time (52, 53). However, in clinical experiments, the reduction of blood platelet aggregation by PUFAs was more specific: in male subjects, EPA was significantly more effective in reducing blood platelet aggregation than placebo but DHA was not, while in female subjects, DHA inhibited aggregation but EPA did not.

Bedi et al. (54) suggest that dietary supplements have the potential to cause bleeding in patients who undergo

TABLE 1 Selected dietary supplements with antiplatelet activity and their other properties

Dietary supplement	Antiplatelet activity	Anti-inflammatory activity	Antioxidant	Effect on blood coagulation	References
Applephenon	No information	No information	No information	No information	(13)
Aronox	Observed (in vitro)	Observed (in vivo and in vitro)	Observed (in vitro)	No information	(14–17)
Delphinol	Observed (in vitro)	Observed (in vitro)	Observed (in vivo)	No effect (in vivo)	(18)
Fruitflow	Observed (in vivo)	Observed (in vivo)	No information	No effect (in vivo)	(6)

surgery. Although the authors found the postoperative blood platelet count to be normal, the study did not include blood platelet function tests. The patients used dietary supplements, i.e., Tab Aretic Sea (Softgel) 3 times/d (containing natural fish oils with olive oil: 375 mg EPA, 150 mg DHA, and 150 mg oleic acid per Softgel) and Tab ForeverGarlic-Thyme (Softgel) 2 times/d (containing 10 mg garlic and 50 mg thyme per Softgel). Both supplements are produced by Forever Living Products (Scottsdale, AZ, USA). The patients took them for 3 mo before surgery, but it important to note that they did not take typical antiplatelet drugs in this time.

Conclusion

Dietary supplements are a common component of the diet in various countries. Stanger et al. (55) recently noted that about half of the adult population of the United States take these components regularly.

Dietary supplements may change hemostasis by various mechanisms, i.e., inhibiting blood platelet activation, especially platelet aggregation, and reducing arachidonic acid metabolism. Moreover, dietary supplements may affect coagulation when taken alone or in combination with antiplatelet drugs (55). Table 1 lists selected commercial dietary supplements with a range of activities including antiplatelet properties, while Figure 2 presents the effects of various components of diet (including fruits—especially berries, vegetables, red wine, and dark chocolate) and dietary supplements (i.e., Aronox, Delphinol, and Fruitflow) as well as the parameters they influence, which may be important in the prophylaxis and treatment of cardiovascular diseases.

It is important to note that hemorrhages, postoperative bleeding, or other diseases have occasionally been associated with the consumption of dietary supplements. However, the number of well-controlled experiments and high-quality human clinical trials is too limited to demonstrate that such supplements have consistent antiplatelet and anticoagulant properties, especially commercial supplements used alone or in combination with drugs such as aspirin, the classic antiplatelet drug. Therefore, it is difficult to determine whether dietary supplements are universally safe and beneficial. Some authors suggest that patients taking supplements with antiplatelet activity, especially before and after surgery, should be monitored with regard to blood platelet count or platelet functions, together with other hemostasis parameters including coagulation times.

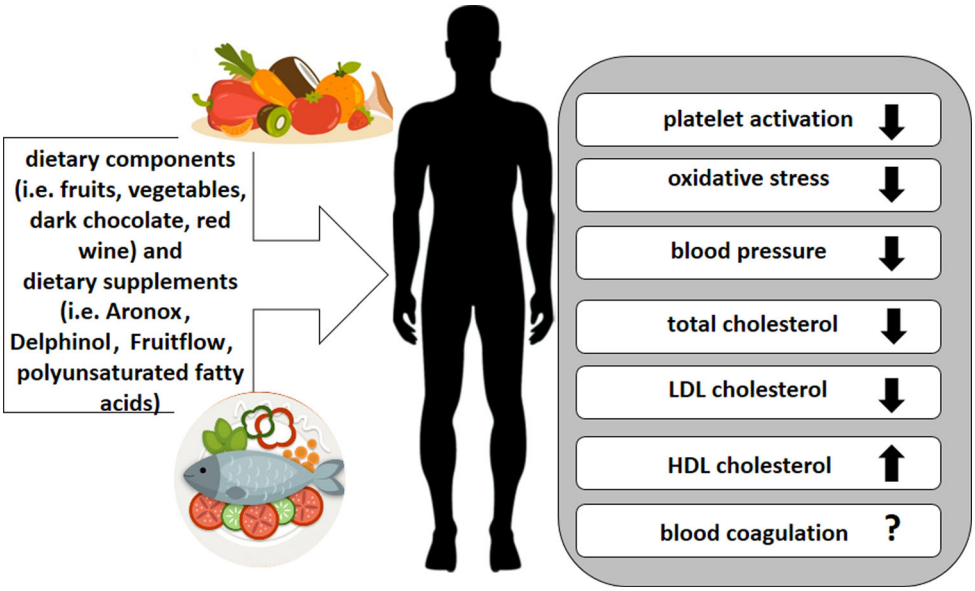

FIGURE 2 Human experiments involving selected dietary supplements in cardiovascular diseases; effects and parameters altered by these supplements.

Acknowledgments

The sole author had responsibility for all parts of the manuscript.

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