

# The effect of vegetarian diet, plant foods, and phytochemicals on hemostasis and thrombosis<sup>1-3</sup>

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**ABSTRACT** Ischemic heart disease (IHD) is multifactorial with a complex etiology. Conventional risk factors including serum lipids account for less than one half of future IHD events. In the past few years, novel risk factors such as hemostatic and thrombotic factors contributing to the development and progression of IHD have been explored. Typically, diet is the first line of consideration in the prevention of IHD, but very little is known about the effect of diet and nutrients on hemostasis and thrombosis. Cross-sectional studies indicate that vegetarians may have a lower concentration of certain markers of hemostasis compared with nonvegetarians. Platelet aggregation, an index of thrombosis, appears to be higher among vegetarians than nonvegetarians, perhaps because of the lower intake of long-chain n-3 fatty acids among vegetarians. Monounsaturated-fat-rich plant foods may have a protective role in hemostasis and may explain in part the lower incidence of IHD in Mediterranean countries where residents consume a diet high in monounsaturated fatty acid. Finally, certain fruits and vegetables such as soy, garlic, and purple grapes may have antithrombotic effects, which may in part be due to the phytochemicals in these foods. Although this review suggests that a plant-based diet with sufficient n-3 fatty acids and certain fruits and vegetables may have a favorable impact on hemostasis and thrombosis, the evidence is neither sufficient nor conclusive at this time to warrant specific recommendations for the public. Clearly, much remains to be done in this area of investigation. *Am J Clin Nutr* 2003;78(suppl):552S-8S.

**KEY WORDS** Hemostasis, thrombosis, vegetarian diet, plant foods, phytochemicals

## INTRODUCTION

Ischemic heart disease (IHD), the major cause of mortality and morbidity in Western countries (1), is multifactorial with a complex etiology. Some of the conventional risk factors extensively studied and documented, such as serum lipids and lipoproteins (2, 3), account for less than one half of future IHD events (4). Moreover, it is possible to develop atherosclerosis even when the serum lipids and lipoprotein values are within the normal range (5). In the past few years, novel risk factors that contribute to the development and progression of IHD have been identified or rediscovered.

Some of these newer risk factors are homocysteine, hemostatic and thrombotic variables, lipoprotein(a), and inflammatory markers. Hemostasis is a process of smooth muscle cell contraction, platelet aggregation, and blood coagulation that occurs at

the site of an injured small vessel to prevent bleeding. It also refers to a balance between blood clotting and lysis. Thrombosis refers to an intravascular blood clot resulting from hyperaggregability of platelets, increased blood viscosity, and impaired fibrinolysis (6, 7). Population-based studies have shown that the prethrombotic state is an important predictor of IHD (8-10). Markers of hemostasis and thrombosis that have been studied more consistently (**Table 1**) include fibrinogen, factor VII, agonist-induced platelet aggregation, and fibrinolysis measured by tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1). A detailed discussion of these markers and their association with IHD and clinical implications appears in other review articles (5, 11, 12).

Dietary modification is the first step in preventing IHD, and the role of diet in modifying some of the risk factors of IHD like blood lipids and lipoproteins is well documented (13, 14). However, the effects of dietary patterns, specific foods, or nutrients on hemostatic and thrombotic variables are less well understood. Thus, the purpose of this review is to describe what is known about the effects of vegetarian diets, plant foods, and phytochemicals on hemostasis and thrombosis.

## VEGETARIAN DIET

Vegetarian dietary practices have been associated with a reduction in many chronic diseases, including cardiovascular disease (CVD) (15, 16). A healthy vegetarian diet is characterized by more frequent consumption of fruits and vegetables, whole grains, legumes, and nuts, resulting in higher intakes of dietary fiber, antioxidants, and phytochemicals compared with nonvegetarian diets. These plant foods and nutrients influence IHD risk factors such as blood lipids, lipoproteins, blood pressure, and lipid peroxidation, thereby reducing the overall mortality from IHD. Although prospective studies such as the Northwick Park Heart Study and the Framingham Study suggest a positive association between high fibrinogen, factor VIIc, factor VIIIc, and risk of IHD

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**TABLE 1**  
Selected markers of hemostasis and thrombosis<sup>1</sup>

Factor	Function
<b>Hemostasis</b>	
Fibrinogen	Structural protein of blood coagulation converted to fibrin network by the action of thrombin
Factor VII	Proenzyme of extrinsic pathway of blood coagulation that activates factor X
Fibrinolysis	Gradual progressive degradation of fibrin into soluble fragments
tPA	Fibrinolytic system activator that converts plasminogen to plasmin
PAI-1	Serine protease inhibitor with high affinity for tPA and ability to inhibit the fibrinolytic system
<b>Thrombosis</b>	
TXA <sub>2</sub> and TXB <sub>2</sub>	Potent platelet aggregators, produced from arachidonic acid
Platelet aggregability	In vitro platelet aggregation induced by agonists such as ADP, thrombin, epinephrine, and collagen

<sup>1</sup>tPA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor 1; TXA<sub>2</sub> and TXB<sub>2</sub>, thromboxane A<sub>2</sub> and B<sub>2</sub>.

(17, 18), the influence of plant-based diets on these factors is not as well understood.

**Table 2** summarizes the findings from 5 cross-sectional studies (19–23) on vegetarian diets and hemostatic and thrombotic factors. Overall, the studies seem to indicate a favorable impact of vegetarian diet on hemostasis. This benefit was shown in terms of either a lower concentration of coagulation factors or an increase in fibrinolysis. Only one study did not show significant differences in hemostatic risk factors between vegetarians and nonvegetarians (20). The differences in the intake of dietary fiber may explain the nonsignificant results in this study. Vegetarians and nonvegetarians (20) in this study had similar but lower intakes of dietary fiber (5–6 g/d), while vegetarians in the other studies (21, 22) had fiber intake that was significantly greater (26–68 g/d) than that of their nonvegetarian (14–28 g/d) counterparts. In fact, fiber has

been shown to decrease factor VIIc in young, middle-aged, and elderly subjects (24, 25).

Two of the studies (22, 23) summarized in Table 2 also measured agonist-induced platelet aggregation, an index of thrombosis. These studies found that vegetarian diets increased platelet aggregation compared with nonvegetarian diets. One explanation for this could be the differences in the intake of long-chain n–3 polyunsaturated fatty acids (LCPUFAs) among vegetarians and nonvegetarians. Frequent consumption of marine fish, a rich source of LCPUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been shown to provide cardio-protection (26, 27). This is brought about by a higher incorporation of EPA in platelet membranes by displacement of arachidonic acid, a precursor to the potent platelet aggregator thromboxane A<sub>2</sub> (28). Li et al (23) reported that vegetarians in comparison to non-vegetarians had lower total plasma phospholipid n–3 fatty acids (4.2% compared with 6.0% of total fatty acids) and a lower ratio of arachidonic acid to EPA (9.8 compared with 17.5). Similar findings were reported by Mezzano et al (22). Unfortunately, these studies did not report dietary intakes of EPA and provide only a speculative explanation for the relation between EPA intake, plasma EPA levels, and platelet aggregation.

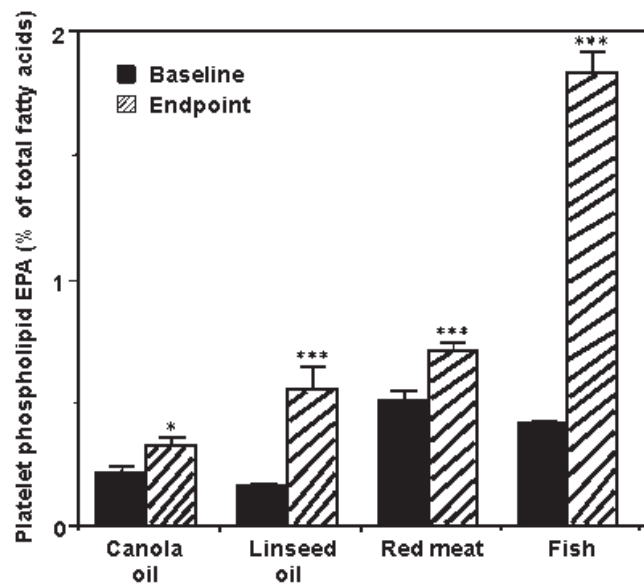
The n–3 PUFA that is present in plant foods is  $\alpha$ -linolenic acid (ALA), which in the body can be converted to EPA and DHA by elongase and desaturase enzymes. However, the efficiency and rate of conversion of ALA to EPA and DHA are typically low (29). The Nurses' Health Study showed that the relative risks of fatal IHD were significantly lower in the highest quintile compared with the lowest quintile of ALA intake even after adjusting for confounders (30). Other prospective studies also show an inverse relation between ALA intake and incidence of IHD mortality (31–33). However, human experimental studies on the effect of ALA on hemostatic and thrombotic factors are sparse.

In a study by Li et al (34), free-living lactoovo vegetarians were randomized into 2 groups, one receiving moderate ALA and the other high ALA for 42 d. The purpose of adding the ALA was to bring the dietary n–3-to-n–6 ratio to 1:3 and 1:1 in the 2 groups,

**TABLE 2**  
Cross-sectional studies on healthy vegetarians and hemostasis and thrombosis factors<sup>1</sup>

Subjects and diet groups	Results	Reference
Great Britain, men and women, 18–65 y old		19
Vegan ( <i>n</i> = 27)	Factor VIIc (V<NV)	
Lactoovo vegetarian ( <i>n</i> = 23)		
NV ( <i>n</i> = 282)		
Taiwanese Buddhist, men and women, <30 y old		20
V ( <i>n</i> = 55)	Factor VIIc (no difference)	
NV ( <i>n</i> = 59)	Fibrinogen (no difference)	
West Africa, men and women, 35–60 y old		21
Vegan ( <i>n</i> = 8)	Fibrinogen (V<NV)	
Lactoovo vegetarian ( <i>n</i> = 28)	Fibrinolysis (V>NV)	
NV ( <i>n</i> = 40)		
Chile, men and women, 27–51 y old		22
Vegan ( <i>n</i> = 3)	Factor VIIc (V<NV)	
Lactoovo vegetarian ( <i>n</i> = 23)	Fibrinogen (V<NV)	
NV ( <i>n</i> = 26)	Platelet aggregation (V>NV)	
Australia, men, 20–50 y old		23
Vegan ( <i>n</i> = 18)	Factor VIIc (V<NV)	
Lactoovo vegetarian ( <i>n</i> = 46)	Platelet aggregation (vegan>NV)	
NV ( <i>n</i> = 83)		

<sup>1</sup>V, vegan and lactoovo vegetarian combined; NV, nonvegetarian. Results are significantly different, *P* < 0.05.



**FIGURE 1.** Effect of 3 different n-3 fatty acid sources on the proportion of EPA in platelet phospholipids: canola oil provided 3.7 g ALA/d; linseed oil provided 15.5 g ALA/d; red meat provided 70 mg EPA/d; and fish provided 847 mg EPA/d. Baseline for canola oil and linseed oil diet groups was 14-d safflower oil-based diet, and that for the red meat and fish groups was 7-d vegetarian diet (34, 36). Endpoint was after 28 d for canola and linseed oil diet groups and 14 d for red meat and fish groups. Significantly different from baseline: \* $P < 0.05$ , \*\*\* $P < 0.001$ . Reprinted with permission from reference 34. ALA,  $\alpha$ -linolenic acid; EPA, eicosapentaenoic acid.

respectively. The variation in the amount of ALA and therefore the n-3-to-n-6 ratio was made possible by the incorporation of modified margarine made from canola and linseed oil provided to all subjects. The proportions of EPA and total n-3 PUFA and the n-3-to-n-6 ratio in platelet phospholipids were greater at the end of the study compared with baseline in both diet groups, but the mean was higher in the high-ALA group compared with the moderate-ALA group. In spite of the higher incorporation of the n-3 PUFA into platelet phospholipid, there were no significant differences in any of the thrombotic factors measured in this study, including agonist-induced platelet aggregation. In contrast, Mezzano et al (35) showed that when lactoovovegetarians are supplemented with 700 mg of EPA and DHA for 8 wk, there is an expected increase in plasma EPA and DHA levels. In addition, supplementation with EPA and DHA reduced platelet aggregation with different agonists significantly compared with placebo-treated lactoovovegetarian subjects.

The EPA content of platelet phospholipids increased from 0.2% to 0.5% of total fatty acids after 15.4 g/d of ALA was consumed for 5 wk (34), while just 2 wk of consuming a diet rich in Atlantic salmon containing 847 mg/d of EPA increased the platelet phospholipid content from 0.4% to 1.9% of total fatty acids (36). A comparison was made between the plant oils canola and linseed (34), providing 3.7 and 15.5 g of ALA per day, respectively, with red meat and fish (36), providing a direct supply of EPA (70 and 847 mg/d, respectively). The incorporation of EPA in platelet phospholipid was significantly higher after consumption of all of the n-3 sources, but it was highest after fish consumption (Figure 1). Although increasing ALA intake increases EPA levels in platelet phospholipids, it seems like the increase is not sufficient

to influence platelet functions. Thus, the biological effects of ALA and EPA are not equivalent with respect to thrombosis. Whether ALA would function as EPA did in these studies if the absolute amount of ALA intake or the duration of feeding a high-ALA diet was increased needs to be explored in the future.

One characteristic difference between vegan and lactoovovegetarian diets is the inclusion of variable servings of dairy and egg products in the lactoovovegetarian diets. The Honolulu Heart Program cohort (37) was followed up after 22 y for the risk of thromboembolic stroke and intake of dietary calcium and milk. Non-drinkers of milk among men had 2 times greater rate of stroke than those that consumed 16 oz milk or more per day. Dietary calcium, sodium, and potassium intake did not account for the differences in the incidence of stroke between milk drinkers and nondrinkers. This suggests that components other than the minerals in milk might be important for stroke risk reduction. An in vitro study showed that casein, the milk protein, and lactoferrin inhibit thrombin-induced platelet aggregation and thrombin-induced secretion of serotonin (38). It is not clear whether these peptides are physiologically released after digestion and absorbed intact. Until further studies can substantiate these findings, the effect of milk products in reducing the risk of thrombosis remains inconclusive. Lactoovovegetarians who use dairy products should choose nonfat or low-fat options from this food group to keep their total and saturated fat intake within the recommendations for a heart-healthy diet.

## PLANT FOODS

The prevalence of IHD is lower in the Mediterranean region compared with the West generally. An olive oil-based diet rich in monounsaturated fatty acid (MUFA) may partly account for this difference in the incidence of IHD. In fact, high dietary intake of MUFA is negatively correlated with IHD mortality (39). When substituted for saturated fat, MUFA is hypocholesterolemic and in comparison to a high-carbohydrate diet significantly reduces serum triacylglycerol concentration (40). These mechanisms explain the reason for the decrease in IHD risk seen with high-MUFA diets. However, it is thought that MUFA from plant oils such as olive oil and canola oil may also have a favorable impact on hemostatic and thrombotic factors, thereby contributing further to IHD risk reduction.

In a randomized controlled crossover study, 18 healthy volunteers were assigned to diets rich in olive oil, sunflower oil, or rapeseed oil for 3 wk each. Olive oil is rich in MUFA, sunflower oil is rich in n-6 PUFA, and rapeseed oil has significant amounts of both MUFA and n-6 PUFA. The olive oil diet was associated with lower nonfasting mean concentration of factor VIIa than the sunflower oil diet. Similar observations were made in comparison with the rapeseed oil diet also, but they were not significant (41). The sunflower oil diet not only had less MUFA than the olive oil diet (7.6% compared with 17% of total energy, respectively) but also had more n-6 PUFA (12.2% energy) than the olive oil diet (2.2% energy). This suggests that besides the MUFA content of the oil, the amount of n-6 fatty acids and the ratio of n-3 to n-6 PUFA in the plant oils may affect hemostatic variables (41, 42).

In another study, the effect of displacing saturated fat with MUFA in the diet on hemostasis and thrombosis was investigated (43). Fifty-one healthy subjects participated in a controlled, parallel-design study that provided a saturated fat (SFA) diet (14.9% energy from SFA, and 12.2% energy from MUFA)

for 8 wk, after which they were administered a MUFA-rich diet (11% energy from SFA, and 15.8% energy from MUFA) for 16 wk. At the end of 8 wk on the MUFA diet, there was a significant reduction in whole blood aggregation in response to ADP, collagen, and arachidonic acid, but by 16 wk these reductions were maintained with only ADP agonist. Sirtori et al (44) reported similar findings, while others (45, 46) showed no significant difference with the type of fatty acid on agonist-induced platelet aggregation, and still others (47, 48) showed that ADP-induced aggregation may be enhanced by olive oil. In contrast, the effect of MUFA on fibrinogen, PAI-1, and tPA activity is more consistent and indicates that the type of fatty acid may not significantly alter these factors.

The measurement techniques of the *ex vivo* agonist-induced platelet aggregation are quite variable and may account for the inconsistent results seen across the different studies. Also, the physiologic relevance of the changes observed in hemostatic variables is not clear because in some instances the changes are quite small for the differences in fatty acid composition. There is some preliminary evidence to suggest that the MUFA-rich olive oil-based Mediterranean diets may contribute to IHD risk reduction via not only lowering blood lipids and lipoproteins but also influencing some of the hemostatic and thrombotic factors. Future studies have to explore how the amount of n-6 PUFA and the n-3-to-n-6 ratio in the diet may modify the effects of MUFA.

Healthy vegetarian diets are also characterized by an increase in the consumption of fruits and vegetables. Cardiovascular health benefits are provided by several fruit and vegetable components, including fiber, antioxidants, and phytochemicals. In a recent study (49), plasma salicylic acid was measured in the serum of vegetarians and nonvegetarians and compared with that of patients consuming a low daily dose of aspirin. Higher salicylate concentration was seen in vegetarians (0.04–2.47 mmol/L) than nonvegetarians (0.02–0.20 mmol/L). Those taking aspirin had several folds higher plasma salicylate concentration (0.23–25.40 mmol/L) than did the nonusers, but there was an overlap in serum salicylate levels between vegetarians and aspirin users. Many fruits and vegetables naturally contain salicylates, but salicylates are particularly high in herbs and spices. Further studies are needed to clarify whether the higher plasma salicylate concentration among vegetarians provides antithrombotic effects similar to those provided by low-dose aspirin.

## PLANT NONNUTRIENTS

Dietary factors play a key role in the development of IHD. Frequent consumption of foods rich in phytochemicals such as allicin, polyphenols, isoflavones, and anthocyanins is associated with reduced incidence of CVD (50–52). Some foods that contain significant amounts of these phytochemicals and have been investigated in human studies include garlic (allicin), cocoa (polyphenols), soy (isoflavones), and red wine and grape juice (anthocyanins). These foods are known to favorably alter some cardiovascular risk factors and thereby decrease the incidence of CVD. The section below discusses some studies with respect to the effect on markers of hemostasis and thrombosis.

### Organosulfur compound

Garlic and extracts prepared from it are known to reduce serum cholesterol levels in humans, inhibit endogenous cholesterol synthesis, and suppress LDL oxidation, thereby reducing the risk of

IHD (50). But the IHD risk-reducing effects are not limited to these mechanisms alone. Garlic intake lowers blood coagulability by reducing fibrinogen, increasing fibrinolysis and prothrombin time, and inhibiting platelet aggregation (53, 54). Two human studies reported reductions in platelet aggregation of 16.4% and 58% with garlic oil obtained from 9–10 g fresh garlic cloves (55, 56). In a randomized double-blind study of normal healthy subjects, the effects of 3 different doses (2 g/d, 4 g/d, or 7.2 g/d) of aged garlic extract (AGE) compared with placebo on platelet aggregation and adhesion were measured after 6 wk of supplementation. AGE supplementation reduced platelet function, and this inhibitory effect was selective, affecting collagen and epinephrine but not ADP-induced aggregation. Also, the dose response was evident with only collagen-induced aggregation, while for other agonists the low dose (2 g/d) was as effective as the higher doses (57).

Not all studies show a favorable effect of garlic on platelet function. A placebo-controlled, double-blind, randomized study on healthy men showed no effect of garlic extract on platelet aggregation, serum thromboxane, and platelet activating factor (58). The inconsistent results are probably due to the use of different garlic preparations and varying amounts of the active constituents in garlic in these studies.

The antithrombotic effects of garlic are attributed to the allyl propyl disulfide, diallyl disulfide, and other sulfur compounds present in the essential oil. Although the exact mechanism by which these compounds alter platelet function is not known, *in vitro* studies suggest that they may act via inhibition of platelet lipooxygenase and cyclooxygenase enzymes, which in turn suppresses the production of thromboxane B<sub>2</sub> (TXB<sub>2</sub>). In fact, researchers in Kuwait found that the daily consumption of 1 clove (3 g) of fresh garlic for 6 mo resulted in a 20% reduction in serum cholesterol and an 80% decrease in serum TXB<sub>2</sub> in middle-aged men (59).

Other members of the Allium family such as onions may also be considered natural anticlotting agents because they possess substances that have fibrinolytic activity and can suppress platelet aggregation. A whole family of sulfinyl disulfides isolated from onions has been shown to inhibit the arachidonic acid cascade in platelets (60). However, the concentration of the sulfur-containing compounds in onions, leeks, and other allium vegetables is much lower than in garlic, and therefore garlic has been most extensively studied in the Allium family.

### Polyphenols

#### *Catechins and procyanidins*

Frequent consumption of polyphenol-rich foods is inversely associated with death from thrombosis and IHD (51). Cocoa, a polyphenol-rich food, contains catechin, epicatechin, and substantial amounts of procyanidin. *Ex vivo* effects of cocoa polyphenols were studied on 10 healthy volunteers by measuring platelet function (61). Consumption of a cocoa drink resulted in the lowering of platelet activation marker expression in response to weak agonists *in vitro* and produced an aspirin-like effect on platelet function. These effects were probably due to the catechin and procyanidin content of cocoa and not due to caffeine, because the caffeine-containing beverage in this study stimulated epinephrine-induced platelet aggregation. This is consistent with *in vitro* studies that document a decrease in platelet aggregation with flavonoids (62).





In contrast, Wan et al (52) reported no significant difference between urinary excretion of TXB<sub>2</sub> and 6-keto-PGF<sub>1α</sub> in a diet enriched with cocoa powder. Measurement of these metabolites is noninvasive and quantifies endogenous eicosanoid production and in vivo thrombosis. This study measured the metabolites in a 24-h urine sample; in contrast, the study by Rein et al (61) measured platelet function 2 h after consumption of a cocoa drink. While inhibition of platelet aggregation is one mechanism by which polyphenols in cocoa may offer cardioprotective benefits, more studies are required to accurately assess the effect of acute compared with chronic intake of cocoa polyphenols on thrombosis.

#### *Anthocyanins*

Red wine and purple grape juices are rich sources of another group of polyphenols called anthocyanins. They also contain catechin. Epidemiologic studies show an inverse correlation between red wine intake and morbidity and mortality from IHD (63). Part of the protective effect of red wine is due to its ability to increase HDL cholesterol. It has been proposed that the polyphenols in red wine and grape juice may also exhibit cardioprotective effects via mechanisms beyond blood lipids. The ex vivo inhibition of platelet activity by purple grape juice (350 mL) seems to be similar to that produced by 700 mL of red wine (64). In fact, dealcoholated red wine demonstrated a significant inhibition of in vitro platelet aggregation that was comparable to phenolic extracts from red wine, especially the catechin-anthocyanidin fraction (65).

Two cups of purple grape juice (450 mL) substantially inhibited platelet activity in healthy subjects (66), while similar amounts of orange juice and grapefruit juice had no such effects. The polyphenols in grape juice are anthocyanins and proanthocyanins, while those in orange and grapefruit juices are mainly flavonones and flavones. Also, grape juice has higher amounts of polyphenols than the other 2 fruit juices. Among the different varieties of grape juice, red and white grape juice (67) do not seem to have any effect on platelet function, in contrast to the antithrombotic function of purple grape juice. Although the agonist used to induce platelet activation was not the same in these various studies, the differences in the effect on platelet function are attributed to the polyphenol content, which is much higher in the purple grape juice than in the other 2 varieties.

#### *Isoflavones*

Isoflavones that are mainly found in soy and soy products are also flavonoids. There are very limited human experimental studies on the effect of soy foods on hemostasis and thrombosis. However, by virtue of the high ALA and fiber content of soy (68), one can speculate that it has some degree of antithrombotic effect. Soy protein intake increases plasma concentration of genistein, an isoflavonoid found in soybeans (69). Genistein has demonstrated several effects in vitro that indicate a role in decreasing thrombosis. Genistein inhibits tyrosine kinase activity, blocking growth factor action; interferes with platelets and thrombin action; and inhibits agonist-induced platelet aggregation (70). However, the relevance of these in vitro effects to human physiology is not clear.

In one double-blind study on perimenopausal women, soy intake (40 g/d) with (80 mg) or without isoflavone did not influence any of the hemostatic or thrombotic factors compared with whey protein (71). However, this study was done on normocholesterolemic, healthy perimenopausal women. The current guideline provided by the Food and Drug Administration (72) to claim soy food as a heart-healthy food is about 25 g/d. This is for individuals

with elevated cholesterol levels. Obviously, much work remains to be done in looking at the effect of similar amounts of soy on cardiovascular risk factors other than blood lipids in patients with elevated levels of these factors.

#### *Quercetin*

Flavonoids such as quercetin, kaempferol, and myricetin naturally occur in fruits and vegetables. A typical diet contains about 23–34 mg of these flavonoids/d (73), the majority of which is quercetin. In a double-blind study (74), healthy men and women were assigned to either a quercetin-supplemented (1 g/d) group or a control group for 28 d. Plasma quercetin was 23-fold higher after quercetin supplementation but did not alter any of the thrombogenic risk factors. Similar observations were made in another randomized crossover study in which volunteers received 220 g onions/d (≈114 mg quercetin) as one of the treatments for 7 d (75).

In vitro, quercetin inhibits platelet aggregation (76, 77), but the levels used range from 20 to 500 mmol/L quercetin, which is several hundred times higher than the plasma levels reached in the human studies. Therefore, it is possible that the inhibitory effect of quercetin on platelet aggregation may require a certain minimum concentration in the plasma. It is also likely that quercetin elicits its cardioprotective effects via mechanisms other than thrombosis.

#### **Summary**


The foods discussed in the section above—including garlic, soy, cocoa, and grape juice—all seem to have some cardioprotective effects. Although these studies have specifically looked at the role of the phytochemical content of these foods, it is reasonable to assume that there may be other constituents of these foods that might confer some of the cardiovascular benefits either alone or in combination with the predominant phytochemical in the food. Also, the results seen in vitro may not be similar to the physiologic response to the intake of these foods or the individual phytochemical. Future intervention studies should consider comparing the whole food to the phytochemical constituents in determining their impact on hemostasis and thrombosis.

#### **CONCLUSIONS**

Identifying novel risk factors for IHD and understanding the role, if any, of dietary components on these markers will help in the development of therapeutic and preventive measures in the future. Normal hemostasis is a result of a complex regulatory process, and to measure the balance among these molecules and their actions, appropriate markers need to be used. Variability in the assay methods used in different labs has resulted in inconsistent results, and this calls for improving means of assessing these markers in the future. Even when the results are consistent, in some instances the protective effects observed are rather small for the differences in diet and the clinical relevance of such small changes is not clear. Another challenge is in the interpretation of the findings on some of the hemostatic factors that are acute phase reactants. Are the changes observed an acute or chronic effect? What are the long-term health implications of the observed changes? These are some of the questions that remain to be addressed in future studies. Because many of the studies on humans have used healthy subjects, clinical trials on patient populations should be considered in the future. It is likely that the



antithrombotic effects of some of these plant foods and nonnutrients may be different in healthy subjects compared with patients with a preexisting cardiovascular disease condition.

There are only limited data to indicate that certain plant foods and nutrients such as fiber, *n*-3 fatty acids, MUFA-rich olive oil, garlic, and soy may favorably modify some of the markers of hemostasis and thrombosis. The evidence is neither conclusive nor sufficient to make specific public health recommendations, and systematic human intervention studies are needed to substantiate the current observations. In the meantime, nutrition education should continue to promote the existing recommendations for a heart-healthy diet, which emphasize eating a variety of fruits and vegetables; increasing MUFA, *n*-3 PUFA, and fiber intake; and reducing saturated fat intake. This type of dietary pattern has been shown to help in the prevention of IHD by favorably affecting several coronary risk factors. 

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