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# Functional Foods as Modifiers of Cardiovascular Disease

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## Abstract

There is growing consensus that systemic inflammation is at the heart of cardiovascular disease (CVD). Inflammation is a key feature of the immune system, functioning to defend tissue integrity and function. However, chronic stimulation of inflammatory mediators leads to lasting vascular reactivity, insulin resistance, hyperlipidemia, and, subsequently, chronic disease. Dietary practices to minimize inflammatory stimuli and CVD risk include regular intakes of fatty fish rich in the eicosapentaenoic and docosahexaenoic acids that compete with the more pervasive membrane fatty acid, arachidonic acid, disrupting the metabolic cascades that stimulate inflammation. Another effective dietary strategy is to consume less arachidonic acid by reducing beef, poultry, fish, and eggs from the diet (e.g., adopting a vegetarian-like diet). Since oxidative stress plays a prominent role in immune system activation, regular ingestion of ample amounts of fruits and vegetables (8+ servings/d) rich in antioxidant compounds, the polyphenols, carotenoids, and vitamin C (e.g., citrus, tomatoes, berries, carrots, and greens), lowers inflammatory mediators and risk for chronic disease. Whole grains, legumes, and nuts have also been demonstrated in clinical trials to effectively reduce inflammatory mediators and risk for CVD. Hence, as proclaimed in antiquity, ‘let food be thy medicine and medicine be thy food’.

### Keywords

functional foods; cardiovascular disease; inflammation

## Background

There is growing scientific consensus that arterial inflammation is at the heart of cardiovascular disease (CVD).[1] Although research portrays inflammation as an instigator of CVD, in reality inflammation is a key feature of the immune system functioning to defend and preserve tissue integrity and function. Pathogen invasion damages vascular tissue initiating the production of oxygen ions and free radicals, collectively termed reactive oxygen species (ROS). These small molecules stimulate the production of eicosanoids from fatty acids located in the phospholipid bylayer of all cell membranes. Eicosanoids are cell signaling molecules that participate in a wide range of physiological processes including immune system activation and the ensuing inflammatory state.2 The activation of white blood cells by eicosanoids enables these cells to adhere to and activate endothelial cells. Both activated leukocytes and endothelial cells in turn release numerous cytokines, small hormone-like mediators with wide ranging effects for cellular metabolism. Collectively, this complex but integrated metabolic cascade results in a rapid and focused offensive to ensure pathogen destruction and the restoration of tissue function.

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The inflammatory cytokines released during the immune response, including tumor necrosis factor alpha (TNF-α), interleukins 1 and 6 (IL-1 and IL-6), and C-reactive protein (CRP), promote glycogenolysis, insulin resistance, and muscle protein catabolism.[3] These metabolic changes ensure a rapid supply of amino acids and glucose to fuel the immune response and enable rapid immune protein synthesis. In addition, inhibition of fat oxidation by inflammatory mediators leads to a state of hyperlipidemia which serves to neutralize viruses and inhibit pathogen infectivity. Once the pathogen is cleared from tissues, the immune system wanes and the inflammatory mediators dissipate leaving tissues healthy and free of infection. However, factors aside from foreign agents also stimulate immune responses such as elevated blood cholesterol or glucose concentrations, cigarette smoke and pollutants, chemical solvents, and even obesity or stress. Since these factors do not disappear or dissipate, the inflammatory mediators are chronically stimulated leading to lasting vascular reactivity, insulin resistance, and hyperlipidemia, and ironically, chronic disease. Individuals should focus on strategies to minimize these factors (e.g., smoking cessation, weight loss, and stress management) to reduce disease risk. In addition, there is substantial evidence that the adoption of certain dietary practices can help control chronic inflammation and minimize CVD disease risk.[4,5]

## Dietary Patterns that Reduce Inflammatory Markers

### Mediterranean diets

A diet rich in foods common to the Mediterranean region prior to the 1960's has been termed the ‘Mediterranean diet’. This diet is high in fruits, vegetables, cereals, beans, nuts and seeds, and olive oil; red meat is rarely eaten, and dairy products, fish and poultry are consumed in low to moderate amounts; and, wine is consumed in moderation. This diet plan gained scientific attention because numerous reports indicated that populations consuming these diets had extraordinary low rates of chronic disease.[6,7] Clinical trials have confirmed the cardiovascular protective effects of this diet plan and that this diet effectively reduces markers of inflammation in high risk populations.[8-10]

In an early study, patients who survived a myocardial infarction within 6 months of enrollment adopted either a Mediterranean-like diet or the standard low-fat therapeutic diet according to random assignment.[11] After a mean follow up of 27 months, overall cardiac mortality was significantly higher (16 versus 3), as was overall mortality (20 versus 8), in the control group versus the Mediterranean diet group. Thus, adoption of a Mediterranean-like diet may reduce inflammation in select populations at high risk for CVD and possibly delay disease progression and need for medical treatment. However, the beneficial effects of Mediterranean-like diets may not extend to patients with established CVD and receiving current standard medical treatments such as statins, betablockers and angiotensin-converting enzyme inhibitors.[12] The mechanisms by which Mediterranean diets reduce inflammatory risk are not well understood but may relate to high intakes of fruits and vegetables which contain antioxidant nutrients and polyphenols that reduce ROS concentrations throughout tissues.

### Vegetarian diets

Diets devoid of flesh foods also reduce risk for CVD and have been demonstrated to reverse coronary atherosclerosis.[13,14] Risk for CVD among vegetarian populations is consistently 20-35% below that for omnivore populations.[15] Much of this benefit is likely related to the low body weights and low blood cholesterol concentrations generally observed for vegetarians due to their lower intakes of saturated fats and calories. Additionally, survey data also indicate that vegetarians have reduced concentrations of inflammatory markers, particularly CRP.[16] In fact, a modified vegetarian diet was demonstrated to reduce CRP concentrations to a greater extent than that achieved by pharmaceutical intervention with a statin drug.[17] Moreover, randomized controlled trials in patients with inflammatory conditions such as atopic dermatitis

or rheumatoid arthritis, have demonstrated that inflammatory markers are reduced and disease symptoms abate following the adoption of a vegetarian diet.[18,19]

Similar to Mediterranean diets, vegetarian diets are high in fruits, vegetables, and nuts, rich sources of the antioxidant nutrients and polyphenols that contribute to the anti-inflammatory potential of these diets. Additionally, fleshless diets are low in arachidonic acid, a fatty acid that rapidly incorporates into cell membrane phospholipids and subsequently becomes the precursor for the inflammatory eicosanoids. Adoption of a vegetarian diet reduces tissue arachidonic acid concentrations 6% after 3 months,[19] and long-term vegetarians may have tissue arachidonic acid concentrations 10-15% lower than that of omnivores. Hence, vegetarian diets reduce risk for CVD by multiple mechanisms: reducing the initial insult in the atherosclerotic pathway (raised cholesterol concentrations), reducing ROS concentrations, reducing production of inflammatory eicosanoids, and reducing markers of inflammatory stress.

## Functional Foods with Anti-Inflammatory Effects

### Fish

Substantial evidence supports the anti-inflammatory benefits of regular fish consumption or fish oil ingestion.[20] The long-chain fatty acids unique to marine foods (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) compete with the more pervasive long-chain fatty acid, arachidonic acid, in cell membranes disrupting the metabolic cascades that stimulate immune responses; consequently the inflammatory sequel is stifled. The anti-inflammatory effects of daily fish oil ingestion are nearly identical to the anti-inflammatory effects demonstrated for low-arachidonic acid diets (i.e., vegetarian diets); and interestingly, the benefits of low-arachidonic acid diets are augmented by fish oil consumption.[19]

In addition to its anti-inflammatory properties, fish oil possesses antithrombotic, triglyceride lowering, and antiarrhythmic effects in patients with CVD.[21] Moreover, fish and fish oil ingestion has been related to a reduced risk for myocardial infarction, which may relate to beneficial effects of EPA and DHA on plaque morphology and stability.[22] In one trial, 188 patients awaiting carotid endarterectomy were randomly assigned to fish oil, sunflower oil, or control groups for a median of 42 days to examine effects on plaque stability.[23] EPA and DHA were rapidly incorporated into carotid plaque in patients receiving fish oil compared to the other groups, and fewer plaques from these patients had signs of inflammation or thin fibrous caps, signs of plaque instability and myocardial infarction risk, compared to the other groups.

A recent meta-analysis of ten qualifying randomized controlled trials, encompassing 14,727 patients, reported that daily fish oil consumption reduced incidence of death due to myocardial infarction by 24% and all cause mortality by 16%.[24] In 2002, the American Heart Association recommended fish consumption (specifically fatty fish: salmon, tuna, herring, halibut, and mackerel) at least twice weekly to reduce risk for heart disease.[25] However, for patients with CVD, or those needing to lower serum triglyceride concentrations, the American Heart Association recommends up to 4 g EPA+DHA daily in supplemental form in consultation with a physician.

### Fruit and vegetables

Oxidative stress plays a prominent role in immune system activation and inflammatory conditions. Individuals consuming diets rich in fruits and vegetables have increased tissue concentrations of the antioxidant nutrients, particularly vitamin C, carotenoids, and polyphenols, and a lower risk for CVD.[26,27] In randomized clinical trials, vitamin C lowered concentrations of the inflammatory mediator CRP 25-35%,[28,29] and this vitamin C induced reduction in CRP was related to clinical improvements in cardiac patients.[29] Citrus, red and

yellow peppers, Brussels sprouts, melons, and strawberries are rich sources of vitamin C. The powerful extracellular and intracellular antioxidant functions of vitamin C serve to reduce tissue ROS concentrations, which in the atherosclerotic condition helps prevent endothelial dysfunction, inhibit vascular smooth muscle proliferation, and reduce oxidized low density lipoprotein (LDL) cholesterol.[30]

The carotenoids, particularly lycopene and beta-carotene concentrated in deeply colored items such as carrots, tomatoes, and dark green vegetables, are other dietary antioxidants that function to reduce oxidative stress in vivo and blood markers of inflammation. In healthy adults, the incorporation of tomato juice into their typical diets (2 cups per day for 2 weeks) significantly reduced plasma concentrations of CRP (-17%) and TNF-α (-43%).31 In patients with grade-1 hypertension, LDL cholesterol oxidation levels in plasma and systolic and diastolic blood pressure measures were significantly reduced following four weeks of daily tomato extract consumption as compared to placebo treatment.32 Many fruits and vegetables (particularly berries and grapes) are rich sources of another category of antioxidants known as the polyphenols, which includes tannins, lignins, and flavonoids. After an overnight fast, patients with CVD were randomly assigned to receive a red grape extract or placebo, and postprandial endothelial cell function was assessed for a 2-hour period by measuring flow-mediated dilation of the brachial artery.33 At 60 to 120 minutes post-treatment, flow-mediated dilation was enhanced 70% for the red grape extract versus placebo. In healthy adults, raisin consumption (1 cup per day for 6 weeks), but not placebo, significantly reduced TNF-α and intra-cellular adhesion molecules.34 Interestingly, tea, coffee and chocolate are also rich sources of polyphenols and have been demonstrated in randomized feeding trials to reduce markers of oxidative stress.

Fruits and vegetables are ranked by their antioxidant capacity, known as the Oxygen Radical Absorbance Capacity (ORAC) score, which reflects the combined antioxidant effects of vitamin C, carotenoids, polyphenols, and other constituents. Fruit with high ORAC scores include blueberries, plums, blackberries, strawberries, raspberries, sweet cherries, avocados, navel oranges, and red grapes; vegetables with high ORAC scores include artichokes, asparagus, red cabbage, spinach, and Russet potatoes.[35] Foods from these lists should be regularly included in the diet to maximize the heart-protective potential of fruit and vegetables consumption.

## Nuts and legumes

Nuts and peanuts have been demonstrated to reduce risk for CVD in numerous large prospective cohort studies,36,37 and the substitution of a serving of nuts for equivalent energy from carbohydrates or saturated fat in the typical diet theoretically reduces risk for CVD by over 30%.37 Nuts are complex foods containing cholesterol lowering mono- and poly-unsaturated fatty acids, arginine (a precursor to the vasodilator nitric oxide), soluble fiber, and several antioxidant polyphenols. In a randomized trial with olive oil as the control treatment, a single portion of walnuts (3 oz) as part of a high saturated fat meal (salami and cheese sandwich with high fat yogurt) reduced postprandial vascular reactivity, an emerging risk factor for CVD, in patients with hypercholesterolemia.[38] Postprandial vascular reactivity is characterized by decreased bioavailability of nitric oxide and increased expression of proinflammatory cytokines and cellular adhesion molecules. Over a longer term, the daily consumption of walnuts (8-13 nuts daily for four weeks) by hypercholesterolemic adults improved endothelial function to a greater degree than the adoption of a Mediterranean-type diet.39

It is not surprising that the evidence supporting the cardio-protective effects of diets high in nuts is robust as multiple mechanisms work together to reduce risk; yet many are hesitant to add nuts to their diet regularly due to their high caloric value. Recent trials specifically examining weight gain in populations adhering to daily nut consumption (1.5 to 3 servings

daily for 8-27 weeks) did not report significant weight gains.[40] It is likely that a portion of the energy in nuts is not assimilated due to poor digestibility and that individuals successfully compensate for the calories in nuts due to their high satiety value.

Legumes are also complex foods rich in soluble fibers and polyphenols, as well as folic acid, a B vitamin that reduces blood homocysteine concentrations, a risk factor for CVD. Despite this favorable nutrient profile, and the fact that legumes are a dietary staple in Mediterranean-like diets, randomized controlled trials examining the potential of legumes to reduce CVD risk are not available. However, a large incident case-control study in Costa Rica concluded that the consumption of 1 serving of legumes daily was associated with a 40% lower risk of myocardial infarction.[41] Interestingly, legumes were the only food group predictive of survival among five long-lived elderly cohorts in Japan, Sweden, Greece, and Australia.[42]

### Whole grains

Whole grain products contain intact grain kernels rich in fiber and trace nutrients. Since grains are predominant in American diets comprising 30-50% total energy, the regular consumption of whole grains markedly improves dietary nutrient and fiber profiles, and there is consistent evidence from epidemiological surveys that whole grain consumption reduces risk for CVD. In a cohort of 14,153 African-American and white adults from the Atherosclerosis Risk in Communities (ARIC) Study, whole grain consumption, but not fruit and vegetable or nut consumption, was associated with a 7% lower risk for heart failure over a 13-year period.[43] A recent meta-analysis based on seven qualifying prospective cohort studies focused on whole grain consumption and cardiovascular outcomes reported that the inverse association between dietary whole grains and incident CVD was strong and consistent across trials.44

In a 12-week intervention trial, fifty individuals at risk for CVD were instructed to follow a therapeutic, hypo-caloric diet for weight loss (5 servings fruits and vegetables, 3 servings low-fat dairy products, 2 servings lean meats, and 4-7 servings grains as based on energy needs); one-half of participants were instructed to consume only refined grains and the remainder consumed only whole grain products.[45] At the end of the trial, both groups of participants lost similar amounts of weight (4-5 kg), but there was a greater degree of abdominal body fat loss in the whole grain group versus the refined grain group. Moreover, CRP concentrations decreased in the whole grain group (-38%) but were unchanged in the refined grain group. Although the anti-inflammatory mechanism is not clear, the reduction in CRP noted in this trial may be related to higher intakes of antioxidant nutrients present in the germ of whole grains. Also, as compared to refined grains, whole grains have a reduced glycemic response following ingestion (i.e., the postprandial rise in blood glucose is lessened), and reductions in postprandial glucose surges have been associated with reduced ROS generation after a meal and reduced postprandial inflammation and CVD risk.46

## Summary

Diet plans rich in fruits and vegetables, nuts and legumes, whole grains, and fish, and low in red and processed meats, refined grains, high fat dairy, and sweets, have consistently been shown to reduce risk of CVD and total mortality. The low morbidity and mortality attributed to populations that adhere to Mediterranean-type diets or vegetarian diets further substantiate the benefits of a plant-based diet. It is now evident, based on the extensive scientific evidence, that constituents in these foods have broad ranging physiologic effects in vivo that lessen inflammatory cascades and vascular reactivity. In many cases, these effects are as powerful as pharmaceutical interventions, albeit much safer. As proclaimed in antiquity: ‘let food be thy medicine and medicine be thy food’.

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