Bioactive Compounds in Foods: Their Role in the Prevention of Cardiovascular Disease and Cancer

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"Bioactive compounds" are extranutritional constituents that typically occur in small quantities in foods. They are being intensively studied to evaluate their effects on health. The impetus sparking this scientific inquiry was the result of many epidemiologic studies that have shown protective effects of plant-based diets on cardiovascular disease (CVD) and cancer. Many bioactive compounds have been discovered. These compounds vary widely in chemical structure and function and are grouped accordingly. Phenolic compounds, including their subcategory, flavonoids, are present in all plants and have been studied extensively in cereals, legumes, nuts, olive oil, vegetables, fruits, tea, and red wine. Many phenolic compounds have antioxidant properties, and some studies have demonstrated favorable effects on thrombosis and tumorogenesis and promotion. Although some epidemiologic studies have reported protective associations between flavonoids or other phenolics and CVD and cancer, other studies have not found these associations. Various phytoestrogens are present in soy, but also in flaxseed oil, whole grains, fruits, and vegetables. They have antioxidant properties, and some studies demonstrated favorable effects on other CVD risk factors, and in animal and cell culture models of cancer. However, because phytoestrogens act both as partial estrogen agonists and antagonists, their effects on cancer are likely complex. Hydroxytyrosol, one of many phenolics in olives and olive oil, is a potent antioxidant. Resveratrol, found in nuts and red wine, has antioxidant, antithrombotic, and anti-inflammatory properties, and inhibits carcinogenesis. Lycopene, a potent antioxidant carotenoid in tomatoes and other fruits, is thought to protect against prostate and other cancers, and inhibits tumor cell growth in animals. Organosulfur compounds in garlic and onions, isothiocyanates in cruciferous vegetables, and monoterpenes in citrus fruits, cherries, and herbs have anticarcinogenic actions in experimental models, as well as cardioprotective effects. In summary, numerous bioactive compounds appear to have beneficial health effects. Much scientific research needs to be conducted before we can begin to make science-based dietary recommendations. Despite this, there is sufficient evidence to recommend consuming food sources rich in bioactive compounds. From a practical perspective, this translates to recommending a diet rich in a variety of fruits, vegetables, whole grains, legumes, oils, and nuts. *Am J Med.* 2002;113(9B):71S–88S. © 2002 by Excerpta Medica, Inc.

Across cultures there are many different dietary patterns, some of which promote health and others that increase risk of chronic disease. Despite cultural differences in cuisines worldwide that are associated with different macronutrient profiles, there are some shared characteristics of healthy dietary patterns. Most notably, they feature fruits and vegetables, legumes, whole grains, and fish, and because of this, all are high in fiber, relatively high in ω-3 fatty acids, and low in saturated fat, trans fat, and dietary cholesterol.[1] There is appreciable epidemiologic evidence that demonstrates a protective role in diets high in fruits and vegetables, legumes, whole grains, and fish on different cancers and cardiovascular diseases.

Interestingly, total dietary fat can vary in a healthy dietary pattern that is low in saturated fat, trans fat, and cholesterol, and meets energy and all nutrient needs.[2] Although the emphasis on reducing saturated fat, trans fat, and cholesterol is to lower low-density lipoprotein (LDL) cholesterol, there is provocative evidence that other dietary constituents can reduce coronary heart disease (CHD) in a manner that is independent of total cholesterol levels.[3] As a result, there is keen interest in assessing the role of food-based bioactive compounds in reducing risk of chronic disease.

As defined by Kitts,[4] bioactive compounds are "extranutritional" constituents that typically are naturally occurring in small quantities in plant products and lipid-rich foods. The purpose of this article is to provide an overview of our present understanding of how foods and their bioactive components affect health. Because of the many plant-based bioactive compounds that have been identified, there have been numerous epidemiologic, clinical, and experimental studies conducted to evaluate

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their health effects. The present article will summarize the current status of the field. The bioactive compounds of plant origin that will be discussed in this review are phenolic compounds, including flavonoids, resveratrol, and phytoestrogens; lycopene; organosulfur compounds; plant sterols; dietary fibers; tea; red wine; isothiocyanates; and monoterpenes. The biological effects and food sources of these compounds are presented in **Table 1**. **Table 2** presents a more comprehensive list of bioactive compounds in common foods.[5] Collectively, the information presented in Tables 1 and 2 illustrates the scope of bioactive compounds found in food.

EPIDEMIOLOGIC EVIDENCE FOR AN ASSOCIATION BETWEEN FOOD AND CHRONIC DISEASE

Numerous epidemiologic studies indicate that an increase in the consumption of fruits and vegetables is associated with a decrease in the incidence of cardiovascular disease (CVD), CHD, and stroke[6–13] (**Table 3**). Results from the Nurses' Health Study and the Health Professionals' Follow-up Study indicate that persons in the highest quintile of fruit and vegetable intake (≥8.0 servings/day) had a relative risk (RR) for CHD of 0.80 (95% confidence interval [CI], 0.69 to 0.93) compared with those in the lowest quintile of intake (<3.0 servings/day), after adjustment for standard CVD risk factors. These results were also equivalent to a 4% reduction in CHD for every 1-serving/day increase in the intake of fruits and vegetables.[8] Green leafy vegetables and vitamin C–rich fruits and vegetables contributed the most to the apparent protective effect of total fruit and vegetable intake, with RR of 0.77 (95% CI, 0.64 to 0.93) and 0.94 (95% CI, 0.88 to 0.99), respectively, for every 1-serving/day increase. Similar results have been reported from the Women's Health Study[10] and the Physicians' Health Study.[9] In addition, comparable data have been reported from studies conducted in Japan[11] and China.[12]

Similar protective effects of fruits and vegetables have been reported for risk of stroke.[6,7,12] Bazzano et al[6] reported that frequency of fruit and vegetable intake was inversely associated with stroke incidence, stroke mortality, ischemic heart disease mortality, and CVD mortality. The incidence of stroke was greatly reduced (RR = 0.73; 95% CI, 0.57 to 0.95) for individuals consuming ≥3 servings/day of fruits and vegetables, compared with the reference group of <1 serving/day. In addition, stroke mortality was also greatly reduced (RR = 0.58; 95% CI, 0.33 to 1.02), from the highest quintile to the lowest.[6] Some investigators, however, have not found that an increase in fruit and vegetable intake is associated with a protective effect on CHD incidence,[11,14] perhaps because of difficulty in collecting accurate self-reported fruit and vegetable consumption data.

More than 200 studies have examined the relation between the consumption of fruits and vegetables and risk of various cancers. A meta-analysis of 26 studies by Gandini et al[15] found an association between risk of breast cancer and intake of fruits and vegetables. When high consumption versus low consumption was compared in these studies, an RR of 0.75 (95% CI, 0.66 to 0.85; $P < 0.001$) was observed from 17 studies on consumption of vegetables, whereas 12 studies involving fruit consumption resulted in an RR of 0.94 (95% CI, 0.79 to 1.11; $P < 0.001$). However, consumption of fruits and vegetables was not significantly associated with a reduced risk of breast cancer in a study by Smith-Warner et al[16] using pooled data from 8 cohort studies (n = 351,825).

A multiethnic case-control study involving 1,619 African American, white, Japanese, and Chinese men with confirmed prostate cancer and 1,618 control subjects examined the protective effects of fruit and vegetable intake on prostate cancer.[17] Whereas risk of prostate cancer was not related to fruit consumption, both cruciferous and yellow-orange vegetable intake were inversely related to prostate cancer. This association was strongest for advanced cases of prostate cancer with an odds ratio (OR) of 0.67 (P for trend = 0.01) for the highest quintile of yellow-orange vegetable intake and an OR of 0.61 (P for trend = 0.006) for the highest quintile of cruciferous vegetable intake. These results were consistent among the various ethnic groups.

Data from the Nurses' Health Study (n = 77,283 women) and the Health Professionals' Follow-up Study (n = 47,778 men) were analyzed to determine the risk of lung cancer in relation to fruit and vegetable consumption.[18] A 21% reduction in risk was observed in women when the highest quintile of fruit and vegetable consumption was compared with the lowest quintile (RR = 0.79; 95% CI, 0.59 to 1.06). Among men, however, a lower risk of lung cancer was not observed with increased fruit and/or vegetable intake (RR = 1.12; 95% CI, 0.74 to 1.69). When smoking status was taken into account, both men and women showed an association between total fruit and vegetable consumption and decreased risk of lung cancer that was not statistically significant (RR = 0.63; 95% CI, 0.35 to 1.12 in the highest tertile).

Both the Nurses' Health Study and the Health Professionals' Follow-up Study were also analyzed to determine the association between total fruit and vegetable consumption and the incidence of colon and rectal cancer.[19] No association between consumption of fruits and vegetables and colon and rectal cancer incidence was observed in either of these 2 cohorts. In men and women combined, a difference of 1 additional serving of fruits and vegetables per day was associated with an RR of 1.02 (95% CI, 0.95 to 1.09) for rectal cancer and an RR of 1.02 (95% CI, 0.98 to 1.09) for colon cancer. The authors of this study stressed that although these large cohort studies

Table 1. Potential Health Benefits of Selected Bioactive Compounds for Cardiovascular Disease and Cancer

Bioactive Compound	Examples	Sources	Putative Beneficial Biological Effects	References
Flavonoids				
Flavonols	Quercetin, kaempferol, catechin	Onion, apple, tea, berries, olives, broccoli, lettuce, red wine, cocoa/chocolate	↓ TC, ↓ LDL-C oxidation, ↑ HDL-C, AOx, antimutagen, ↓ tumor initiation/promotion, ↓ platelet aggregation, ↓ eicosanoid synthesis	38, 40, 74–77, 79, 83, 84
Flavonols	Epicatechin, epigallocatechin, epicatechin-3-gallete, epigallocatechin-3-gallete	Green/black tea, cocoa/chocolate	AOx, carcinogen detox, antimutagen, ↓ tumor initiation/promotion, apoptosis, ↓ LDL-C oxidation, ↓ platelet aggregation	65–72, 174–176, 178, 179, 181, 182, 186
Phytoestrogens				80, 97–99
Lignans, coumestran	Enterolactone, enterodial, coumestrol	Flaxseed oil, lucerne, clover	↓ LDL-C, AOx, estrogen/antiestrogen; adverse effect (CVD): pro-oxidant activity with partially defatted flaxseed	114, 115
Isoflavones	Genistein, daidzein	Soybeans, legumes	↓ TC and LDL-C, ↓ LDL-C oxidation, ↓ TG, ↑ HDL-C, ↓ thrombosis, AOx, estrogen/antiestrogen, antimutagen; ↓ angiogenesis, ↑ apoptosis; adverse effect: procarcinogen potential?	100, 101, 105, 108–112, 117, 118
Resveratrol		Grapes, red wine, peanuts	↓ LDL-C oxidation, ↓ platelet aggregation/thrombosis, ↓ eicosanoid synthesis, AOx, carcinogen detoxification, antimutagen, ↓ tumor initiation/promotion, estrogen/antiestrogen	46, 70, 119–122
Lycopene		Tomatoes, tomato products	↓ LDL-C and LDL-C oxidation, AOx, antimutagen	123–125, 129–132
Organosulfur compounds	Allicin, diallyl sulfide, diallyl disulfide, allyl mercaptan	Garlic, onion, leek	↓ TC and LDL-C, ↓ TG, ↓ cholesterol and FA synthesis, ↓ BP, ↓ thrombosis, AOx, carcinogen detoxification, ↓ tumor promotion; adverse effect: tumor promotion potential?	138, 139, 142, 143, 148–153
Soluble dietary fibers	β-Glucan, pectin, psyllium	Oats, barley, yeast, fruit, vegetables, psyllium seed, fortified cereals and grains	↓ TC, TG, LDL-C	170–173
Isothiocyanates (ITC)	Phenethyl (PEITC), benzyl (BITC), sulforaphanes	Cruciferous vegetables (e.g., watercress, broccoli)	↓ Tumor initiation/promotion, ↓ carcinogen activation, carcinogen detoxification	188–191
Monoterpenes	d-Limonene, perillic acid	Essential oils of citrus fruit, cherries, mint, herbs	↓ TC and LDL-C, carcinogen detoxification, ↓ tumor initiation/promotion, ↓ HMGR	192–195
Plant sterols	Sitostanol, stigmasterol, campesterol	Tall oil, soybean oil, rice bran oil	↓ TC and LDL-C, AOx, ↓ cholesterol absorption; adverse effect: ↓ carotenoid absorption	155–163, 165, 166
Olive oil	Tyrosol, hydroxytyrosol, oleoeuropeine, caffeic acid, cumaric acid	Extra virgin olive oil	AOx, ↓ LDL-C oxidation	85–90, 92, 93, 95, 96

AOx = antioxidant activity; BP = blood pressure; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HMGR = HMG CoA reductase; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

Table 2. Bioactive Compounds in Fruits and Vegetables, Cereals, and Oilseeds and Oils

Fruits and vegetables	
Apples	Quercetin, epicatechin, chlorogenic acid, *p*-coumaric acid, phloridzin
Citrus fruits	Naringenin, hesperetin, hesperedin, eriocitrin, naringin, meoeriocitrin, natrituin, *p*-coumaric acid, caffeic acid, ferulic acid
Grapes	Tannic acid, quercetin, procyanidines, other phenolics
Onion	Quercetin, myricetin
Carrots	Lignin, carotene
Tomato	Quercetin, lycopene, rutin, prunin
Garlic	*S*-Allyclcysteine, *S*-allylmercaptocysteine
Horseradish	Sinigrin
Azuki beans	Procyanidin dimers
Oilseeds and oil crops	
Cocoa	Catechin, epicatechin, chlorogenic acid
Soybean	Genistein, daidzein, glycitein, phenolic acids, tocopherols, amino acids, peptides
Sesame seed	Sesamol, sesaminol, tocopherol, sesamolinol
Cottonseed	Quercetin, rutin, kaempferol, gossypeti, heracetin, dihydroquercetin, quercetrin, isoquercetrin
Peanuts	Taxifolin
Mustard seed	Sinigrin, phenolic acids, sinapic acid methyl ester
Cereal crops	
Rice	Orizanol, isovitexin, cyanidine-3-*O*-β-D-glycopyranoside, pinoresinol, other phenolics
Wild rice	Phytic acid, luteolin glycoside, *p*-hydroxy acetophenone glycoside, 3,4,5-trimethoxycinnamin acid
Barley leaves	2′-*O*-Glucosylisovitexin
Oat	Esters of caffeic and ferulic acids

Adapted from *Isolation, Identification and Evaluation of Natural Antioxidants from Aromatic Herbs in Lithuania*.[5]

(Nurses' Health Study, n = 88,764 women; Health Professionals' Follow-up Study, n = 47,325) did not show a protective effect of fruits and vegetables against colon and rectal cancers, a diet rich in these foods is advisable because of the protection they confer against other chronic diseases.

A recent meta-analysis of 12 population-based cohort studies found that whole-grain foods significantly reduced the risk of CHD by approximately 26% after adjustment for multiple CHD risk factors.[20] The inverse association of whole grains was stronger than for cereal fiber, fruits, or vegetables, suggesting that 3 servings of whole grains per day may be important to cardiovascular health. Several epidemiologic studies have reported reductions in CVD risk of similar magnitude (25% to 40%) in individuals consuming 1 to 3 servings of whole grains per day (Table 3[21–28]). Overall, epidemiologic studies lend support to the hypothesis that individuals with a higher intake of whole grains have a lower risk of CVD than those who consume a diet poor in whole grains.

Along with whole grains, legumes have been understudied in their relationship to CHD. The majority of studies focus on specific nutritional components of legumes and not the total dietary intake of legumes. A new report that used the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study database found that legume consumption was inversely associated with risk of CHD and CVD.[29] Individuals with an intake of legumes at least 4 times a week had a 22% lower risk of CHD (RR = 0.78; 95% CI, 0.68 to 0.90; $P = 0.002$) and an 11% lower risk of CVD (RR = 0.89; 95% CI, 0.80 to 0.98; $P = 0.02$) compared with those consuming legumes less than once a week.

A large number of studies have consistently found that moderate alcohol consumption (1 to 3 drinks/day) is associated with a decreased risk of CHD.[30] Several studies have reported a protective effect of wine consumption.[31,32] A recent analysis of >24,000 men and women in Denmark found that wine drinkers had a relative risk for death from CHD of 0.58 (95% CI, 0.47 to 0.72) and light drinkers who avoided wine had a relative risk of 0.76 (95% CI, 0.63 to 0.92) compared with nondrinkers.[33] In addition, Klatsky et al[34] reported that wine intake was inversely related to CHD among persons consuming ≥3 drinks/day, but beer or liquor were not. Likewise, Criqui and Ringel,[35] using data from 21 developed countries, found that beer and spirits consumption was only weakly correlated with CHD after adjusting for other dietary components, whereas a strong and consistent inverse correlation was found between wine and CHD. The relation between alcohol and stroke is less certain. However, analysis of data from the Copenhagen City Heart Study found that weekly consumption of wine reduced the risk of stroke by about 35%, whereas neither beer nor spirits intake was associated with stroke risk.[36] Despite the studies demonstrating cardioprotective effects of wine versus spirits and beer, there is some evidence that there is no additional cardioprotective effect of wine versus other types of alcohol.[37]

Collectively, the epidemiologic studies evaluating associations between intake of a variety of plant-based foods indicate a protective effect, both on CVD and certain cancers. Possible constituents in food that account for these protective effects are discussed in subsequent sections of this review.

PHENOLIC COMPOUNDS

Phenolic compounds, commonly referred to as polyphenols, are present in all plants and, thus, are in the diet.[38] There are >8,000 phenolic structures that have been identified that vary structurally from being simple molecules (e.g., phenolic acids with a C6 ring structure) to being highly polymerized compounds (i.e., tannins). More than 10 classes of polyphenols have been defined on the basis of chemical structure.[38] The flavonoids are the most common polyphenolic compounds present in plant food. Sampson et al[39] recently reported an analysis of specific flavonoids in fruits and vegetables grown in the United States and the Netherlands. Flavonoids can be categorized into 13 classes comprising >5,000 compounds. The most common flavonoids are flavones, flavonols, and their glycosides.[38] The vast majority of plant phenolics are simple phenols and flavonoids.

Although polyphenols are present in virtually all plant foods, their levels vary enormously among diets depending on the type and quantity of plant foods in the diet. For example, some plant foods and beverages that are particularly rich in polyphenols are red wine, apple and orange juices, and legumes. There also can be marked variability in the polyphenolic compounds within a food; polyphenolic compounds in sorghum can vary by approximately 6-fold. The variability is influenced largely by genetic factors and environmental conditions.

The primary phenols in cereals and legumes are flavonoids, phenolic acids, and tannins. The major polyphenols in wine include phenolic acids, anthocyanins, tannins, and other flavonoids. The most abundant phenolic compound in fruits is flavonol. Nuts are rich in tannins.[38] Olive oil contains both phenolic acids and hydrolyzable tannins. The predominant flavonoid in onions is quercetin glycoside, whereas in tea and apples it is quercetin-3-rutinoside.

The dietary intake data for polyphenolic compounds, although limited, show that the intake reported is highly variable among the population groups studied.[40] Moreover, these data are questionable because of the omission of many polyphenolic compounds from nutrient databases. Nonetheless, although we presently have a poor understanding of the intake of total polyphenolic compounds, as well as the specific classes and individual polyphenols, it is evident that a diet rich in plant foods and beverages will be high in these compounds.

Several population studies have reported an inverse association between flavonoid intake and risk of coronary disease[41–44] and cancer.[42] In the Zutphen Elderly Study, a high intake of flavonoids (approximately 30 mg/day) was associated with approximately a 50% reduction in CHD mortality rate compared with individuals who had a low flavonoid intake (<19 mg/day). Similar results were reported in a cohort study also conducted in Finland[43] with 5,133 men and women, aged 30 to 69 years. In this study, onions and apples, rich sources of dietary flavonoids, were associated with a reduction in coronary mortality. Individuals in the highest quartile for apple intake had an approximately 50% reduction in coronary mortality. Likewise, a similar reduction was reported for individuals in the highest quartile of onion consumption. In a prospective study of 34,492 postmenopausal women in Iowa,[44] total flavonoid intake was associated with a decreased risk (RR = 0.62) in the group with the highest flavonoid intake. In contrast, in the Health Professionals' Study with 34,789 men, Rimm et al[45] did not find an association between new diagnosis of nonfatal myocardial infarction in 496 patients and flavonol and flavone intake. They did, however, report a significant association (RR = 0.63) between flavonoid intake and subsequent coronary mortality in 4,814 men with existing CHD. Thus, much of the epidemiologic evidence (albeit limited) suggests that flavonoids have a protective effect against coronary mortality. For those studies that have reported an association, putative mechanisms of action include inhibition of LDL oxidation (measured in vitro)[46] and inhibition of platelet aggregation and adhesion.[47] However, a recent study[48] reported no effect of onion (220 g/day) or parsley (5 g dried/day) on platelet aggregation.

Red wine is a rich and concentrated source of polyphenolic substances and >200 individual phenolic compounds have been identified to date.[49] Studies have shown that red wine inhibits oxidation of LDL in vitro[46,50] and increases antioxidant capacity of plasma.[51] The antioxidants identified in red wine include phenolic acids, flavonols, monomeric catechins, and polymeric anthocyanidins. Catechin, a flavan-3-ol compound, is one of the most abundant phenolic compounds in red wine and is present at concentrations up to 300 mg/L.[52] In contrast, red wine contains about 30 mg/L of flavonols (quercetin and kaempferol) and 140 mg/L of phenolic acids. All of these phenolic compounds, including resveratrol and grape extract, have been shown to have antioxidant properties in vitro.[53–61] Collectively, there is evidence emerging that phenolic compounds have antithrombotic effects that appear to be the result of reduced susceptibility of platelet aggregation, reduced synthesis of prothrombotic and proinflammatory mediators, decreased expression of adhesion molecules, and tissue factor activity (reviewed by Rotondo and de Gaetano[62] and Wollin and Jones[63]). In addition, there is some evidence that wine polyphenols can modulate the production of nitric oxide by the vascular endothelium, resulting in vasorelaxation.[62] The effects of polyphenols are independent of whether the food source is wine or grape juice. Freedman et al[64] found that juice from purple grapes (7 mL/kg body weight per day for 14 days) decreased platelet aggregation (58% vs. 39%), increased platelet-

Table 3. Association Between Plant Foods and Cardiovascular Disease and Coronary Heart Disease Risks: Selected Epidemiologic Studies

Reference	Study	Country	Population	Food Assessed	Association	Outcome
Joshipura et al 2001[8]	Nurses' Health Study and the Health Professionals' Follow-Up Study	USA	N = 126,399; 42,148 (M), 84,251 (W)	F and V / legumes	− / 0	CHD risk
Bazzano et al 2001[6] and Bazzano et al 2002[29]	NHANES I	USA	N = 9,632 (M, W)	F and V / legumes	−* / −*	CVD risk
			N = 9,608 (M, W)		− / −†	CHD risk
Zhao and Chen 2001[12]	Review	China	49 rural counties in China	F and V / legumes	−* (V only) / −†	CHD mortality
					−* (V only) / −†	Stroke mortality
Menotti et al 1999[13]	Seven Countries Study	See legend‡	N = 12,763 (M)	F and V / legumes	−† / −†	CHD mortality
Liu et al 2000[10]	Women's Health Study	USA	N = 39,876 (W)	F and V	−	CVD mortality
Liu et al 2001[9]	Physicians' Health Study	USA	N = 22,071 (M)	F and V	−†	CHD risk
Rosengren et al 1999[14]	Worldwide WHO MONICA Project	Sweden	N = 1,583 (M, W)	F and V	0	CHD incidence
					0	CHD mortality
Sasazuki et al 2001[11]		Japan	N = 1,937	F and V	+ (V only)	MI
					− (F only)	
Gillman et al 1995[7]	Framingham Study	USA	N = 832 (M)	F and V	−*	Stroke
Criqui and Ringel 1994[35]		21 developed countries		F and V / wine	− / −	CHD risk
					0 / −†	CHD mortality
					−† (F only) / 0	Total mortality
Pietinen et al 1996[21]	Alpha-Tocopherol, Beta-Carotene Prevention Study	Finland	N = 21,930 (M, W)	F and V / rye bread / cereal products	−* / −† / 0	CHD mortality
					0 / 0 / 0	CHD events
Fraser et al 1992[22]	Seventh-day Adventist Study	USA	N = 31,208 (M, W)	F and V / WW bread / legumes	− / −* / 0	Nonfatal MI
					− / 0 / 0	Fatal CHD
Liu et al 1999[23] and Liu et al 2000[24]	Nurses' Health Study	USA	N = 75,521 (W)	Whole grains	−†	CHD risk
					−†	Ischemic stroke
McKeown et al 2002[25]	Framingham Offspring Study	USA	N = 2,941; 1,338 (M), 1,603 (W)	Whole grains	−†	CVD risk factors§
Jacobs et al 2000[26]	Iowa Women's Health Study	USA	N = 11,040 (postmenopausal W)	Whole grains	−	CHD mortality
					−	Other CVD mortality
					−	All-cause mortality

Jacobs et al 1998[27]	Iowa Women's Health Study	USA	N = 34,492 (postmenopausal W)	Whole grains	–†	IHD mortality
Jacobs et al 1999[28]	Iowa Women's Health Study	USA	N = 38,740 (postmenopausal W)	Whole grains	–†	CHD mortality
					–†	All CVD mortality
					–	Stroke
Truelsen et al 1998[36]	The Copenhagen City Heart Study	Denmark	N = 13,329 (M, W)	Wine	–†	Stroke risk
Gronbaek et al 2000[33]	Copenhagen City Heart Study and Copenhagen County Centre of Preventive Medicine	Denmark	N = 24,523; 13,064 M, 11,459 W	Wine	–⋆	CHD mortality
Artalejo et al 1997[31]		Spain	50 provinces	Wine	–†	CVD mortality
Klatsky et al 1997[34]		USA	N = 128,934 (M, W)	Wine	–⋆	CHD risk
Stampfer et al 1988[32]	Nurses' Health Study	USA	N = 87,526 (W)	Wine	–†	CHD risk
					–†	Ischemic stroke

– = inverse association; + = positive association; 0 = no association; CHD = coronary heart disease; CVD = cardiovascular disease; F and V = fruits and vegetables; IHD = ischemic heart disease; M = men; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; W = women; WHO MONICA = World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease; WW = whole wheat.

⋆ $P \leq 0.01$.

† $P \leq 0.05$.

‡ = USA, Finland, the Netherlands, Italy, former Yugoslavia, Greece, and Japan.

§ = Waist–hip ratio, LDL cholesterol, fasting insulin concentration.

derived nitric oxide release (3.5 pmol/10^8 platelets vs. 6.0 pmol/10^8 platelets), and suppressed superoxide production (30 vs. 19 U). Thus, the inhibition of platelet-mediated thrombosis was independent of alcohol consumption. Cocoa and chocolate are also rich sources of polyphenolic compounds. In fact, 41 g of chocolate milk contain nearly as much phenol as 140 mL of red wine.[65] Major phenolic compounds include quercetin, epicatechin, procyanidin, and cocoa-red, the color component of cocoa (which is also found in red wine). Chocolate also contains cacao liquor polyphenol, an enriched polyphenol fraction purified from cacao liquor, a major constituent of chocolate.[66]

Both cocoa powder and chocolate have antioxidant activity. A recent study found that chocolate consumption (80 g semisweet) resulted in a decrease in basal plasma oxidation products.[67] Several studies have shown that chocolate decreases LDL oxidation susceptibility.[65,68,69] Cacao liquor polyphenol has been reported to inhibit both hydrogen peroxide and superoxide anion production in humans, possibly by scavenging excess reactive oxygen species.[66] In addition to antioxidant effects, the polyphenols of cocoa and chocolate have been shown to inhibit cyclooxygenase activity, thus reducing platelet aggregation and thrombotic tendencies.[70] Consistent with this is evidence that cocoa consumption suppresses unstimulated and stimulated platelet activation.[67,71] In addition, a recent study found that high-procyanidin chocolate increased plasma prostacyclin and decreased plasma leukotrienes,[72] thereby favorably altering eicosanoid synthesis.

Quercetin is the predominant flavonoid in the diet[73] and is found in fruits, vegetables, nuts, seeds, flowers, and bark. There is epidemiologic evidence for a protective effect against CVD of foods providing 16 to 24 mg/day of quercetin.[41–43] Quercetin inhibits platelet aggregation in vitro[74] and reduces thromboxane synthesis in vivo.[75] However, 2 clinical studies[76,77] found that despite a 23-fold increase in plasma quercetin concentration in the supplement study, there were no beneficial effects on plasma lipids and lipoproteins, platelet aggregation, platelet thromboxane B_2 production, and blood pressure.

Current research suggests a role for quercetin and other flavonoids in cancer prevention. Epidemiologic studies consistently have demonstrated an inverse relation between flavonoid consumption and risks for certain types of cancer. Several in vitro and in vivo experiments have shown that flavonoids may interrupt various stages of the cancer process.[78] It appears that these phytochemicals possess antioxidant activity as well as other anticarcinogenic properties.[79–81]

Flavonoids may exert their antioxidant activity in several ways. They may directly scavenge some radical species by acting as chain-breaking antioxidants.[77] They may suppress lipid peroxidation by recycling other antioxi-

dants, such as α-tocopherol, by donating a hydrogen atom to the tocopherol molecule.[77] In addition, some flavonoids can chelate pro-oxidant metal ions, such as iron and copper, thus preventing free radical formation from these pro-oxidants while simultaneously retaining their own free-radical scavenging capability.[77] The powerful antioxidant activity of flavonoids suggests a protective role for these compounds in carcinogenesis.

Flavonoids may act in a variety of ways beyond their antioxidant properties to interfere with carcinogenesis, such as protecting DNA from oxidative damage, deactivating carcinogens, and inhibiting the expression of mutated genes and the activity of enzymes that promote carcinogenesis, as well as promoting detoxification of xenobiotics.[81,82] For example, experimental studies have shown that quercetin can inhibit initiation, promotion,[83] and hyperproliferation of tumors[84] in animal models.

OLIVE OIL PHENOLICS

Olive oil has been shown to reduce LDL oxidizability[85–90] in the postprandial state[91] rather than the fasting state.[91,92] In part, this reflects its fatty acid profile (high in monounsaturated fatty acids) that is less susceptible to lipid peroxidation than polyunsaturated fatty acids. α-Tocopherol also may contribute to the antioxidant effects of olive and other vegetable oils.

Antioxidant effects of olive oil also appear to be the result of phenolic compounds. Olive oil, in particular, the first-pressed or better known "extra virgin" type, has a high content of phenolic components, which have been shown to be powerful antioxidants.[93] Olive oil phenols are a complex mixture of compounds that include 3,4-dihydroxyphenylethanol (hydroxytyrosol), 4-hydroxyphenylethanol (tyrosol), 4-hydroxyphenylacetic acid, protocatechuic acid, syringic acid, vanillic acid, caffeic acid, and p-coumaric acid. The concentration of the phenolic fraction in olive oil varies depending on the cultivar, climate, and degree of ripeness of the fruit; the average concentration is 500 mg/L in extra virgin olive oil.[94] Of the various phenolic constituents of olive oil, hydroxytyrosol seems to be among the most important. It is present in free form and also as a constituent of complex molecules (i.e., oleuropein). Its in vitro antioxidant potency is greater than butylated hydroxytoluene.[95] In addition, olive oil phenols have greater antioxidant potency than other vegetable oils.[95,96] High phenolic olive oil compared with high oleic sunflower oil reduced LDL peroxidation in hypercholesterolemic postmenopausal women.[89]

PHYTOESTROGENS

Phytoestrogens, or estrogenic compounds in plants, are divided into 3 main classes: isoflavonones, coumestans, and lignans.[97] Structurally, all are diphenolic compounds that are similar to estrogen and, as might be expected, bind to the estrogen receptor. Surprisingly, however, they act both as partial estrogen agonists and antagonists, thereby having similar and opposing actions compared with estrogen.[98] The isoflavones, genistein and daidzein, are found predominantly in legumes, namely soybeans.[97,99] Coumestrol is found in lucerne, alfalfa, and clovers and at low concentrations in beans and peas.[97,99] Lignans are the most ubiquitous phytoestrogens, because they exist as minor constituents of many plants, where they are involved in plant cell wall formation. The primary dietary source of lignans is flaxseed oil, but it can be found in varying concentrations in soybeans, seaweed, whole grains, fruits, and vegetables.[97,99]

Isoflavonoids are the most extensively studied phytoestrogens with respect to CVD. Because soy foods are the most significant dietary source of isoflavones, many studies with humans and nonhuman primates have been conducted evaluating the effects of soy foods and constituents of soy foods on numerous CVD risk factors. Soy foods have been shown to have favorable effects on plasma lipids and lipoproteins. A meta-analysis of 38 clinical studies reported that total cholesterol was decreased by 9%, LDL cholesterol by 13%, and triglycerides by 11% when an average of 47 g of soybean protein was consumed,[100] with a greater response observed in subjects having a higher baseline cholesterol level. High-density lipoprotein (HDL) cholesterol was increased modestly (i.e., 2.4%; not significant). The active components of soy protein that are thought to account for these effects are the isoflavones genistein and daidzein.[101] In this study, monkeys fed soybean protein containing isoflavones had lower serum total and LDL cholesterol levels compared with those fed an isoflavone-free soybean protein. However, there are reports showing that an isoflavone supplement rich in genistein[102] and genistein plus daidzein[103] had no effect on plasma cholesterol levels in healthy, normocholesterolemic subjects or in postmenopausal women.[104] In contrast, Crouse et al[105] found that soy protein containing isoflavones significantly reduced total and LDL cholesterol levels by 4% and 6%, respectively, in hypercholesterolemic subjects (LDL cholesterol, 140 to 200 mg/dL). Moreover, when the soy protein was stripped of isoflavones by ethanol extraction, the cholesterol-lowering effect was lost. It is important to note that isoflavone bioavailability is dependent on gut microflora activity. Thus, isoflavone absorption and its beneficial effects may be highly variable and could explain discrepant study results.[106] Soy phytoestrogens decrease the extent of atherosclerotic lesion formation in nonhuman primates,[107,108] reduce LDL oxidative susceptibility in humans,[109] and decrease thrombin formation.[110] In addition, they have been shown to improve systemic arterial compliance.[111] There is also some evidence that isofla-

vone-containing soy foods have a modest blood pressure–lowering effect.[112]

Research to date shows multiple beneficial effects of soy that appear to be the result of isoflavones. However, further studies are needed to resolve the biological effects that individual isoflavones have on CVD risk and the mechanisms that account for these effects. Furthermore, it will be important to reconcile these beneficial effects of soy protein with recent evidence indicating potentially adverse effects of soy protein with isoflavones on lipoprotein (a) and brachial artery flow–mediated dilation.[113] The adverse effects reported in the latter study occurred despite favorable effects on LDL cholesterol and the LDL cholesterol:HDL cholesterol ratio.

Lignans have weak estrogenic and antiestrogenic activity that is comparable to soy isoflavones. Flaxseed is a rich source of lignans. A recent clinical study has shown that partially defatted flaxseed (containing lignans and flaxseed gum) lowers LDL cholesterol approximately 8%.[114] In addition, lignans possess antioxidant activity.[115] However, surprisingly, partially defatted flaxseed has pro-oxidant activity.[114] Epidemiologic research has shown that the rate of hormone-related cancers is higher in populations with Western lifestyles that include relatively high fat, low-fiber (low in phytoestrogens) diets, compared with Asian populations with Eastern lifestyles that include plant-based diets high in phytoestrogens.[97,99] Evidence is mounting that these phytoestrogens might play a significant role in protection against a wide range of clinical conditions, including breast, prostate, colon, and other cancers, in addition to CVD, menopausal symptoms, and osteoporosis.[97–99] These plant-based phytoestrogens, particularly isoflavones, appear to compete with endogenous estrogen for receptor binding, yet they stimulate weaker estrogenic responses, and at certain concentrations they exert antiestrogenic actions.[97–99] Phytoestrogen action as an estrogen agonist or antagonist is dependent on the dietary concentration of these compounds, endogenous estrogen levels, sex, and menopausal status.[80] This weak estrogenic effect may be protective against hormone-related diseases.[80,97,99] For example, a shorter menstrual cycle is associated with an increased risk of breast cancer secondary to the increased exposure to estrogen.[98] Phytoestrogens stimulate sex hormone–binding globulin, which reduces the amount of circulating estrogen, and inhibit gonadotropin output to increase the duration of the menstrual cycle. The combined effect of a longer menstrual cycle and lower estrogen levels leads to a lower integrated lifetime exposure to estrogen and may protect against breast cancer development.[80,97–99]

Like other phytochemicals, phytoestrogens possess antioxidant properties. They have been shown to suppress tumor promoter–induced hydrogen peroxide and superoxide anion formation.[97–99] In addition to its own antioxidant actions, genistein also enhances the activity of a number of antioxidant enzymes, including catalase, glutathione peroxidase, glutathione reductase, and superoxide dismutase.[97]

Despite the reported protective effects of phytoestrogens against cancer development, some studies indicate a need for caution when supplementing with these phytochemicals. A report by McMichael-Phillips et al[116] showed an increase in proliferation of breast lobular epithelium, whereas another study documented an increase in estradiol levels and increased frequency of hyperplastic cells in aspirated breast fluid after supplementation with soybeans.[117] Allred et al[118] reported that soy protein diets containing varying concentrations of genistein stimulated the growth of estrogen-dependent breast cancer cells in vivo in a dose-dependent manner.

The current evidence suggests that phytoestrogens may play a role in the prevention and treatment of several types of cancer. Many of these effects are considered to be protective in nature, although a few potentially adverse effects have been reported. Of note is that many of the effects, positive and negative, have been shown with very high concentrations and not at levels likely to be achieved by eating foods containing phytoestrogens.[97,99] Additionally, the role of such factors as bioavailability, phytoestrogen absorption, duration of exposure, and the potential influence of other dietary components remains uncertain at this time.

RESVERATROL

Resveratrol is a polyphenol (3,5,4'-trihydroxystilbene), thought to be a phytoalexin, one of a group of compounds produced during times of environmental stress or pathogenic attack.[119] It is found principally in the skin of grapes and is produced in other plants, including peanuts. Red wine is a rich source of resveratrol and is thought to confer the cardioprotective effects associated with moderate consumption of wine. There is evidence to suggest that resveratrol inhibits both LDL oxidative susceptibility in vitro[46] and platelet aggregation as well as eicosanoid synthesis.[70] Resveratrol also has been shown to inhibit the expression of the tissue factor gene[120]; tissue factor protein initiates the coagulation cascade resulting in thrombus formation. Thus, the evidence to date suggests that resveratrol may decrease CVD risk by multiple mechanisms. Preinfusion of resveratrol prevents reperfusion-induced arrhythmias and mortality in rats, possibly because of its antioxidant, free radical–scavenging activity and its ability to increase nitric oxide release.[121]

Resveratrol functions as a chemopreventive agent as well. It has been shown to inhibit ribonucleotide reductase and certain other cellular events associated with initiation, promotion, and progression of carcinogenesis.[119] Administration of 25 μmol of resveratrol reduced the

number of skin tumors in mice by 98% and reduced the number of mice with tumors by 88%.[119] Resveratrol serves, in a dose-dependent manner, as both an antioxidant and an antimutagen.[119,122]

Resveratrol also has been categorized as a phytoestrogen, because at low concentrations it is a partial estrogen receptor agonist, yet at higher levels, in the presence of 17-β-estradiol (E_2), it antagonizes the growth-stimulatory effect of E_2.[122] As an antiestrogen compound, it has been shown to inhibit proliferation of estrogen receptor–positive human breast cancer MCF-7 cells and to stimulate tumor growth factor–β messenger RNA expression 15-fold.[122] Although the metabolism of resveratrol is not clear, it has been suggested that 2 glasses of red wine could elevate plasma resveratrol concentrations into the micromolar range, where most of these pharmacologic effects have been observed.[123]

LYCOPENE

Lycopene is an acyclic carotenoid found primarily in tomatoes and tomato products (about 80% of dietary lycopene in the United States[124]). Other minor food sources include apricots, grapefruit, guava, watermelon, and papaya. Tomato lycopene levels vary widely among different varieties and stages of ripeness.[124,125] Bioavailability is enhanced by cooking food sources of lycopene, particularly in the presence of oil or fats.[124–126]

There is some evidence that lycopene may have a protective effect against CVD. In the European Community Multicenter Study on Antioxidant, Myocardial Infarction, and Breast Cancer (EURAMIC) Study,[127] adipose tissue lycopene concentrations were independently protective (OR = 0.52 for the 10th vs. the 90th percentile) against myocardial infarction. These results differ from an earlier case-control study in smokers that assessed serum carotenoids and risk of myocardial infarction.[128] In that study,[128] low serum levels of carotenoids were associated with an increased risk of subsequent myocardial infarction in smokers. The difference between the 2 studies may reflect the different study populations. There is limited evidence that dietary supplementation of lycopene lowers LDL cholesterol levels by about 14%,[129] possibly because of an inhibition of cholesterol synthesis and increased LDL degradation (reviewed by Arab and Steck[130]). In addition, lycopene reduces LDL oxidative susceptibility in vitro.[131] There also is some evidence that lycopene intake, as measured by adipose tissue concentrations, is associated with reduced intimal wall thickness and risk of myocardial infarction.[130]

Experimental studies are limited at this point, but epidemiologic studies suggest that lycopene consumption may also protect against various forms of cancer, including cancer of the prostate,[124,125,132] cervix,[124–126] pharynx and esophagus,[125,133,134] stomach,[124,125,133,134] bladder,[125] and colon and rectum.[124–126,133,134] Interestingly, it appears that lycopene also may play a protective role against ultraviolet light exposure and cigarette smoke, although more research is needed.[124]

The anticarcinogenic mechanisms of lycopene remain speculative, but its antioxidant properties are believed to play a role, because oxidative stress is linked to carcinogenesis. It appears that it may interfere with oxidative damage to lipids, DNA, and lipoproteins.[124,135,136] Lycopene has been shown to be a more potent inhibitor than either α- or β-carotenes of tumor cell growth and proliferation in cell cultures and animal models.[124,133]

ORGANOSULFUR COMPOUNDS

Most of the CVD research conducted with food sources of organosulfur compounds has evaluated the effects of garlic oil and garlic on various risk factors. A number of studies have shown, in general, that garlic favorably affects important risk factors for CVD. Garlic oil and garlic consumption have been shown to decrease total and LDL cholesterol and triglyceride levels. Consumption of 0.5 to 1 clove of garlic per day lowers cholesterol levels approximately 10%.[137,138] Mechanisms that explain the observed effects of garlic include a decrease in cholesterol and fatty acid synthesis and cholesterol absorption.[139] However, there is some evidence that garlic powder does not lower cholesterol levels,[140] which may reflect either a loss of active compound(s) during processing or an inhibition in the release of active components in garlic. The formation of these active compounds is influenced by crushing garlic, duration of the drying process, the temperature at which garlic is dried, and humidity.[141] Garlic extracts also have been shown to elicit antithrombotic effects and modestly decrease blood pressure (i.e., 5.5% decrease in systolic blood pressure and a slight decrease in diastolic blood pressure).[142] There also is evidence that aged garlic extracts, including water and lipid-soluble compounds, have antioxidant effects.[143] Aged garlic extract results from the prolonged extraction of fresh garlic at room temperature and contains allyl amino acid derivatives, stable lipid-soluble allyl sulfides, flavonoids, and saponins.[144] The water-soluble organosulfur compounds, S-allylcysteine and S-allylmercaptocyteine, have potent antioxidant properties.[143] In addition, aged garlic extract contains lipid-soluble compounds that have antioxidant effects. These include diallyl sulfide, triallyl sulfide, diallyl disulfide, diallyl polysulfides, and others. However, much variability has been observed between different studies because of differences in duration of treatment with garlic, total quantity of garlic consumed, and lack of consistency when preparing garlic.[145–147]

The use of garlic as an effective remedy for tumors has been documented as early as 1550 BC.[148] More recently, animal and cell culture studies have shown garlic to be a

potent inhibitor of tumorigenesis.[149] However, as of yet, epidemiologic studies have not shown a strong effect of garlic intake on cancer prevention.[149]

Diallyl disulfide and diallyl sulfide appear to be the bioactive components of garlic that exert the anticarcinogenic effects.[148,150] These allylic compounds stimulate glutathione S-transferase activity in the liver. This transferase binds to and detoxifies potential carcinogens.[150] Allicin has been found to cause a transient decrease in glutathione (GSH), which was correlated with its antiproliferative action.[151] Organosulfur compounds derived from garlic function as antioxidants with free radical–scavenging properties to inhibit lipid peroxidation.[148,152] Diallyl sulfide may function to suppress the tumor promotion phase of carcinogenesis by reducing polyamine formation by means of inhibition of ornithine decarboxylase and possibly by stimulating DNA repair.[148] In contrast, Fukushima et al[150] reported that diallyl sulfide promoted rather than inhibited liver carcinogenesis. An additional mechanism by which garlic may suppress carcinogenesis is through a depression in nitrosamine formation.[153] Although many studies report chemopreventive effects of garlic, further studies are needed to clarify its role in cancer prevention.

PLANT STEROLS AND BIOACTIVE CONSTITUENTS

Phytosterols are naturally occurring plant sterols that are present in the nonsaponifiable fraction of plant oils. Structurally, plant sterols are similar to cholesterol except that there always are some substitutions on the sterol side chain at the C24 position. They are not synthesized in humans, are poorly absorbed, and are excreted faster from the liver than cholesterol, which explains their low abundance in human tissues.[154] The primary plant sterols in the diet are sitosterol, stigmasterol, and campesterol. Typical consumption of plant sterols is approximately 200 to 400 mg/day. The most abundant plant sterol in Western diets is β-sitosterol.

Studies with sitosterol or mixtures of plant sterols (approximately 1 g/day) have shown that they reduce serum cholesterol levels in humans by approximately 10%.[155] This discovery has resulted in subsequent research to evaluate the effects of sitosterol derivatives on cholesterol absorption and serum cholesterol levels. Sitostanol (a 5-α saturated sitosterol) was shown to be more potent in reducing cholesterol absorption and serum cholesterol levels than sitosterol.[156] These findings provided the basis for the current era of research evaluating the effects of sitostanol and sitostanol esters from different plant oil sources. Special margarines are the primary food source of plant sterols/stanols. The plant sterol mixtures are derived from different oil sources, including pine tree wood pulp (tall oil), soybean oil, rice bran oil, and shea nut oil. Benecol margarine (Raisio Inc, Raisio, Finland) is comprised of stanol esters derived from tall oil. Take Control margarine (Lipton, Unilever Bestfoods, Englewood Cliffs, NJ) contains sterol esters from soybeans. The stanol/stanol ester margarine studies have fed approximately 2 to 3 g/day of stanols either as the free or esterified form in full-fat or lower fat margarines or mayonnaise. Typically, there is an approximate 10% reduction in total cholesterol and about a 14% decrease in LDL cholesterol and no change in HDL cholesterol or triglyceride levels.[157–162] With a reduced-fat spread (40% fat) providing 1.1 or 2.2 g/day of plant sterol esters, LDL cholesterol was reduced 7.6% and 8.1% beyond that achieved with a National Cholesterol Education Program Step 1 diet in subjects with mild-to-moderate hypercholesterolemia.[163] Thus, both plant stanol and sterol esters evoke a significant serum cholesterol–lowering response beyond that attained with a cholesterol-lowering diet. The cholesterol-lowering effects have been observed in long-term studies (for 1 year[160]) as well as in shorter term trials[156] with mildly hypercholesterolemic subjects. Moreover, efficacy has been demonstrated in subjects with previous myocardial infarction on a statin.[162]

The reduction in total and LDL cholesterol is the result of a decrease in cholesterol absorption and an alteration of enzymes involved in cholesterol metabolism and excretion (reviewed by Jones and Ntanios[164]). A potentially adverse effect associated with consumption of stanol esters is a dose-dependent decrease in plasma carotenoid levels from decreased carotenoid absorption and possibly other as-yet unidentified mechanisms.

There is some emerging evidence that the sterols present in the unsaponfiable fraction of rice bran oil, oryzanols (a group of ferulate esters of triterpene alcohols and phytosterols), decrease plasma cholesterol levels[165] and that tocotrienols, another group of phytosterols present in rice bran oil, may have important antioxidant properties.[166] Further work is needed to evaluate the effects of rice bran oil to establish its efficacy as a source of plant sterols that lower CVD risk.

β-GLUCAN, PSYLLIUM, AND PECTIN

Epidemiologic studies have suggested that dietary fiber protects against CHD. In the Scottish Heart Health Study, increased fiber intake was associated with both a reduced risk of CHD and decreased mortality.[167] In the Nurses' Health Study, a 10-g/day increase in total fiber intake was associated with a 20% reduction in CHD events.[168] In the latter study, only cereal fiber was strongly associated with decreased risk of CHD. In contrast, based on a meta-analysis, Anderson et al[169] reported that cereal fiber derived from refined cereal products was not associated with a cardioprotective effect.

β-Glucan, psyllium, and pectin are soluble dietary fibers that have been shown to lower total and LDL cholesterol levels. β-Glucan is found in oats, barley, and yeast; pectin is present in fruits and vegetables; and psyllium is derived from the husks of blond psyllium seed and currently is being added to some foods, including cereals and other grain products. Fiber from 2 servings of oats (approximately 2.6 g of soluble fiber) elicits a 2% to 3% cholesterol-lowering effect beyond what is achieved by a serum cholesterol–lowering diet.[170] A meta-analysis of 8 studies has shown that approximately 10 g/day of psyllium lowers total cholesterol 4% and LDL cholesterol 7%.[169] Another soluble fiber, flaxseed gum, has been shown to lower LDL cholesterol by 7% to 8% when 5 to 6 g/day is consumed.[114] Another meta-analysis has shown that the cholesterol-lowering effects of β-glucan, psyllium, and pectin are comparable.[171] Because different foods have varying amounts of these soluble fibers, the cholesterol-lowering response expected will depend on the quantity of soluble fiber consumed. Thus, soluble fiber has a modest cholesterol-lowering effect that goes beyond what can be achieved by lowering saturated fatty acid and cholesterol.

In addition to lowering serum cholesterol levels, a high fiber intake prevents or attenuates the hypertriglyceridemic response to a high-carbohydrate diet.[172] Chandalia et al[173] reported that increasing dietary fiber from 10 to 22 g/1,000 calories was associated with a 10% reduction in fasting serum triglyceride levels. Thus, dietary fiber can reduce risk of heart disease in multiple ways.

TEA

Tea is a rich source of antioxidant polyphenols (i.e., catechins, flavonols, theaflavins, and thearubigins) and may confer a cardioprotective effect by decreasing LDL oxidative susceptibility.[174] The epidemiologic evidence, however, for an association between regular consumption of tea and CHD is equivocal.[175,176] Some prospective epidemiologic studies have shown a clear protective effect of flavonols, whereas one showed only a protective effect in a cohort with a history of CHD (reviewed by Hollman et al[175]); another study found that flavonols (mainly from tea) actually increased risk of CHD (reviewed by Hollman et al[175]). In the Boston Area Health Study, consumption of ≥1 cup of black tea per day was associated with a 50% reduction in risk of heart attack.[177] A cross-sectional study with men and women with coronary artery disease found a protective association between green tea consumption and coronary atherosclerosis in men but not women.[177] There is evidence that tea polyphenols inhibit LDL lipid peroxidation.[175,176,178,179] However, other investigators have not observed this.[180] There is some evidence that black and green tea consumption may decrease platelet aggregation but appear to have no effect on hemostasis (reviewed by Tijburg et al[181]).

Whether tea has chemopreventive effects in humans is unclear. In a Japanese prospective cohort study of 8,552 individuals, consumption of >10 cups of green tea a day was associated with delayed onset of cancer by 8.7 years in women and 3.0 years in men compared with those who consumed <3 cups per day.[182] In addition, a lower RR was observed for lung, colon, and liver cancers. Likewise, a prospective study in postmenopausal women found that those who consumed ≥2 cups of tea (primarily black tea) had a slightly lower risk for all cancers compared with women who never or only occasionally consumed tea.[183] On the other hand, Nagano et al[184] found no protective relationship between tea consumption and cancer (all sites) in 38,540 Japanese men and women. The primary sources of polyphenols in green tea are (35% to 52%) catechins and flavonols, which include epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate.[182,185] In addition, tea contains smaller concentrations of quercetin and theaflavins (black tea).[186] Thearubigens are the major fraction of black tea polyphenols and account for >20% of the solids in brewed tea.[187] Human studies have established that these antioxidant polyphenols, in particular epigallocatechin-3-gallate, protect against carcinogenesis.[185] In animals, green tea significantly increased activity of antioxidants and detoxifying enzymes, such as glutathione S-transferase, catalase, and quinone reductase, in the lungs, liver, and small intestine.[185] Topical administration of epigallocatechin-3-gallate, subsequent to ultraviolet radiation, significantly reduced tumor induction in mice.[185]

ISOTHIOCYANATES

Isothiocyanates are found in a number of cruciferous vegetables, including broccoli, Brussels sprouts, cabbage, and cauliflower, and are released upon chewing.[188] Some naturally occurring forms of this phytochemical include 2-phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphanes.[188] These compounds have gained much attention because of their marked chemopreventive capacity in animals and human cell cultures. α-Napthyl, β-napthyl, 2-phenethyl isothiocyanate, benzyl isothiocyanate, and other arylalkyl isothiocyanates have been reported to protect against tumorogenesis in the lung, breast, liver, stomach, and esophagus.[189] Isothiocyanates, particularly 2-phenethyl isothiocyanate, have been recommended as a chemopreventive strategy to reduce lung cancer in smokers.[188] Most anticarcinogenic activity was reported to occur before or during carcinogen administration but not after.[188]

The specific effects of isothiocyanates, however, seem to be dependent on the experimental conditions, the form of isothiocyanate, treatment regimen, and target tis-

sue being assessed. More importantly, it has been shown that uptake of isothiocyanates is markedly reduced when the vegetables are cooked because of inactivation of myrosinase.[190,191] The anticarcinogenic potential of cruciferous vegetables requires further study, because most are consumed in the cooked form.

MONOTERPENES

Monoterpenes are naturally occurring isoprenoids found in the essential oils of citrus fruits, cherries, mint, and herbs.[192–194] D-limonene comprises 90% to 95% of orange oil and is a prevalent flavoring agent in many foods and beverages.[192] The monoterpenes, limonene and perillyl alcohol, have shown efficacy in both cancer prevention and therapy.[192,193]

Monoterpenes have been reported to decrease the incidence of chemically induced tumors in the skin, liver, lung, breast, and forestomach of rats.[192–194] Chemotherapeutic use of these compounds is encouraging, because they caused complete regression in >80% of mammary carcinomas in rats.[192,195] However, 1 study reported no beneficial effect of perillyl alcohol and was even shown to have tumor-promoting activity similar to that of phenobarbital.[196]

CONCLUSION

Impressive progress is being made in defining the role of bioactive compounds in reducing the risk of major chronic diseases and the underlying biological mechanisms that account for these effects. An ever-expanding list of bioactive compounds is being scientifically evaluated. As discussed herein, numerous bioactive compounds appear to have beneficial health effects. On the basis of a large population database, there is sufficient evidence to recommend a diet high in food sources rich in bioactive compounds. From a practical perspective, this means recommending a diet rich in a variety of fruits, vegetables, whole grains, legumes, and nuts that are prepared in different ways.

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