Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Actis-Goretta, L.	Actis-Goretta, L.; Ottaviani, J. I.; Fraga, C. G., Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *J Agric Food Chem* **2006,** 54, (1), 229-34.	2006	Angiotensin converting enzyme (ACE) activity was evaluated in the presence of flavanol-rich foods, i.e., wines, chocolates, and teas, and of purified flavonoids. All foods assayed inhibited ACE activity, red wines being more effective than white wine, and green tea more effective than black tea. The **inhibition of ACE activity was associated with both phenolic and flavanol content in the foods**. When isolated polyphenols were assayed, **procyanidins (dimer and hexamer)** and **epigallocatechin significantly inhibited enzyme activity**; similar concentrations of (+)-catechin, (-)-epicatechin, gallic acid, chlorogenic acid, caffeic acid, quercetin, kaempferol, and resveratrol were ineffective. When ACE activity was assayed in rat kidney membranes in the presence of chocolate extracts or purified procyanidins, it was observed that the inhibition depended on the chocolate content of flavanols and the number of flavanol units constituting the procyanidin. These experiments demonstrate that flavanols either isolated or present in foods could inhibit ACE activity. The occurrence of such inhibition in vivo needs to be determined, although is supported by the association between the consumption of flavanol-rich foods and reductions in blood pressure observed in several experimental models.				X
	Andriambeloson,E.	Andriambeloson, E.; Magnier, C.; Haan-Archipoff, G.; Lobstein, A.; Anton, R.; Beretz, A.; Stoclet, J. C.; Andriantsitohaina, R., Natural dietary polyphenolic compounds cause endothelium-dependent vasorelaxation in rat thoracic aorta. *J Nutr* **1998,** 128, (12), 2324-33.	1998	This study investigated the possible active principles which support the endothelial nitric oxide-dependent relaxation produced by red wine and other plant polyphenolic compounds in thoracic aorta from male Wistar rats (12-14 wk old). Relaxation experiments were recorded isometrically on vessels precontracted with norepinephrine. Ten different chromatographic fractions (3-18 mg) isolated from red wine polyphenolic compounds (RWPC) and some available defined polyphenols (10-15 mg) were tested. Fractions enriched into either anthocyanins or oligomeric condensed tannins exhibited endothelium-dependent vasorelaxant activity (maximal relaxation in the range of 59-77%) comparable to the original RWPC. However, polymeric condensed tannins elicited a weaker vasorelaxant activity than the original RWPC (maximal relaxation ranged between 20-47%, $P < 0.01$). Moreover, the representative of either phenolic acid derivatives (benzoic acid, vanillic acid, gallic acid), hydroxycinnamic acid (p-coumaric acid, caffeic acid) or the flavanol [(+)-epicatechin] classes failed to induce this type of response. Among the anthocyanins, delphinidin (maximal relaxation being 89%), but not malvidin or cyanidin, showed endothelium-dependent vasorelaxation. These results show that anthocyanins and oligomeric-condensed tannins exhibited a pharmacological profile comparable to the original RWPC. These compounds may be involved in the reduction of cardiovascular mortality related to the presence of wine, fruits and vegetables in the diet.				X

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Beecher, G. R	Beecher, G. R., Proanthocyanidins: Biological activities associated with human health. *Pharmaceutical Biology* **2004,** 42, 2-20.	2004	Proanthocyanidins, also called condensed tannins, are oligomers and polymers of monomeric flavans linked through specific single (B linkages) and double (A linkages) bonds. These secondary plant metabolites have substantial antioxidant activity. They are prevalent in some foods and dietary supplements including several **berries**, red grapes and their wines, and seeds, baking chocolate, cinnamon, pycnogenol, and Ginkgo biloba. Calculations based on limited food composition data suggest daily intakes of about 54 mg/day per person in the United States. Similar data are unavailable to estimate intakes from dietary supplements. Studies on digestion of proanthocyanidins indicates only monomers and dimers are absorbed; however, preliminary evidence suggests hydroxylated phenolic acids are important products of gastrointestinal microflora activity that also may be absorbed. Several types of investigations support improved vascular health after short- or long-term consumption of proanthocyanidins or foods and supplements that contain them. These effects include vasodilation, presumably as a result of increased NO production, decreased platelet aggregation, reduced sensitivity of low-density lipoproteins (LDL) to oxidization, and modulation of several reactions associated with inflammation. Studies with cranberries and cinnamon, both of which contain uniquely linked proanthocyanidins, support a role for bacterial antiadhesion and improved glucose metabolism in type 2 diabetics, respectively. Results from a variety of experiments indicate proanthocyanidins may modulate several reactions involved in cancer processes. A crucial research need is to identify further biologically active components of proanthocyanidins so that mechanisms of action at the tissue, cellular, and subcellular levels.				
	Blomhoff, R.	Blomhoff, R., Dietary antioxidants and cardiovascular disease. *Curr Opin Lipidol* **2005,** 16, (1), 47-54.	2005	PURPOSE OF REVIEW: Oxidative damage is involved in **cardiovascular diseases**. Intervention with alpha-tocopherol, ascorbic acid and beta-carotene does not appear to reduce pathogenesis. The purpose of this review is to describe alternative antioxidant mechanisms that may be involved. RECENT FINDINGS: Antioxidants with different chemical properties may recharge each other in an antioxidant network. The total antioxidant content of dietary plants may therefore be a useful tool for testing the "antioxidant network" hypothesis. Several berries, fruits, nuts, seeds, vegetables, drinks and spices have been found to be high in total antioxidants. Initial studies in animals and humans are supportive as to the beneficial effects of dietary plants rich in total antioxidants. Additionally, antioxidants and other plant compounds may also improve the endogenous antioxidant defence through induction of antioxidant and phase 2 enzymes. Dietary plants rich in such compounds include broccoli, Brussels sprouts, cabbage, kale, cauliflower, carrots, onions, tomatoes, spinach and garlic. SUMMARY: Although initial studies have indicated that antioxidants may reduce oxidative stress, **human intervention studies do not support** **a beneficial effect of antioxidant supplements**. Further research is needed to clarify whether other plant antioxidants, plants rich in a combination of antioxidants, or plant compounds that induce the endogenous antioxidant defence can reduce pathogenesis of cardiovascular disease and other oxidative stress-related diseases.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Jalili, T.	Jalili, T.; Carlstrom, J.; Kim, S.; Freeman, D.; Jin, H.; Wu, T. C.; Litwin, S. E.; David Symons, J., Quercetin-supplemented diets lower blood pressure and attenuate cardiac hypertrophy in rats with aortic constriction. *J Cardiovasc Pharmacol* **2006,** 47, (4), 531-41.	2006	**Quercetin (Q**), a flavonoid **found in berries** and onions, can reduce blood pressure in hypertensive animals and inhibit signal transduction pathways in vitro that regulate cardiac hypertrophy. We hypothesized that quercetin could prevent cardiovascular complications in **rats** with abdominal aortic constriction (AAC). Rats consumed standard or Q-supplemented chow (1.5 g Q/kg chow) for 7 days before AAC or sham surgery (SHAM, n = 15; AAC, n = 15; SHAMQ, n = 15; AACQ, n = 14). Fourteen days after surgery, plasma and liver Q concentrations were elevated ($P < 0.05$) and hepatic lipid oxidation was reduced ($P < 0.05$) in Q-treated versus untreated rats. **Carotid arterial blood pressure and cardiac hypertrophy were attenuated** ($P < 0.05$), and cardiac protein kinase C betaII translocation was normalized ($P < 0.05$) in AACQ versus AAC. Expression of cardiac beta-myosin heavy-chain mRNA was also reduced in AACQ versus AAC ($P < 0.05$). However, extracellular regulated kinase 1/2 phosphorylation was similar in AAC versus AACQ. The level of aortic endothelial dysfunction (wire myography) was also similar between AAC and AACQ, in spite of reduced aortic thickening in AACQ. Importantly, Q-treated rats did not show any deleterious changes in myocardial function (echocardiography). Our **data supports an antihypertensive** **and antihypertrophic effect of Q** in vivo in the absence of changes concerning vascular and myocardial function.			X	
	Mennen, L. I.	Mennen, L. I.; Sapinho, D.; de Bree, A.; Arnault, N.; Bertrais, S.; Galan, P.; Hercberg, S., Consumption of foods rich in flavonoids is related to a decreased cardiovascular risk in apparently healthy French women. *J Nutr* **2004,** 134, (4), 923-6.	2004	A high consumption of flavonoids may lower cardiovascular risk through their antioxidant capacity. This study evaluated the relation between consumption of foods rich in flavonoids and estimated cardiovascular risk. A cross-sectional analysis was performed in **1286 women and 1005 men of the SU.VI.MAX Study (an 8-y trial evaluating the effect of antioxidant supplementation on the incidence of major chronic diseases)**. Dietary intakes were estimated using six 24-h dietary records collected during the year between the clinical measurement of blood pressure, weight and height and the biological measurement of total serum cholesterol and fasting plasma glucose. The relation between flavonoid rich food consumption and cardiovascular risk factors was evaluated with analyses of covariance and the effect on cardiovascular risk with logistic regression analyses. In women, flavonoid-rich food consumption was inversely related to systolic blood pressure ($P = 0.005$). **No relation between risk factors and flavonoid-rich food consumption was seen in men.** Women in the highest tertile of flavonoid-rich food consumption were at lower risk for cardiovascular disease [odds ratio (OR): 0.31; 95%CI: 0.14, 0.68], whereas a positive tendency was seen in men (OR: 1.38; 95%CI: 0.96, 2.00). These **results indicate that in women, a high consumption of flavonoid-rich foods may prevent cardiovascular disease**.	X			

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Morton, L. W	Morton, L. W.; Abu-Amsha Caccetta, R.; Puddey, I. B.; Croft, K. D., Chemistry and biological effects of dietary phenolic compounds: relevance to cardiovascular disease. *Clin Exp Pharmacol Physiol* **2000,** 27, (3), 152-9.	2000	1. There has been considerable recent interest in the possibility that increased intake of dietary anti-oxidants may protect against cardiovascular disease. This is partly due to the knowledge that oxidative events in vivo may play a role in the pathogenesis of atherosclerosis. 2. While dietary anti-oxidants, such as vitamins E and C, have received considerable attention in this regard, relatively little is known about a similar anti-oxidant role for plant-derived polyphenolic compounds, such as the flavonoids and phenolic acids. A review of the distribution, bioavailability and biological activity of these compounds suggests that they may have a physiological role as anti-oxidants. 3. Human trials on the anti-oxidant effects of beverages rich in polyphenolics, such as red wine, fruit juice or tea, have been limited and results are, at present, inconclusive. This is due, in part, to poor methodologies available to measure oxidative damage in vivo. 4. There is a sound rationale for considering polyphenolics as important contributors to the dietary anti-oxidant intake derived from fruits and vegetables. However, **continuing research is needed using appropriate biomarkers of oxidant damage in vivo before these compounds can be conclusively considered as dietary anti-oxidants with nutritional benefit.**				
	Rissanen, T. H.	Rissanen, T. H.; Voutilainen, S.; Virtanen, J. K.; Venho, B.; Vanharanta, M.; Mursu, J.; Salonen, J. T., Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. *J Nutr* **2003,** 133, (1), 199-204.	2003	Diets rich in fruits and vegetables have been of interest because of their potential health benefits against chronic diseases such as cardiovascular disease (CVD) and cancer. The aim of this work was to assess the association of the dietary intake of a food group that includes fruits, berries and vegetables with all-cause, CVD-related and non-CVD-related mortality. The subjects were **Finnish men aged 42-60 y examined in 1984-1989 in the prospective Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study**. Dietary intakes were assessed by 4-d food intake record during the baseline phase of the KIHD Study. The risk of all-cause and non-CVD-related deaths was studied in 2641 men and the risk of CVD-related death in 1950 men who had no history of CVD at baseline. During a mean follow-up time of 12.8 y, **cardiovascular as well as noncardiovascular and all-cause mortality were lower among men with the highest consumption of fruits, berries and vegetables.** After adjustment for the major CVD risk factors, the relative risk for men in the highest fifth of fruit, berry and vegetable intake for all-cause death, CVD-related and non-CVD-related death was 0.66 [95% confidence interval (CI) 0.50-0.88], 0.59 (0.33-1.06), and 0.68 (0.46-1.00), respectively, compared with men in the lowest fifth. These **data show that a high fruit, berry and vegetable intake is associated with reduced risk of mortality in middle-aged Finnish men.** Consequently, the findings of this work indicate that diets that are rich in plant-derived foods can promote longevity.	X			

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Scalbert, A.	Scalbert, A.; Manach, C.; Morand, C.; Remesy, C.; Jimenez, L., Dietary polyphenols and the prevention of diseases. *Crit Rev Food Sci Nutr* **2005,** 45, (4), 287-306.	2005	Polyphenols are the most abundant antioxidants in the diet and are widespread constituents of fruits, vegetables, cereals, dry legumes, chocolate, and beverages, such as tea, coffee, or wine. Experimental studies on animals or cultured human cell lines support a role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, diabetes, or osteoporosis. However, **it is very difficult to predict from these results the effects of polyphenol intake on disease prevention in humans**. One of the reasons is that these studies have often been conducted at doses or concentrations far beyond those documented in humans. The few clinical studies on biomarkers of oxidative stress, cardiovascular disease risk factors, and tumor or bone resorption biomarkers have often led to contradictory results. Epidemiological studies have repeatedly shown an inverse association between the risk of myocardial infarction and the consumption of tea and wine or the intake level of some particular flavonoids, but no clear associations have been found between cancer risk and polyphenol consumption. More human studies are needed to provide clear evidence of their health protective effects and to better evaluate the risks possibly resulting from too high a polyphenol consumption.				
	Stewart, D.	Stewart, D., Role of berries in human health. *Acta Hort. (ISHS)* **2004,** 649, 35-38.	2004	The in vitro efficacy of specific fruit extracts at inhibiting the initial stages of atherosclerosis was determined. Using the oxidation of human low-density lipoprotein (LDL) as an appropriate model it was found that when extracts from soft fruit were analysed on an equivalent Vitamin C (Vit. C) basis the ability to inhibit LDL oxidation was as follows: Rubus>Fragaria>Ribes>Vit. C (alone). However, when analogous experiments were performed on an equivalent phenolic-content basis content the ranking changed to Rubus>Ribes>Fragaria> Vit. C (alone). This showed that the **phenolic compounds in soft fruit are more powerful and/or durable antioxidants than Vit. C**. In addition, the variation in efficacy between extracts from Rubus, Ribes and Fragaria reflected the relative differences in phenolic composition and should, with further more detailed experiments, yield specific targets for plant breeders to produce nutritionally enhanced fruit.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Stoclet, J. C.	Stoclet, J. C.; Chataigneau, T.; Ndiaye, M.; Oak, M. H.; El Bedoui, J.; Chataigneau, M.; Schini-Kerth, V. B., Vascular protection by dietary polyphenols. *Eur J Pharmacol* **2004,** 500, (1-3), 299-313.	2004	Consumption of polyphenol-rich foods, such as fruits and vegetables, and beverages derived from plants, such as cocoa, red wine and tea, may represent a beneficial diet in terms of cardiovascular protection. Indeed, epidemiological studies demonstrate a significant inverse correlation between polyphenol consumption and cardiovascular risk. Among the numerous plausible mechanisms by which polyphenols may confer cardiovascular protection, improvement of the endothelial function and inhibition of angiogenesis and cell migration and proliferation in blood vessels have been the focus of recent studies. These studies have indicated that, in addition to and independently from their antioxidant effects, plant polyphenols (1) enhance the production of vasodilating factors [nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin] and inhibit the synthesis of vasoconstrictor endothelin-1 in endothelial cells; and (2) inhibit the expression of two major pro-angiogenic factors, vascular endothelial growth factor (VEGF) and matrix metalloproteinase-2 (MMP-2) in smooth muscle cells. The mechanisms of these effects involve: (1) in endothelial cells, increased Ca(2+) level and redox-sensitive activation of the phosphoinositide 3 (PI3)-kinase/Akt pathway (leading to rapid and sustained activation of nitric oxide synthase and formation of EDHF) and enhanced expression of nitric oxide synthase; and (2) in smooth muscle cells, both redox-sensitive inhibition of the p38 mitogen-activated protein kinase (p38 MAPK) pathway activation (leading to inhibition of platelet-derived growth factor (PDGF)-induced VEGF gene expression) and redox-insensitive mechanisms (leading to inhibition of thrombin-induced MMP-2 formation). The current evidence suggests that all these mechanisms are triggered by **polyphenols with specific structures**, although the structural requirements may be different from one effect to the other, and that they all contribute to the **vasoprotective, anti-angiogenic, anti-atherogenic, vasorelaxant and anti-hypertensive effects of acute or chronic administration of plant polyphenols found in vivo in animals and in patients.**		X		X
	Wang, J.	Wang, J.; Mazza, G., Effects of anthocyanins and other phenolic compounds on the production of tumor necrosis factor alpha in LPS/IFN-gamma-activated RAW 264.7 macrophages. *J Agric Food Chem* **2002,** 50, (15), 4183-9.	2002	Flavonoids have been reported to demonstrate their benefits in lowering oxidative stress and beneficial effects on cardiovascular and chronic inflammatory diseases. Common phenolic compounds, including **phenolic acids, flavonols, isoflavones, and anthocyanins, present in fruits, vegetables, and grains were investigated for their effects on the production of tumor necrosis factor alpha (TNF-alpha) in LPS/IFN-gamma-activated RAW 264.7 macrophages**. Gallic acid and (+)-catechin showed small but significant effects, whereas chlorogenic acid had no effect on TNF-alpha production. The flavonol **quercetin inhibited TNF-alpha production, but kaempferol and myricetin induced the secretion of TNF-alpha**. The isoflavone genistein was an inhibitor of TNF-alpha, whereas daidzein induced TNF-alpha production. Glycosylation of genistein changed its inhibitory effects to TNF-alpha induction, and glycosylation of daidzein had no effect on its activity. **Anthocyanidins/anthocyanins and anthocyanin-rich extracts induced TNF-alpha production and acted as modulators of the immune response in activated macrophages. This is the first study to report the effects of anthocyanins and berry extracts on TNF-alpha production**.				X

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Youdim, K. A.	Youdim, K. A.; Joseph, J. A., A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. *Free Radic Biol Med* **2001,** 30, (6), 583-94.	2001	It is rare to see a day pass in which we are not told through some popular medium that the population is becoming older. Along with this information comes the "new" revelation that as we enter the next millennium there will be increases in age-associated diseases (e.g., cancer, cardiovascular disease) including the most devastating of these, which involve the nervous system (e.g., Alzheimer's disease [AD] and Parkinson's disease [PD]). It is estimated that within the next 50 years approximately 30% of the population will be aged 65 years or older. Of those between 75 and 84 years of age, 6 million will exhibit some form of AD symptoms, and of those older than 85 years, over 12 million will have some form of dementia associated with AD. What appears more ominous is that many cognitive changes occur even in the absence of specific age-related neurodegenerative diseases. Common components thought to contribute to the manifestation of these disorders and normal age-related declines in brain performance are increased susceptibility to long-term effects of oxidative stress (OS) and inflammatory insults. Unless some means is found to reduce these age-related decrements in neuronal function, health care costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse age-related neuronal deficits as well as their subsequent, behavioral manifestations. Fortunately, the growth of knowledge in the biochemistry of cell viability has opened new avenues of research focused at identifying new therapeutic agents that could potentially disrupt the perpetual cycle of events involved in the decrements associated with these detrimental processes. In this regard, a new role in which certain dietary components may play important roles in alleviating certain disorders are beginning to receive increased attention, in particular those involving phytochemicals found in fruits and vegetables.				
	Yu, Y.-M.	Yu, Y.-M.; Chang, W.-C.; Wu, C.-H.; Chiang, S.-Y., Reduction of oxidative stress and apoptosis in hyperlipidemic rabbits by ellagic acid. *The Journal of Nutritional Biochemistry* **2005,** 16, (11), 675-681.	2005	Oxidative stress is one of the major risk factors for coronary artery disease. Ellagic acid is a phenolic compound present in fruits and nuts, and has been found to have antioxidative property. Twenty-four New Zealand white (NZW) rabbits were assigned randomly into four dietary groups. The normal group was fed regular rabbit chow, and the cholesterol group was fed a high fat and cholesterol diet. The ellagic acid (E) group and probucol group were fed the same diet as the cholesterol group plus the addition of 1% (w/w diet) ellagic acid and probucol, respectively. Oxidative stress [as measured by plasma lipids, oxygen free radicals and thiobarbituric acid reactive substances (TBARS)] increased in the cholesterol group compared with the normal group; however, it decreased in the probucol and E groups compared with the cholesterol group. Forty-five percent of the intimal surface of the thoracic aorta was covered with atherosclerotic lesions in the cholesterol group, but only 2-3% was covered in the E and probucol groups. The aortic level of 8-(OH)dG and the expression of caspase-8, caspase-9 and Fas ligand were also suppressed after ellagic acid supplement. These results indicated that ellagic acid could prevent atherosclerosis via suppression of oxidative stress and apoptosis in hyperlipidemic rabbits.			X	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Mullen, W.	Mullen, W.; McGinn, J.; Lean, M. E.; MacLean, M. R.; Gardner, P.; Duthie, G. G.; Yokota, T.; Crozier, A., Ellagitannins, flavonoids, and other phenolics in red raspberries and their contribution to antioxidant capacity and vasorelaxation properties. J Agric Food Chem 2002, 50, (18), 5191-6.	2002	Analysis of extracts of Glen Ample **raspberries (Rubus idaeus L.)** by gradient, reverse phase HPLC with diode array and tandem mass spectrometry identified eleven anthocyanins, including cyanidin-3-sophoroside, cyanidin-3-(2(G)-glucosylrutinoside), cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3-sophoroside, pelargonidin-3-(2(G)-glucosylrutinoside), and pelargonidin-3-glucoside. Significant quantities of an **ellagitannin, sanguiin H-6**, with an M(r) of 1870 were detected along with lower levels of a second ellagitannin, lambertianin C, which has an M(r) of 2804. Other phenolic compounds that were detected included trace levels of ellagic acid and its sugar conjugates along with one kaempferol- and four quercetin-based flavonol conjugates. Fractionation by preparative HPLC revealed that sanguiin H-6 was a major contributor to the antioxidant capacity of raspberries together with vitamin C and the anthocyanins. **Vasodilation activity was restricted to fractions containing lambertianin C and sanguiin H-6.**				