

Clinical Studies on Benefits of Quercetin, Catechins, and other Flavonoids Found in FRS

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ALLERGIES

1. Fisetin, A F-flavonol, exhibits T_H2-type cytokine production by activated human basophils.
Shinji Higa MD, et al. *J of Allergy and Clin Immunology*. Vol. 111 Is. 6, June 2003, Pages 1299-130.
We sought to determine the potency of flavonoids (astragaloside, fisetin, kaempferol, myricetin, quercetin and rutin) for the inhibition of cytokine expression and synthesis by human basophils. The results provide evidence of a novel activity of the flavonoids that suppresses the expression of T_H2-type cytokines (IL-4, IL-13, and IL-5) by basophils. Among these cytokines, IL-4, IL-13, and IL-5 have major roles in allergic inflammation.
2. Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal mast cells
Pearce, F. PhD. *Journal of Allergy and Clinical Immunology* Vol. 73, Issue 6, June 1984, Pages 819-823.
Quercetin is structurally related to the antiallergic drug disodium cromoglycate. We observed that quercetin inhibits anaphylactic histamine release from MMC (Mucosal Mast Cells) isolated from the small bowel LP of the rat previously infected with the nematode *Nippostrongylus brasiliensis*.

ASTHMA

1. Diet and Chronic Obstructive Pulmonary Disease: Independent Beneficial effects of Fruits, Whole Grains and Alcohol.
Tabak, et. al., The MORGEN Study, *Am J Resp and Crit Care Med*, Vol. 164, pp61-64.
Intake of solid fruits containing flavonoids and green tea catechins reduced effects of Chronic Obstructive Pulmonary Disease, COPD. Data was taken from 13, 651 adults.
2. Dietary Antioxidants and Asthma in Adults.
Shaheen, et.al. *Am J Resp and Crit Care Med*, Vol. 164
Increased apple and red wine intake reduce frequency and severity of asthma attacks, and may indicate a protective effect of flavonoids.
3. Exercise-Induced Asthma (EIA) therapy is reduced by increased antioxidant intake.
Boljevic, et.al. *Bronchial Asthma, Free Radicals, and Antioxidant Activity*; Moscow Medical Academy.
4. Antioxidants may cut Children's Asthma Risk
Coenen, Susan Smith. *Prevention*, March 2005, Vol. 57 Issue 3, p60
Researchers at Cornell University reviewed nutrition data for more than 7,500 kids and found that those who had higher blood levels of vitamin C, beta-carotene, and selenium were 10 to 20% less likely to have asthma than kids who had lower levels of these antioxidants. Antioxidants may reduce inflammation in the airways.
5. Antioxidant-independent ascorbate enhancement of catecholamine-induced contraction of vascular smooth muscle.
Dillon, P. *American Journal of Physiology: Heart & Circulatory Physiology* Jun2004, Vol. 55 Issue 6, p42353.
Ascorbate reduces the oxidation rate of catecholamines and, by an independent mechanism, enhances rabbit aortic ring contractions initiated by catecholamines. Ascorbate may play a role in

shock and asthma treatments and potentiate the cardiovascular health consequences of PPA and Eph.

6. Serum Antioxidants Concentrations Amongst U.S. Adults With Self-Reported Asthma.
Ford, Earl. *Journal of Asthma*, April 2004, Vol. 41 Issue 2, p179
Antioxidants may protect the lungs of people with asthma against oxidative stress.
7. Serum Total Antioxidant Status in Severe Exacerbation of Asthma: Correlation with the Severity of the Disease.
Katsoulis, K. *Journal of Asthma* Dec2003, Vol. 40 Issue 8, p847
Oxidative processes, mediated by oxygen free radicals, are recognized to contribute significantly to the inflammatory pathology of bronchial asthma. An imbalance between oxidants and antioxidants has also been proposed in this disease. Decreased Antioxidant Status was observed during asthma attacks, probably due to increased oxidative stress.
8. Reducing Agents Inhibit the Contractile Response of Isolated Guinea-Pig Main Bronchi.
Casoni, G. *Clinical & Experimental Allergy* Jul2003, Vol. 33 Issue 7, p999.
Our findings find that GSH [reduced glutathione, one of the most important antioxidant compounds against oxidant free radicals] decreases bronchial smooth muscle contraction is reduced to different stimuli, and that oxidant free radicals are produced during bronchial smooth muscle contraction. We suggest that oxidants are involved in the mechanisms in bronchoconstriction and that reducing agents could be a possible therapeutic option for airway obstruction sustained by bronchospasm.
9. Dietary Antioxidants and Ozone-Induced Bronchial Hyper-responsiveness in Adults with Asthma.
Trenga, Carol. *Archives of Environmental Health* May/Jun2001, Vol. 56 Issue 3, p242
In a study with seventeen subjects results showed that dietary supplementation with vitamins E and C may benefits asthmatic adults who are exposed to air pollutants
10. Double-blind intervention trial on modulation of ozone effects on pulmonary function by antioxidant supplements.
Grievink, Linda. *American Journal of Epidemiology* Feb 15, 1999, Vol. 149 issue 4, p306(9).
A study done on 38 cyclists showed that the antioxidant vitamins, [100 mg of Vitamin E and 500 mg of Vitamin C, offer some protection against acute effects of ozone on (forced expiratory volume)/second.
11. Antioxidants: (NUTRACEUTICALS RESEARCH)(Brief Article).
Nutraceuticals World April 2005, Vol. 8 Issue 4, p59(1)
A study using 2,000 women show that, maternal dietary antioxidant intakes during pregnancy may modify the risks of developing wheeze and eczema during early childhood. Vitamin C showed a positive correlation to lowering the risk of asthma, but vitamin E showed negative results.
12. Asthma-Healing Antioxidants. (Fast Tips For Smart Eaters)
McCord, Holly. *Prevention* May2003, Vol. 55 Issue 5, p68
Pollution triggers asthma attacks in children by draining protective antioxidants from the lining of their lungs. A new study found that getting more antioxidant vitamins C and E might help asthmatic kids breathe easy in high-pollution areas.

BOWEL FUNCTION

1. Mechanism of Quercetin as an Anti-diarrheal agent.
Zhang, et.al. *Pub Med* 2003 Oct Vol. 23 Issue 10 pp1029-31.
Quercetin inhibits intestinal movement and reduces capillary permeability in the abdominal cavity, which may be the anti-diarrheal mechanism of plant-based agents such as *Psidium guajava* L extract.
2. Effect of Quercetin on the Acute and Chronic experimental Colitis in the rat.
Medina, et.al. *J Pharmacological Expert Therapy* 1996 Aug; Vol. 278 issue 2, pp771-9
When tested in chronic colitis (2 and 4 weeks), quercetin treatment decreased colonic damage and the incidence of diarrhea, and normalized colonic fluid transport.
3. The Independent Sept 21, 2000, p8
Drinking tea also increases fluid intake preventing constipation and cystitis.
4. Vitamin C (VC) and vitamin E (VE) in plasma as well as activities of superoxide dismutase (SOD) and catalase (CAT) in erythrocytes were determined by spectrophotometric analytical methods were measured.
Wang, W. and Z. Zhou. *Biomedical and Environmental Sciences*. September 2004, Vol. 17 Issue 3: 266-272.
The findings in the present study using children with chronic constipation suggest that chronic childhood constipation causes oxidative stress and potential free radical damage to children with chronic constipation.

CANCER

1. Quercetin, a natural substance found in apples, onions, tea, and red wine, may be a potentially novel approach for preventing and treating prostate cancer, according to a laboratory research study conducted at Mayo Clinic in Rochester, MN. *Mayo Clinic News* 2001.
2. Quercetin blocks androgen (hormone) activity in androgen-responsive human prostate cell lines. By blocking these cell lines, prostate cancer cells can be prevented or stopped. Quercetin has been studied scientifically for 30 years. It's documented as safe and having relatively low toxicity.
3. Mayo Clinic Researchers Discover that Green Tea Component Helps Kill Leukemia Cells. Epigallocatechin gallate (EGCG) interrupts the communication signals that leukemia cells need to survive. *Mayo Clinic News*, March 31, 2004.
4. *Am J of Clin Nutrition*, Vol. 71, No. 6, 1698S-1702S, June 2000.
Studies of rats, mice, and hamsters showed that flavonoid components of tea protect against lung, stomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin cancers caused by chemical carcinogens. Other studies showed the preventive effect of tea flavonoids against atherosclerosis, coronary heart disease, high cholesterol, and high blood pressure.
5. Food-derived polyphenols (flavonoids quercetin, genistein, rutin) inhibit pancreatic cancer growth through mitochondrial cytochrome C release and apoptosis. *Wiley Interscience Journal*, 2 Nov 2001.

6. Quercetin Bests Vitamin C as Cancer Preventing Researchers at Cornell University and Seoul National University discovered that Vitamin C blocks cancer cell intercommunication. Vitamin C is a potent cancer fighter; however, scientists also found that quercetin works in the same manner but it even more powerful.
7. Ames, Bruce, UC Berkeley, *Mutation Research* 475 (2001) 7-20.
DNA Damage from Micronutrient deficiency is likely a Major Cause of Cancer. Antioxidant and vitamin intake is an important weapon in the prevention of cancer.
8. Intake of Flavonoids and Lung Cancer: These Findings suggest that foods rich in certain flavonoids (quercetin from onions and apples and naringin from white grapefruit) may protect against certain forms of lung cancer and that decreased bioactivation of carcinogens by inhibition of certain enzyme variants should be explored as a possible underlying mechanism.
9. Tea Consumption and Cancer Incidence in a Prospective Cohort Study of Postmenopausal Women. Zheng et. al. *Am J of Epidemiology*, Vol 144 Issue 2 pp175-182.
The study of 35,369 postmenopausal women suggests that tea flavonoids may protect against some cancers. There was a slight decrease in the rate of all cancers combined.
10. Quercetin Leads to Growth Inhibition and apoptosis of Pancreatic Tumor Cells.
Lee LT, et. al. *Anticancer Res* 2002 May-Jun, Vol. 22 Issue 3 pp1615 – 27.
11. Perturbation of Microtubule Polymerization by Quercetin.
Guptka and Panda, *Biochemistry* 2002 Oct 29; Vol. 41 Issue 43 13029-38.
The flavonoid quercetin has a broad range of biological activities, including potent anti-tumor activity against several types of tumors. Recently, it has been shown that quercetin inhibits cancer cells proliferation by depleting cellular microtubules.
12. Antioxidants and Digestive-Tract Cancers.
(Adapted from the *American Journal of Epidemiology*, November 1, 1995) *Nutrition Research Newsletter* Jan 1996, Vol. 15, Issue 1, p7(1).
A study following 33,691 women from ages 55-60 for 7 years indicate that foods rich in antioxidant vitamins, especially carotene, may be important in the prevention of cancers of the upper digestive tract, especially stomach cancer. It is unclear, however, whether the antioxidants themselves are the active agents or whether they are surrogate measures of the overall levels of intake of certain types of vegetables and fruits.
13. Steinmetz, Kristi A. *Journal of the American Dietetic Association* Oct 1996, v96, n10, p1027(13)
To summarize the 174 case-control studies, the evidence is convincing for a protective effect of vegetables and fruit against cancers of the lung, stomach, and esophagus. The evidence for other sites is either less abundant or less consistent, but suggests a probable protective effect against cancers of the oral cavity and pharynx, colon, breast, pancreas, and bladder. The exception is prostate cancer; several studies have been undertaken, yet none has shown a protective association. Flavonoids, such as quercetin and kaempferol, are polyphenolic antioxidants that occur in vegetables, fruit, tea, and wine. In addition to being antioxidants, flavonoids may defend cells against carcinogens via their ability to increase the pump-mediated efflux of certain carcinogens from cells (90) or via induction of detoxification enzymes (64). Furthermore, quercetin may reduce cell proliferation (91).

14. Substance in Strawberries Destroys Cancer Cells.
PR Newswire March 22, 2005, pNA.
Quercetin and strawberry extract were also shown to arrest the cell cycle progression of human hepatoma prior to cell death. This means that cancer cell proliferation was retarded; thus, strawberries and their major phytonutrient, quercetin, may have protective actions at several steps in the process of cancer development.
15. Development of Gamma-Tocopherol as a colorectal cancer chemopreventive agent.
Sharon Campbell et al. *Critical Reviews in Oncology/Hematology*. Vol. 47 Issue 3 Nov. 2003. pp 249-259.
The cell membrane (lipid) soluble antioxidant Vitamin E may play a role in preventing colorectal cancer by decreasing the formation of mutagens arising from the oxidation of fecal lipids.
16. cAMP independent protein kinase activity is correlated with growth of rat mammary tumors.
Sharoni, Y, et al. *European Journal of Cancer and Clinical Oncology* Vol. 20 Issue 2. February 1984, Pages 277-281
An important portion of the protein kinase activity in the 7,12-dimethylbenz (a)anthracene (DMBA) induced rat mammary tumor is inhibited by the bioflavonoid quercetin (10^{-4} M).
17. Type II Estrogen-Binding Sites in Human Ovarian Cancer: Correlation with Estrogen, Progesterone, and Epidermal Growth Factor Receptor.
Ferrandina, G. M.D et al. *Gynecologic Oncology* Vol. 49, Issue 1, April 1993, Pages 67-72.
It has been demonstrated that bioflavonoids, most notably quercetin, through the interaction with Type II EBS, may exert a growth inhibitory activity both alone or in combination with chemotherapeutic agents on ovarian cancer cell lines and primary tumors.
18. Inhibitory effect of quercetin on primary ovarian and endometrial cancers and synergistic activity with cis-diamminedichloroplatinum(II)
G. Scambia et al. *Gynecologic Oncology* Vol. 45, Issue 1, April 1992, Pages 13-19
It has been demonstrated that the flavonoid quercetin (3,3',4',5,7-pentahydroxyflavone) inhibits the growth of several cancer cell lines and that the antiproliferative activity of this substance is mediated by so-called type II estrogen binding sites. Moreover it has been observed that quercetin enhances the antiproliferative activity of cis-diamminedichloroplatinum(II) (CDDP) and busulfan both in vitro and in vivo.
19. Diet and risk of cancer of the upper aerodigestive tract—II. Nutrients
E. De Stefani et al. *Oral Oncology* Vol. 35, Issue 1, January 1999, Pages 22-26
Non-nutritive substances, like flavonoids displayed a marked reduction in upper aerodigestive tract cancer risk of 70%.
20. Oxidant and antioxidant activity changes in patients with oral cancer and treated with radiotherapy
Sabitha, K. and C. Shyamaladevi. *Oral Oncology* Vol. 35, Issue 3, May 1999, Pages 273-277.
Radiation induces lipid peroxidation by inactivating the antioxidant enzymes, thereby rendering the system inefficient in management of the free radical attack. Thus, the degree of radiation affects the extent of the depression of the antioxidant enzyme activities and increases lipid peroxidation.

21. The Radiation-Induced Fibroatrophic Process: Therapeutic Perspective Via the Antioxidant Pathway. Delanian, S. and J. Lefaix. *Radiotherapy and Oncology* Vol. 73, Issue 2, November 2004. Pp 119-131
Antioxidant therapy of superoxide dismutase and combined pentoxifylline-tocopherol treatment reduced or reversed the process of radiation-induced fibro-atrophy in both clinical practice and animal experiments. The efficacy of this antioxidant treatment was reinforced in clinical trials.
22. Potential role of lipid peroxidation derived DNA damage in human colon carcinogenesis: studies on exocyclic base adducts as stable oxidative stress markers
Bartsch, H PhD and Jagadeesan N PhD. *Cancer Detection and Prevention* Vol. 26, Issue 4, October 2002, Pages 308-312
23. Cardiotoxicity of Cytotoxic Drugs
Schimmel, K. et al. *Cancer Treatment Reviews* Vol. 30, Issue 2, April 2004, Pages 181-191
The mechanism of anthracycline induced cardiotoxicity seems to involve the formation of free radicals leading to oxidative stress. Addition of the antioxidant and iron chelator dexrazoxane to anthracycline therapy has shown to be effective in lowering the incidence of anthracycline induced cardiotoxicity.
24. Pros and cons of antioxidant use during radiation therapy
Prasad, K. et al. *Cancer Treatment Reviews* Vol. 28, Issue 2, April 2002, Pages 79-91
Two opposing hypotheses, based on conceptual framework, regarding the use of supplementation with high doses of multiple micronutrients including high dose dietary antioxidants during radiation therapy have been proposed. One states that high doses of antioxidants may improve the efficacy of radiation therapy by increasing tumor response and decreasing some of its toxicity on normal cells. The other suggests that antioxidants should not be used during radiation therapy, because they would protect cancer cells against radiation damage. This review indicates that high doses of the antioxidants: Vitamin C, Vitamin E and Beta-Carotene can be used adjunctively with radiation therapy.
25. CYP1A1 genotype-selective inhibition of benzo[a]pyrene activation by quercetin
Schwarz, D. et al. *European Journal of Cancer* Vol. 41, Issue 1, January 2005, Pages 151-158
Epidemiological studies suggest that foods rich in quercetin and naringin may protect against certain types of lung cancer, and that genotype dependent inhibition of cytochrome P450 1A1 (CYP1A1)-mediated bioactivation of procarcinogens could be the underlying mechanism. We studied the inhibitory effects of quercetin and naringin on the terminal bioactivation step on a lung carcinogen. We found that quercetin potently inhibited diol-epoxide formation by all CYP1A1 types with IC₅₀ values between 1.6 and 7.0 nano-M. Our data support the hypothesis that quercetin may have a stronger chemopreventive effect in individuals carrying wild-type compared with variant CYP1A1 genes.

CATARACTS

1. Quercetin Metabolism in the lens: role in inhibition of hydrogen peroxide induced cataracts.
Cornish, et.al. *Free Radical Biol Medicine* 2002 July 1;33(1):63-70 .
Quercetin, a major flavonoid in the diet, inhibits lens opacification in a lens organ culture oxidative model of cataract. Dietary quercetin and metabolites are active in inhibiting oxidative damage in the lens and thus could play a role in prevention of cataract formation.

2. Studies show that the eye may be damaged by active oxygen (free radicals). Formation of cataracts can be thwarted by metabolic and dietary antioxidants.
Varma, SD, University of Maryland School of Medicine.
3. Antioxidants may lower the rate at which cataracts get worse.
Nutrition Action Health Letter Sept 2002, Vol. 29 issue 7, p10 (1).
297 adults with early stage cataracts got an antioxidant supplement (beta-carotene (18 mg, or 30,000 IU), vitamin C (750 mg), and vitamin E (600 IU)), and the control got a placebo. After three years, the antioxidant-takers had slightly less severe cataracts than the placebo group, though the cataracts in both groups got worse. The researchers hypothesize that if subjects in the supplemented group continued antioxidant treatments for the next 21 years, they could achieve a 10 percent reduction in cataract progression.
4. Researchers at Ohio State University have demonstrated in the laboratory that certain antioxidants found in our diets in dark leafy green vegetables--not only spinach but also kale and collard greens--can help prevent cataracts, at least in the test tube.
Tufts University Health & Nutrition Letter March 2005, Vol. 23 issue 1, p2(1 Inverse association of tea and flavonoid intakes with incident of myocardial infarction).
5. You can prevent cataracts now
Sodhi, Virender, *Natural Health* August 2003, Vol. 33 issue 6, p34(2)
Antioxidants from supplements and foods can quench free radicals, which cause the proteins to clump in the eyes. Many studies show that the antioxidants vitamin E, vitamin C, selenium, and carotenoids help prevent cataracts.
6. High-dose antioxidant supplementation and cataract risk
Mares, Julie A. *Nutrition Reviews* Jan 2004, Vol. 62 issue 1, p28(5).
Although a large body of observational evidence suggests that supplement use is associated with lower risk for cataract, there is insufficient evidence that high-dose antioxidants slow the progression of cataracts beyond that provided by multivitamins or healthful diets
7. Vitamin C is associated with reduced risk of cataract in a Mediterranean population
Valero, Maria, and Fletcher, Astrid E. *The Journal of Nutrition* June 2002, Vol. 132 issue 6, p1299(8)
We conducted a case-control study to investigate the association of antioxidant vitamins (vitamin C, vitamin E, vitamin A, [beta]-carotene, [alpha]-carotene, [beta]-cryptoxanthin, lycopene, zeaxanthin and lutein) and minerals (zinc and selenium) and risk of cataract in a Mediterranean population. Cases with cataract (343) and 334 age/sex frequency-matched controls aged 55 to 74 y were selected from an ophthalmic outreach clinic in Valencia, Spain. There is evidence for a protective role for vitamin C on the aging lens as this effect was seen in a population characterized by high vitamin C intakes.
8. Pelton, Ross. *American Druggist* May 1999, v216 i5, p50(2).
Studies show that antioxidants and nutrients can significantly improve eye health. Individuals who take vitamins C and E, for instance, reduce their risk of cataracts by over 50%. Vitamin A prevents the night vision problems and xerophthalmia, which is the drying and hardening of epithelial cellular membranes leading to blindness. The herb bilberry also contains antioxidant and anti-inflammatory properties which protects joints and blood vessels.

9. Oxidation of Lens Proteins Plays a Central Role in the Formation of Age-Related Cataracts, Willett, Walter C, *Am J Clin Nutr* 1999 Vol. 70 pp509-16.
During 761762 person-years of follow-up, 1471 cataracts were extracted. After age, smoking, and other potential cataract risk factors were controlled for, those with the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those in the lowest quintile. Oxidation of lens proteins plays a central role in the formation of age-related cataracts, suggesting that dietary antioxidants may play a role in prevention. Lutein and zeaxanthin and foods rich in these carotenoids may decrease the risk of cataracts severe enough to require extraction.
10. Tufts Study Finds Antioxidant Vitamin C May Reduce Risk of Cataracts By 77 Percent in Women. *PR Newswire* Oct 20, 1997, p1020DCM022.

CHOLESTEROL

1. Dietary Intake of Flavonoids by Japanese Women and the Inverse Correlation between Quercetin Intake and LDL cholesterol levels.
Arai et.al. *Journal of Nutrition* 2000 Vol. 130 pp2243-2250. Results show that a high consumption of both flavonoids and isoflavones from soy by Japanese women may contribute to their low incidence of coronary heart disease compared to women of other countries.
2. *Men's Health* June 2004, Vol. 19 issue 5, p40.
An 18-month study on 575 people indicate that those who eat yellow and orange fruits and vegetables are four times less likely to develop atherosclerosis. Yellow and orange foods carry high concentrations of antioxidants such as lutein, zeaxanthin, and beta-cryptoxanthin, says lead researcher Maura Paul-Labrador, Ph.D., of the University of Southern California's school of medicine. Unlike other antioxidants, these can hitch rides on cholesterol and help keep arteries smooth and flexible.
3. Metabolic intervention with L-arginine and antioxidants together with graduated and moderate exercise training may reduce atherosclerotic lesion formation.
Napoli, Claudio. *Proceedings of the National Academy of Sciences of the United States* June 8, 2004, Vol. 101 Issue 23, p8797(6).
Mice on a high cholesterol diet, some were supplemented with Antioxidants (1.0% vitamin E added to the chow and 0.05% vitamin C added to the drinking water) and L-arginine (6% in drinking water) and exercise. There was a reduced number that developed atherosclerosis compared with untreated exercised mice.

CROHN'S DISEASE

1. Lipid peroxidation and plasma antioxidant micronutrients in Crohn's Disease, Wendland et.al. *Am J of Clin Nutrition*, Vol 74 Issue 2, pp259
In Crohn's Disease, increased production of free radicals may reduce blood concentration of antioxidant vitamins and result in increased oxidative stress. This indicates that increased antioxidant consumption may help reduce symptoms of the disease.

2. Altered Lipid Oxidant and antioxidant status in pediatric Crohn's Disease.
Am J of Clin Nutrition, Vol 71, No. 3 807-815.
Activation of inflammatory cells and excessive production of free radicals may affect circulating lipids.
[This indicates why FRS may be helpful in reducing symptoms of the disease]
3. Fish oil and antioxidants alter the composition and function of circulating mononuclear cells in Crohn's disease.
Trebbles, T.M. *Alternative Medicine Review* March 2005, Vol. 10 issue 1, p70(1).
Dietary supplementation with fish oil plus antioxidants is associated with reducing disease activity by modified PBMC composition and lower production of PGE(2) and IFN-gamma by circulating monocytes or macrophage.
4. Antioxidants inhibit the in vitro production of inflammatory cytokines in Crohn's disease and ulcerative colitis.
Reimund. *European Journal of Clinical Investigation* Feb98, Vol. 28 Issue 2, p145.
This study shows that supplementation of the three antioxidants, BHA, THP, and NDGA, significantly inhibit the production of some inflammatory cytokines using PBMCs (peripheral blood) and inflamed colonic mucosa from active IBD patients.
5. Status of lipid-soluble antioxidants and TRAP in patients with Crohn's disease and healthy controls.
Genser, D. *European Journal of Clinical Nutrition* Sep99, Vol. 53 Issue 9, p675.
Reactive oxygen metabolites (free radicals) cause tissue injury in patients with Crohn's disease. They have a lower level of antioxidant enzymes in their intestines.

DIABETES

1. Quercetin, an antioxidant flavonoid, reduces diabetic kidney disease in rats.
Anjaneyulu M, et. al. *Clin Exp Pharmacol Physiol*. 2004 Apr; 31(4):244-8.
Studies have indicated that oxidative stress [from free radicals] is one of the major mechanisms involved in the development of diabetic nephropathy. Rats induced with diabetes and exhibiting kidney disease were treated with quercetin and showed significantly reduced kidney disease and oxidative stress.
2. Quercetin reduces pain from diabetic kidney disease.
Anjaneyulu, et.al. *Prog Neuropsychopharmacol Biol Psychiatry*, 2003 Sep, Vol. 27 issue 6, pp1001- 5.
3. Effects of combined quercetin and CoQ10 treatment on oxidative stress in normal and diabetic rats.
Coldiron et. al. *J Biochem Mol Toxicology*, 2002; Vol. 16 issue 41, pp97-202.
Free radicals may be actively involved in development of heart disease, cancer, and diabetes. Quercetin may be effective in reducing some effects of diabetes.
4. Quercetin alleviates oxidative stress in diabetic rats.
Mahesh and Menon. *Phytother Res*. 2004 Feb Vol. 18 issue 2, pp 123-7.
Oral administration of quercetin to diabetic rats resulted in a decrease in the levels of blood glucose... Quercetin also resulted in the activities of superoxide dismutase coming to near normal, along with the levels of Vitamins C and E. Quercetin in lower doses was found to be more effective. The results indicate that quercetin reduced the diabetes indices changes in oxidative stress.

5. Dietary antioxidant intake and risk of type 2 diabetes.
Montonen J, Jarvinen R, Knekt P, Reunanen A: *Diabetes Care* 2004 Vol.27, pp 362-366.
The risk of Type II diabetes may be reduced by the intake of antioxidants in the diet.
A study using 2,285 men and 2,019 women aged 40-69 without diabetes to begin with measured the nutritional history of the subjects, predominately their intake of vitamin C, tocopherol-a (Vitamin E), tocotrienols, and carotenoids. After 23 years 164 men and 219 women developed type II diabetes.
6. A salen-manganese catalytic free radical scavenger inhibits type 1 diabetes and islet allograft rejection
Olcott, Angelica P. *Immunology and Transplantation* Oct 2004, Vol. 53 issue 10, p2574(7)
Reactive oxygen and nitrogen species contribute to the pathoetiology of both spontaneous type 1 diabetes and allograft rejection. Antioxidants designed to prevent the formation of both cytotoxic reactive oxygen and nitrogen species may effectively protect [beta]-cells from spontaneous autoimmunity and alloresponses.
7. Paradoxical effects of green tea (*Camellia sinensis*) and antioxidant vitamins in diabetic rats: improved retinopathy and renal mitochondrial defects but deterioration of collagen matrix glycoxidation and cross-linking.
Mustata, Georgian T. *Diabetes* Feb 2005, Vol. 54 issue 2, p517(10).
Green tea extract, vitamin C or vitamin E (with tap water control), when treated on diabetic rats, showed an improvement in several diabetes related cellular dysfunctions (retinal superoxide production, acellular capillaries, pericypte ghosts, and lens crystalline), but showed either no change or a negative change in matrix glycoxidation in selected tissues (tendon, aorta, and plasma). The body weights of the diabetic rats decreased after 12 months on the vitamins (antioxidants) and green tea extract.
8. Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis
Quilliot, Didier. *American Journal of Clinical Nutrition* May 2005, Vol. 81 issue 5, p1117(9)
Patients with Chronic Pancreatitis (CP) are at high risk of antioxidant deficiencies, which causes an increase in oxidative stress*. Diabetes mellitus lowers the total antioxidant levels in patients with CP. In these patients, a vitamin E deficiency and an elevated plasma glucose concentration were associated with significantly higher LDL oxidizability.
9. MnSOD and catalase transgenes demonstrate that protection of islets from oxidative stress does not alter cytokine toxicity.
Chen, Hainan, Epstein, Paul N., Li, Xiaoyan. *Diabetes* May 2005, v54 i5, p1437(10)
Antioxidants increased beta cell survival and scavenging as well as improved p-cell survival after treatment with reactive oxygen species. Antioxidants may be effective in reducing cytokine-induced reactive oxygen species. They may not reduce cytokine toxicity.
10. Quercetin may regenerate pancreatic islets and increase insulin release in strptozocin-induced diabetic rats. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats.
Diabetes Week Nov 3, 2003, p4 from *Comp Biochem Physiol* 2003, Vol. 13 issue3 pp357-364

HEART DISEASE

1. Flavonoids in chocolate can favorably alter eicosanoid synthesis in humans, reduce platelet aggregation in humans by favorably altering, thereby reducing atherosclerosis.
Schramm, et.al, Chocolate Procyanidins Decrease... *Am J of Clin Nutrition* January 2001, Vol. 73, issue 1 pp36-40.
2. Flavonoids in Tea May Reduce the Risk of Death after Heart Attack.
CNN Medical Unit, May 6, 2002.
Flavonoids found in green and black tea protect the heart by relaxing the blood vessels so blood can flow more easily. Further, evidence shows that flavonoids reduce levels of bad cholesterol.
3. Inverse association of tea and flavonoid intakes with incident of myocardial infarction.
Geleijnse, et.al. *The Rotterdam Study Am J of Clin Nutrition* May 2002, Vol. 75, No 5, pp880-886.
An increased intake of tea and flavonoids may contribute to the primary prevention of ischemic heart disease. The risk of heart attack was lower in tea drinkers than in non-tea drinkers. Dietary flavonoids may protect against cardiovascular disease.
4. The flavonoids quercetin and catechins synergistically inhibit platelet function and decrease the risk of cardiovascular disease.
Pignatelli et.al. *Am J of Clin Nutrition* November 2000, Vol. 72, No. 5, pp1150-1155.
5. Catechins, whether from tea or other sources, may reduce the risk of ischemic heart disease mortality but not of stroke.
Arts, IJla et.al. The Zutphen Elderly Study. *Am J of Clin Nutrition* August 2001, Vol. 74, No. 2, pp227-232.
6. The risk of some chronic diseases may be lower at higher dietary flavonoid intakes. Flavonoid Intake and the Risk of Diseases,
Knekt, et. al, *Am J of Clin Nutrition* September 2002, Vol. 76, No. 3, pp560-568.
7. *Methods and Findings in Experimental and Clinical Pharmacology*, Vol. 24, Suppl A, 2002, pp 59-60
Flavonoids, together with other antioxidants, constitute two lines of defense in protecting cell walls against injury owing to oxidation of LDL. At the LDL level, they inhibit LDL oxidation due to their free radical scavenger activity; at the cellular level, they protect the cells directly by increasing their resistance to damage by oxidized LDL cholesterol. Recent studies have shown that flavonoids prevent the adhesion of molecules that attract toxic molecules.
8. Quercetin inhibits human vascular smooth muscle cell proliferation and migration.
Alocer, et. al, *Surgery* February 2002; Vol. 131 issue 2 pp198-204.
This finding provides support for the use of quercetin in treating cardiovascular diseases.
9. Flavonoid Intake and Coronary Mortality in Finland, a Cohort Study.
Knekt, et. al. National Public Health Institute, Helsinki, Finland.
Results suggest that people with low flavonoid intakes have a higher risk of coronary diseases.

10. Dietary Flavonoids, Antioxidant vitamins, and the incidence of stroke: The Zutphen Study: The habitual intake of flavonoids and their major source (tea) may protect against stroke. *Archives of Internal Medicine* Vol. 156 Issue 6, pp637.
11. Mitochondrial Function is improved, thereby protecting the heart, by low oral doses of quercetin. Brookes, P et al. *Free Radical Biological Medicine* 2002 June 1, Vol.32 issue 11 pp1220-8. Compounds in red wine, such as the flavonoid quercetin, are thought to protect the heart through mechanisms not yet clearly understood. Improved mitochondrial function is likely.
12. Flavonoid intake and risk of chronic diseases. Knekt, Paul. *American Journal of Clinical Nutrition* Sept 2002, Vol. 76 issue 3, p560(9) A study done on 10,054 men and women indicated that people with higher intakes of the flavonoid quercetin had lower mortality from ischemic heart disease.
13. Mulberry (*Morus alba* L.) leaves and their major flavonol quercetin 3-(6-malonylglucoside) attenuate atherosclerotic lesion development in LDL receptor-deficient mice. Enkhmaa, Byambaa. *The Journal of Nutrition* April 2005, Vol. 135 issue 4, pp729(6) An 8-week trial on male mice showed that oxidative modification was decreased by 43%. In mulberry (3g)supplemented mice atherosclerotic lesion was reduced by 53%, whereas the quercetin (.05g) group no protective effects were observed.

INFLAMMATION

1. Quercetin inhibits substances that lead to inflammation. Sato M, et.al., *J Rheumatol* 1997 Sep, Vol. 24 issue 9 pp1680-4.
2. Antioxidants may contribute in the fight against aging. Hu HL, et. al. *Mechanisms of Ageing and Development* January 2001 Vol. 121, Issues 1-3, 20, Pages 217-230. Data suggest that dietary antioxidants could play a significant role in the reduction of inflammatory responses.
3. Dietary supplementation with vitamin E alone reduces the baseline inflammatory status that is indicated by the CRP concentration in healthy adult baboons. Co-supplementation with Co[Q.sub.10], however, significantly enhances this anti-inflammatory effect of vitamin E. Wang, Xing Li. *American Journal of Clinical Nutrition* Sept 2004, Vol. 80 issue 3, p649(7) We explored the effects of a high-fat, high-cholesterol (HFHC) diet on vascular responses in 21 baboons and the potential response-attenuating effects of vitamin E and coenzyme [Q.sub.10] (Co[Q.sub.10]) supplementation.

MEMORY

1. Protective Effect of Flavonoids against ageing and cognitive Impairment in Mice. Patil, et. al. *Pharmacology* October 2003, Vol. 69 issue 2, p59-67. Flavonoids are known to inhibit formation of substances that can lead to many degenerative neuro diseases including Alzheimer's, viral and bacterial meningitis, dementia, and stroke. Experiments

showed that treatment with flavonoids (quercetin and apigenin) reverses cognitive deficits in aged. The study concluded that flavonoids might be important in the prevention of memory deficits.

2. Oxidative Stress and Alzheimer Disease.
 Christen, Y. *Am J of Clin Nutrition*, Vol. 71 issue 2, pp621 S.
 Scientists hypothesize that free radical damage of neurons, which are extremely sensitive to free radical attack, is involved in AD. Many free radical scavengers have produced promising results in relation to AD.
3. Natural Extracts as Possible Protective Agents of Brain Aging.
 Bastianetto, S. and R. Quirion, *Neurobiology of Aging*, 2002 Sep-Oct; Vol. 23 issue 5, pp891-97.
 A growing number of studies indicated that natural extracts and phytochemicals have a positive impact on brain aging. Bioflavonoids protected against brain cell death due to their antioxidant activity. The results show that dietary intake of natural plant flavonoids may be beneficial in normal aging of the brain.
4. An Apple a Day May Keep the Doctor Away. (Alzheimer's Disease).
 Toops, Diane. *USA Today*, (Magazine) from Cornell Research Feb 2005, Vol. 133 issue 2717, p5(1).
 A potent antioxidant abundant in apples and some other fruits and vegetables appears to protect brain cells against oxidative stress, a tissue-damaging process associated with Alzheimer's disease and other neuro-degenerative disorders, according to a study of rat brain cells conducted by researchers at Cornell University, Ithaca, N.Y. "On the basis of serving size, fresh apples have some of the highest levels of [the antioxidant] quercetin when compared to other fruits and vegetables and may be among the best food choices for fighting Alzheimer's," contends C.Y. Lee, professor and chairman of the Department of Food Science & Technology.
5. β -Amyloid (1-42)-induced learning and memory deficits in mice: involvement of oxidative burdens in the hippocampus and cerebral cortex
 Jhoo, J et al. *Behavioural Brain Research* 6 December 2004, Vol. 155, Issue 2, Pages 185-196
 In the present study, we examined whether oxidative stress contributes to the memory deficits induced by intracerebroventricular injection of $A\beta$ (1-42) in mice... Treatment with antioxidant α -tocopherol significantly prevented memory impairment induced by $A\beta$ (1-42)... Therefore, our results suggest that the oxidative stress contributes to the $A\beta$ (1-42)-induced learning and memory deficits in mice.
6. Quercetin, a natural flavonoid, attenuates vacuolar formation in the optic tract in rat chronic cerebral hypoperfusion model
 Takizawa, S. et al. *Brain Research* 1 August 2003, Vol. 980, Issue 1, pp 156-160.
 We investigated whether quercetin attenuates white matter damage in rats with chronic cerebral hypoperfusion, as a model of vascular dementia. The present results are consistent with the idea that chronic treatment with quercetin could be protective against at least a part of ischemic white matter damage.
7. Neuroprotective effects of antioxidative flavonoids, quercetin, (+)-dihydroquercetin and quercetin 3-methyl ether, isolated from *Opuntia ficus-indica* var. *saboten*
 Hyang, D. et al. *Brain Research* 7 March 2003, Vol. 965, Issues 1-2, Pp130-136.
 We evaluated their protective effects against oxidative neuronal injuries induced in primary cultured rat cortical cells and their antioxidant activities by using three different cell-free bioassays. The results

indicate that quercetin, (+)-dihydroquercetin, and quercetin 3-methyl ether are the active antioxidant principles in the fruits and stems of *Opuntia ficus-indica* var. *saboten* exhibiting neuroprotective actions against the oxidative injuries induced in cortical cell cultures. Furthermore, quercetin 3-methyl ether appears to be the most potent neuroprotectant of the three flavonoids isolated from this plant.

8. Antioxidants may contribute in the fight against ageing: an in vitro model
Heng-Long, et al. *Mechanisms of Ageing and Development* Vol. 121, Issues 1-3, 20 January 2001, Pages 217-230.
We investigated the potential of the dietary antioxidant, quercetin, to reverse the age related influences of GSH depletion and oxidative stress using in vitro human umbilical vein endothelial cells (HUVEC) and human skin fibroblast (HSF) cell models. In conclusion, these data suggest that dietary antioxidants could play a significant role in the reduction of inflammatory responses.

OBESITY

1. Efficacy of Green Tea Extract Rich in Catechins and Caffeine in Increasing Energy Expenditure and Fat Oxidation in Humans.
Dulloo et. al. *Am J of Clin Nutrition*, Vol. 70. No. 6 1040-45; Dec 1999.
Results: Green Tea Extract has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both.

OSTEOPOROSIS

1. Tea Drinking and Bone Mineral Density in Older Women,
Hegarty et. al. *Am J of Clin Nutrition*, Vol. 71 issue 4, pp1003.
Older women who drank tea had higher bone mineral densities than those who did not drink tea. Nutrients found in tea, such as bioflavonoids, may influence bone density. Tea flavonoids may protect against osteoporosis in older women.
2. Potential Inhibitory Effects of naturally occurring flavonoids quercetin and kaempferol on bone loss.
Wattel, A. et. al. *Biochemical Pharmacology* January 2003, Vol. 65, Issue 1, pp 35-42.
Recent studies suggest that flavonoids have a protective effect on postmenopausal bone loss. Both quercetin and kaempferol reduce bone loss in a time and dose-dependent manner.
3. Study Shows Tea May Strengthen Bones.
Tea and Coffee Trade Journal July 20, 2002, Vol. 174 issue 7, p11(1)
Researchers from National Cheng Kung University Hospital in Taiwan may have found that drinking tea over time may strengthen bones. Benefits occurred in people who drank an average of nearly two cups a day of black, green or oolong tea for at least six years. The Flavonoids in tea include estrogen-like plant derivatives that may enhance bone strength. The study tested 1, 037 men and women 30 and older, and measured hipbone density.
4. Role of Dietary Lipid and Antioxidants in Bone Metabolism
Seifert, M. and B. Watkins. *Nutrition Research* July 1997, Vol. 17, Issue 7, Pages 1209-28.
Recent investigations and clinical studies suggest that dietary lipids and antioxidant nutrients influence bone formation and cartilage biology.

5. Bone metabolism and oxidative stress in postmenopausal rats with iron overload
Isomura, H. et al. *Toxicology* Vol. 197, Issue 2, 15 April 2004, Pages 92-99.
We investigated the relationship between ROS and bone metabolism in young female and postmenopausal rats, by using dietary iron overload and several indices including bone metabolic markers, oxidative stress and antioxidant markers, and cytokines. Taken together, these results suggest for the first time that oxidative stress could be involved in the pathogenesis of metabolic bone diseases such as osteoporosis as demonstrated by analysis of the relationship between bone metabolism and oxidative stress.
6. Micronutrients in Women's Health and Immune Function
Bendich, A. PhD, FACN. *Nutrition* Vol. 17, Issue 10, October 2001, Pages 858-867.
Antioxidants such as vitamins C and E have been shown to reduce the risk of fracture in women smokers. Multivitamins have been shown to enhance many aspects of immune response, and antioxidant micronutrients consistently have been found to enhance lymphocyte-proliferative responses and skin-test responses, especially in the elderly.

OXIDATIVE STRESS

1. Comparison of antioxidant Effects of grape juice flavonoids on Oxidative Stress.
O'Byrne, et.al. *Am J of Clin Nutrition*, Vol 76, No. 6, 1367-1374 Dec 2002.
Flavonoids in grape juice increased serum antioxidant capacity. These flavonoids are potent antioxidants that may protect against oxidative stress and reduce the risk of free radical damage and chronic diseases.
2. Flavonoids Protect Against Oxidative Damage to LDL; benefits of a flavonoid-rich diet.
O'Reilly, et.al., *Free Radical Res* 2000 Oct, Vol. 33 issue 4, pp 419-26.
Overall quercetin was the most effective inhibitor of oxidative damage to LDL in vitro.
2. Quercetin inhibits C-Fos, heat shock protein, and fibrillary acidic protein expression in injured astrocytes.
Wu and Yu; *Wiley Interscience Journal*; August 2000.
Quercetin exhibits properties that aid in the prevention of injury shock and improve healing.
3. Fruits and Vegetables in the Prevention of Cellular Oxidative Damage
Prior, RL. *Am J of Clin Nutrition*, Vol. 78, No. 3, 570S-578S, Sep 2003.
Flavonoids from fruits and vegetables exhibit inhibitory effects on cellular oxidative damage. Quercetin is better absorbed than anthocyanins, and appears to maintain its antioxidant properties in the body.
4. Quercetin Protects Cutaneous Cell Types from Oxidative Stress.
Skaper, et.al., *Free Radical Biology and Medicine*, Vol 22, No. 4 pp 669-678, 1997.
Lipid peroxides and free radicals are likely involved in numerous pathological events including inflammation, radiation damage, metabolic disorders, cellular aging, and reperfusion damage. Flavonoids such as quercetin may delay oxidant injury and cell death by scavenging oxygen radicals, protecting against lipid oxidation and thereby terminating the chain-radical reaction, chelating metal ions, to form inert complexes that cannot cause cell damage.

5. Structure–activity relationships of quercetin in antagonizing hydrogen peroxide-induced calcium dysregulation in PC12 cells
Wang, H. and J. Joseph, *Free Radical Biol Med.* 1999 Sept; Vol. 27 issues 5-6 pp683-94.
The study showed that the particular structure of the quercetin molecule provided its strong antioxidant property of protecting cells against H₂O₂-induced oxidative stress and calcium dysregulation.

PROSTATITIS

1. Quercetin in Men with Category III Chronic Prostatitis: a preliminary prospective, double blind, placebo –controlled trial.
Shoskes, et. al. *Urology*, Dec 1999 Vol. 54 issue 6 pp, 960-963.
Bioflavonoids recently have been shown to reduce symptoms of prostatitis. Conclusion of Study: Therapy with the bioflavonoid quercetin is well tolerated and provides significant symptomatic improvement in most men with chronic pelvic pain syndrome.