

Life Extension Magazine April 2009

REPORT

Quercetin

Enhanced Antioxidant Protection Against Heart Disease, Cancer, Allergies, and More

By Julius Goepp, MD

News of the disease-protective and longevity benefits of red wine has grabbed headlines around the world during the past few years. Red wine contains a number of beneficial polyphenols, such as the much-publicized resveratrol as well as quercetin¹—a compound that is now also making news of its own.

Long known for its anti-inflammatory and anti-allergic effects,^{2,3} recent scientific breakthroughs reveal that quercetin may help promote longevity by mimicking the effects of caloric restriction.^{4,5} Furthermore, this powerful antioxidant demonstrates multifaceted protective effects against cardio-vascular disease, metabolic syndrome, and even cancer.^{2,3}

While quercetin can be obtained through red wine and other dietary sources such as apples, onions, grapefruit, tea, green vegetables, and beans,⁶ highly purified supplements make it possible to acquire the bio-logically meaningful doses that have shown promise in tightly controlled studies. In the words of the German nutrition expert Professor Stephan C.

Bischoff, ***“Quercetin is a most promising compound for disease prevention and therapy.”***⁷ Let's take a look at some of the compelling evidence that has accumulated over the past few years for quercetin's role in health management and disease prevention.

ANTI-INFLAMMATORY AND ANTI-ALLERGY EFFECTS

At the core of most of quercetin's remarkable properties is its ability to modulate inflammation. Since we now understand that inflammation is involved in virtually every chronic human disease and many acute ones—having an inflammatory modulator like quercetin in our armamentarium is likely to prove very useful indeed.

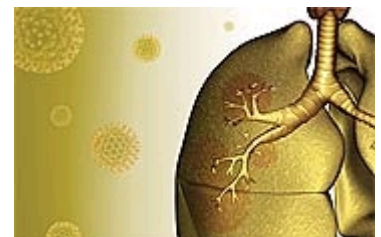
Korean researchers in 2007 showed how quercetin inhibits the production of inflammatory cytokines by blocking the effects of the powerful cellular mediator NF-kappaB, long associated with both cancer and chronic inflammatory conditions.⁸

Quercetin's anti-inflammatory effects may arise in part from its inhibitory effects on the inflammation-producing enzymes cyclooxygenase (COX) and lipo-oxygenase (LOX). This in turn leads to a decrease in inflammatory mediators such as prostaglandins and leukotrienes.^{2,9} Pharmaceutical agents that block the COX enzymes are often used in the management of painful conditions like arthritis, while LOX inhibitors are employed in the management of asthma.

Additionally, quercetin exerts anti-allergy and anti-inflammatory effects by helping prevent the release of histamine from mast cells and basophils, thus acting as a natural antihistamine.² This is similar to the mechanism of action of the drug cromolyn, which is used to manage allergy-related asthma.

Researchers in both Brazil¹⁰ and Korea¹¹ protected animals from fatal allergic reactions to common food allergens by pre-treating them with quercetin in oral or inhaled forms.

Quercetin's ability to prevent allergic effects has tremendous implications for the treatment and prevention of asthma and bronchitis, conditions for which quercetin-rich foods have had long traditional roles.¹² Several studies since 2007 have shown that animals pre-treated with quercetin or related compounds have dramatically reduced reactions to chemicals that trigger asthma attacks.¹³⁻¹⁵ In a dramatic, eye-opening study in 2008, Korean researcher Hee Moon compared inhaled quercetin head-to-head with prescription asthma drugs in guinea-pigs.¹⁶ Remarkably, the nutrient-derived quercetin treatment reduced airway resistance



(difficulty breathing) more than the adrenaline-like drug albuterol, and had equivalent effects to the anti-inflammatory cromolyn as well as the potent steroid dexamethasone.

In a form of epidemiological detective work, nutrition scientists from Michigan State University explored the impact of dietary flavonoids such as quercetin in their more general roles as systemic anti-inflammatory agents.¹⁷ Basing their work on knowledge that intake of certain foods can lower levels of the inflammatory risk factor *C-reactive protein* (CRP), they went looking for the most potent food components, studying more than 8,000 adults. They found that higher flavonoid intake was associated with lower CRP levels—and quercetin headed the list of specific flavonoid compounds that had the strongest protective effect. Since elevated CRP levels are associated with numerous disease states such as obesity, heart disease, and lupus, this provides compelling reason to explore quercetin's potential for preventing death and disability from a host of major killers.

IMMUNE-MODULATING EFFECTS

Quercetin is one of nearly 200 beneficial compounds found in garlic,¹⁸ which has been used for millennia in treating and preventing infectious disease such as viral syndromes.¹⁹ Indeed, modern science confirms quercetin's benefits in helping fight off viral invaders.

In laboratory studies, quercetin has been found to reduce the replication and infectivity of numerous viruses, including respiratory syncytial virus (a common cause of children's upper respiratory infection) and parainfluenza virus type 3.²

Italian researchers just last year showed that they could use a quercetin-rich extract to *up-regulate* the antiviral immune response in cells infected with herpes viruses.²⁰ Additionally, an animal study last year showed that supplementation with quercetin helped protect mice against influenza infection following exercise-induced stress.²¹ These findings make quercetin an intriguing candidate for preventing and managing viral infections in susceptible individuals.

OBESITY

The rampant rise of overweight and obesity poses one of the greatest global health threats today. Scientists are now eagerly exploring quercetin's potential as a means of controlling fat accumulation.

Fat, long considered to be an inert, biologically uninteresting tissue, is now known to be a virtual beehive of metabolic and endocrine activity, producing myriad hormones, inflammatory cytokines, and other molecules that influence health for better or for worse.²² Fat tissue mass is essentially the product of new fat cells, their accumulation of fat triglycerides, and their programmed death by the process of apoptosis.²³ Each of these processes can be affected by various natural dietary components, and as University of Georgia nutritionist Srujana Rayalam recently observed, ***“Therapy employing compounds that target different stages of the adipocyte [fat cell] life cycle might prove beneficial for decreasing adipose tissue volume by inducing apoptosis or by inhibiting adipogenesis [fat accumulation] or both.”***²³ What is so exciting about quercetin is recent evidence that this flavonoid, alone or in combination with resveratrol and genistein, is capable of exerting just such multiple effects directly on fat tissue!

Quercetin inhibits fat accumulation in maturing human fat cells in culture, for example, while also suppressing the maturation of new fat cells and simultaneously triggering apoptosis (programmed destruction) in existing fat cells.^{24,25} Quercetin actually blocks the uptake of glucose from the blood, depriving fat cells of the raw material they need to manufacture and accumulate fat molecules.²⁶ In remarkable work published in mid-2008, the University of Georgia group found that while they could block fat cell production and enhance fat cell death dramatically using either quercetin or resveratrol (another powerful flavonoid) alone, when they used the two in combination they decreased lipid accumulation in cultured fat cells by nearly 70%, while increasing fat apoptosis by a whopping 310%!²⁷

Just a few months later, the same research team found that resveratrol and genistein synergize with quercetin to decrease lipid accumulation in human fat cells. While genistein, quercetin, and resveratrol decreased lipid accumulation in fat cells by 17%, 20%, and 17%, respectively, the combination of all three agents decreased lipid accumulation by an impressive 80%.²⁵

Studies in animals lend support to the potential anti-obesity effects of quercetin. In mice fed a high-fat diet, quercetin produced a transient increase in energy expenditure,²⁸ while another study showed that high-dose quercetin supplementation was associated with reduced body weight gain in obese, insulin-resistant mice.³

It's no surprise then that quercetin—alone or in combination with other nutraceuticals—is drawing the attention of researchers searching for novel strategies for fighting obesity via numerous mechanisms.



WHAT YOU NEED TO KNOW: QUERCETIN

- Despite being the most common and best studied of the polyphenols, quercetin has been largely neglected in the public eye until recently, as new research has revealed its astonishing potential as a health-promoting, disease-preventing supplement.
- Quercetin's powerful antioxidant effects directly reduce tissue damage and have now been shown to prevent diseases such as cancer and cardiovascular disease.
- Independent effects of quercetin directly reduce fat tissue growth and development, and even reduce the bulk of body fat stores, promoting health through weight reduction.
- Quercetin shows promise in fighting the numerous components of the metabolic syndrome, including hypertension, insulin resistance, and adverse lipid profiles.
- Quercetin's antioxidant effects lead to anti-inflammatory and anti-allergy effects, augmenting its role in chronic disease prevention and treatment.
- Quercetin directly extends the life span of laboratory organisms, in part by mimicking the beneficial effects of caloric restriction, and opening the door to a new approach to life extension itself.
- Health care practitioners recommend quercetin in doses ranging from 50 mg to 500 mg, one to three times daily.^{2,55}

CARDIOVASCULAR DISEASE

Increased dietary intake of flavonoids—particularly from quercetin-rich foods—has been linked with decreased heart disease mortality and decreased stroke incidence.² In 2000, Spanish scientists showed that red wine, laden with quercetin and related antioxidants, prevented activity of inflammation-promoting NF-kappaB in human volunteers, providing a big part of the explanation of how red wine reduces cardiovascular mortality.²⁹

In 2004, British researchers demonstrated that humans who took quercetin supplements had substantially reduced platelet aggregation, suggesting that another of quercetin's cardiovascular health benefits was related to a reduced risk of clotting.³⁰ These researchers later showed that dietary ingestion of quercetin from onion soup also helped inhibit platelet aggregation.³¹ And in a study of 30 men who already had coronary heart disease, Greek cardiologists showed that a red grape polyphenol extract rich in quercetin caused an increase in **flow-mediated dilation** of major arteries, a potent indicator of improved endothelial health.³²



The natural next step was to study quercetin supplements alone and their effect on blood pressure, a study undertaken at the University of Utah in 2007.³³ They studied 19 patients with pre-hypertension and 22 with *stage 1 (early) hypertension*, supplementing them with placebo or 730 mg quercetin/day for 28 days. There was no effect on the pre-hypertensive patients, but the hypertensive group enjoyed reductions in both systolic and diastolic blood pressure (average 7 mmHg and 5 mmHg reductions, respectively)—meaningful changes that lower vascular disease risk.

In 2008, a randomized, placebo-controlled crossover trial in 12 healthy men showed biochemical evidence of improved endothelial function (such as augmentation of nitric oxide status) with as little as 200 mg/day of quercetin.³⁴

Together, these effects point to an important role for quercetin in protecting cardiovascular health.

METABOLIC SYNDROME AND DIABETES

Chinese folk medicine has long used a quercetin-rich plant called *Euonymus alatus* to treat type 2 diabetes.³⁵ Not surprisingly, modern research is finding that quercetin may hold applications in managing metabolic syndrome—a cluster of risk factors that is associated with an elevated risk of diabetes.

Spanish researchers publishing in the journal *Obesity* showed in 2008 that quercetin given to obese, insulin-resistant rats produced a reduction in systolic blood pressure, plasma lipids, and insulin levels, while improving the over-aggressive inflammatory status these rats develop.³ The higher of two experimental quercetin doses also led to increased expression of endothelial *nitric oxide synthase*—the enzyme that generates blood vessel-protective *nitric oxide*. These findings suggest that quercetin may protect against numerous components of the common and deadly *metabolic syndrome*.

REPORT

Quercetin

Enhanced Antioxidant Protection Against Heart Disease, Cancer, Allergies, and More

By Julius Goepp, MD

CANCER

Quercetin's ability to suppress cell proliferation, to promote programmed cell death, and to minimize DNA damage has made it of natural interest as a cancer-preventive nutrient as well,^{36,37} and epidemiologic studies strongly suggest that quercetin and other flavonoid intake is correlated with a reduced risk of certain cancers.³⁸⁻⁴³ Researchers have demonstrated quercetin's ability to prevent or slow tumor development in experiments involving cancers of the brain, liver, colon, and other tissues.⁴⁴⁻⁴⁷



Clinical evidence of quercetin's usefulness in cancer prevention and therapy is rapidly accumulating. An early Phase I clinical trial of quercetin in patients with various cancer types demonstrated a decrease in activity of enzymes required for tumor growth in nine of 11 patients studied.⁴⁸ Two patients with advanced cancers that had failed to respond to standard chemotherapy experienced significant drops in chemical tumor markers during the study.

More recently, Cleveland Clinic oncologists investigated quercetin in patients who had *familial adenomatous polyposis*, an inherited condition producing hundreds of colonic polyps that ultimately turn to cancer.⁴⁹ They combined the quercetin with curcumin, another nutrient with known anti-inflammatory and tumor-blocking potential, in five patients, treating and following them for six months. All patients had a reduction in both size (60%) and number of polyps (51%) over the course of treatment, with minimal adverse effects and no evidence of laboratory abnormalities. The researchers strongly encouraged larger controlled trials to further explore the supplements' potential cancer-fighting abilities.

LONGEVITY

The diverse and multiple effects of quercetin on specific disease processes are overwhelming, and are certain to have an effect on longevity simply by reducing the impact of chronic illness. But there seems to be something else going on with this surprising polyphenol—something independent of its disease-preventing activity. Hard as it may be to believe, there is actually evidence that quercetin has a direct effect on prolonging life span, at least in simple laboratory organisms. For example, a Portuguese biochemistry research group has shown that, by increasing resistance to oxidative stress, quercetin supplements prolong the life span of laboratory yeast cells in culture by 60%!⁴



Biologists at Humboldt University in Berlin took these findings several steps further in their work on a simple roundworm *C. elegans*, demonstrating that feeding the tiny worms flavonoid-rich diets improved overall health and longevity.⁵⁰ Digging deeper, the same group traced this powerful effect to the quercetin content of the supplement—they've even identified a set of four specific genes that seem to be activated by quercetin, pinpointing the precision with which this nutrient acts.^{50,51} Other scientists have found evidence that quercetin may mimic many beneficial biological effects of caloric restriction, which extends life span in animals and possibly in humans.^{5,52,53} The immediate impact on humans has also been shown by neuroscientists in Kentucky, who discovered that they could protect brain cells from the devastating effects of the toxic protein found in Alzheimer's disease, beta-amyloid, by pre-treating the cells with quercetin, apparently through reduction in free radical damage caused by the deadly protein.⁵⁴

DOSAGE AND SAFETY

Health care practitioners recommend quercetin in doses ranging from 50 mg to 500 mg, one to three times daily.^{2,55}

Quercetin is generally considered safe and well tolerated. Pregnant or nursing women should speak with a physician before using quercetin.²

SUMMARY

Quercetin, a ubiquitous polyphenol found especially in apples, onions, and red grapes has been ignored for years while other members of its class took the limelight. In just the past two years, however, a virtual explosion of information has emerged about this versatile molecule. We now understand that it can fundamentally affect disease processes as different as obesity, cardiovascular disease, cancer, and asthma, through its powerful antioxidant effects that reduce inflammation throughout the body. Even more astonishingly, it is now clear that quercetin may have a direct and independent effect on prolonging life itself, through mechanisms that are becoming less mysterious as scientists focus their attention deep inside cellular processes.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

References

1. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. *Eur J Pharmacol.* 2008 May 13;585(2-3):325-37.
2. No authors listed. Quercetin. Monograph. *Altern Med Rev.* 1998 Apr;3(2):140-3.
3. Rivera L, Moron R, Sanchez M, Zarzuelo A, Galisteo M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. *Obesity (Silver Spring).* 2008 Sep;16(9):2081-7.
4. Belinha I, Amorim MA, Rodrigues P, et al. Quercetin increases oxidative stress resistance and longevity in *Saccharomyces cerevisiae*. *J Agric Food Chem.* 2007 Mar 21;55(6):2446-51.
5. Barger JL, Kayo T, Pugh TD, Prolla TA, Weindruch R. Short-term consumption of a resveratrol-containing nutraceutical mixture mimics gene expression of long-term caloric restriction in mouse heart. *Exp Gerontol.* 2008 Sep;43(9):859-66.
6. Formica JV, Regelson W. Review of the biology of Quercetin and related bioflavonoids. *Food Chem Toxicol.* 1995 Dec;33(12):1061-80.
7. Bischoff SC. Quercetin: potentials in the prevention and therapy of disease. *Curr Opin Clin Nutr Metab Care.* 2008 Nov;11(6):733-40.
8. Min YD, Choi CH, Bark H, et al. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line. *Inflamm Res.* 2007 May;56(5):210-5.
9. Warren CA, Paulhill KJ, Davidson LA, et al. Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. *J Nutr.* 2009 Jan;139(1):101-5.
10. Cruz EA, Da-Silva SA, Muzitano MF, et al. Immunomodulatory pretreatment with *Kalanchoe pinnata* extract and its quercitrin flavonoid effectively protects mice against fatal anaphylactic shock. *Int Immunopharmacol.* 2008 Dec 10;8(12):1616-21.
11. Park HJ, Lee CM, Jung ID, et al. Quercetin regulates Th1/Th2 balance in a murine model of asthma. *Int Immunopharmacol.* 2008 Dec 2.
12. Chaabi M, Freund-Michel V, Frossard N, et al. Anti-proliferative effect of *Euphorbia stenoclada* in human airway smooth muscle cells in culture. *J Ethnopharmacol.* 2007 Jan 3;109(1):134-9.
13. Jiang JS, Chien HC, Chen CM, Lin CN, Ko WC. Potent suppressive effects of 3-O-methylquercetin 5,7,3',4'-O-tetraacetate on ovalbumin-induced airway hyperresponsiveness. *Planta Med.* 2007 Sep;73(11):1156-62.
14. Jung CH, Lee JY, Cho CH, Kim CJ. Anti-asthmatic action of quercetin and rutin in conscious guinea-pigs challenged with aerosolized ovalbumin. *Arch Pharm Res.* 2007 Dec;30(12):1599-607.
15. Rogerio AP, Kanashiro A, Fontanari C, et al. Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma. *Inflamm Res.* 2007 Oct;56(10):402-8.
16. Moon H, Choi HH, Lee JY, et al. Quercetin inhalation inhibits the asthmatic responses by exposure to aerosolized-ovalbumin in conscious guinea-pigs. *Arch Pharm Res.* 2008 Jun;31(6):771-8.
17. Chun OK, Chung SJ, Claycombe KJ, Song WO. Serum C-reactive protein concentrations are inversely associated with

dietary flavonoid intake in U.S. adults. *J Nutr.* 2008 Apr;138(4):753-60.

18. Ayaz E, Alpsoy HC. Garlic (*Allium sativum*) and traditional medicine. *Turkiye Parazitol Derg.* 2007;31(2):145-9.
19. Josling P. Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. *Adv Ther.* 2001 Jul-Aug;18(4):189-93.
20. Arena A, Bisignano G, Pavone B, et al. Antiviral and immunomodulatory effect of a lyophilized extract of *Capparis spinosa* L. buds. *Phytother Res.* 2008 Mar;22(3):313-7.
21. Davis JM, Murphy EA, McClellan JL, Carmichael MD, Gangemi JD. Quercetin reduces susceptibility to influenza infection following stressful exercise. *Am J Physiol Regul Integr Comp Physiol.* 2008 Aug;295(2):R505-9.
22. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab.* 2008 Nov;93(11 Suppl 1):S64-73.
23. Rayalam S, La-Fera MA, Baile CA. Phytochemicals and regulation of the adipocyte life cycle. *J Nutr Biochem.* 2008 Nov;19(11):717-26.
24. Ahn J, Lee H, Kim S, Park J, Ha T. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochem Biophys Res Commun.* 2008 Sep 5;373(4):545-9.
25. Park HJ, Yang JY, Ambati S, et al. Combined effects of genistein, quercetin, and resveratrol in human and 3T3-L1 adipocytes. *J Med Food.* 2008 Dec;11(4):773-83.
26. Strobel P, Allard C, Perez-Acle T, et al. Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. *Biochem J.* 2005 Mar 15;386(Pt 3):471-8.
27. Yang JY, la-Fera MA, Rayalam S, et al. Enhanced inhibition of adipogenesis and induction of apoptosis in 3T3-L1 adipocytes with combinations of resveratrol and quercetin. *Life Sci.* 2008 May 7;82(19-20):1032-9.
28. Stewart LK, Soileau JL, Ribnicky D, et al. Quercetin transiently increases energy expenditure but persistently decreases circulating markers of inflammation in C57BL/6J mice fed a high-fat diet. *Metabolism.* 2008 Jul;57(7 Suppl 1):S39-46.
29. Blanco-Colio LM, Valderrama M, Alvarez-Sala LA, et al. Red wine intake prevents nuclear factor-kappaB activation in peripheral blood mononuclear cells of healthy volunteers during postprandial lipemia. *Circulation.* 2000 Aug 29;102(9):1020-6.
30. Hubbard GP, Wolfram S, Lovegrove JA, Gibbins JM. Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. *J Thromb Haemost.* 2004 Dec;2(12):2138-45.
31. Hubbard GP, Wolfram S, de Vos R, Bovy A, Gibbins JM, Lovegrove JA. Ingestion of onion soup high in quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in man: a pilot study. *Br J Nutr.* 2006 Sep;96(3):482-8.
32. Lekakis J, Rallidis LS, Andreadou I, et al. Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. *Eur J Cardiovasc Prev Rehabil.* 2005 Dec;12(6):596-600.
33. Edwards RL, Lyon T, Litwin SE, et al. Quercetin reduces blood pressure in hypertensive subjects. *J Nutr.* 2007 Nov;137(11):2405-11.
34. Loke WM, Hodgson JM, Proudfoot JM, et al. Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. *Am J Clin Nutr.* 2008 Oct;88(4):1018-25.
35. Fang XK, Gao J, Zhu DN. Kaempferol and quercetin isolated from *Euonymus alatus* improve glucose uptake of 3T3-L1 cells without adipogenesis activity. *Life Sci.* 2008 Mar 12;82(11-12):615-22.
36. Choi EJ, Bae SM, Ahn WS. Antiproliferative effects of quercetin through cell cycle arrest and apoptosis in human breast cancer MDA-MB-453 cells. *Arch Pharm Res.* 2008 Oct;31(10):1281-5.
37. Boyle SP, Dobson VL, Duthie SJ, Kyle JA, Collins AR. Absorption and DNA protective effects of flavonoid glycosides from an

onion meal. *Eur J Nutr.* 2000 Oct;39(5):213-23.

38. Gates MA, Tworoger SS, Hecht JL, et al. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. *Int J Cancer.* 2007 Nov 15;121(10):2225-32.

39. Gates MA, Vitonis AF, Tworoger SS, et al. Flavonoid intake and ovarian cancer risk in a population-based case-control study. *Int J Cancer.* 2008 Nov 11.

40. Gerhauser C. Cancer chemopreventive potential of apples, apple juice, and apple components. *Planta Med.* 2008 Oct;74(13):1608-24.

41. Garcia-Closas R, Agudo A, Gonzalez CA, Riboli E. Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr Cancer.* 1998;32(3):154-8.

42. Nothlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Flavonols and pancreatic cancer risk: the multiethnic cohort study. *Am J Epidemiol.* 2007 Oct 15;166(8):924-31.

43. Nothlings U, Murphy SP, Wilkens LR, et al. A food pattern that is predictive of flavonol intake and risk of pancreatic cancer. *Am J Clin Nutr.* 2008 Dec;88(6):1653-62.

44. Siegelin MD, Reuss DE, Habel A, Rami A, von DA. Quercetin promotes degradation of survivin and thereby enhances death-receptor mediated apoptosis in glioma cells. *Neuro Oncol.* 2008 Oct 29.

45. Tan S, Wang C, Lu C, et al. Quercetin is able to demethylate the p16INK4a gene promoter. *Chemotherapy.* 2009;55(1):6-10.

46. Vasquez-Garzon VR, Rellanes-Robledo J, Garcia-Roman R, Paricio-Bautista DI, Villa-Trevino S. Inhibition of reactive oxygen species and pre-neoplastic lesions by quercetin through an antioxidant defense mechanism. *Free Radic Res.* 2008 Dec 29;1-10.

47. Warren CA, Paulhill KJ, Davidson LA, et al. Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. *J Nutr.* 2009 Jan;139(1):101-5.

48. Ferry DR, Smith A, Malkhandi J, et al. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clin Cancer Res.* 1996 Apr;2(4):659-68.

49. Cruz-Correa M, Shoskes DA, Sanchez P, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol.* 2006 Aug;4(8):1035-8.

50. Pietsch K, Saul N, Menzel R, Sturzenbaum SR, Steinberg CE. Quercetin mediated lifespan extension in *Caenorhabditis elegans* is modulated by age-1, daf-2, sek-1 and unc-43. *Biogerontology.* 2008 Nov 29.

51. Saul N, Pietsch K, Menzel R, Steinberg CE. Quercetin-mediated longevity in *Caenorhabditis elegans*: is DAF-16 involved? *Mech Ageing Dev.* 2008 Oct;129(10):611-3.

52. Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. *Rejuvenation Res.* 2007 Jun;10(2):179-90.

53. Ghosh HS. The anti-aging, metabolism potential of SIRT1. *Curr Opin Investig Drugs.* 2008 Oct;9(10):1095-102.

54. Ansari MA, Abdul HM, Joshi G, Opii WO, Butterfield DA. Protective effect of quercetin in primary neurons against Abeta(1-42): relevance to Alzheimer's disease. *J Nutr Biochem.* 2008 Jul 3.

55. Egert S, Wolfram S, Bosy-Westphal A, et al. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. *J Nutr.* 2008 Sep;138(9):1615-21.

your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.