

Journal
ABSTRACTS**Butterbur, Rosmarinic Acid****TREATING INTERMITTENT ALLERGIC RHINITIS: A PROSPECTIVE, RANDOMIZED, PLACEBO AND ANTIHISTAMINE-CONTROLLED STUDY OF BUTTERBUR EXTRACT ZE 339.**

BACKGROUND: Intermittent allergic rhinitis (IAR) causes patients distress and impairs their work performance and quality of life. A variety of medicines are used by sufferers whose anguish frequently leads to trying new treatments, increasingly from herbal sources. **METHODS:** Prospective, randomized, double-blind, parallel group comparison study of Butterbur extract (Ze 339; 8 mg total petasine; one tablet thrice-daily), fexofenadine (Telfast 180, one tablet once-daily) and placebo in 330 patients. Protocol and analysis were according to the latest guidelines on new treatments for allergic rhinitis. The primary efficacy variable was a change in symptoms from baseline to endpoint during daytime. The secondary efficacy variables were: (a) as per primary variable (evening/night); (b) Physician's global assessment; (c) Responder rates. Safety was closely monitored. **FINDINGS:** Both active treatments were individually significantly superior to placebo ($p < 0.001$) in improving symptoms of IAR, while there were no differences between the two active treatments ($p = 0.37$). Superiority to placebo was similarly shown during the evening/night ($p < 0.001$), by physicians' own assessment and by responder rates. Both treatments were well tolerated. **INTERPRETATION:** Butterbur Ze 339 and Fexofenadine are comparably efficacious relative to placebo. Despite being a herbal drug, Butterbur Ze 339 has now been subject to a series of well controlled trials and should be considered as an alternative treatment for IAR.

Phytother Res. 2005 Jun;19(6):530-7

BUTTERBUR ZE339 FOR THE TREATMENT OF INTERMITTENT ALLERGIC RHINITIS: DOSE-DEPENDENT EFFICACY IN A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY.

OBJECTIVES: To investigate whether the efficacy and safety of Butterbur extract Ze339 are related to dosage when administered to patients with intermittent allergic rhinitis. **DESIGN:** Prospective, randomized, double-blind, placebo-controlled, parallel-group comparison. **SETTING:** Multicenter, including 6 outpatient general medicine and allergy clinics. **PATIENTS:** One hundred eighty-six patients were randomized (Butterbur Ze339 high dose, 60; low dose, 65; and placebo, 61 patients). Established diagnostic criteria for intermittent allergic rhinitis were confirmed by skin allergy tests in all patients. **INTERVENTIONS:** High-dose group, 1 tablet 3 times daily; low-dose group, 1 tablet twice daily; or matching placebo. All groups were treated for 2 consecutive weeks. **MAIN OUTCOME MEASURES:** The main efficacy variable was change in symptoms from baseline to end point during the daytime. The secondary efficacy variables were Clinical Global Impression score, change in symptoms from baseline to treatment day 7, and responder rates. Statistical analysis was prospective, on an intention-to-treat basis. **RESULTS:** Improvement in the main efficacy variable was significantly superior in the Butterbur Ze339 groups, relative to placebo, and a significant dose relationship was observed between the 2 Butterbur doses. The clinicians' assessment of efficacy and the overall responder rates were significantly superior for the active groups compared with placebo. The incidence and type of adverse events were indistinguishable across the herbal treatment and placebo groups. **CONCLUSIONS:** Butterbur Ze339 is an effective treatment for intermittent allergic rhinitis symptoms and is well tolerated. The effects of this herbal medicine are clear to patients and physicians in a double-blind evaluation against placebo.

Arch Otolaryngol Head Neck Surg. 2004Dec;130(12):1381-6

A PLACEBO-CONTROLLED EVALUATION OF BUTTERBUR AND FEXOFENADINE ON OBJECTIVE AND SUBJECTIVE OUTCOMES IN PERENNIAL ALLERGIC RHINITIS.

BACKGROUND: There are presently no placebo-controlled data regarding the effects of butterbur (BB) on subjective and objective outcomes in patients with perennial allergic rhinitis. **OBJECTIVE:** We performed a placebo-controlled evaluation of the effects of BB and fexofenadine (FEX) on subjective and objective outcomes in patients with perennial allergic rhinitis. **METHODS:** Sixteen patients with perennial allergic rhinitis and house dust mite sensitization were randomized in double-blind cross-over fashion to receive for 1 week either BB 50 mg twice daily, FEX 180 mg once daily and placebo (PL) once daily, or PL twice daily. The peak nasal inspiratory flow (PNIF) response to adenosine monophosphate (AMP) challenge administered as a single 400 mg/mL dose was measured over a 60-min period after challenge, and domiciliary total nasal symptom score was recorded.

RESULTS: Pre-challenge values for mean \pm SEM PNIF (L/min) were significantly different comparing all groups; BB (138 \pm 8), FEX (140 \pm 9), and PL (138 \pm 8). The maximum % PNIF fall from baseline after nasal AMP challenge was significantly attenuated ($P<0.05$) compared to PL (46 \pm 3), with BB (34 \pm 3) and FEX (39 \pm 3). The area under the 60-min time-response curve (%.min) was also significantly attenuated ($P<0.05$) compared to PL (1734 \pm 156), with BB (1052 \pm 258) and FEX (1194 \pm 161). There was also a significant reduction ($P<0.05$) in total nasal symptom score with BB (1.8 \pm 0.4) and FEX (1.8 \pm 0.4), compared to PL (2.8 \pm 0.5). There were no significant differences between BB and FEX for any outcomes. **CONCLUSION:** BB and FEX, in comparison to PL, were equally effective in attenuating the nasal response to AMP and in improving nasal symptoms, highlighting a potential role for BB in the treatment of allergic rhinitis.

Clin Exp Allergy. 2004 Apr;34(4):646-9

ROSMARINIC ACID INDUCES P56LCK-DEPENDENT APOPTOSIS IN JURKAT AND PERIPHERAL T CELLS VIA MITOCHONDRIAL PATHWAY INDEPENDENT FROM FAS/FAS LIGAND INTERACTION.

Apoptosis is one way of controlling immune responses, and a variety of immunosuppressive drugs suppress harmful immune responses by inducing apoptosis of lymphocytes. In this study we observed that rosmarinic acid, a secondary metabolite of herbal plants, induced apoptosis in an p56(lck) (Lck)-dependent manner; Lck(+) Jurkat T cells undergo apoptosis in response to rosmarinic acid (RosA) treatment, whereas Lck(-) Jurkat subclone J.CaM1.6 cells do not. J.CaM1.6 cells with various Lck mutants indicated that Lck SH2 domain, but not Lck kinase activity, was required for RosA-induced apoptosis. RosA induced apoptosis in the absence of a TCR stimulus, and this was not prevented by interruption of the Fas/Fas ligand interaction. Instead, RosA-mediated apoptosis involved a mitochondrial pathway as indicated by cytochrome c release and the complete blockage of apoptosis by an inhibitor of mitochondrial membrane depolarization. Both caspase-3 and -8 were indispensable in RosA-induced apoptosis and work downstream of mitochondria and caspase-9 in the order of caspase-9/caspase-3/caspase-8. In freshly isolated human PBMC, RosA specifically induced apoptosis of Lck(+) subsets such as T and NK cells, but not Lck-deficient cells, including B cells and monocytes. Moreover, RosA's ability to kill T and NK cells was restricted to actively proliferating cells, but not to resting cells. In conclusion, Lck-dependent apoptotic activity may make RosA an attractive therapeutic tool for the treatment of diseases in which T cell apoptosis is beneficial.

J Immunol. 2004 Jan 1;172(1):79-87

ROSMARINIC ACID IN PERILLA EXTRACT INHIBITS ALLERGIC INFLAMMATION INDUCED BY MITE ALLERGEN, IN A MOUSE MODEL.

BACKGROUND: Perilla and its constituent rosmarinic acid have been suggested to have anti-allergic activity. However, few studies have examined the effects on allergic asthma. **OBJECTIVE:** The purpose of this study was to evaluate the effect of oral administration of perilla leaf extract, which contains high amount of rosmarinic acid, on a murine model of allergic asthma induced by house dust mite allergen. **METHODS:** C3H/He mice were sensitized by intratracheal administration of *Dermatophagoides farinae* (Der f). Mice were orally treated with rosmarinic acid in perilla extract (PE) (1.5 mg/mouse/day). **RESULTS:** Der f challenge of sensitized mice elicited pulmonary eosinophilic inflammation, accompanied by an increase in lung expression of IL-4 and IL-5, and eotaxin. Daily treatment with rosmarinic acid in PE significantly prevented the increases in the numbers of eosinophils in bronchoalveolar lavage fluids and also in those around murine airways. Rosmarinic acid in PE treatment also inhibited the enhanced protein expression of IL-4 and IL-5, and eotaxin in the lungs of sensitized mice. Der f challenge also enhanced allergen-specific IgG1, which were also inhibited by rosmarinic acid in PE. **CONCLUSION:** These results suggest that oral administration of perilla-derived rosmarinic acid is an effective intervention for allergic asthma, possibly through the amelioration of increases in cytokines, chemokines, and allergen-specific antibody.

Clin Exp Allergy. 2004 Jun;34(6):971-7

EXTRACT OF PERILLA FRUTESCENS ENRICHED FOR ROSMARINIC ACID, A POLYPHENOLIC PHYTOCHEMICAL, INHIBITS SEASONAL ALLERGIC RHINOCONJUNCTIVITIS IN HUMANS.

Extract of *Perilla frutescens* enriched for rosmarinic acid, a polyphenolic phytochemical, suppresses allergic immunoglobulin responses and inflammation caused by polymorphonuclear leukocytes (PMNL) in mice. However, few placebo-controlled clinical trials have examined the efficacy and safety of polyphenolic phytochemicals for treatment of allergic inflammatory diseases in humans. The present study determined whether oral supplementation with rosmarinic acid is an effective intervention for patients with seasonal allergic rhinoconjunctivitis (SAR). In this 21-day, randomized, double-blind, age-matched, placebo-controlled parallel group study, patients with mild SAR were treated daily with extract of *Perilla frutescens* enriched for rosmarinic acid (200 mg [n=10] or 50 mg [n=9] or placebo (n=10). Patients recorded symptoms daily in a diary. Profiles of infiltrating cells and concentrations of eotaxin, IL-1 β , IL-8, and histamine were measured in nasal lavage fluid. Serum IgE concentrations and routine blood tests were also examined. As compared with placebo supplementation, supplementation with extract of *Perilla frutescens* enriched for rosmarinic acid resulted in a significant increase in responder rates for itchy nose, watery eyes, itchy eyes, and total symptoms ($P<0.05$). Active treatment significantly decreased the numbers of neutrophils and eosinophils in nasal

lavage fluid ($P < 0.05$ vs. placebo). Patients reported no adverse events, and no significant abnormalities were detected in routine blood tests. In conclusion, extract of *Perilla frutescens* enriched for rosmarinic acid can be an effective intervention for mild SAR at least partly through inhibition of PMNL infiltration into the nostrils. Use of this alternative treatment for SAR might reduce treatment costs for allergic diseases.

Exp Biol Med (Maywood). 2004Mar;229(3):247-54100

ANTI-INFLAMMATORY AND ANTI-ALLERGIC EFFECT OF ROSMARINIC ACID (RA); INHIBITION OF SEASONAL ALLERGIC RHINOCONJUNCTIVITIS (SAR) AND ITS MECHANISM.

The present study was undertaken to determine whether oral supplementation with rosmarinic acid (RA) is an effective intervention for patients with SAR. In addition, the anti-inflammatory mechanism of RA also estimated in the ear edema models. **CLINICAL TRIAL:** Patients were treated daily with RA (200 mg or 50 mg) or placebo for 21 days. Patients recorded symptoms daily and profiles of infiltrating cells and concentration of cytokines were measured in nasal lavage fluid. Compared to placebo, supplementation with RA resulted in a significant decrease in responder rates for each symptom. RA also significantly decreased the numbers of neutrophils and eosinophils in nasal lavage fluid. **ANIMAL STUDY:** Topical application RA showed anti-inflammatory activity 5-hours after 12-tetradecanoylphorbol 13-acetate (TPA) treatment with marked inhibition of neutrophil infiltration. Up regulation of ICAM-1, VCAM-1 cyclooxygenase-2 (COX-2), KC and MIP-2 by TPA were markedly reduced by pretreatment with extract of perilla (PE) or RA. Reactive oxygen radical production detected as thiobarbituric acid reactive substance (TBARS), lipid peroxide (LPO) and 8-hydroxy-2'-deoxyguanosine (8OH-dG), by double treatment of TPA was reduced by pretreatment with PE or RA. RA is an effective intervention for SAR that is mediated by inhibition of PMNL infiltration. This effect of RA is due to two independent mechanisms: inhibition of the inflammatory response and scavenging of ROS.

Biofactors. 2004;21(1-4):127-31

PETASITES HYBRIDUS (BUTTERBUR ROOT) EXTRACT IN THE TREATMENT OF ASTHMA--AN OPEN TRIAL.

The efficacy and tolerability of a butterbur root extract (Petadolex) for the treatment of asthma was analyzed in a prospective, non-randomized, open trial. Subjects included 64 adults and 16 children/adolescents treated for two months with the extract, followed by two months during which the intake of the extract was optional. Concomitant asthma medication was permitted. The number, duration, and severity of asthma attacks decreased, while peak flow, forced expiratory volume (FEV1), and all measured symptoms improved during therapy. In addition, more than 40 percent of patients using asthma medications at baseline reduced intake of these medications by the end of the study. This study suggests the *Petasites hybridus* extract Petadolex is an effective and safe therapy for the treatment of asthma.

Altern Med Rev. 2004 Mar;9(1):54-62M

BIOMARKERS OF CARDIOVASCULAR DISEASE AS RISK FACTORS FOR AGE-RELATED MACULAR DEGENERATION.

PURPOSE: To measure and contrast 2 biomarkers of cardiovascular disease, C-reactive protein (CRP) and plasma homocysteine, in individuals with age-related macular degeneration (AMD) and control individuals without AMD. **DESIGN:** Case-control study. **PARTICIPANTS:** Seventy-nine affected individuals and 77 unaffected individuals from the AMD Genetic Study Group returned to obtain CRP and homocysteine levels. **METHODS:** Both affected and unaffected individuals underwent testing for CRP and homocysteine. A detailed cardiovascular history was taken. **MAIN OUTCOME MEASURES:** Mean CRP and homocysteine levels in affected and unaffected individuals. **RESULTS:** Mean CRP levels for affected and unaffected individuals were 3.42 and 2.30 mg/l, respectively ($P = 0.03$). Mean homocysteine levels for affected and unaffected individuals were 11.72 and 8.88 micromol/l, respectively ($P < 0.0001$). In logistic regression models, older age, higher CRP, and higher homocysteine were risk factors for AMD. There were no significant differences between cases and controls in terms of gender, diabetes, hypertension, use of statin drugs, and smoking. The control group was significantly younger and had a lower rate of vitamin usage than the affected group. **CONCLUSIONS:** Elevated CRP and homocysteine levels are associated with AMD and implicate the role of chronic inflammation and atherosclerosis.

Ophthalmology. 2005 Dec;112(12):2076-80

DIETARY INTAKE OF ANTIOXIDANTS AND RISK OF AGE-RELATED MACULAR DEGENERATION.

CONTEXT: Age-related macular degeneration (AMD) is the most prevalent cause of irreversible blindness in developed countries. Recently, high-dose supplementation with beta carotene, vitamins C and E, and zinc was shown to slow the progression of AMD. **OBJECTIVE:** To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD. **DESIGN:** Dietary intake was assessed at baseline in the Rotterdam Study (1990-1993) using a semiquantitative food frequency questionnaire. Incident AMD until final follow-up in 2004 was determined by grading fundus color transparencies in a masked way according to the International Classification and Grading System. **SETTING:** Population-based cohort of all inhabitants aged 55 years or older in a middle-class suburb of Rotterdam, the Netherlands. **PARTICIPANTS:** Of 5836 persons at risk of AMD at baseline, 4765 had reliable dietary data and 4170 participated in the follow-up. **MAIN OUTCOME MEASURE:** Incident AMD, defined as soft distinct drusen with pigment alterations, indistinct or reticular drusen, geographic atrophy, or choroidal neovascularization. **RESULTS:** Incident AMD occurred in 560 participants after a mean follow-up of 8.0 years (range, 0.3-13.9 years). Dietary intake of both vitamin E and zinc was inversely associated with incident AMD. The hazard ratio (HR) per standard deviation increase of intake for vitamin E was 0.92 (95% confidence interval [CI], 0.84-1.00) and for zinc was 0.91 (95% CI, 0.83-0.98). An above-median intake of all 4 nutrients, beta carotene, vitamin C, vitamin E, and zinc, was associated with a 35% reduced risk (HR, 0.65; 95% CI, 0.46-0.92) of AMD. Exclusion of supplement users did not affect the results. **CONCLUSION:** In this study, a high dietary intake of beta carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of AMD in elderly persons.

JAMA. 2005 Dec 28;294(24):3101-7

EVALUATION OF PLASMA HOMOCYSTEINE AND RISK OF AGE-RELATED MACULAR DEGENERATION.

PURPOSE: To assess the relationship between plasma levels of homocysteine and age-related macular degeneration (AMD). **DESIGN:** Cross-sectional, case-control study. **METHODS:** Fasting plasma homocysteine levels were measured at two centers in 934 individuals who were participating in an ancillary study of the Age-Related Eye Disease Study. There were 547 cases and 387 control subjects, who were determined by fundus photography. Conditional logistic regression analyses were conducted to assess the association of homocysteine with AMD. **RESULTS:** Median values of homocysteine were higher among advanced AMD cases (9.51 mmol/l) compared with persons with no AMD (8.81 mmol/l; $P = .01$). Values of >12 mmol/l vs $< \text{or} = 12$ mmol/l were also associated with an increased risk of AMD ($P = .023$), when controlled for other covariates. **CONCLUSION:** Results are consistent with a possible small, independent association between higher homocysteine levels and AMD. Homocysteine may be a modifiable risk factor for AMD.

Am J Ophthalmol. 2006 Jan;141(1):201-3

First isolated and characterized in 1900 by Gulewitsch, carnosine (beta-alanyl-L-histidine) is a dipeptide commonly present in mammalian tissue, and in particular in skeletal muscle cells; it is responsible for a variety of activities related to the detoxification of the body from free radical species and the by-products of membrane lipids peroxidation, but recent studies have shown that this small molecule also has membrane-protecting activity, proton buffering capacity, formation of complexes with transition metals, and regulation of macrophage function. It has been proposed that carnosine could act as a natural scavenger of dangerous reactive aldehydes from the degradative oxidative pathway of endogenous molecules such as sugars, polyunsaturated fatty acids (PUFAs) and proteins. In particular, it has been recently demonstrated that carnosine is a potent and selective scavenger of alpha,beta-unsaturated aldehydes, typical by-products of membrane lipids peroxidation and considered second messengers of the oxidative stress, and inhibits aldehyde-induced protein-protein and DNA-protein cross-linking in neurodegenerative disorders such as Alzheimer's disease, in cardiovascular ischemic damage, in inflammatory diseases. The research for new and more potent scavengers for HNE and other alpha,beta-unsaturated aldehydes has produced a consistent variety of carnosine analogs, and the present review will resume, through the scientific literature and the international patents, the most recent developments in this field.

Curr Med Chem. 2005;12(20):2293-315

ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND AGE-RELATED MACULAR DEGENERATION.

CONTEXT: C-reactive protein (CRP) is a systemic inflammatory marker associated with risk for cardiovascular disease (CVD). Some risk factors for CVD are associated with age-related macular degeneration (AMD), but the association between CRP and AMD is unknown. **OBJECTIVE:** To test the hypothesis that elevated CRP levels are associated with an increased risk for AMD. **DESIGN, SETTING, AND PARTICIPANTS:** A total of 930 (91%) of 1026 participants at 2 centers in the Age-Related Eye Disease Study (AREDS), a multicenter randomized trial of antioxidant vitamins and minerals, were enrolled in this case-control study. There were 183 individuals without any maculopathy, 200 with mild maculopathy, 325 with intermediate disease, and 222 with advanced AMD (geographic atrophy or neovascular AMD). The AMD status was assessed by standardized grading of fundus photographs, and stored fasting blood specimens drawn between January 1996 and April 1997 were analyzed for high-sensitivity CRP levels. **MAIN OUTCOME MEASURE:** Association between CRP and AMD. **RESULTS:** The CRP levels were significantly higher among participants with advanced AMD (case patients) than among those with no AMD (controls; median values, 3.4 vs 2.7 mg/L; $P = .02$). After adjustment for age, sex, and other variables, including smoking and body mass index, CRP levels were significantly associated with the presence of intermediate and advanced stages of AMD. The odds ratio (OR) for the highest vs the lowest quartile of CRP was 1.65 (95% confidence interval [CI], 1.07-2.55; P for trend = .02). The OR for CRP values at or above the 90th percentile (10.6 mg/L) was 1.92 (95% CI, 1.20-3.06), and the OR for CRP values at or above the mean plus 2 SDs (16.8 mg/L) was 2.03 (95% CI, 1.03-4.00). A trend for an increased risk for intermediate and advanced AMD with higher levels of CRP was seen for smokers (OR, 2.16; 95% CI, 1.33-3.49) and those who never smoked (OR, 2.03; 95% CI, 1.19-3.46) with the highest level of CRP. **CONCLUSION:** Our results suggest that elevated CRP level is an independent risk factor for AMD and may implicate the role of inflammation in the pathogenesis of AMD.

JAMA. 2004 Feb 11;291(6):704-10

C-REACTIVE PROTEIN CONCENTRATION AND CONCENTRATIONS OF BLOOD VITAMINS, CAROTENOIDS, AND SELENIUM AMONG UNITED STATES ADULTS.

OBJECTIVE: To examine the relationships between circulating concentrations of C-reactive protein and concentrations of retinol, retinyl esters, vitamin C, vitamin E, carotenoids, and selenium. **DESIGN:** Cross-sectional study using National Health and Nutrition Examination Survey III (1988-1994) data. **SETTING:** United States population. **SUBJECTS:** Up to 14 519 US noninstitutionalized civilian men and women aged ≥ 20 y. **RESULTS:** C-reactive protein concentration (dichotomized at the sex-specific 85th percentile) was inversely and significantly associated with concentrations of retinol, retinyl esters, vitamin C, alpha-carotene, beta-carotene, cryptoxanthin, lutein/zeaxanthin, lycopene, and selenium after adjustment for age, sex, race or ethnicity, education, cotinine concentration, body mass index, leisure-time physical activity, and aspirin use. **CONCLUSIONS:** These results suggest that the inflammatory process, through the production of reactive oxygen species, may deplete stores of antioxidants. Whether increased consumption of foods rich in antioxidants or supplementation with antioxidants can provide health benefits to people characterized by elevated C-reactive protein concentrations may be worthy of further study.

Eur J Clin Nutr. 2003 Sep;57(9):1157-63

LUTEIN, BUT NOT ALPHA-TOCOPHEROL, SUPPLEMENTATION IMPROVES VISUAL FUNCTION IN PATIENTS WITH AGE-RELATED CATARACTS: A 2-Y DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY.

OBJECTIVE: We investigated the effect of long-term antioxidant supplementation (lutein and alpha-tocopherol) on serum levels and visual performance in patients with cataracts. **METHODS:** Seventeen patients clinically diagnosed with age-related cataracts

were randomized in a double-blind study involving dietary supplementation with lutein (15 mg; n = 5), alpha-tocopherol (100 mg; n = 6), or placebo (n = 6), three times a week for up to 2 y. Serum carotenoid and tocopherol concentrations were determined with quality-controlled high-performance liquid chromatography, and visual performance (visual acuity and glare sensitivity) and biochemical and hematologic indexes were monitored every 3 mo throughout the study. Changes in these parameters were assessed by General Linear Model (GLM) repeated measures analysis. RESULTS: Serum concentrations of lutein and alpha-tocopherol increased with supplementation, although statistical significance was reached only in the lutein group. Visual performance (visual acuity and glare sensitivity) improved in the lutein group, whereas there was a trend toward the maintenance of and decrease in visual acuity with alpha-tocopherol and placebo supplementation, respectively. No significant side effects or changes in biochemical or hematologic profiles were observed in any of the subjects during the study. CONCLUSIONS: Visual function in patients with age-related cataracts who received the lutein supplements improved, suggesting that a higher intake of lutein, through lutein-rich fruit and vegetables or supplements, may have beneficial effects on the visual performance of people with age-related cataracts.

Nutrition. 2003 Jan;19(1):21-4

EFFICACY OF N-ACETYLCARNOSINE IN THE TREATMENT OF CATARACTS.

PURPOSE: To evaluate the effects of 1% N-acetylcarnosine (NAC) solution on lens clarity over 6 and 24 months in patients with cataracts. **TRIAL DESIGN:** Randomised, placebo-controlled study. **PARTICIPANTS:** 49 subjects (76 affected eyes) with an average age of 65.3 +/- 7.0 years with a diagnosis of senile cataract with minimum to advanced opacification in various lens layers. **METHODS:** 26 patients (41 eyes) were allocated to topical NAC 1% eyedrops twice daily. The control group consisted of 13 patients (21 eyes) who received placebo eyedrops and 10 patients (14 eyes) who did not receive eyedrops. **MAIN OUTCOME MEASURES:** All patients were evaluated at entry and followed up every 2 months for a 6-month period (trial 1), or at 6-month intervals for a 2-year period (trial 2), for best-corrected visual acuity and glare testing. In addition, cataract was measured using stereocinematographic slit-images and retro-illumination examination of the lens. Digital analysis of lens images displayed light scattering and absorbing centres in two- and three-dimensional scales. **RESULTS:** The overall intra-reader reproducibility of cataract measurements (image analysis) was 0.830, and glare testing 0.998. After 6 months, 90% of NAC-treated eyes showed improvement in best corrected visual acuity (7 to 100%) and 88.9% showed a 27 to 100% improvement in glare sensitivity. Topographic studies indicated fewer areas of posterior subcapsular lens opacity and 41.5% of treated eyes had improvement in image analysis characteristics. The overall ratios of image analysis characteristics at 6 months compared with baseline measures were 1.04 and 0.86 for the control and NAC-treated group, respectively ($p < 0.001$). The apparent benefits of treatment were sustained after 24 months' treatment. No treated eyes demonstrated worsening of vision. The overall visual outcome in the control group showed significant worsening after 24 months in comparison with both baseline and the 6-month follow-up examination. The overall clinical results observed in the NAC-treated group by the 24-month period of examination differed significantly ($p < 0.001$) from the control group in the eyes with cortical, posterior subcapsular, nuclear or combined lens opacities. Tolerability of NAC eyedrops was good in almost all patients, with no reports of ocular or systemic adverse effects. **CONCLUSION:** Topical NAC shows potential for the treatment and prevention of cataracts.

Drugs R D. 2002;3(2):87-103

ALPHA TOCOPHEROL SUPPLEMENTATION DECREASES SERUM C-REACTIVE PROTEIN AND MONOCYTE INTERLEUKIN-6 LEVELS IN NORMAL VOLUNTEERS AND TYPE 2 DIABETIC PATIENTS.

Type 2 diabetic subjects have an increased propensity to premature atherosclerosis. Alpha tocopherol (AT), a potent antioxidant, has several anti-atherogenic effects. There is scanty data on AT supplementation on inflammation in Type 2 diabetic subjects. The aim of the study was to test the effect of RRR-AT supplementation (1200 IU/d) on plasma C-reactive protein (CRP) and interleukin-6 (IL-6) release from activated monocyte in Type 2 diabetic patients with and without macrovascular complications compared to matched controls. The volunteers comprised Type 2 diabetic subjects with macrovascular disease (DM2-MV, n = 23), Type 2 diabetic subjects without macrovascular complications (DM2, n = 24), and matched controls (C, n = 25). Plasma high sensitive CRP (Hs-CRP) and Monocyte IL-6 were assayed at baseline, following 3 months of supplementation and following a 2 month washout phase. DM2-MV subjects have elevated HsCRP and monocyte IL-6 compared to controls. AT supplementation significantly lowered levels of C-reactive protein and monocyte interleukin-6 in all three groups. In conclusion, AT therapy decreases inflammation in diabetic patients and controls and could be an adjunctive therapy in the prevention of atherosclerosis.

Free Radic Biol Med. 2000 Oct 15;29(8):790-2

THE ANTIOXIDANT ACTIVITY OF STANDARDIZED EXTRACT OF GINKGO BILOBA (EGB 761) IN RATS.

The standardized extract of ginkgo biloba (EGb 761) has been widely employed for its significant benefit in neurodegenerative disorders. Although antioxidative actions have been attributed to this extract, the mechanisms of the multiple principles involved in this pharmacological activity are not completely established. Parkinson's and Alzheimer's diseases are frequently associated

with oxidative stress and defects in the cellular protective mechanisms. In this study, the lipid peroxidation (LPO) and the activity of the antioxidant enzymes, catalase (CAT) and superoxide dismutase (SOD) were evaluated in the hippocampus, striatum and substantia nigra (SN) of rats treated with EGb 761. An increase in the CAT and SOD activities in the hippocampus, striatum and SN, and a decrease of the LPO in the hippocampus were observed. These data are additional to the antioxidant properties of EGb 761 reported in the literature and indicate a possible role for the extract in the treatment of diseases involving free radicals and oxidative damage.

Phytother Res. 2001 Aug;15(5):449-51

EFFECTS OF OMEGA-3 FATTY ACID SUPPLEMENTATION AND EXERCISE ON LOW-DENSITY LIPOPROTEIN AND HIGH-DENSITY LIPOPROTEIN SUBFRACTIONS.

The purpose of this study was to examine the effect of combining exercise with omega-3 fatty acids (n-3fa) supplementation on lipoprotein subfractions and associated enzymes. Subjects were 10 recreationally active males, aged 25 +/- 1.5 years (mean +/- SE), who supplemented n-3fa (60% eicosapentaenoic acid [EPA] and 40% docosahexaenoic [DHA]) at 4 g/d for 4 weeks. Before and after supplementation, subjects completed a 60-minute session of treadmill exercise at 60% Vo(2)max. Following a 24-hour diet and activity control period, blood was collected immediately before and after the exercise session to assess lipid variables: high-density lipoprotein cholesterol (HDL-C) and subfractions, low-density lipoprotein cholesterol (LDL-C) and subfractions and particle size, lecithin:cholesterol acyltransferase (LCAT) activity, and cholesterol ester transfer protein (CETP) activity. Supplementation with n-3fa alone increased total HDL-C and HDL(2)-C, while exercise alone increased total HDL-C, HDL(3)-C, and total LDL-C. LDL subfractions, particle size, and LCAT and CETP activities were not affected by supplementation. Combination treatment resulted in an additive effect for HDL(3)-C only and also increased LDL(1)-C versus baseline. LCAT and CETP activities were not affected by treatments. These results suggest that n-3fa supplementation or an exercise session each affect total HDL-C and subfractions but not LDL-C or subfractions. In addition, the combination of n-3fa and exercise may have additional effects on total HDL-C and LDL-C subfractions as compared to either treatment alone in active young men.

Metabolism. 2004 Jun;53(6):749-54

ASSOCIATION BETWEEN SMALL DENSE LOW-DENSITY LIPOPROTEIN AND POSTPRANDIAL ACCUMULATION OF TRIGLYCERIDE-RICH REMNANT-LIKE PARTICLES IN NORMOTRIGLYCERIDEMIC PATIENTS WITH MYOCARDIAL INFARCTION.

BACKGROUND: Although the small dense low-density lipoprotein (sd-LDL) is associated with hypertriglyceridemia, more than 60% of myocardial infarction (MI) patients are normotriglyceridemic in the fasting state. This study was aimed to investigate the relationship between the low-density lipoprotein (LDL) phenotype and postprandial hyperlipemia (PPL) in MI patients. **METHODS AND RESULTS:** Oral fat tolerance tests were performed in 71 patients with acute MI and fasting triglyceride concentrations below 200 mg/dl. Postprandial changes in the LDL particle diameter (LDL-PD) and lipids over a 6-h period after a meal were compared among 4 groups of patients classified according to fasting triglyceride levels (A, B as <150, and C, D as > or =150) and postprandial triglyceride levels (A, C as <230 and B, D as > or =230). Although fasting concentrations of triglyceride and remnant-like particle (RLP)-triglyceride were significantly higher in group C than in group B, the areas under the curves of the RLPs were significantly higher in group B. The triglyceride-to-cholesterol ratio in the RLPs was significantly higher in the PPL group than in the nonPPL group postprandially. The prevalence of sd-LDL (LDL-PD < or =25.5 nm) was significantly higher in group D but similar between groups B and C (23%, 42%, 50% and 83% in groups A, B, C and D, respectively). **CONCLUSION:** These results suggest that postprandial accumulation of triglyceride-rich lipoproteins is strongly associated with sd-LDL in MI patients without hypertriglyceridemia.

Circ J. 2004 Dec;68(12):1165-72

CONTRIBUTION OF POSTPRANDIAL LIPEMIA TO THE DIETARY FAT-MEDIATED CHANGES IN ENDOGENOUS LIPOPROTEIN-CHOLESTEROL CONCENTRATIONS IN HUMANS.

BACKGROUND: Dietary fats alter LDL and HDL cholesterol while serving as precursors of postprandial triacylglycerol-rich lipoproteins (TRLs). **OBJECTIVE:** We hypothesized that the saturated fatty acid (SFA)-mediated increase and the polyunsaturated fatty acid (PUFA)-mediated decrease in endogenous lipoprotein cholesterol are promoted by postprandial TRLs. **DESIGN:** We performed a 16-d crossover diet study to examine the effect of PUFA-rich [ratio of PUFAs to SFAs (P:S) = 2.0] and SFA-rich (P:S = 0.25) diets on fasting and postprandial plasma lipid and lipoprotein-cholesterol concentrations in 16 normolipidemic subjects. **RESULTS:** Fasting plasma cholesterol decreased significantly after a PUFA-rich diet because of a decrease in LDL (-12.3%; P < 0.05) and HDL (-3.8%; NS), but did not change after an SFA-rich diet. The appearance of postprandial TRLs in plasma at 4 h was linked to a significant lowering of both LDL (-7.4%) and HDL (-4.8%) after a PUFA-rich diet; no such effect was observed after the SFA-rich diet. At 7 h, LDL and HDL cholesterol returned to near fasting concentrations without postprandial TRL accumulation after a PUFA-rich diet but with a significant postprandial TRL accumulation after an SFA-rich diet. Thus, the in vivo postprandial clearance of cholesterol in LDL+HDL was greater after a PUFA-rich diet than after an

SFA-rich diet. The appearance of postprandial TRLs in plasma increased the cholesteryl ester transfer protein-mediated transfer of cholesteryl ester from LDL+HDL to TRLs in vitro without a significant influence from dietary fat. **CONCLUSION:** Dietary fat-mediated alterations in the rate of hepatic removal of postprandial TRLs, which carry cholesterol accepted from LDL+HDL via cholesteryl ester transfer protein in vivo, may contribute to the dietary fat-mediated change in endogenous lipoprotein cholesterol.

Am J Clin Nutr. 2004 Nov;80(5):1145-58

LIPOPROTEIN(A): AN ELUSIVE CARDIOVASCULAR RISK FACTOR.

Lipoprotein (a) [Lp(a)], is present only in humans, Old World nonhuman primates, and the European hedgehog. Lp(a) has many properties in common with low-density lipoprotein (LDL) but contains a unique protein, apo(a), which is structurally different from other apolipoproteins. The size of the apo(a) gene is highly variable, resulting in the protein molecular weight ranging from 300 to 800 kDa; this large variation may be caused by neutral evolution in the absence of any selection advantage. Apo(a) influences to a major extent metabolic and physicochemical properties of Lp(a), and the size polymorphism of the apo(a) gene contributes to the pronounced heterogeneity of Lp(a). There is an inverse relationship between apo(a) size and Lp(a) levels; however, this pattern is complex. For a given apo(a) size, there is a considerable variation in Lp(a) levels across individuals, underscoring the importance to assess allele-specific Lp(a) levels. Further, Lp(a) levels differ between populations, and blacks have generally higher levels than Asians and whites, adjusting for apo(a) sizes. In addition to the apo(a) size polymorphism, an upstream pentanucleotide repeat (TTTTA(n)) affects Lp(a) levels. Several meta-analyses have provided support for an association between Lp(a) and coronary artery disease, and the levels of Lp(a) carried in particles with smaller size apo(a) isoforms are associated with cardiovascular disease or with preclinical vascular changes. Further, there is an interaction between Lp(a) and other risk factors for cardiovascular disease. The physiological role of Lp(a) is unknown, although a majority of studies implicate Lp(a) as a risk factor.

Arterioscler Thromb Vasc Biol. 2004Dec;24(12):2219-26

VARIABLE HYPOCOAGULANT EFFECT OF FISH OIL INTAKE IN HUMANS: MODULATION OF FIBRINOGEN LEVEL AND THROMBIN GENERATION.

OBJECTIVE: The beneficial effect of dietary fish oil, rich in omega-3 polyunsaturated fatty acids (PUFAs), on cardiovascular disease is multifactorial and may partly rely on their anticoagulant action. We studied how fish oil intake influenced thrombin generation in plasma and which factors were involved herein. **METHODS AND RESULTS:** Twenty-five healthy males with borderline overweight received 3.0 g omega-3 PUFAs daily for 4 weeks. Fish oil intake reduced plasma triglycerides and lowered platelet integrin activation, as well as plasma levels of fibrinogen and factor V, but had no effect on vitamin K-dependent coagulation factors. Before fish oil intake, thrombin generation (reflecting the coagulant potential) considerably varied between plasmas from individual subjects, which were partly explained by variation in prothrombin, antithrombin, fibrinogen, and factor V levels. Fish oil intake reduced thrombin generation in the presence and absence of platelets. This reduction correlated with the fish oil effect on fibrinogen and factor V levels. Interestingly, the lowering effect of fish oil on thrombin generation and fibrinogen clustered around subjects with high fibrinogen carrying a structural fibrinogen alpha-chain polymorphism. **CONCLUSIONS:** Dietary omega-3 PUFAs provoke a hypocoagulant, vitamin K-independent effect in humans, the degree of which may depend on fibrinogen level. Intake of fish oil reduced fibrinogen and factor V levels as well as thrombin generation in plasma. The effects on thrombin generation and fibrinogen clustered around subjects with high fibrinogen carrying alpha-chain fibrinogen polymorphism. Thus, dietary fish oil can provoke a hypocoagulant effect depending on the fibrinogen level.

Arterioscler Thromb Vasc Biol. 2004Sep;24(9):1734-40

GLYCEMIC AND INSULINEMIC MEAL RESPONSES MODULATE POSTPRANDIAL HEPATIC AND INTESTINAL LIPOPROTEIN ACCUMULATION IN OBESE, INSULIN-RESISTANT SUBJECTS.

BACKGROUND: Exacerbated postprandial lipemia is a risk factor for cardiovascular disease and is linked to insulin status. Limited data on the effect of dietary carbohydrate on postprandial lipoprotein accumulation are available. **OBJECTIVE:** We tested the hypothesis that dietary carbohydrates with different glucose availability alter postprandial lipoprotein metabolism differently in obese, insulin-resistant subjects. **DESIGN:** After an overnight fast, 9 subjects with central obesity and insulin resistance but normal triacylglycerolemia randomly ingested 2 test meals with comparable amounts of fat (28-29 g) and digestible carbohydrate (91-94 g) but with different quantities of slowly available glucose (SAG) in cereal products (17 or 2 g SAG/100 g for biscuits and wheat flakes, respectively). Blood samples were collected before and for 6 h after meal intakes. **RESULTS:** The postmeal 0-2-h areas under the curve (AUCs) for glycemia and insulinemia were significantly lower ($P < 0.05$) after the biscuit meal than after the flakes meal. Plasma triacylglycerol concentrations increased significantly after the flakes meal but not after the biscuit meal (1.5-fold higher 0-6-h AUC for the flakes meal). Apolipoprotein B-100 concentrations in the triacylglycerol-rich lipoprotein fraction increased significantly 2 h after the flakes meal but not after the biscuit meal (3-fold higher 0-6-h AUC for the flakes meal). Apolipoprotein B-48 concentrations increased ($P < 0.05$) 4 h after the flakes meal but not after the biscuit meal (2.3-fold higher 0-6-h AUC for the flakes meal). **CONCLUSION:** Mixed meals containing slowly digestible carbohydrate that induces low glycemic

and insulinemic reduce the postprandial accumulation of both hepatically and intestinally derived triacylglycerol-rich lipoproteins in obese subjects with insulin resistance.

Am J Clin Nutr. 2004 Oct;80(4):896-902

PREVENTING MYOCARDIAL INFARCTION IN THE YOUNG ADULT IN THE FIRST PLACE: HOW DO THE NATIONAL CHOLESTEROL EDUCATION PANEL III GUIDELINES PERFORM?

OBJECTIVES: The purpose of this study was to investigate the utility of the new National Cholesterol Education Program (NCEP) III guidelines in a group of young adults. **BACKGROUND:** These guidelines have been hailed as an improvement in their potential to identify individuals at risk for coronary heart disease (CHD) complications. Compared with the NCEP II, the new guidelines will increase the number of patients who qualify for medical management. However, the effectiveness of these guidelines to identify young adults at risk for a cardiac event is yet to be studied. **METHODS:** A retrospective review of clinical data from young adults (age ≤ 55 years for men and ≤ 65 years for women) hospitalized for acute myocardial infarction over a three-year period was conducted. Patients with a history of CHD or CHD equivalent were excluded. Using the NCEP III guidelines, we calculated a 10-year risk for coronary events on all patients. **RESULTS:** A total of 222 patients met criteria for inclusion. The mean age was 50 years and 25% were women. Mean lipid levels were all within the normal range; however, rates of smoking and obesity were high. When the 10-year risk of these patients was stratified by the number of risk factors and low-density lipoprotein cholesterol level, only 25% met criteria to qualify for pharmacotherapy. For women in this population, only 18% met criteria for treatment. **CONCLUSIONS:** The new guidelines offer multiple new features but have a tendency to underappreciate the risk for disease in young adults. To improve performance in young adults, statistical adjustments may be necessary.

J Am Coll Cardiol. 2003 May 7;41(9):1475-9

DOSE RESPONSE OF ALMONDS ON CORONARY HEART DISEASE RISK FACTORS: BLOOD LIPIDS, OXIDIZED LOW-DENSITY LIPOPROTEINS, LIPOPROTEIN(A), HOMOCYSTEINE, AND PULMONARY NITRIC OXIDE: A RANDOMIZED, CONTROLLED, CROSSOVER TRIAL.

BACKGROUND: Although recent studies have indicated that nut consumption may improve levels of blood lipids, nuts are not generally recommended as snacks for hyperlipidemic subjects because of their high fat content. Furthermore, the effective dose is still unknown. **METHODS AND RESULTS:** The dose-response effects of whole almonds, taken as snacks, were compared with low-saturated fat ($<5\%$ energy) whole-wheat muffins (control) in the therapeutic diets of hyperlipidemic subjects. In a randomized crossover study, 27 hyperlipidemic men and women consumed 3 isoenergetic (mean 423 kcal/d) supplements each for 1 month. Supplements provided 22.2% of energy and consisted of full-dose almonds (73 \pm 3 g/d), half-dose almonds plus half-dose muffins, and full-dose muffins. Fasting blood, expired air, blood pressure, and body weight measurements were obtained at weeks 0, 2, and 4. Mean body weights differed <300 g between treatments. The full-dose almonds produced the greatest reduction in levels of blood lipids. Significant reductions from baseline were seen on both half- and full-dose almonds for LDL cholesterol (4.4 \pm 1.7%, $P=0.018$, and 9.4 \pm 1.9%, $P<0.001$, respectively) and LDL:HDL cholesterol (7.8 \pm 2.2%, $P=0.001$, and 12.0 \pm 2.1%, $P<0.001$, respectively) and on full-dose almonds alone for lipoprotein(a) (7.8 \pm 3.5%, $P=0.034$) and oxidized LDL concentrations (14.0 \pm 3.8%, $P<0.001$), with no significant reductions on the control diet. No difference was seen in pulmonary nitric oxide between treatments. **CONCLUSIONS:** Almonds used as snacks in the diets of hyperlipidemic subjects significantly reduce coronary heart disease risk factors, probably in part because of the nonfat (protein and fiber) and monounsaturated fatty acid components of the nut.

Circulation. 2002 Sep 10;106(11):1327-32

REPORT OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE WORKSHOP ON LIPOPROTEIN(A) AND CARDIOVASCULAR DISEASE: RECENT ADVANCES AND FUTURE DIRECTIONS.

It has been estimated that approximately 37% of the US population judged to be at high risk for developing coronary artery disease (CAD), based on the National Cholesterol Education Program guidelines, have increased plasma lipoprotein(a) [Lp(a)], whereas Lp(a) is increased in only 14% of those judged to be at low risk. Therefore, the importance of establishing a better understanding of the relative contribution of Lp(a) to the risk burden for CAD and other forms of vascular disease, as well as the underlying mechanisms, is clearly evident. However, the structural complexity and size heterogeneity of Lp(a) have hindered the development of immunoassays to accurately measure Lp(a) concentrations in plasma. The large intermethod variation in Lp(a) values has made it difficult to compare data from different clinical studies and to achieve a uniform interpretation of clinical data. A workshop was recently convened by the National Heart, Lung, and Blood Institute (NHLBI) to evaluate our current understanding of Lp(a) as a risk factor for atherosclerotic disorders; to determine how future studies could be designed to more clearly define the extent to which, and mechanisms by which, Lp(a) participates in these processes; and to present the results of the NHLBI-supported program for the evaluation and standardization of Lp(a) immunoassays. This report includes the most recent data presented by the workshop participants and the resulting practical and research recommendations.

MOLECULAR EFFECTS OF THE ISOFLAVONOID GENISTEIN IN PROSTATE CANCER.

Differences in diet have been proposed to be at least partially responsible for the low rate of prostate cancer in Asian populations compared with men in Western countries. One of the compounds that occurs in a greater quantity in the Eastern diet is genistein, an isoflavonoid found in high concentrations in serum after ingestion of soy-rich foods. Extensive molecular studies have been performed to determine its potential health benefits. The mechanism of action of genistein is complex and includes several cellular pathways. In addition to its estrogenic and/or antiestrogenic activities, genistein has been reported to inhibit steroidogenesis and block several protein tyrosine kinases, including epidermal growth factor receptor and src tyrosine kinases. Moreover, it arrests the cell cycle, induces apoptosis, and has antiangiogenic and antimetastatic properties and antioxidant activity. Herein, we review the current literature on the molecular mechanisms of genistein in relation to its effects on prostate cancer cells.

Clin Prostate Cancer. 2005 Sep;4(2):124-9

SOY ISOFLAVONE SUPPLEMENTATION ELEVATES ERYTHROCYTE SUPEROXIDE DISMUTASE, BUT NOT PLASMA CERULOPLASMIN IN POSTMENOPAUSAL BREAST CANCER SURVIVORS.

Soy isoflavone antioxidant effects may help prevent breast cancer re-occurrence, but isoflavone estrogen-like actions may increase breast cancer risk. These isoflavone actions can be reflected by effects on two copper enzymes activities, superoxide dismutase 1 (SOD 1), which has antioxidant function relevant to breast cancer prevention, and ceruloplasmin, which has its synthesis up-regulated by estrogen, and for which high values are associated with high breast cancer risk. A soy isoflavone-rich concentrate supplement was examined for effects on these two copper enzyme activities in post-menopausal breast cancer survivors (n = 7) in a crossover design with a placebo (24 days on supplement or placebo; 14 day wash out). The soy concentrate, but not the placebo, increased erythrocyte SOD 1 activities, but not ceruloplasmin activities or protein. The effect on superoxide dismutase activities was not likely due to increased copper intake since analysis of the soy extract showed little copper. The effect on superoxide dismutase was not accompanied by a change in urinary contents of 8-deoxyhydroxyguanosine, a DNA oxidant product, though perhaps this would change with a longer intervention. In summary, in regard to two copper enzyme activities, an isoflavone-rich soy concentrate showed an antioxidant effect considered relevant to breast cancer, but not an effect associated with estrogenic activity and increased breast cancer risk.

Breast Cancer Res Treat. 2005 Feb;89(3):251-5

NOVEL TEMPEH (FERMENTED SOYABEAN) ISOFLAVONES INHIBIT IN VIVO ANGIOGENESIS IN THE CHICKEN CHORIOALLANTOIC MEMBRANE ASSAY.

Anti-angiogenic strategies are emerging as an important tool for the treatment of cancer and inflammatory diseases. In the present investigation we isolated several isoflavones from a tempeh (fermented soyabean) extract. The isolated isoflavones were identified as 5,7,4'-trihydroxyisoflavone (genistein), 7,4'-dihydroxyisoflavone (daidzein), 6,7,4'-trihydroxyisoflavone (factor 2), 7,8,4'-trihydroxyisoflavone (7,8,4'-TriOH) and 5,7,3',4'-tetrahydroxyisoflavone (orobol). The effects on angiogenesis of these isoflavones were evaluated in the chicken chorioallantoic membrane assay; their capacity to inhibit vascular endothelial growth factor-induced endothelial cell proliferation and expression of the Ets 1 transcription factor, known to be implicated in the regulation of new blood vessel formation, were also investigated. We found that all isoflavones inhibited angiogenesis, albeit with different potencies. Compared with negative controls, which slightly inhibited in vivo angiogenesis by 6.30%, genistein reduced angiogenesis by 75.09%, followed by orobol (67.96%), factor 2 (56.77%), daidzein (48.98%) and 7,8,4'-TriOH (24.42%). These compounds also inhibited endothelial cell proliferation, with orobol causing the greatest inhibition at lower concentrations. The isoflavones also inhibited Ets 1 expression, providing some insight into the molecular mechanisms of their action. Furthermore, the chemical structure of the different isoflavones suggests a structure-activity relationship. Our present findings suggest that the new isoflavones might be added to the list of low molecular mass therapeutic agents for the inhibition of angiogenesis.

Br J Nutr. 2005 Mar;93(3):317-23

THE SOY ISOFLAVONE GENISTEIN PROMOTES APOPTOSIS IN MAMMARY EPITHELIAL CELLS BY INDUCING THE TUMOR SUPPRESSOR PTEN.

The isoflavone genistein (GEN), a biologically active component of soy foods, is associated with reduced breast cancer risk in women who consume soy-rich diets. GEN has been reported to influence many biological processes, of which suppression of cell proliferation and stimulation of apoptosis are considered to be the major pathways underlying its inhibition of tumorigenesis. This study evaluated the mechanism by which diets containing GEN promote mammary epithelial cell death. We report that mammary glands of young adult female rats exposed from gestation day 4 to postnatal day 50, to AIN-93G diets containing as sole protein source, casein (CAS) supplemented with GEN, or soy protein isolate (SPI+) had increased apoptosis, relative to rats fed CAS diet devoid of GEN. Mammary gland proliferation was unaffected by diet. The increased apoptotic index in mammary glands of GEN and SPI+ rats was accompanied by increased levels of the tumor suppressor protein PTEN (phosphatase and tensin homolog deleted in chromosome ten), albeit enhanced mammary expression of the pro-apoptotic p21, Bax and Bok genes was observed only in GEN-fed rats. GEN-induced apoptosis in MCF-7 cells was concomitant with increased PTEN expression, and this was abrogated by PTEN siRNA. MCF-7 cells treated with serum from GEN- or SPI(+)-fed rats had increased apoptosis as well as increased levels of the PTEN transcript. PTEN siRNA attenuated the increased apoptotic response of MCF-7 cells to serum from rats fed SPI+ or GEN, although the inhibition to basal (CAS serum) apoptotic levels was achieved only for cells treated with GEN serum. Decreased p21 and Bok gene expression accompanied the inhibition of apoptosis by PTEN siRNA. Data implicate PTEN in the induction of apoptosis by GEN and suggest that the promotion of apoptosis leading to inhibition of tumorigenesis in vivo by diets containing GEN may also involve the distinct activities of yet unknown GEN metabolite(s) and/or other systemic factors induced by GEN.

Carcinogenesis. 2005 Oct;26(10):1793-803

IMPACT OF DIET ON PROSTATE CANCER: A REVIEW.

Epidemiological studies suggest that environmental factors may mediate the transformation of latent prostate cancer into clinically apparent tumors and that diet appears to influence this progression. Close correlations between average per capita fat intake and prostate cancer mortality internationally generated interest in underlying mechanisms for this link, such as through serum levels of androgens, free radicals, proinflammatory fatty acid metabolites, or insulin-like growth factor. Much interest currently lies in the potential of HMG-CoA reductase inhibitors (statins) to play a chemopreventative role in prostate cancer. Lycopene, a potent antioxidant found in tomatoes, may exert a protective effect in the prostate. Selenium and vitamin E have also been shown to decrease the risk of prostate cancer in some men. Calcium may support vitamin D-related antiproliferative effects in prostate cancer. Certain soy proteins, common in the Asian diet, have been shown to inhibit prostate cancer cell growth. Finally, green tea may also have a chemopreventive effect by inducing apoptosis. Despite confounding factors present in clinical studies assessing the effect of diet on cancer risk, the data remain compelling that a variety of nutrients may prevent the development and progression of prostate cancer.

Prostate Cancer Prostatic Dis. 2005;8(4):304-10

META-ANALYSIS OF SOY FOOD AND RISK OF PROSTATE CANCER IN MEN.

There has been considerable interest in recent years in the role of soy in cancer etiology. The purpose of this meta-analysis was to evaluate epidemiologic studies available to date that related soy consumption to the risk of prostate cancer in men. We conducted a thorough Medline search for English-language publications, supplemented with hand-searching of articles' bibliographies and nonindexed medical and professional journals, on epidemiologic studies of soy and prostate cancer. We identified 2 cohort and 6 case-control studies that met the following criteria for meta-analysis: a study must have assessed soy as a food and provided a risk estimate (relative risk or odds ratio) and its 95% confidence interval. Data from the same study population appearing in different journals were only used once with the most recent publication chosen for the analysis. Studies on fermented soy food were not included. We conducted the meta-analysis using a random-effects model. An analysis of these studies yielded an overall risk estimate of 0.70 (95% CI = 0.59-0.83; $p < 0.001$). No publication bias was detected. In summary, results of the analysis showed that consumption of soy food was associated with a lower risk of prostate cancer in men.

Int J Cancer. 2005 Nov 20;117(4):667-9

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY IN MEN WITH PROSTATE CANCER AND RISING PSA: EFFECTIVENESS OF A DIETARY SUPPLEMENT.

OBJECTIVES: Epidemiological studies have shown significant relationships between the use of dietary components and prostate cancer incidence and mortality. Large studies of primary prevention, which confirm these findings, are desirable but costly and difficult to design. The present tertiary prevention study reports on the effect of a dietary supplement in comparison with placebo on the rate of increase of prostate-specific antigen (PSA). **METHODS:** 49 patients with a history of prostate cancer and rising PSA levels after radical prostatectomy ($n = 34$) or radiotherapy ($n = 15$) participated in a randomised, double-blind, placebo-controlled crossover study of a dietary supplement. Ethical approval of the protocol was obtained. Treatment periods of 10 weeks were separated by a 4-week washout period. The supplement consisted of soy, isoflavones, lycopene, silymarin and antioxidants

as main ingredients. Changes in the rate of increase of PSA (PSA slope and doubling time) were the primary parameters of efficacy. Analyses according to intention to treat (ITT) and per protocol (PP) were carried out. RESULTS: Baseline parameters did not differ between randomised groups. Five participants were lost to follow-up, however 46 could be evaluated in an ITT analysis. PP analysis could be performed in 42 men with at least 5 PSA measurements. Per protocol analysis showed a significant decrease in PSA slope ($p = 0.030$) and $(2)\log$ PSA slope ($p = 0.041$). This translates into a 2.6 fold increase in the PSA doubling time from 445 to 1150 days for the supplement and placebo periods. No treatment-based changes in safety parameters were observed during the study. CONCLUSIONS: The soy-based dietary supplement utilised in this study was shown to delay PSA progression after potentially curative treatment in a significant fashion. More extensive studies of the supplement may be indicated.

Eur Urol. 2005 Dec;48(6):922-30.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from 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.