

Dermal wound healing properties of redox-active grape seed proanthocyanidins.

Khanna S, Venojarvi M, Roy S, et al.
Free Radic Biol Med 2002;33:1089.

Angiogenesis plays a central role in wound healing. Among many known growth factors, vascular endothelial growth factor (VEGF) is believed to be the most prevalent, efficacious, and long-term signal that is known to stimulate angiogenesis in wounds. The wound site is rich in oxidants, such as hydrogen peroxide, mostly contributed by neutrophils and macrophages. We proposed that oxidants in the wound microenvironment support the repair process. Proanthocyanidins or condensed tannins are a group of biologically active polyphenolic bioflavonoids that are synthesized by many plants. Previously we have reported that a grape seed proanthocyanidin extract containing 5000 ppm resveratrol (GSPE) potently upregulates oxidant and tumor necrosis factor- α inducible VEGF expression in human keratinocytes (*Free Radic. Biol. Med.* 31:38-42, 2001). Our current objective was to follow up on that finding and test whether GSPE influences dermal wound healing in vivo. First, using a VEGF promoter-driven luciferase reporter construct we observed that the potentiating effect of GSPE on inducible VEGF expression is at the transcriptional level. The reporter assay showed that GSPE alone is able to drive VEGF transcription. Next, two dermal excisional wounds were inflicted on the back of mice and the wounds were left to heal by secondary intention. Topical application of GSPE accelerated wound contraction and closure. GSPE treatment was associated with a more well-defined hyperproliferative epithelial region, higher cell density, enhanced deposition of connective tissue, and improved histological architecture. GSPE treatment also increased VEGF and tenascin expression in the wound edge tissue. Tissue glutathione oxidation and 4-hydroxynonenal immunostaining results supported that GSPE application enhanced the oxidizing environment at the wound site. Oxidants are known to promote both VEGF as well as tenascin expression. In summary, our current study provides firm evidence to support that topical application of GSPE represents a feasible and productive approach to support dermal wound healing.

Genistein and vitamin D synergistically inhibit human prostatic epithelial cell growth.

Rao A, Woodruff RD, Wade WN, et al.
J Nutr 2002;132:3191-3194.

We performed studies to test synergism between the growth inhibitory effects of genistein and vitamin D compounds on prostatic epithelial cells. Isobolographic analysis demonstrated that genistein, in combination with the hormonally active form of cholecalciferol, 1- α , 25-dihydroxycholecalciferol, synergistically inhibited the growth of primary human prostatic epithelial cells (HPEC) and prostate cancer cells. Synergistic growth inhibition of HPEC was also observed between genistein and the low-calcemic vitamin D compound 25-hydroxycholecalciferol. Flow cytometry with HPEC indicated that genistein induced arrest in the G(2)M phase, whereas 1- α , 25-dihydroxycholecalciferol or 25-hydroxycholecalciferol induced arrest in the G(1)0 phase of the cell cycle. Combining genistein with either vitamin D compound resulted in both G(2)M and G(1)0 arrest in HPEC. In contrast, flow cytometry of prostate cancer cells indicated that both genistein and 1 α ,25-dihydroxycholecalciferol induced a G(1)0 arrest either alone or in combination. These are the first studies that demonstrate synergism between the prostatic cell growth inhibition elicited by genistein and that elicited by vitamin D compounds.

A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report.

Hong B, Ji YH, Hong JH, et al. *J Urol* 2002;168:2070-2073.

PURPOSE: We investigated the efficacy of Korean red ginseng for erectile dysfunction using the International Index of Erectile Function, RigiScan (UroHealth Systems, Laguna Niguel, California), hormonal levels and penile duplex ultrasonography with audiovisual sexual stimulation. **MATERIALS AND METHODS:** A total of 45 patients with clinically diagnosed erectile dysfunction were enrolled in a double-blind, placebo controlled, crossover study (8 weeks on treatment, 2 weeks of washout and 8 weeks on treatment) in which the effects of Korean red ginseng and a vehicle placebo were compared using multiple variables. The ginseng dose was 900 mg, 3 times daily. **RESULTS:** Mean International Index of Erectile Function scores were significantly higher in patients treated with Korean red ginseng than in those who received placebo (baseline 28.0 +/- 16.7 and 38.1 +/- 16.6 versus 30.9 +/- 15.7, $p < 0.01$). Scores on questions 3 (penetration) and 4 (maintenance) were significantly higher in the ginseng than in the placebo group ($p < 0.01$). In response to the global efficacy question 60% of the patients answered that Korean red ginseng improved erection ($p < 0.01$). Among other variables penile tip rigidity on RigiScan showed significant improvement for ginseng versus placebo. **CONCLUSIONS:** Our data show that Korean red ginseng can be as effective alternative for treating male erectile dysfunction.

Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand.

Scholey AB, Kennedy DO. *Hum Psychopharmacol* 2002;17:35-44.

The present paper describes three studies examining the acute effects of single doses of Ginkgo biloba (GK501), Ginseng (G115) and their combination (Ginkoba M/E, Pharmaton SA) on the performance of healthy young adults (mean age 21 years) during serial arithmetic tasks with differing cognitive load. In each double-blind, placebo-controlled study three different treatment doses and a placebo were administered, according to a balanced crossover design, with a 7-day washout period between each dose. Participants' scores on two computerised serial subtraction tasks (Serial Threes and Serial Sevens) were assessed pre-dosing and at 1, 2.5, 4 and 6 h thereafter. A number of significant time, dose and task-specific effects were associated with each treatment. There was a dose-dependent improvement in speed of responding during Serial Threes following Ginkgo biloba. Different doses of Ginseng improved accuracy and slowed responses during Serial Sevens. The most striking result, however, was a highly significant and sustained increase in the number of Serial Sevens responses following 320 mg of the Ginkgo-Ginseng combination at all post-treatment testing times. This was accompanied by improved accuracy during Serial Sevens and Serial Threes following the 640 mg and the 960 mg dose, respectively. The paper concludes with speculation into the possible mechanisms underlying these effects.

Antiherpes simplex virus type 2 activity of casuarinin from the bark of *Terminalia arjuna* Linn.

Cheng HY, Lin CC, Lin TC. *Antiviral Res* 2002;55:447-455.

Casuarinin, a hydrolyzable tannin isolated from the bark of *Terminalia arjuna* Linn. (Combretaceae), was investigated for its antiviral activity on herpes simplex type 2 (HSV-2) in vitro. Results showed that the IC(50) of casuarinin in XTT and plaque reduction assays were 3.6+/-0.9 and 1.5+/-0.2 microM, respectively. The 50% cytotoxic concentration for cell growth (CC(50)) was 89+/-1 microM. Thus, the selectivity index (SI) (ratio of CC(50) to IC(50)) of casuarinin was 25 and 59 for XTT and plaque reduction assays, respectively. Casuarinin continued to exhibit antiviral activity even added 12 h after infection. During the attachment assay, casuarinin was shown to prevent the attachment of HSV-2 to cells. Furthermore, casuarinin also exhibited an activity in inhibiting the viral penetration. Interestingly, casuarinin was virucidal at a concentration of 25 microM, reducing viral titers up to 100,000-fold. This study concludes that casuarinin possesses anti-herpesvirus activity in inhibiting viral attachment and penetration, and also disturbing the late event(s) of infection.

Ginger syrup as an antiemetic in early pregnancy.

Keating A, Chez RA. *Altern Ther Health Med* 2002;8:89-91.

CONTEXT: Ginger (*Zingiber officinale*) has been used to ameliorate symptoms of nausea. A beverage containing ginger in a syrup may be easier to consume than a capsule or solid food. OBJECTIVE: To determine if ginger syrup mixed in water is an effective remedy for the relief of nausea and vomiting in the first trimester of pregnancy. DESIGN: Double-blind, placebo-controlled, randomized clinical trial. SETTING: Subjects were enrolled from the University of South Florida department of obstetrics and gynecology private practice office. PATIENTS: 26 subjects in the first trimester of pregnancy. INTERVENTION: Subjects ingested 1 tablespoon of commercially prepared study syrup (or placebo) in 4 to 8 ounces of hot or cold water 4 times daily. MAIN OUTCOME MEASURES: Duration and severity of nausea and vomiting over a 2-week period measured on a 10-point scale. RESULTS: After 9 days, 10 of the 13 (77%) subjects receiving ginger had at least a 4-point improvement on the nausea scale. Only 2 of the 10 (20%) remaining subjects in the placebo group had the same improvement. Conversely, no woman in the ginger group, but 7 (70%) of the women in the placebo group, had a 2-point or less improvement on the nausea scale. Eight of the 12 (67%) women in the ginger group who were vomiting daily at the beginning of the treatment stopped vomiting by day 6. Only 2 of the 10 (20%) women in the placebo group who were vomiting stopped by day 6. CONCLUSION: The ingestion of 1 g of ginger in syrup in a divided dose daily may be useful in some patients experiencing nausea and vomiting in the first trimester of pregnancy.

Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes.

Jayagopal V, Albertazzi P, Kilpatrick ES, et al. *Diabetes Care* 2002;25:1709-1714.

OBJECTIVE: Phytoestrogen consumption has been shown to reduce risk factors for cardiovascular disease. Type 2 diabetes confers an adverse cardiovascular risk profile particularly in women after menopause. The aim of this study was to determine whether a dietary supplement with soy protein and isoflavones affected insulin resistance, glycemic control, and cardiovascular risk markers in postmenopausal women with type 2 diabetes. **RESEARCH DESIGN AND METHODS:** A total of 32 postmenopausal women with diet-controlled type 2 diabetes completed a randomized, double blind, cross-over trial of dietary supplementation with phytoestrogens (soy protein 30 g/day, isoflavones 132 mg/day) versus placebo (cellulose 30 g/day) for 12 weeks, separated by a 2-week washout period. **RESULTS:** Compliance with the dietary supplementation was >90% for both treatment phases. When compared with the mean percentage change from baseline seen after 12 weeks of placebo, phytoestrogen supplementation demonstrated significantly lower mean values for fasting insulin (mean +/- SD 8.09 +/- 21.9%, P = 0.006), insulin resistance (6.47 +/- 27.7%, P = 0.003), HbA(1c) (0.64 +/- 3.19%, P = 0.048), total cholesterol (4.07 +/- 8.13%, P = 0.004), LDL cholesterol (7.09 +/- 12.7%, P = 0.001), cholesterol/HDL cholesterol ratio (3.89 +/- 11.7%, P = 0.015), and free thyroxine (2.50 +/- 8.47%, P = 0.004). No significant change occurred in HDL cholesterol, triglycerides, weight, blood pressure, creatinine, dehydroepiandrosterone sulfate, androstenedione, and the hypothalamic-pituitary-ovarian axis hormones. **CONCLUSIONS:** These results show that dietary supplementation with soy phytoestrogens favorably alters insulin resistance, glycemic control, and serum lipoproteins in postmenopausal women with type 2 diabetes, thereby improving their cardiovascular risk profile.

Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants.

Chattopadhyay S, Bhaumik S, Purkayastha M, et al. *Toxicol Lett* 2002;136:65.

Epidemiological studies on arsenic contamination in drinking water indicated presence of arsenic in fetal tissues. Experiments on human fetal brain explants on exposure to arsenic in culture showed disturbance in lipid peroxidation, generation of nitric oxide (NO), reactive oxygen species (ROS) and apoptosis. The oxidative stress challenged by antioxidant vitamins C, E or chelator dimercaptosuccinic acid (DMSA) may reverse arsenic toxicity on neuronal development. The concept was tested with the models: (A) human fetal brain explants exposed to arsenic, 0.3 mg/l in culture for 24 h; (B) rat neonatal brain explants from 1-day-old litters exposed to 0.3 mg/l arsenic in drinking water during gestation. Rats (n=10) were given oral administration of vitamin C, 2.5 mg/kg/day, vitamin E, 148 mcg/kg/day during gestation and DMSA, 50 mg/kg for 2 days at the end of gestation. (A) The arsenic induced in human fetal brain explants increase in production of NO, 20% and ROS, 25%, and decrease in DNA, 62% and protein, 54% synthesis. The morphological analyses showed growth of viable cells, neural networking vis-a-vis apoptosis on exposure to arsenic for 24 h and necrosis and loss of ground matrix on arsenic exposure for 18 days. The occurrence of two processes of apoptosis and necrosis in different neurons of same culture indicated existence of a selective cellular defense against arsenic toxicity. (B) The rats exposed to arsenic showed increased generation of NO, 25% and ROS, 22%, loss of glutathione content from 42 to 35 mcg/mg protein, 40% increase in lipid peroxidation and decreased superoxide dismutase at 32%. The administration of vitamins C, E and DMSA showed partial reversal of the effects indicating possible protection from arsenic toxicity.

Soy isoflavones: no effects on bone mineral content and bone mineral density in healthy, menstruating young adult women after one year.

Anderson JJ, Chen X, Boass A, et al. *J Am Coll Nutr* 2002;21:388-393.

BACKGROUND: The effects of isoflavone-enriched soy protein on human bone mineral content (mass) and density in healthy, menstruating young adult females have not been examined in a comparative prospective investigation. Peri- and post-menopausal women have been reported to show beneficial effects of isoflavones on bone measurements. Therefore, young women may also be able to improve their accrual of peak bone mineral content (BMC) and bone mineral density (BMD) during the early adult years of bone consolidation with an isoflavone-enriched diet. **OBJECTIVES:** In this controlled, double-blind intervention, we tested the hypothesis that an isoflavone-rich soy protein diet increases BMC and BMD in young adult females over a period of one year in comparison to a control group receiving soy protein that has isoflavones removed. **DESIGN:** Young healthy women of any ethnic background, 21 to 25 years of age, were divided into two groups, placebo (n = 13) and supplement (n = 15). The soy protein supplement was enriched with isoflavones (approximately 90 mg of total isoflavones/day), whereas the control protein diet was isoflavone-deficient, even though it contained the same amount of soy protein and other ingredients as the isoflavone-rich diet. Dual-energy x-ray absorptiometric (DXA) measurements of BMC and BMD were made at baseline and at 6 and 12 months. DXA estimates of body composition, including fat mass and lean body mass, were generated from whole-body BMC measurements. BMI was calculated as weight (kg) over height (m) squared. Physical activity was assessed, and three-day dietary records were taken at entry (baseline) and at 6 and 12 months. **RESULTS:** No changes in BMD after 12 months were found in either the isoflavone-treated (treatment) group or the isoflavone-deficient (control) group. Other variables also remained essentially constant over the 12-month period, including normal menstrual patterns in both the

treatment and control groups. **CONCLUSIONS:** The isoflavone-rich soy preparation had no effects on BMC and BMD over a 12-month period in young healthy adult females with normal menses. An isoflavone-rich supplement appears to have little or no effect on bone in young adult women with normal ovarian function, at least over this 12-month study period.

Effects of *Cordyceps sinensis* on T lymphocyte subsets and hepatofibrosis in patients with chronic hepatitis B.

Gong HY, Wang KQ, Tang SG. *Hunan Yi Ke Da Xue Xue Bao* 2000;25:248-250. [Article in Chinese]

In order to find an effective drug to cure patients with chronic hepatitis B, *Cordyceps sinensis* had been used to treat 25 patients with chronic hepatitis B. The comprehensive index, including T lymphocyte subsets (CD4, CD8), hyaluronic acid(HC) and precollagen type III(PC III), were observed before and after treatment. After 3 months of treatment, CD4 and CD4/CD8 ratio increased significantly($P < 0.05$), while HA and PC III decreased significantly($P < 0.05$) compared with the control. The results suggest that the beneficial effects might be obtained by using *Cordyceps sinensis* to adjust the T lymphocyte subsets level and to treat hepatic fibrosis on patients with chronic hepatitis B.

Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine.

Burke BE, Olson RD, Cusack BJ. *Biomed Pharmacother* 2002;56:283-288.

Approximately 30% of women afflicted with migraine have menstrually associated attacks. These migraines are often refractory to treatment. Evidence suggests estrogen and progestin fluctuations may influence menstrual migraine. Phytoestrogens have demonstrated estrogenic effects in some tissues, but are without stimulation of the endometrium, suggesting decreased risk with long-term use. This study was undertaken to assess the efficacy of a phytoestrogen combination in the prophylactic treatment of menstrual migraine. Forty-nine patients were randomized to receive either placebo, or a daily combination of 60 mg soy isoflavones, 100 mg dong quai, and 50 mg black cohosh, with each component standardized to its primary alkaloid. Patients received study medication for 24 weeks. Average frequency of menstrually associated migraine attacks during weeks 9-24 was reduced from 10.3 +/- 2.4 (mean +/- s.e.m.) in placebo treated patients to 4.7 +/- 1.8 ($P < 0.01$) in patients treated with the phytoestrogen preparation.

Effects of American ginseng berry extract on blood glucose levels in ob/ob mice.

Xie JT, Aung HH, Wu JA, et al. *Am J Chin Med* 2002;30:187-194.

In this study, we evaluated antihyperglycemic effects of American ginseng berry extract in diabetic ob/ob mice. Animals received daily intraperitoneal (IP) injections of the extract 150 mg/kg for 12 days. On days 5 and 12, the extract-treated ob/ob mice had significantly lower fasting blood glucose levels compared to day 0 (both $p < 0.05$). Glucose tolerance improved significantly, which was shown by overall glucose excursion, calculated as area under the curve (AUC) during the two-hour IP glucose tolerance test. The AUC decreased by 31.8% on day 12 compared to day 0 ($p < 0.01$). In addition, after 12 days of the berry extract treatment, a significant reduction in body weight ($p < 0.01$ compared to day 0) and a significant increase in body temperature ($p < 0.01$ compared to day 0) was noticeable. Our results support in vivo antihyperglycemic and antiobese activity of American ginseng berry extract that may prove to be of clinical importance in the prevention and treatment of Type 2 diabetes.

Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study.

Holick CN, Michaud DS, Stolzenberg-Solomon R, et al. *Am J Epidemiol* 2002;156:536-547.

Findings from several beta-carotene supplementation trials were unexpected and conflicted with most observational studies. Carotenoids other than beta-carotene are found in a variety of fruits and vegetables and may play a role in this important malignancy, but previous findings regarding the five major carotenoids are inconsistent. The authors analyzed the associations between dietary beta-carotene, beta-carotene, lutein/zeaxanthin, lycopene, beta-cryptoxanthin, vitamin A, serum beta-carotene, and serum retinol and the lung cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male smokers conducted in southwestern Finland between 1985 and 1993. Of the 27,084 male smokers aged 50-69 years who completed the 276-food item dietary questionnaire at baseline, 1,644 developed lung cancer during up to 14 years of follow-up. Cox proportional hazards models were used to estimate relative risks and 95% confidence intervals. Consumption of fruits and vegetables was associated with a lower lung cancer risk (relative risk = 0.73, 95% confidence interval: 0.62, 0.86, highest vs. lowest quintile). Lower risks of lung cancer were observed for the highest versus the lowest quintiles of lycopene (28%), lutein/zeaxanthin (17%), beta-cryptoxanthin (15%), total carotenoids (16%), serum beta-carotene (19%), and serum retinol (27%). These findings suggest that high fruit and vegetable consumption, particularly a diet rich in carotenoids, tomatoes, and tomato-based products, may reduce the risk of lung cancer.

Vitamin A as an anti-inflammatory agent.

Reifen R. *Proc Nutr Soc* 2002;61:397-400.

Vitamin A is necessary for normal differentiation of epithelial tissues, the visual process and reproduction, and is vital for the optimal maintenance and functioning of the innate and adaptive immune system. Vitamin A deficiency is one of the most profuse nutritional deficiencies worldwide. It is associated with increased susceptibility to infectious diseases in both man and animal models. Vitamin A also has a role as an anti-inflammatory agent. Supplementation with vitamin A has been found to be beneficial in a number of inflammatory conditions, including skin disorders such as acne vulgaris, broncho-pulmonary dysplasia and some forms of precancerous and cancer states. The present review suggests that vitamin A deficiency induces inflammation and aggravates existing inflammatory states. Supplementation with vitamin A in selected cases could ameliorate inflammation. The two main mechanisms which appear to be involved in the prevention of disease are the effects of vitamin A on the immune system and the effect on epithelial integrity.

Betaine supplementation decreases plasma homocysteine concentrations but does not affect body weight, body composition, or resting energy expenditure in human subjects.

Schwab U, Torronen A, Toppinen L, et al. *Am J Clin Nutr* 2002;76:961-967.

BACKGROUND: Betaine (trimethylglycine) is found in several tissues in humans. It is involved in homocysteine metabolism as an alternative methyl donor and is used in the treatment of homocystinuria in humans. In pigs, betaine decreases the amount of adipose tissue. **OBJECTIVE:** The aim of the study was to examine the effect of betaine supplementation on body weight, body composition, plasma homocysteine concentrations, blood pressure, and serum total and lipoprotein lipids. **DESIGN:** Forty-two obese, white subjects (14 men, 28 women) treated with a hypoenergetic diet were randomly assigned to a betaine-supplemented group (6 g/d) or a control group given placebo for 12 wk. The intervention period was preceded by a 4-wk run-in period with a euenergetic diet. **RESULTS:** Body weight, resting energy expenditure, and fat mass decreased significantly in both groups with no significant difference between the groups. Plasma homocysteine concentrations decreased in the betaine group (+/- SD: 8.76 +/- 1.63 micro mol/L at 4 wk, 7.93 +/- 1.52 micro mol/L at 16 wk; P = 0.030 for the interaction of time and treatment). Diastolic blood pressure decreased without a significant difference between the groups. Serum total and LDL-cholesterol concentrations were higher in the betaine group than in the control group (P < 0.05). **CONCLUSION:** A hypoenergetic diet with betaine supplementation (6 g daily for 12 wk) decreased the plasma homocysteine concentration but did not affect body composition more than a hypoenergetic diet without betaine supplementation did.

Pros and cons of antioxidant use during radiation therapy.

Prasad KN, Cole WC, Kumar B, Che Prasad K. *Cancer Treat Rev* 2002;28:79-91.

Radiation therapy is one of the major treatment modalities in the management of human cancer. While impressive progress like more accurate dosimetry and more precise methods of radiation targeting to tumor tissue has been made, the value of radiation therapy in tumor control may have reached a plateau. At present, two opposing hypotheses regarding the use of antioxidants during radiation therapy have been proposed. One hypothesis states that supplementation with high doses of multiple micronutrients including high dose dietary antioxidants (vitamins C and E, and carotenoids) may improve the efficacy of radiation therapy by increasing tumor response and decreasing some of its toxicity on normal cells. The other hypothesis suggests that antioxidants (dietary or endogenously made) should not be used during radiation therapy, because they would protect cancer cells against radiation damage. Each of these hypotheses is based on different conceptual frameworks that are derived from results obtained from specific experimental designs, and thus, each may be correct within its parameters. The question arises whether any of these concepts and experimental designs can be used during radiation therapy to improve the management of human cancer by this modality. This review has analyzed published data that are used in support of each hypothesis, and has revealed that the current controversies can be resolved, if the results obtained from one experimental design are not extrapolated to the other. This review has also discussed the scientific rationale for a micronutrient protocol that includes high doses of dietary antioxidants (vitamin C, vitamin E succinate and natural beta-carotene) which can be used adjunctively with radiation therapy.

Complementary and alternative medical treatment of breast cancer: a survey of licensed North American naturopathic physicians.

Standish LJ, Greene K, Greenlee H, et al. *Altern Ther Health Med* 2002;8:68-70; 72-75.

CONTEXT: Complementary and alternative medicine (CAM) use is on the rise in the United States, especially for breast cancer patients. Many CAM therapies are delivered by licensed naturopathic physicians using individualized treatment plans. **OBJECTIVE:** To describe naturopathic treatment for women with breast cancer. **DESIGN:** Cross-sectional mail survey in 2 parts: screening form and 13-page survey. **SETTING:** Bastyr University Cancer Research Center, Kenmore, Wash. **PARTICIPANTS:** All licensed naturopathic physicians in the United States and Canada (N=1,356) received screening forms; 642 (47%) completed the form. Of the respondents, 333 (52%) were eligible, and 161 completed the survey (48%). **MAIN OUTCOME MEASURES:** Demographics of naturopathic physicians, development of treatment plans, CAM therapies used, perceived efficacy of therapeutic interventions. **RESULTS:** Of those respondents screened, 497 (77%) had provided naturopathic care to women with breast cancer, and 402 (63%) had treated women with breast cancer in the previous 12 months. Naturopaths who were women were more likely than men to treat breast cancer ($P < \text{or} = .004$). Of the survey respondents, 104 (65%) practiced in the United States, and 57 (35%) practiced in Canada; 107 (66.5%) were women, and 54 (33.5%) were men. To develop naturopathic treatment plans, naturopathic physicians most often considered the stage of cancer, the patient's emotional constitution, and the conventional therapies used. To monitor patients clinically, 64% of the naturopathic physicians used diagnostic imaging, 57% considered the patient's quality of life, and 51% used physical examinations. The most common general CAM therapies used were dietary counseling (94%), botanical medicines (88%), antioxidants (84%), and supplemental nutrition (84%). The most common specific treatments were vitamin C (39%), coenzyme Q-10 (34%), and Hoxsey formula (29%).

Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function.

Chappell LC, Seed PT, Kelly FJ, et al. *Am J Obstet Gynecol* 2002;187:777-784.

OBJECTIVE: We have previously reported a reduced incidence of preeclampsia in women who were at risk and were taking vitamin C (1000 mg/d) and vitamin E (400 IU/d) supplements. In this study, we determined whether supplementation in the same cohort was associated with an improvement in indices of placental dysfunction and oxidative stress toward values determined in women who were at low risk of preeclampsia. **STUDY DESIGN:** Seventy-nine women who were at high risk and who were taking vitamin supplements and 81 who were taking placebos were compared with 32 women who were at low risk and who were not taking supplements who were studied simultaneously. **RESULTS:** Indices of oxidative stress and placental function were abnormal in the placebo group. When the placebo group was compared with the women who were at low risk, ascorbic acid, plasminogen activator inhibitor-2, and placenta growth factor concentrations were decreased; and 8-epi-prostaglandin F(2alpha), leptin, and the plasminogen activator inhibitor-1/-2 ratio were increased. In the group that received vitamin supplements, ascorbic acid, 8-epi-prostaglandin F(2alpha), leptin, and plasminogen activator inhibitor-1/-2 values were similar to women who were at low risk. **CONCLUSION:** Antioxidant supplementation in women who were at risk of preeclampsia was associated with improvement in biochemical indices of the disease.

Coronary endothelial function in hyperhomocysteinemia: improvement after treatment with folic acid and cobalamin in patients with coronary artery disease.

Willems FF, Aengevaeren WR, Boers GH, et al. *J Am Coll Cardiol* 2000;40:766-772.

OBJECTIVES: We evaluated the effect of therapy with folic acid and cobalamin on coronary endothelial function, expressed as a change in volumetric coronary blood flow (CBF), in hyperhomocysteinemic patients with coronary artery disease (CAD). **BACKGROUND:** Hyperhomocysteinemia is an independent risk factor for CAD. The mechanism responsible for this increased risk is unclear, but it is generally assumed that hyperhomocysteinemia causes endothelial dysfunction. It is unknown whether lowering plasma homocysteine levels with folic acid and cobalamin improves coronary endothelial function in patients with hyperhomocysteinemia and symptomatic CAD. **METHODS:** Fifteen patients scheduled for elective percutaneous transluminal coronary angioplasty (PTCA) with plasma homocysteine levels of ≥ 16 micromol/l were randomized for six months of treatment with folic acid 5 mg and cobalamin 400 microg daily or placebo. Coronary endothelial function was evaluated in a non-PTCA vessel using acetylcholine infusion in dosages of 10(-8) M, 10(-7) M, and 10(-6) M. Endothelium-dependent CBF is determined using intracoronary Doppler velocity and quantitative coronary angiography at baseline and after six months. **RESULTS:** In the folic acid/cobalamin treated group, CBF increased after acetylcholine infusion with 96% (standard deviation 54; 95% confidence interval [CI]: 44% to 154%) compared with a decrease of 16% (standard deviation 35; 95% CI: -20% to +30%) of the CBF in the placebo-treated group ($p < 0.005$). **CONCLUSIONS:** This is the first prospective randomized placebo-controlled intervention study evaluating coronary endothelial function in hyperhomocysteinemic patients with CAD. Our results suggest that coronary endothelial function improves after treatment with folic acid and cobalamin.

Therapeutic effects of psyllium in type 2 diabetic patients.

Sierra M, Garcia JJ, Fernandez N, et al. *Eur J Clin Nutr* 2002;56:830-842.

OBJECTIVE: The aim of this study was to evaluate the effects of psyllium in type 2 diabetic patients. **DESIGN:** The study included three phases: phase 1 (1 week), phase 2 (treatment, 14 g fibre/day, 6 weeks) and phase 3 (4 weeks). At the end of each phase a clinical evaluation was performed after the ingestion of a test breakfast of 1824.2 kJ (436 kcal). Measurements included concentrations of blood glucose, insulin, fructosamine, GHbA(1c), C-peptide and 24 h urinary glucose excretion. In addition, uric acid, cholesterol and several mineral and vitamin concentrations were also evaluated. **SETTING:** The study was performed at the Department of Pharmacology, Toxicology and Nursing at the University of Leon (Spain). **SUBJECTS:** Twenty type 2 diabetic patients (12 men and 8 women) participated in the study with a mean age of 67.4 y for men and 66 y for women. The mean body mass index of men was 28.2 kg/m(2) and that of women 25.9 kg/m(2). **RESULTS:** Glucose absorption decreased significantly in the presence of psyllium (12.2%); this reduction is not associated with an important change in insulin levels (5%). GHbA(1c), C-peptide and 24 h urinary glucose excretion decreased (3.8, 14.9 and 22.5%, respectively) during the treatment with fibre (no significant differences) as well as fructosamine (10.9%, significant differences). Psyllium also reduced total and LDL cholesterol (7.7 and 9.2%, respectively, significant differences), and uric acid (10%, significant difference). Minerals and vitamins did not show important changes, except sodium that increased significantly after psyllium administration. **CONCLUSIONS:** The results obtained indicate a beneficial therapeutic effect of psyllium (Plantaben(R)) in the metabolic control of type 2 diabetics as well as in lowering the risk of coronary heart disease. We also conclude that consumption of this fibre does not adversely affect either mineral or vitamin A and E concentrations. Finally, for a greater effectiveness, psyllium treatment should be individually evaluated.

Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients.

Goeters C, Wenn A, Mertes N, et al. *Crit Care Med* 2002;30:2032-2037.

OBJECTIVE: Glutamine is recognized as a conditionally indispensable amino acid. The purpose of the current study was to investigate whether supplemental l-alanyl-l-glutamine to parenteral nutrition can alter clinical outcome in intensive care unit patients. **DESIGN:** Prospective, open, randomized trial. **SETTING:** Postoperative intensive care unit of a university hospital. **PATIENTS:** Male and female critically ill patients with indications for parenteral nutrition and an expected stay on intensive care unit for ≥ 5 days. **INTERVENTIONS:** Patients were randomized to receive either standard parenteral nutrition or supplemented parenteral nutrition with l-alanyl-l-glutamine (0.3 g.kg.body weight [bw] per day). Total amount of amino acids comprised 1.5 g.kg.bw per day. Caloric support was managed by metabolic variables (glucose and triglyceride plasma values). Target values for energy supply were 3 g.kg.bw carbohydrates and 1 g.kg.bw fat per day. **MEASUREMENTS AND MAIN RESULTS:** Medical treatment, nutritional therapy, vital variables, and biochemical data were recorded. Clinical outcome was measured by average length of stay in the intensive care unit and hospital and the mortality in the intensive care unit and within 30 days and 6 months. A total of 144 patients were randomized; 95 patients were treated for ≥ 5 days and 68 patients for ≥ 9 days under standardized conditions. In the treatment group, plasma glutamine concentrations significantly increased within 6-9 days. Six-month survival was significantly improved for patients treated for ≥ 9 days (66.7% [glutamine supplemented] vs. 40% [control]). **CONCLUSION:** Study results support the hypothesis that replacement of glutamine deficiency may correct the excess mortality in intensive care unit patients caused by inadequate parenteral nutrition.

L-carnitine reduces lymphocyte apoptosis and oxidant stress in HIV-1-infected subjects treated with zidovudine and didanosine.

Moretti S, Famularo G, Marcellini S, et al. *Antioxid Redox Signal* 2002;4:391-403.

Apoptosis is critical to the progression of human immunodeficiency virus-1 (HIV-1) infection. It appears reasonable that antiretroviral therapies may not achieve a full control of the infection in the absence of an impact on apoptosis. We assigned 20 asymptomatic HIV-infected subjects with advanced immunodeficiency to receive either zidovudine (AZT), and didanosine (DDI) or the same regimen plus L-carnitine, a known antiapoptotic drug, for 7 months. Immunologic and virologic parameters were measured at baseline and after 15, 60, 120, and 210 days of treatment. We assessed on each time point the following: (a) the frequency of peripheral blood apoptotic CD4 and CD8 lymphocytes, CD4 and CD8 cells with disrupted mitochondrial membrane potential, and CD4 and CD8 cells undergoing oxidant stress; (b) the expression of the molecular markers of apoptosis Fas and caspase-1; and (c) the expression of p35/cdk-5 regulatory subunit that is involved in regulating cell survival and apoptosis. Absolute CD4 and CD8 counts and plasma viremia were also measured. Apoptotic CD4 and CD8 cells, lymphocytes with disrupted mitochondrial membrane potential, and lymphocytes undergoing oxidant stress were greatly reduced in subjects treated with AZT and DDI plus L-carnitine compared with those who did not receive L-carnitine. Fas and caspase-1 were down-expressed and p35 over-expressed in lymphocytes from patients of the L-carnitine group. No difference was found in CD4 and CD8 counts and viremia between the groups. No toxicity of L-carnitine was recognized. The addition of L-carnitine is safe and allows apoptosis and oxidant stress to be greatly reduced in lymphocytes from subjects treated with AZT and DDI.

Magnesium supplementation prevents experimental chronic cyclosporine A nephrotoxicity via renin-angiotensin system independent mechanism.

Asai T, Nakatani T, Yamanaka S, et al. *Transplantation* 2002;74:784-791.

BACKGROUND: We have previously shown that correction of hypomagnesemia by magnesium (Mg) supplementation ameliorates chronic cyclosporine A (CsA) nephropathy via inhibiting gene expression of fibrogenic molecules. Experiments were conducted to further elucidate upstream mechanism of the beneficial effects upon CsA nephrotoxicity. **METHODS:** CsA (15 mg/kg/day, subcutaneous [SC]) was administered daily to rats maintained on low sodium diet for 7, 14, and 28 days. Because blockade of renin-angiotensin system improves chronic CsA nephropathy, the effects of Mg supplementation and those of angiotensin-converting enzyme inhibitor (ACEI) were compared on renal function, renal histology, mononuclear cell infiltration, and gene expression profile. **RESULTS:** CsA induced a decline in glomerular filtration and developed characteristic striped fibrosis that were mostly evident at day 28. Mg attenuated CsA-induced impaired renal function, whereas ACEI did not. Interstitial inflammation as evidenced by monocyte/macrophage infiltration preceded the renal fibrosis and increased progressively with the CsA treatment period. Concomitantly, CsA markedly up-regulated expression of chemoattractant proteins, osteopontin, and monocyte chemoattractant protein-1. These changes were abolished by Mg but were only partially affected with ACEI. CsA promoted renal mRNA expression of fibrogenic molecules and extracellular matrices that were almost completely abolished by Mg but partially suppressed by ACEI. Similarly, CsA-induced chronic fibrotic lesion was markedly attenuated by Mg supplementation but was partially attenuated by ACEI. **CONCLUSION:** Mg supplementation abolished CsA-induced precedent interstitial inflammation possibly via inhibition of chemoattractants expression and consequently attenuated tubulointerstitial fibrosis. In this protective mechanism, factors independent of the renin-angiotensin system appears to be mainly involved.

Tocotrienols are needed for normal bone calcification in growing female rats.

Norazlina M, Ima-Nirwana S, Abul Gapor MT, Abdul Kadir Khalid B. *Asia Pac J Clin Nutr* 2002;11:194-199.

In this study the effects of vitamin E deficiency and supplementation on bone calcification were determined using 4-month-old female Sprague-Dawley rats. The rats weighed between 180 and 200 g. The study was divided in three parts. In experiment 1 the rats were given normal rat chow (RC, control group), a vitamin E deficient (VED) diet or a 50% vitamin E deficient (50% VED) diet. In experiment 2 the rats were given VED supplemented with 30 mg/kg palm vitamin E (PVE30), 60 mg/kg palm vitamin E (PVE60) or 30 mg/kg pure alpha-tocopherol (ATF). In experiment 3 the rats were fed RC and given the same supplements as in experiment 2. The treatment lasted 8 months. Vitamin E derived from palm oil contained a mixture of ATF and tocotrienols. Rats on the VED and 50% VED diets had lower bone calcium content in the left femur compared to the RC group (91.6 +/- 13.3 mg and 118.3 +/- 26.0 mg cf 165.7 +/- 15.2 mg; $P < 0.05$) and L5 vertebra (28.3 +/- 4.0 mg and 39.5 +/- 6.2 mg compared with 51.4 +/- 5.8 mg; $P < 0.05$). Supplementing the VED group with PVE60 improved bone calcification in the left femur (133.6 +/- 5.0 mg compared with 91.6 +/- 13.3 mg; $P < 0.05$) and L5 vertebra (41.3 +/- 3.3 mg compared with 28.3 +/- 4.0 mg; $P < 0.05$) while supplementation with PVE30 improved bone calcium content in the L5 vertebra (35.6 +/- 3.1 mg compared with 28.3 +/- 4.0 mg; $P < 0.05$). However, supplementation with ATF did not change the lumbar and femoral bone calcium content compared to the VED group. Supplementing the RC group with PVE30, PVE60 or ATF did not cause any significant changes in bone calcium content. In conclusion, vitamin E deficiency impaired bone calcification. Supplementation with the higher dose of palm vitamin E improved bone calcium content, but supplementation with pure ATF alone did not. This effect may be attributed to the tocotrienol content of palm vitamin E. Therefore, tocotrienols play an important role in bone calcification.

Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline.

Shults CW, Oakes D, Kieburtz K, et al. *Arch Neurol* 2002;59:1541-1550.

BACKGROUND: Parkinson disease (PD) is a degenerative neurological disorder for which no treatment has been shown to slow the progression. **OBJECTIVE:** To determine whether a range of dosages of coenzyme Q10 is safe and well tolerated and could slow the functional decline in PD. **DESIGN:** Multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging trial. **SETTING:** Academic movement disorders clinics. **PATIENTS:** Eighty subjects with early PD who did not require treatment for their disability. **INTERVENTIONS:** Random assignment to placebo or coenzyme Q10 at dosages of 300, 600, or 1200 mg/d. **MAIN OUTCOME MEASURE:** The subjects underwent evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and 1-, 4-, 8-, 12-, and 16-month visits. They were followed up for 16 months or until disability requiring treatment with levodopa had developed. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit. **RESULTS:** The adjusted mean total UPDRS changes were +11.99 for the placebo group, +8.81 for the 300-mg/d group, +10.82 for the 600-mg/d group, and +6.69 for the 1200-mg/d group. The P value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was .09, which met our prespecified criteria for a positive trend for the trial. A prespecified, secondary analysis was the comparison of each treatment group with the placebo group, and the difference between the 1200-mg/d and placebo groups was significant (P = .04). **CONCLUSIONS:** Coenzyme Q10 was safe and well tolerated at dosages of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q10 than in those assigned to placebo, and the benefit was greatest in subjects receiving the highest dosage. Coenzyme Q10 appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

Glutathione, iron and Parkinson's disease.

Bharath S, Hsu M, Kaur D, et al. *Biochem Pharmacol* 2002;64:1037-1048.

Parkinson's disease (PD) is a progressive neurodegenerative disease involving neurodegeneration of dopaminergic neurons of the substantia nigra (SN), a part of the midbrain. Oxidative stress has been implicated to play a major role in the neuronal cell death associated with PD. Importantly, there is a drastic depletion in cytoplasmic levels of the thiol tripeptide glutathione within the SN of PD patients. Glutathione (GSH) exhibits several functions in the brain chiefly acting as an antioxidant and a redox regulator. GSH depletion has been shown to affect mitochondrial function probably via selective inhibition of mitochondrial complex I activity. An important biochemical feature of neurodegeneration during PD is the presence of abnormal protein aggregates present as intracytoplasmic inclusions called Lewy bodies. Oxidative damage via GSH depletion might also accelerate the build-up of defective proteins leading to cell death of SN dopaminergic neurons by impairing the ubiquitin-proteasome pathway of protein degradation. Replenishment of normal glutathione levels within the brain may hold an important key to therapeutics for PD. Several reports have suggested that iron accumulation in the SN patients might also contribute to oxidative stress during PD.

Effects of combined quercetin and coenzyme Q10 treatment on oxidative stress in normal and diabetic rats.

Coldiron AD Jr, Sanders RA, Watkins JB 3rd. *J Biochem Mol Toxicol* 2002;16:197-202.

Reactive oxygen species may be actively involved in the genesis of various pathological states such as ischemia-reperfusion injury, cancer, and diabetes. Our objective was to determine if subacute treatment with combined antioxidants quercetin and coenzyme Q(10) (10 mg/kg/day ip for 14 days) affects the activities of antioxidant enzymes in normal and 30-day streptozotocin-induced diabetic Sprague-Dawley rats. Quercetin treatment raised blood glucose concentrations in normal and diabetic rats, whereas treatment with coenzyme Q(10) did not. Liver, kidney, heart, and brain tissues were excised and the activities of catalase, glutathione reductase, glutathione peroxidase, superoxide dismutase, and concentrations of oxidized and reduced glutathione were determined. In the liver of diabetic rats, superoxide dismutase, glutathione peroxidase, and levels of both oxidized and reduced glutathione were significantly decreased from the nondiabetic control, and these effects were not reversed when antioxidants were administered. In kidney, glutathione peroxidase activity was significantly elevated in the diabetic rats as compared to nondiabetic rats, and antioxidant treatment did not return the enzyme activity to nondiabetic levels. In heart, catalase activity was increased in diabetic animals and restored to normal levels after combined treatment with quercetin and coenzyme Q(10). Cardiac superoxide dismutase was lower than normal in quercetin- and quercetin + coenzyme Q(10)-treated diabetic rats. There were no adverse effects on oxidative stress markers after treatment with quercetin or coenzyme Q(10) singly or in combination. In spite of the elevation of glucose, quercetin may be effective in reversing some effects of diabetes, but the combination of quercetin + coenzyme Q(10) did not increase effectiveness in reversing effects of diabetes.

Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism.

Khalil DA, Lucas EA, Juma S, et al. *J Nutr* 2002;132:2605-2608.

Recent studies suggest that soy protein (SP) protects bone in women; however, its effects on bone metabolism in men have not been investigated. Healthy men (59.2 +/- 17.6 y) were assigned to consume 40 g of either SP or milk-based protein (MP) daily for 3 mo in a double-blind, randomized, controlled, parallel design. Serum insulin-like growth factor-I (IGF-I), which is associated with higher rates of bone formation, was greater ($P < 0.01$) in men supplemented with SP than in those consuming MP. Serum alkaline phosphatase and bone-specific alkaline phosphatase activities, markers of bone formation, and urinary deoxypyridinoline excretion, a specific marker of bone resorption, were not different between the SP and MP groups. Furthermore, because substantial reductions in bone density occur in men at approximately 65 y of age, data were analyzed separately for men ≥ 65 y and those < 65 y of age. The response to protein supplementation was consistent in the two age groups. The effects of SP on serum IGF-I levels suggest that SP may positively influence bone in men. Longer-duration studies examining the effects of SP or its isoflavones on bone turnover and bone mineral density and content in men are warranted.

Further investigation of the modifying effect of various chemopreventive agents on apoptosis and cell proliferation in human colon cancer cells.

Zheng Q, Hirose Y, Yoshimi N, et al. *J Cancer Res Clin Oncol* 2002;128:539-546.

PURPOSE. Recent preclinical assays using animal models have shown that naturally-occurring and synthetic chemicals such as auraptene (AUR), nobiletin (NOB), hesperidin (HE), diosmin (DIO), indole-3-carbinol (I3C), 1'-acetoxychavicol acetate (ACA), 2,5-di-O-acetyl-D-1,4-glucaro-6,3-dilactone (ACE), D-glucuronic acid gamma-lactone (GL), chlorogenic acid (CGA), protocatechuic acid (PA), and sinigrin (SIN) are possible preventive agents against the development of cancer. However, the mode of action of such preventive agents remains to be elucidated. The current study, therefore, was conducted to analyze whether these agents induce apoptosis and/or inhibit DNA synthesis in human colorectal cancer cell lines. **METHODS.** We performed an 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium assay to evaluate the modifying effects of the chemicals on cell viability as the first screening. Then, induction of apoptosis was detected by means of a DNA fragmentation assay, a quantitative enzyme immunoassay, and morphological analysis using 4-diamidino-2-phenylindole staining. In addition, the modulating effects of the compounds on DNA synthesis of the cells with fixed doses of the compounds were analyzed by scoring the 5-bromo-2'-deoxyuridine labeling index. **RESULTS.** AUR, NOB, I3C, ACA, and ACE had apoptosis-inducing effects in a concentration- and time-dependent manner, some of which were followed by a reduction in replicating DNA synthesis. CGA, PA, SIN, GL, DIO, and HE had little modulating effect on cell viability, apoptosis, and DNA synthesis in this cell system. **CONCLUSIONS.** Our results suggest that AUR, I3C, ACA, NOB, and ACE might exert tumor-preventive action through apoptosis- and/or cell proliferation-dependent mechanisms and, on the other hand, CGA, PA, SIN, HE, DIO, and GL might be apoptosis- and cell proliferation-independent. These assays provided an initial tool for further mechanical studies of tumor-preventive agents and future applications to mechanism-based chemopreventive studies.

Antioxidant nutrients and adriamycin toxicity.

Quiles J, Huertas J, Battino M, et al. *Toxicology* 2002;180:79.

The anthracycline antibiotic adriamycin (doxorubicin) is one of the most effective chemotherapeutic agents against a wide variety of cancers. However, its use is seriously limited by the development in the heart of acute and chronic toxic effects. Mechanisms of action and toxicity of adriamycin are briefly revised in this review. Among followed strategies to attenuate adriamycin toxicity are dosage optimisation, synthesis and use of analogues or combined therapy with antioxidants. The most promising results come from the combination of the drug delivery together with an antioxidant in order to reduce oxidative stress. Many antioxidants have been assayed with very different results. Among these molecules, metal ions chelators and low-molecular-mass agents that scavenge reactive oxygen species and that are synthesised in vivo have been widely studied. However, the present review will be exclusively focused on the antioxidants that are derived from the diet, in particular the role of vitamin E, vitamin C, vitamin A, coenzyme Q, flavonoids, antioxidant components of virgin olive oil and selenium.

Oxidative stress induced by phenylketonuria in the rat: Prevention by melatonin, vitamin E, and vitamin C.

Martinez-Cruz F, Pozo D, Osuna C, et al. *J Neurosci Res* 2002;69:550-558.

Phenylketonuria (PKU) is an autosomal recessive disorder caused by a deficiency of the phenylalanine hydroxylation system and is characterized by a block in the conversion of phenylalanine (PHE) to tyrosine. We examined the effects of maternal hyperphenylalaninemia on the morphological and biochemical development of pup rat brain and cerebellum. In our model of PKU we evaluated a number of markers of oxidative stress such as Ehrlich adducts formation, lipid peroxidation, as well as the levels of reduced and oxidized glutathione, and the activities of the enzymes glutathione peroxidase and glutathione reductase. We also studied the expression of heme-oxygenase-1 and mitogen-activated protein kinase 1/2 (MAPK 1/2) as additional markers of oxidative stress. We demonstrate that PKU strongly increased most of the oxidative stress markers studied and induced significant morphological damage. We also showed that daily administration of melatonin (20 mg/kg BW), vitamin E (30 mg/kg BW), and vitamin C (30 mg/kg BW) until delivery prevented the oxidative biomolecular damage in the rat brain and cerebellum. Although no significant differences were observed among the antioxidants studied, it should be noted that the doses of melatonin were less than those for vitamins E and C. We conclude that PKU induces a clear state of oxidative stress that is somehow involved in the brain and body damage occurring in this inborn error. Moreover, melatonin and other antioxidants are capable of preventing completely the damage induced by PKU.

Effects of berberine on glucose metabolism in vitro.

Yin J, Hu R, Chen M, et al. *Metabolism* 2002;51:1439-1443.

The action of berberine was compared with metformin and troglitazone (TZD) with regard to the glucose-lowering action in vitro. HepG2 cell line, phenotypically similar to human hepatocytes, was used for glucose consumption (GC) studies. Cell proliferation was measured by methylthiotetrazole (MTT) assay. In moderate high glucose concentration (11.1 mmol/L), GC of HepG2 cells was increased by 32% to 60% ($P < .001$ to $P < .0001$) with 5×10^{-6} mol/L to 1×10^{-4} mol/L berberine, which was comparable to that with 1×10^{-3} mol/L metformin. The glucose-lowering effect of berberine decreased as the glucose concentration increased. The maximal potency was reached in the presence of 5.5 mmol/L glucose, and it was abolished when the glucose concentration increased to 22.2 mmol/L. The effect was not dependent on insulin concentration, which was similar to that of metformin and was different from that of TZD, whose glucose-lowering effect is insulin dependent. TZD had a better antihyperglycemic potency than metformin when insulin was added ($P < .001$). In the meantime, a significant toxicity of the drug to HepG2 cells was also observed. The betaTC3 cell line was used for insulin release testing, and no secretagogue effect of berberine was observed. These observations suggest that berberine is able to exert a glucose-lowering effect in hepatocytes, which is insulin independent and similar to that of metformin, but has no effect on insulin secretion.

Ginkgo biloba neuroprotection: Therapeutic implications in Alzheimer's disease.

Luo Y. *J Alzheimers Dis* 2001;3:401-407.

An extract of Ginkgo biloba leaves, EGb761, is becoming one of the most popular dietary supplements in the United States to enhance memory. In Europe it is a commonly prescribed drug for treatment of age-related deterioration, including degenerative dementias of the Alzheimer type (AD). Substantial experimental evidence indicates that EGb761 has neuroprotective potency under conditions such as ischemia, seizures and peripheral nerve damage. However, the mechanisms of such neuroprotective effects remain unknown, partially because of the complex chemical composition of EGb761 and the resulting so-called "polyvalent" action. This review focuses on cellular and molecular approaches towards understanding the polyvalent action of EGb761 neuroprotective effect. Two potential mechanisms of action, reducing oxidative damage and stimulating cell survival machinery, are discussed. Better understanding of the neuroprotective mechanisms of EGb761 will provide impetus for possible combination therapies and for the design of rational, "mechanism-based" strategies that target age-related neurodegeneration and Alzheimer's disease.

Effect of Angelica sinensis on the proliferation of human bone cells.

Yang Q, Populo SM, Zhang J, et al. *Clin Chim Acta* 2002;324:89-97.

BACKGROUND: Angelica sinensis, an herbal medicine known for its effect to purify blood quality and improve circulation, frequently appears as the main ingredient in prescriptions for bone injuries. Currently, how pharmacologically it contributes to the reformation of bone is unclear. **METHODS:** The effect of the aqueous extract of Angelica sinensis on bone cells was investigated in vitro for the first time. The human osteoprecursor cells (OPC-1) were incubated in the medium with different concentrations of the aqueous extract of Angelica sinensis and the cell proliferation was studied. **RESULTS:** When the concentration of Angelica sinensis aqueous extract was <125 microg/ml, the proliferation of OPC-1 was enhanced. However, the proliferation of OPC-1 was inhibited by Angelica sinensis extract with the concentrations >250 microg/ml. Under most treatments, the cells presented very pale expression for cyclooxygenase-2 (Cox 2) protein; slightly intensified band showed at the highest Angelica sinensis concentration, 1.0 mg/ml during the course of culture. **CONCLUSION:** The aqueous extract of Angelica sinensis was found to directly stimulate the proliferation, alkaline phosphatase (ALP) activity, protein secretion and particularly type I collagen synthesis of OPC-1 at dose-dependent manner.