

### **Vitamin C supplement use and bone mineral density in postmenopausal women.**

Morton DJ, Barrett-Connor EL, Schneider DL. *J Bone Miner Res* 2001;16:135-140.

Vitamin C is known to stimulate procollagen, enhance collagen synthesis, and stimulate alkaline phosphatase activity, a marker for osteoblast formation. Studies of dietary vitamin C intake and the relation with bone mineral density (BMD) have been conflicting, probably because of the well-known limitations of dietary nutrient assessment questionnaires. The purpose of this study was to evaluate the independent relation of daily vitamin C supplement use with BMD in a population-based sample of postmenopausal women. Subjects were 994 women from a community-based cohort of whom 277 women were regular vitamin C supplement users. Vitamin C supplement use was validated. Daily vitamin C supplement intake ranged from 100 to 5,000 mg; the mean daily dose was 745 mg. Average duration of use was 12.4 years; 85% had taken vitamin C supplements for more than 3 years. BMD levels were measured at the ultradistal and midshaft radii, hip, and lumbar spine. After adjusting for age, body mass index (BMI), and total calcium intake, vitamin C users had BMD levels approximately 3% higher at the midshaft radius, femoral neck, and total hip ( $p < 0.05$ ). In a fully adjusted model, significant differences remained at the femoral neck ( $p < 0.02$ ) and marginal significance was observed at the total hip ( $p < 0.06$ ). Women taking both estrogen and vitamin C had significantly higher BMD levels at all sites. Among current estrogen users, those also taking vitamin C had higher BMD levels at all sites, with marginal significance achieved at the ultradistal radius ( $p < 0.07$ ), femoral neck ( $p < 0.07$ ), and total hip ( $p < 0.09$ ). Women who took vitamin C plus calcium and estrogen had the highest BMD at the femoral neck ( $p = 0.001$ ), total hip ( $p = 0.05$ ), ultradistal radius ( $p = 0.02$ ), and lumbar spine. Vitamin C supplement use appears to have a beneficial effect on levels of BMD, especially among postmenopausal women using concurrent estrogen therapy and calcium supplements.

### **Activity of purified diosmin in the treatment of hemorrhoids.**

Diana G, Catanzaro M, Ferrara A, Ferrari P. *Clin Ter* 2000;151:341-344.  
[Article in Italian]

Several theories on the etio-pathogenesis and physio-pathology of hemorrhoids have been up to now proposed. From the fisio-pathological viewpoint, particular importance is retained by the vascular factor, which in its turn is influenced by mechanical and sphincteric factors, that impair the venous back-flow. In the evidence of an hemorrhoidal crisis, characterized by local oedema, pain and bleeding, the use of bioflavonoid drugs is deemed to be the first choice. We investigated the use of purified diosmin, given at a dose of two 450 mg tablets bid for the first 7 days, then at 1 tablet bid for up to 2 months, in a group of 66 patients suffering from primitive hemorrhoids of grade 1-4. Our results confirmed diosmin efficacy in decreasing both pain and bleeding: reduction rates of 79% and 67%, respectively, were reached in the first treatment week. In the second week, figures were 98% and 86%, respectively. Diosmin tolerability was excellent: this characteristic makes the drug very easy to handle by the general practitioner and also useful to the proctologist in the preparation of patient to further treatments.

### **Inhibition of inducible nitric oxide synthesis by the herbal preparation Padma 28 in macrophage cell line.**

Moeslinger T, Friedl R, Volf I, et al. *Can J Physiol Pharmacol* 2000;78:861-866.

Padma 28 is a mixture of herbs used in traditional Tibetan medicine with anti-inflammatory activities. We investigated the effects of Padma 28 on nitric oxide (NO) production by the inducible nitric oxide synthase (iNOS) in lipopolysaccharide stimulated mouse macrophages (RAW 264.7). Padma 28 (0-900 microg/mL) induced a concentration dependent inhibition of inducible nitric oxide synthesis. iNOS protein expression showed a concentration dependent reduction as revealed by immunoblotting when cells were incubated with increasing amounts of Padma 28. Padma 28 decreased iNOS mRNA levels as shown by RT-PCR. Aqueous extracts from *costi amari radix* (costus root, the dried root of *Saussurea lappa*) and the outer cover of *myrobalani fructus* (the dried fruit of *Terminalia chebula*), constituents of the complex herb preparation Padma 28, were found to inhibit inducible nitric oxide synthesis by decreasing iNOS protein and iNOS mRNA levels. The inhibition of inducible nitric oxide synthesis might contribute to the anti-inflammatory activities of Padma 28.

**A trial of oolong tea in the management of recalcitrant atopic dermatitis.**

Uehara M, Sugiura H, Sakurai K. *Arch Dermatol* 2001;137:42-43.

**BACKGROUND:** Mild cases of atopic dermatitis (AD) generally improve with standard treatment. However, standard treatment fails many patients with recalcitrant AD skin lesions. Study results in animal models have demonstrated that the administration of tea (ie, green, black, or oolong) has suppressed type I and type IV allergic reactions. **OBJECTIVE:** To test the effectiveness of oolong tea in the treatment of recalcitrant AD. **PATIENTS:** Although 121 patients with recalcitrant AD were enrolled in the study, 118 patients completed the open study. **METHODS:** Patients were asked to maintain their dermatological treatment. However, they were also instructed to drink oolong tea made from a 10-g teabag placed in 1000 mL of boiling water and steeped for 5 minutes. This amount was then divided into 3 equal servings and 1 serving was drunk daily after 3 regular meals. Photographs of 2 or 3 representative lesion sites were taken at baseline and at 1 and 6 months and the severity of pruritus was assessed on a 6-point Lickert-like scale ranging from markedly improved (>50% improvement) to worsened. **RESULTS:** After 1 month of treatment 74 (63%) of the 118 patients showed marked to moderate improvement of their condition. The beneficial effect was first noticed after 1 or 2 weeks of treatment. A good response to treatment was still observed in 64 patients (54%) at 6 months. **CONCLUSION:** The therapeutic efficacy of oolong tea in recalcitrant AD may well be the result of the antiallergic properties of tea polyphenols.

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## Recently Published Abstracts

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### **Germinated barley foodstuff feeding. A novel nutraceutical therapeutic strategy for ulcerative colitis.**

Kanauchi O, Iwanaga T, Mitsuyama K. *Digestion* 2001;63:S60-S67.

A germinated barley foodstuff (GBF) contained glutamine-rich protein and the hemicellulose-rich fiber was made from brewer's spent grain by physical isolation (milling and sieving). Both in vivo and in vitro studies demonstrated that the fiber fraction of GBF supports maintenance of epithelial cell populations, facilitates epithelial repair, and suppresses epithelial nuclear factor kappaB-DNA binding activity through generating increased short-chain fatty acid (especially butyrate) production by luminal microflora which includes Bifidobacterium and Eubacterium, thereby preventing experimental colonic injury. The fiber fraction also modulates stool water content by its high water-holding capacity. The protein fraction which contains larger glutamine prevents experimental small bowel injury. Based on these observations, clinical studies were initiated in patients with mild to moderate active ulcerative colitis. The patients who had been unresponsive to or intolerant of standard treatment received 30 grams of GBF feeding daily in a nonrandomized, open-label fashion. At 4 weeks, this treatment resulted in a significant clinical and endoscopic improvement independent of disease extent. The improvement was associated with an increase in stool butyrate concentrations and in luminal Bifidobacterium and Eubacterium levels. After the end of GBF treatment the patients had an exacerbation of the disease. GBF was safe and well tolerated. These results indicate that GBF feeding is a potentially attractive treatment in patients with ulcerative colitis.

### **Effect of melatonin and pineal extracts on human ovarian and mammary tumor cells in a chemosensitivity assay.**

Bartsch H, Buchberger A, Franz H, et al. *Life Sci* 2000;67:2953-2960.

Pinealectomy enhances tumor growth and metastatic spread in experimental animals. This effect is only in part due to melatonin since melatonin-free pineal extracts containing yet unidentified pineal substances have also shown tumor inhibiting activity. Despite numerous reports suggesting melatonin as a potential anti-cancer agent there have not been sufficient clinical trials to define the actual therapeutic potential of melatonin for the treatment of human cancers. To help fill this gap, we used a chemosensitivity assay designed to test the sensitivity of tumors from individual patients towards chemotherapeutic drugs for assessing the effect of melatonin and pineal extracts on primary human tumor cells. Primary cell cultures from seven ovarian and six mammary tumors were incubated with melatonin, the pineal extract YC05R (containing substances between 500 and 1000 daltons) and chemotherapeutic drugs. The pineal extract YC05R inhibited growth of all tumors in a dose-dependent manner. Physiological concentrations of melatonin ( $10(-8)$ - $10(-10)$  M) inhibited the growth of one out of six mammary carcinomas in a dose-dependent manner. Primary cell cultures from three ovarian tumors were affected by melatonin in different ways, i.e., two were inhibited and one was slightly stimulated. There was no correlation between sensitivity towards melatonin and sex steroid receptor status, stage or grade of the tumor. It is concluded that, 1), melatonin may be an inhibitor of human mammary and ovarian carcinoma in individual cases and, 2), the pineal gland contains very active anti-tumor substances inhibiting both, the mammary and ovarian tumors, tested. These substances require chemical and biological identification.

### **Loss of skeletal muscle in cancer: biochemical mechanisms.**

Tisdale MJ. *Front Biosci* 2001;6:D164-D174.

Patients with cancer often undergo a specific loss of skeletal muscle mass, while the visceral protein reserves are preserved. This condition known as cachexia reduces the quality of life and eventually results in death through erosion of the respiratory muscles. Nutritional supplementation or appetite stimulants are unable to restore the loss of lean body mass, since protein catabolism is increased mainly as a result of the activation of the ATP-ubiquitin-dependent proteolytic pathway. Several mediators have been proposed. An enhanced protein degradation is seen in skeletal muscle of mice administered tumour necrosis factor (TNF), which appears to be mediated by oxidative stress. There is some evidence that this may be a direct effect and is associated with an increase in total cellular-ubiquitin-conjugated muscle proteins. Another cytokine, interleukin-6 (IL-6), may play a role in muscle wasting in certain animal tumours, possibly through both lysosomal (cathepsin) and non-lysosomal (proteasome) pathways. A tumour product, proteolysis-inducing factor (PIF) is produced by cachexia-inducing murine and human tumours and initiates muscle protein degradation directly through activation of the proteasome pathway. The action of PIF is blocked by eicosapentaenoic acid (EPA), which has been shown to attenuate the development of cachexia in pancreatic cancer patients. When combined with nutritional supplementation EPA leads to accumulation of lean body mass and prolongs survival. Further knowledge on the biochemical mechanisms of muscle protein catabolism will aid the development of effective therapy for cachexia.

**Detrimental effect of cancer preventive phytochemicals silymarin, genistein and epigallocatechin 3-gallate on epigenetic events in human prostate carcinoma DU145 cells.**

Bhatia N, Agarwal R.  
*Prostate* 2001;46:98-107.

**BACKGROUND:** Targeting epigenetic events associated with autonomous growth of advanced prostate cancer (PCA) is a practical approach for its control, prevention, and treatment. Recently we showed that treatment of prostate carcinoma DU145 cells with cancer preventive flavonoid silymarin at 100-200  $\mu$ M doses inhibits erbB1-Shc mitogenic signaling and modulates cell cycle regulators leading to a G(1) arrest and inhibition of cell growth and anchorage-independent colony formation. Here, we asked the question whether these important findings could be extended to other cancer preventive flavonoids and isoflavones such as epigallocatechin 3-gallate (EGCG) and genistein. **METHODS:** DU145 cells were treated with similar doses (100-200  $\mu$ M) of silymarin, genistein or EGCG, cell lysates prepared, and levels of activated signaling molecules (erbB1-Shc-ERK1/2) and cell cycle regulators (CDKIs, CDKs, and cyclins) analyzed employing immunoprecipitation and/or immunoblotting techniques. Cell growth studies were done by cell counting during 5 days of treatment with these agents, and cell death was determined by Trypan blue staining. **RESULTS:** Treatment of cells with silymarin, genistein or EGCG at 100-200  $\mu$ M resulted in a complete inhibition of TGF $\alpha$ -caused activation of erbB1

followed by a moderate to strong inhibition (10-90%) of Shc activation without an alteration in their protein levels. Silymarin and genistein, but not EGCG, also inhibited (10% to complete) ERK1/2 activation suggesting that these agents impair erbB1-Shc-ERK1/2 signaling in DU145 cells. In other studies, silymarin, genistein or EGCG caused a strong induction of Cip1/p21 (up to 2.4-fold) and Kip1/p27 (up to 150-fold), and a strong decrease in CDK4 (40-90%) but had moderate effect on CDK2, and cyclins D1 and E. An enhanced level of CDKIs also led to an increase in their binding to CDK4 and CDK2. Treatment of cells with silymarin, genistein or EGCG also resulted in 50-80% cell growth inhibition at lower doses, and complete inhibition at higher doses. In contrast to silymarin, higher doses of genistein showed cytotoxic effect causing 30-40% cell death. A more profound cytotoxic effect was observed with EGCG accounting for 50% cell death at lower doses and complete loss of viability at higher doses. **CONCLUSIONS:** These results suggest that similar to silymarin, genistein and EGCG also inhibit mitogenic signaling pathway(s) and alter cell cycle regulators, albeit at different levels, leading to growth inhibition and death of advanced and androgen-independent prostate carcinoma cells. More studies are, therefore, needed with these agents to explore their anti-carcinogenic potential against human prostate cancer.

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### **Ruscus aculeatus (butcher's broom) as a potential treatment for orthostatic hypotension, with a case report.**

Redman DA. *J Altern Complement Med* 2000;6:539-549.

**CONTEXT:** Chronic orthostatic hypotension (OH) is frequently a severely debilitating disease that affects large groups of the population with autonomic insufficiency—the elderly; patients with diabetes, Parkinson's disease, and chronic fatigue syndrome; and anyone on drugs that affect the autonomic nervous system. Unfortunately, even though more than 60 medications are currently being used to treat OH, none of them is particularly or consistently effective. *Ruscus aculeatus*, a phytotherapeutic agent that is well known in Europe, may, however, change this. Its vasoconstrictive and venotonic properties make it ideally suited to treat the pooling of blood in the limbs, lack of venous tone, and lack of neurally mediated vasoconstriction that frequently characterize OH. Although it has never been suggested as a treatment for OH, it already has a long, proven record of use in Europe for treating a variety of circulatory disorders. **OBJECTIVE:** To provide evidence for what appears to be an effective, safe, inexpensive botanical therapy for OH and encourage further studies on the efficacy of *Ruscus* for OH patients. **DESIGN:** Review of OH and therapies currently available for OH and evaluation of the properties of *Ruscus aculeatus*, its mechanism of action, and its suitability as a therapeutic agent for treatment of OH. **RE-**

**SULTS:** A review of the many pharmacologic and nonpharmacologic agents for treating OH reveals that all of the drug therapies are disappointing and marginally useful. Although nonpharmacologic management is preferred, in the many cases in which OH becomes debilitating, pharmacologic intervention becomes a last resort. But drug therapy may not always be necessary, because *Ruscus aculeatus*, a phytotherapeutic agent containing ruscogenins and flavonoids, may prove useful for the treatment of OH if denervation is not so advanced that it has compromised receptor activity at the venous wall. *Ruscus aculeatus* is an alpha-adrenergic agonist that causes venous constriction by directly activating postjunctional alpha1- and alpha2-receptors, in turn stimulating the release of noradrenaline at the level of the vascular wall. It also possesses venotonic properties: it reduces venous capacity and pooling of blood in the legs and exerts protective effects on capillaries, the vascular endothelium, and smooth muscle. Its flavonoid content strengthens blood vessels, reduces capillary fragility, and helps maintain healthy circulation. Unlike most of the drug therapies used to treat OH, *Ruscus aculeatus* does not cause supine hypertension. It also appears to do something no other therapy can offer—alleviate the worsening effects of OH in environmentally hot conditions. Finally, it is an extremely safe, inexpensive, over-the-counter botanical medicine. **CONCLUSION:** With proven phlebotherapeutic properties, including vasoconstrictive action and venotonic properties, *Ruscus aculeatus* shows great promise for ameliorating the symptoms of OH and improving the quality of life for large groups in the population. It clearly deserves to be the object of wider research and study as a treatment for OH.

**Melatonin counteracts potentiation by homocysteine of kcl-induced vasoconstriction in human umbilical artery: relation to calcium influx.**

Okatani Y, Wakatsuki A, Reiter RJ. *Biochem Biophys Res Commun* 2001;280:940-944.

Homocysteinemia is a major and independent risk factor for vascular disease. Oxidative stress is a possible mechanism for homocysteine (HCY)-induced vascular disease. Herein, we evaluated the antioxidant property of melatonin (MLT) in relation to the vasoconstrictive effect of HCY on the human umbilical artery. Helical umbilical arterial strips without endothelium were obtained at elective Cesarean delivery near term. Changes in potassium chloride (KCl)-induced vasoconstriction were measured. Arterial strips were treated with HCY (10 or 100  $\mu$ M) plus FeSO<sub>4</sub> (10  $\mu$ M) alone or pretreated with a hydroxyl radical ( $\cdot$ OH) scavenger, mannitol (20 mM), or MLT (1 or 10  $\mu$ M). The effect of HCY on the response of arterial strips to external calcium (Ca<sup>2+</sup>) in the presence of KCl (20 mM) was determined. HCY plus FeSO<sub>4</sub> potentiated KCl-induced vasoconstriction in a concentration-dependent manner; pretreatment with mannitol significantly reduced this vasospastic effect. HCY (100  $\mu$ M) significantly augmented the contractile response to external Ca<sup>2+</sup>. MLT (10  $\mu$ M) significantly suppressed the contractile response to external Ca<sup>2+</sup>. These results suggest that HCY potentiates KCl-induced umbilical artery vasoconstriction, in part by increasing Ca<sup>2+</sup> influx in vascular smooth muscle cells via activation of Ca<sup>2+</sup> channels. MLT significantly suppressed the vasoconstrictive effect of HCY, probably by scavenging  $\cdot$ OH arising from HCY autooxidation.

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**Cholinesterase inhibitors and Ginkgo extracts—are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration.**

Wettstein A. *Phytomedicine* 2000;6:393-401.

The efficacy of four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, metrifonate) and Ginkgo special extract EGb 761 in Alzheimer's disease were compared. The differences in the effects of the active substance and placebo on cognition were measured on the ADAS-Cog scale, taking into account the different degrees of dementia in the various studies and the dropout rate due to adverse drug reactions. Efficacy, expressed as the delay in symptom progression or the difference in response rate between active substance and placebo, showed no major differences between the four cholinesterase inhibitors and the Ginkgo special extract. Only tacrine exhibited a high dropout rate due to adverse drug reactions. In view of this, the subject of new prescriptions should be critically reviewed. Second-generation cholinesterase inhibitors (donepezil, rivastigmine, metrifonate) and Ginkgo special extract EGb 761 should be considered equally effective in the treatment of mild to moderate Alzheimer's dementia.

**Relation of serum antioxidant vitamins to the risk of colorectal adenoma.**

Breuer-Katschinski B, Nemes K, Marr A, et al. *Digestion* 2001;63:43-48.

The relation between risk of colorectal adenoma and serum concentrations of vitamins A, C, E and carotene was examined in a population-based case-control study of 105 cases of colorectal adenoma and a similar number of hospital controls showing no polyps at colonoscopy and a second control group of population controls. There were no significant associations with serum concentrations of vitamins C and E and carotene. Serum concentrations of vitamin A were significantly inversely related to the risk of colorectal adenoma when cases were compared with both control groups. After adjustment for energy intake, smoking, alcohol, estrogen therapy, body-mass-index and social class the inverse association between vitamin A and colorectal adenoma was even more marked. For the highest versus the lowest quartile of serum levels the adjusted RR was 0.23 (0.07-0.73) in relation to hospital controls and 0.08 (0.02-0.25) in relation to population controls. These findings suggest that the risk of developing colorectal adenomas is reduced in those with high vitamin A levels.

### **Deficiency in peripheral glutamine production in pediatric patients with burns.**

Gore DC, Jahoor F. *J Burn Care Rehabil* 2000;21:171-177.

Plasma glutamine levels decrease in association with severe injury, which suggests that the consumption of glutamine exceeds the production of glutamine or possibly represents a deficit in the release of glutamine from skeletal muscle. The goal of this study was to assess the peripheral glutamine kinetic response to prolonged stress in children with critical injuries. To accomplish this purpose, we quantitated peripheral glutamine kinetics in vivo with the use of 5N15 glutamine in 5 children with severe burns (total body surface area, 74% +/-14%; mean +/- SEM) and 3 children who underwent elective scar reconstruction. In the children with severe burns, leg blood flow was significantly elevated (16.2 +/-2.1 vs 7.5 +/-0.3 mL/min/100 mL leg volume,  $P < .02$ ) and the arterial concentration of glutamine was significantly reduced (0.31 +/-0.04 vs 0.84 +/-0.05 mmol/L,  $P < .001$ ). The rate of glutamine turnover within the leg was significantly reduced in the patients with acute burns, whereas the net efflux of glutamine was similar between the 2 groups. These findings suggest that plasma glutamine concentrations decrease during severe stress as a result of a deficit in peripheral glutamine release in conjunction with an increased central consumption. This preliminary study supports the notion that exogenous glutamine supplementation in pediatric patients with severe injuries may be needed because of this inadequate skeletal muscle response.

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### **Doxorubicin toxicity to the skin: possibility of protection with antioxidants enriched yeast.**

Korac B, Buzadzic B. *J Dermatol Sci* 2001;25:45-52.

The possibility of skin protection against doxorubicin toxicity was examined after oral antioxidative pretreatment of the rats with yeast supplemented with selenium and vitamins E, C and A for 15 days. The activity and level of antioxidative defense components were monitored in the skin and blood 48 h after i.v. applied doxorubicin. In the blood, increased glutathione peroxidase activity in the erythrocytes, and amounts of vitamin E and glutathione in the plasma were found after the antioxidative treatment. It also led to an increase of the reductive capacity in the skin (increased thioredoxin reductase activity and reduced glutathione level). Doxorubicin alone, depleted reductive capacity, i.e. decreased the activity of thioredoxin reductase in the skin, as well as the content of reduced glutathione both in the skin and blood plasma. Depletion of reductive capacity represents one of the first harmful doxorubicin effects to the skin at the time when the changes of other antioxidative enzyme activities were not detectable. Reductive capacity in the skin of animals given antioxidative pretreatment was maintained elevated upon doxorubicin application in comparison with the corresponding control. Oral supplementation with antioxidants thus prevents toxic effects of doxorubicin in the skin and may contribute to the alleviation of its secondary cytotoxicity during the chemotherapy.

### **Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women.**

Somekawa Y, Chiguchi M, Ishibashi T, Aso T. *Obstet Gynecol* 2001;97:109-115.

**Objective:** To evaluate the effects of dietary isoflavones in soy products on menopausal symptoms, lipid profiles, and bone mineral densities in postmenopausal Japanese women. **Methods:** We estimated the daily intakes of isoflavones in the diets of 478 postmenopausal Japanese women who reported soy consumption. We recorded serum values of fasting total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and apolipoproteins. Bone mineral density was measured at the lumbar spine (L2-L4) by dual energy x-ray absorptiometry. Women were assigned to two groups according to years since menopause (early and late postmenopausal groups), and each group was subcategorized into four groups according to dietary isoflavone intake. Relationships between isoflavone intake, menopausal symptoms, lipid profiles, and bone mineral density were examined in each group. **Results:** The mean estimated intake of isoflavones among 478 women was 54.3 mg/day. With stepwise regression analysis we found that weight and years since menopause were significant independent predictors of bone mineral density. Bone mineral densities adjusted to years since menopause and weight were significantly different in the highest intake compared with lowest intake category ( $P < .001$ ) within the early and late postmenopausal groups. In the early postmenopausal group, significant differences were found in palpitation and backaches between the high and low intake categories but were not significant in the late postmenopausal group. **Conclusion:** High consumption of soy products is associated with increased bone mass in postmenopausal women and might be useful for preventing hypoestrogenic effects.

**Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women.**

Wangen KE, Duncan AM, Xu X, Kurzer MS. *Am J Clin Nutr* 2001;73:225-231.

**BACKGROUND:** Soy-protein consumption is known to reduce plasma total and LDL cholesterol concentrations. However, the responsible soy component or components and the magnitude of effects in normocholesterolemic and mildly hypercholesterolemic subjects are unclear. **OBJECTIVE:** The present study examined the effects of soy isoflavone consumption on plasma concentrations of triacylglycerol, apolipoprotein (apo) A-I, apo B, lipoprotein(a), and total, LDL, and HDL cholesterol and on LDL peak particle diameter in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. **DESIGN:** In a randomized crossover trial, fasting plasma samples were obtained from 18 postmenopausal women throughout three 93-d periods of daily isolated soy protein (ISP) consumption providing an average of 7.1 +/- 1.1 (control), 65 +/- 11 (low isoflavone), or 132 +/- 22 (high isoflavone) mg isoflavones/d. **RESULTS:** Compared with values measured during the control diet, the plasma LDL cholesterol concentration was 6.5% lower ( $P < 0.02$ ) during the high-isoflavone diet and the ratio of LDL to HDL cholesterol was 8.5% and 7.7% lower during the low- and high-isoflavone diets, respectively ( $P < 0.02$ ). Isoflavone consumption did not significantly affect plasma concentrations of total or HDL cholesterol, triacylglycerol, apo A-I, apo B, or lipoprotein(a) or the LDL peak particle diameter. **CONCLUSIONS:** Consumption of isoflavones as a constituent of ISP resulted in small but significant improvements in the lipid profile in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Although the effects were small, it is possible that isoflavones may contribute to a lower risk of coronary heart disease if consumed over many years in conjunction with other lipid-lowering strategies.

**Chemopreventive effects of grape seed proanthocyanidin extract on Chang liver cells.**

Joshi SS, Kuszynski CA, Bagchi M, Bagchi D.  
*Toxicology* 2000;155:83-90.

In an attempt to ameliorate the chemotherapy associated normal cell toxicity, in this study a known antioxidant, grape seed proanthocyanidin extract (GSPE) using Chang liver cells has been used. Chang liver cells were treated in vitro with idarubicin (Ida) (30 nM) and 4-hydroxyperoxycyclophosphamide (4-HC) (1 microg/ml) with or without proanthocyanidin (25 microg/ml). The cells were grown in vitro and the growth rate of the cells were determined using MTT assay. The results showed that the GSPE decreased growth inhibitory effects of Ida and 4-HC on Chang liver cells in vitro. Since these chemotherapeutic agents are known to induce apoptosis in the target cells, these cells were also analyzed for presence of apoptotic cells using flow cytometry. The GSPE decreased the number of apoptotic cell population induced by either chemotherapy. In an attempt to determine the mechanisms of ameliorating effects of proanthocyanidin, the expression of apoptosis/cell cycle/growth related genes, Bcl-2, p53 and c-myc was determined in the treated and control cells using Western blotting or reverse transcriptase-polymerase chain reaction (RT-PCR) techniques. There was an increased expression of Bcl-2 in the cells treated with GSPE. However, there was a significant decrease in the expression of other cell cycle related genes such as p53 and c-myc in these cells following treatment with GSPE. Thus, these results indicate that proanthocyanidin can be a potential candidate to ameliorate the toxic effects associated with chemotherapeutic agents used in treatment of cancer.

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### **Novel approaches to chemoprevention of skin cancer.**

Bickers DR, Athar M. *J Dermatol* 2000;27:691-695.

Protection against sun-induced damage leading to photocarcinogenesis in skin is a highly desirable goal. Among various strategies, chemopreventive approaches utilizing non-toxic agents to prevent the occurrence of precancerous lesions or their surrogate markers are potentially attractive. Epidemiological and experimental studies provide evidence that some naturally occurring chemical agents in the human diet can diminish cancer risk. Aside from water, tea is the most common beverage consumed worldwide. Black tea accounts for nearly 80% of total tea production. Black tea and green tea are derived from the same plant, *Camelia sinensis*. Green tea contains monomeric polyphenols known as flavanols and black tea contains dimeric flavanols and polymeric polyphenols known as theaflavins (TFs) and thearubigins (TRs). Over the past fifteen years our laboratory has been exploring the feasibility of using tea and its constituents as an approach to skin cancer prevention. We demonstrated that green tea, black tea and constituent polyphenols protect against chemical- and ultraviolet B (UVB)-induced carcinogenesis and reduce the growth of established tumors in skin. We have also shown the efficacy of green and black tea extracts against UVB and psoralen + ultraviolet A (PUVA)-induced early damage in

skin. Although PUVA is highly effective in treating certain skin diseases, careful follow-up studies of cohorts of patients have shown that similar to UVB, PUVA treatment increases the risk for cutaneous squamous cell carcinoma and melanoma. We have found that oral administration of a standardized green tea extract (SGTE) prior to and during treatment of SKH-1 mice diminished PUVA-induced skin hyperplasia and hyperkeratosis. SGTE-treatment also inhibited PUVA-induced accumulation of c-fos and p53 proteins and epithelial hyperproliferation. Both topical application and oral administration of SGTE after PUVA-treatment reduced skin inflammation and cell hyperproliferation. Topical application of SGTE to human skin prior to PUVA-treatment inhibited the delayed skin inflammatory response. Similarly, oral and topical administration of standardized black tea extract (SBTE) and its two major polyphenolic sub-fractions protect against UVB-induced erythema in SKH-1 mice. Furthermore, topical application of tea extracts to human volunteers protects against UVB-induced erythema. In summary, these studies indicate that tea extracts are effective in reducing UVB- and PUVA-mediated DNA damage, expression of early response genes and early inflammatory changes in skin. These studies verify a conceptual rationale for employing naturally occurring dietary constituents as an approach to cancer chemoprevention.

**Clinical and pharmacological studies on liver diseases treated with Kampo herbal medicine.**

Cyong JC, Ki SM, Iijima K, et al. *Am J Chin Med* 2000;28:351-360.

Hepatitis C virus (HCV) infection frequently causes chronic hepatitis, which is linked to the development of liver cirrhosis and hepatocellular carcinoma. Most physicians who practice Kampo medicine in Japan have observed that Kampo medicine can be as effective as interferon therapy in the treatment of chronic hepatitis C. In the present study, to evaluate the effect of Kampo medicine on chronic hepatitis C, clinical treatment was assessed in short-term and long-term study, and it was shown that ninjin-yoei-to (Formula ginseng compositae: TJ-108) was very effective. Therefore, to find the most active herbal component of TJ-108 in the treatment of HCV, Citrus Unshiu Peel, Schisandra Fruit, and Polygala Root, which are specific to TJ-108, were screened using an in vitro HCV infection model. Among the three herbs, Schisandra Fruit was found to be most active. In the next step, Gomisin A, an active component of Schisandra Fruit, was studied using an in vitro model with MOLT-4 cells and an animal model of immunologically induced acute hepatic failures. It is concluded that the therapeutic effect of TJ-108 on chronic hepatitis C is from the inhibitory effect on HCV infection, and also from the protective effect on immunological hepatopathy of Schisandra Fruit and its lignan component, Gomisin A.

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### **Cocoa powder enhances the level of antioxidative activity in rat plasma.**

Baba S, Osakabe N,  
Natsume M, et al. *Br J Nutr*  
2000;84:673-680.

The aims of the present study were to determine the level of (-)-epicatechin (EC) and its metabolites in rat plasma after oral administration of cocoa powder and to evaluate the protective effect of cocoa powder in terms of suppressing the oxidation of plasma components. Rats were orally administered 1 g cocoa powder/kg body weight, containing 7.80 mg EC, and their blood was collected before administration and at designated time intervals thereafter. The EC and its metabolites in plasma were treated with beta-glucuronidase and/or sulfatase, then analysed by HPLC and by liquid chromatography-MS. Several EC-related compounds were detected in plasma such as free EC, and glucuronide, sulfate, and glucuronide-sulfate conjugates of non-methylated or methylated EC. All EC metabolites showed a maximum concentration in plasma at 30-60 min post-administration. Glucuronide conjugates of both non-methylated and methylated EC were found in high concentration in plasma. Moreover, administration of cocoa powder significantly reduced the accumulation of lipid peroxides in plasma and significantly reduced the consumption of alpha-tocopherol in plasma oxidized by treatment with 2,2'-azobis-(2-amidinopropane) dihydrochloride (AAPH (25 mmol/l)) or CuSO<sub>4</sub> (100 μmol/l) compared with that in the case of plasma obtained before administration. The total EC concentration in plasma was negatively correlated with the level of accumulation of lipid peroxides in plasma oxidized by treatment with AAPH (25 mmol/l) and was positively correlated with the level of residual alpha-tocopherol in plasma oxidized by treatment with CuSO<sub>4</sub> (100 μmol/l). These results indicate that EC in cocoa powder was absorbed from the digestive tract, that various conjugated forms of EC were generated in the digestive tract and distributed to the plasma, and that these enhanced the antioxidative activity of plasma.

### **Neuroprotective effect of vitamin E on the early model of Parkinson's disease in rat: behavioral and histochemical evidence.**

Roghani M, Behzadi G.  
*Brain Res* 2001;892:211-217.

There is strong evidence that oxidative stress participates in the etiology of Parkinson's disease (PD). We designed this study to investigate the neuroprotective effect of vitamin E in the early model of PD. For this purpose, unilateral intrastriatal 6-hydroxydopamine (12.5 µg/5 µl) lesioned rats were pretreated intramuscularly with D-alpha-tocopheryl acid succinate (24 I.U./kg, i.m.) 1 h before and three times per week for 1 month post-surgery. Apomorphine- and amphetamine-induced rotational behavior was measured postlesion fortnightly. A parallel tyrosine hydroxylase immunoreactivity and wheat germ agglutinin-horse radish peroxidase (WGA-HRP) tract-tracing study was performed to evaluate the vitamin E pretreatment efficacy. Tyrosine hydroxylase-immunohistochemical analyses showed a reduction of 18% in ipsilateral substantia nigra pars compacta (SNc) cell number of the vitamin E-pretreated lesioned (L+E) group comparing with contralateral side. The cell number dropped to 53% in the lesioned (L+V) group. In addition, retrograde-labeled neurons in ipsilateral SNc were reduced by up to 30% in the L+E group and 65% in the L+V group. Behavioral tests revealed that there are 74% and 68% reductions in contraversive and ipsiversive rotations in the L+E group, respectively, as compared with the L+V group. Therefore repeated intramuscular administration of vitamin E exerts a rapid protective effect on the nigrostriatal dopaminergic neurons in the early unilateral model of PD.

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### **Exocrine pancreatic insufficiency in tropical sprue.**

Morales M, Galvan E, Mery CM. *Digestion* 2001;63:30-34.

**Background:** Pancreatic insufficiency may appear secondary to several intestinal disorders. It may contribute to malabsorption in tropical sprue (TS). **Methods:** The exocrine pancreatic function was evaluated with the indirect pancreolauryl test (PT) in 56 patients with TS. The PT results were analyzed and correlated with serum albumin levels, degree of intestinal atrophy, and steatorrhea. **Results:** Abnormally low values were found in 36 (64.2%) cases. A significant relationship was not observed between PT and hypoalbuminemia. Patients with more severe damage by intestinal biopsy tended to have lower PT values. No relationship was found between pancreatic insufficiency and steatorrhea (expressed as g/24 h), but patients with pancreatic insufficiency had increased stool fat concentrations (expressed as percentage of wet stool weight). All patients responded favorably to treatment with folic acid and tetracycline. Fifteen patients with abnormal initial PT values underwent a repeat PT after a 6-week therapy; all of them showed normalization of PT values. **Conclusions:** The abnormal exocrine pancreatic function found with an indirect test in patients with TS is probably secondary to a low pancreatic hormonal stimulation due to intestinal damage, as occurs in celiac sprue. These abnormalities are reversible after specific treatment for TS.

**Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production.**

Wang W, Basinger A, Neese RA, et al. *Am J Physiol Endocrinol Metab* 2001;280:E540-E547.

Our objective was to examine very low density lipoprotein-triglyceride (VLDL-TG) kinetics after chronic and acute administration of nicotinic acid (NA). Incorporation of [1,2,3,4-(13)C(4)]palmitate and [2-(13)C(1)]glycerol into VLDL-TG was measured in five healthy, normolipidemic women. Each subject was studied twice; the 4-day hospital stays were separated by 1 mo, during which time doses of NA were increased to 2 g/day (500 mg, 4 times/day). During posttreatment study, 500 mg of NA were administered acutely at 0800. Under baseline postabsorptive conditions, incorporation curves from (13)C-labeled free fatty acid (FFA) and (13)C-labeled glycerol were superimposable, and VLDL-TG kinetics were in agreement ( $t(1/2) = 1.4 \pm 0.3$  and  $1.3 \pm 0.3$  h, and production rates =  $27.2 \pm 6.1$  and  $28.5 \pm 5.3$  g/day, respectively). In the postabsorptive state after chronic NA therapy, VLDL-TG concentrations and production rates were lower despite a trend toward elevated plasma FFA concentrations and fluxes. After the acute dose of NA, plasma FFA concentrations and flux fell dramatically, and there was a virtual halt to VLDL-TG production, which continued throughout the 6-h period after NA, despite a marked rebound overshoot in serum FFA concentrations and flux after hour 2. Plasma homocysteine concentrations increased 68% ( $P < 0.001$ ) in the NA phase, consistent with chronic increased transmethylation demand. We conclude that 1) NA acutely and chronically decreases VLDL-TG production rate in normal women; 2) the acute effect on VLDL-TG production is associated with an initial suppression of lipolysis but persists for several hours after the antilipolytic action of NA has abated and is observed in the basal postabsorptive state, when lipolytic rates are not reduced; and 3) the effect of NA on VLDL-TG production, therefore, cannot be completely explained by its antilipolytic actions.

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### **Diet and bladder cancer: a meta-analysis of six dietary variables.**

Steinmaus CM, Nunez S, Smith AH. *Am J Epidemiol* 2000;151:693-702.

In 1996, more than 300,000 new cases of bladder cancer were diagnosed worldwide. Besides tobacco smoking, occupation, and other factors, diet may play a role in causation of this illness. The authors performed a meta-analytical review of epidemiologic studies linking six dietary factors to bladder cancer. These factors include retinol, beta-carotene, fruits, vegetables, meat, and fat. Increased risks of bladder cancer were associated with diets low in fruit intake (relative risk (RR) = 1.40, 95% confidence interval (CI): 1.08, 1.83), and slightly increased risks were associated with diets low in vegetable intake (RR = 1.16, 95% CI: 1.01, 1.34). Elevated risks were identified for diets high in fat intake (RR = 1.37, 95% CI: 1.16, 1.62) but not for diets high in meat intake (RR = 1.08, 95% CI: 0.82, 1.42). No increased risks were found for diets low in retinol (RR = 1.01, 95% CI: 0.83, 1.23) or beta-carotene (RR = 1.10, 95% CI: 0.93, 1.30) intake. These results suggest that a diet high in fruits and vegetables and low in fat intake may help prevent bladder cancer, but the individual dietary constituents that reduce the risks remain unknown.

### **Effect of vitamin A therapy on serologic responses and viral load changes after influenza vaccination in children infected with the human immunodeficiency virus.**

Hanekom WA, Yogev R, Heald LM, et al. *J Pediatr* 2000;136:550-552.

Vitamin A administered to children infected with the human immunodeficiency virus before influenza vaccination in a double-blind randomized study did not enhance vaccine serologic responses but did dampen the increase in the human immunodeficiency virus viral load 14 days after immunization (vitamin A, decrease of 0.13 +/- 0.09 log(10) copies/mL; placebo, increase of 0.14 +/- 0.08, P = .02).

**Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis.**

Gabriele S, Alberto P, Sergio G, et al. *Toxicology* 2000;155:1-15.

Oxidative stress, favoring disease progression by a rapid degeneration of endothelial cell function is deeply involved in Systemic Sclerosis (SSc) pathogenesis. Raynaud's phenomenon (RP), present in 90% of patients with SSc, provoking frequent daily episodes of hypoxia-reperfusion injury, produces several episodes of free radicals-mediated endothelial derangement. These events results in a positive feedback effect of luminal narrowing and ischemia and therefore to the birth of a vicious cycle of oxygen free radicals (OFR) generation, leading to endothelial damage, intimal thickening and fibrosis. Thus ischemia and reperfusion are two criticals events that may induce oxidative stress and inactivation of antioxidant enzymes. In RP and SSc, a reduced concentration of ascorbic acid, alpha-tocopherol and beta-carotene as well as low values of Selenium have been reported. This antioxidative potential deficiency increases the propensity to oxidative stress, favoring the development of injury mediated by OFR. We reviewed several antioxidant compounds, aiming at their capacity of reverting endothelial dysfunction and damage, scavenging lipid peroxidation and reducing multiple episodes of hypoxia-reperfusion injury. In order to interrupt SSc vicious cycle, we propose a main strategy for SSc treatment by a supplementation of antioxidants and different kind of drugs with antioxidant property, such as Lazaroids, Resveratrol, Melatonin and Probucol.

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### **Low-energy diet in atopic dermatitis patients: clinical findings and DNA damage.**

Kouda K, Tanaka T, Kouda M. *J Physiol Anthropol Appl Human Sci* 2000;19:225-228.

Undernutrition without malnutrition (low-energy diet) increases maximum longevity, reduces the incidence of several cancers and delays their onset, in animal studies. It has also been demonstrated by experimental study that caloric restriction provides a beneficial effect on various inflammatory diseases. In this study, we offered a low-energy diet to patients with atopic dermatitis (AD). Nineteen adult patients (5 males and 14 females aged 15 to 36 years) were enrolled in the study which lasted 8 weeks. The energy intake was 55% of nutritional requirements; protein was 75%, calcium 180%, iron 130%, vitamin A 105%, vitamin C 250% and vitamin E 110% of the daily requirement. No patient experienced adverse reaction, and none dropped out of the trial. Body weight, body mass index (BMI), and systolic blood pressure had decreased significantly by the end of study. The SCORAD (scoring atopic dermatitis) index, which combines objective (extent and intensity of lesions) and subjective (daytime pruritus and sleep loss) criteria, was reduced significantly. In 11 patients with severe AD, there was a significant reduction in oxidative DNA damage. The change in the inflammatory intensity score and the change in BMI caused by energy restriction showed a significant positive correlation. The change in oxidative DNA damage levels and the change in BMI showed a positive correlation. These results clarify the relationship between weight loss and the improvement of AD. It may be hypothesized that this low-energy diet which included several additional nutrients has a possibility to reduce inflammatory symptoms of patients with AD.

**Folate deficiency in vitro induces uracil misincorporation and DNA hypomethylation and inhibits DNA excision repair in immortalized normal human colon epithelial cells.**

Duthie SJ, Narayanan S, Blum S, et al. *Nutr Cancer* 2000;37:245-251.

Epidemiological studies have indicated that folic acid protects against a variety of cancers, particularly cancer of the colorectum. Folate is essential for efficient DNA synthesis and repair. Moreover, folate can affect cellular S-adenosylmethionine levels, which regulate DNA methylation and control gene expression. We have investigated the mechanisms through which folate affects DNA stability in immortalized normal human colonocytes (HCEC). DNA strand breakage, uracil misincorporation, and DNA repair, in response to oxidative and alkylation damage, were determined in folate-sufficient and folate-deficient colonocytes by single cell gel electrophoresis. In addition, methyl incorporation into genomic DNA was measured using the bacterial enzyme Sss1 methylase. Cultured human colonocyte DNA contained endogenous strand breaks and uracil. Folate deficiency significantly increased strand breakage and uracil misincorporation in these cells. This negative effect on DNA stability was concentration dependent at levels usually found in human plasma (1-10 ng/ml). DNA methylation was decreased in HCEC grown in the absence of folate. Conversely, hypomethylation was not concentration dependent. Folate deficiency impaired the ability of HCEC to repair oxidative and alkylation damage. These results demonstrate that folic acid modulates DNA repair, DNA strand breakage, and uracil misincorporation in immortalized human colonocytes and that folate deficiency substantially decreases DNA stability in these cells.

**An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients.**

Galban C, Montejo JC, Mesejo A, et al. *Crit Care Med* 2000;28:643-648.

**OBJECTIVE:** To determine whether early enteral feeding in a septic intensive care unit (ICU) population, using a formula supplemented with arginine, mRNA, and omega-3 fatty acids from fish oil (Impact), improves clinical outcomes, when compared with a common use, high protein enteral feed without these nutrients. **DESIGN:** A prospective, randomized, multicentered trial. **SETTING:** ICUs of six hospitals in Spain. **PATIENTS:** One hundred eighty-one septic patients (122 males, 59 females) presenting for enteral nutrition in an ICU. **INTERVENTIONS:** Septic ICU patients with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of  $>$  or  $=10$  received either an enteral feed enriched with arginine, mRNA, and omega-3 fatty acids from fish oil (Impact), or a common use, high protein control feed (Precitene Hiperproteico). **MEASUREMENTS AND MAIN RESULTS:** One hundred seventy-six (89 Impact patients, 87 control subjects) were eligible for intention-to-treat analysis. The mortality rate was reduced for the treatment group compared with the control group (17 of 89 vs. 28 of 87;  $p < .05$ ). Bacteremias were reduced in the treatment group (7 of 89 vs. 19 of 87;  $p = .01$ ) as well as the number of patients with more than one nosocomial infection (5 of 89 vs. 17 of 87;  $p = .01$ ). The benefit in mortality rate for the treatment group was more pronounced for patients with APACHE II scores between 10 and 15 (1 of 26 vs. 8 of 29;  $p = .02$ ). **CONCLUSIONS:** Immune-enhancing enteral nutrition resulted in a significant reduction in the mortality rate and infection rate in septic patients admitted to the ICU. These reductions were greater for patients with less severe illness.

### **Characterization and antimutagenic activity of soybean saponins.**

Berhow MA, Wagner ED, Vaughn SF, Plewa MJ. *Mutat Res* 2000;448:11-22.

An extract was prepared from a commercial soybean-processing by-product (soybean molasses) and was fractionated into purified chemical components. In previous work, this extract (phytochemical concentrate, PCC) repressed induced genomic DNA damage, whole cell clastogenicity and point mutation in cultured mammalian cells. In the current study, a chemical fraction was isolated from PCC using preparative high-performance liquid chromatography (HPLC). This fraction, PCC100, repressed 2-acetoxyacetylaminofluorene (2AAAF)-induced DNA damage in Chinese hamster ovary (CHO) cells as measured by single cell gel electrophoresis (alkaline Comet assay). Using liquid chromatography-electrospray ionization-mass spectroscopy and <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) spectroscopy, PCC100 was shown to consist of a mixture of group B soyasaponins and 2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP) soyasaponins. These include soyasaponins I, II, III, IV, V, Be, betag, betaa, gammag and gammaa. Purified soyasapogenol B aglycone prepared from fraction PCC100 demonstrated significant antigenotoxic activity against 2AAAF. To our knowledge, these data demonstrate for the first time the antimutagenic activity of soybean saponins in mammalian cells.

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**The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands.**

Yao Z, Drieu K,  
Papadopoulos V. *Brain Res*  
2001;889:181-190.

beta Amyloid (Abeta) treatment induced free radical production and increased glucose uptake, apoptosis and cell death in PC12 nerve cells. Addition of the standardized extract of Ginkgo biloba leaves, EGb 761 together with the Abeta protein prevented, in a dose-dependent manner, the Abeta-induced free radical production, increased glucose uptake, apoptosis and cell death. However, pretreatment of the cells with EGb 761 did not rescue the cells from the Abeta-induced toxicity although it prevented the Abeta-induced reactive oxygen species generation. Moreover, the terpene and flavonoid-free EGb 761 extract, HE 208, although inhibited the Abeta-induced increased glucose uptake, it failed to protect the cells from apoptosis and cytotoxicity induced by Abeta. In conclusion, these results indicate that the terpenoid and flavonoid constituents of EGb 761, acting probably in combination with components present in HE 208, are responsible for rescuing the neuronal cells from Abeta-induced apoptosis and cell death; their mechanism of action being distinct of their antioxidant properties. Because pre- and post-treatment with EGb 761 did not protect the cells from Abeta-induced neurotoxicity, we examined whether EGb 761 interacts directly with Abeta. Indeed, in vitro reconstitution studies demonstrated that EGb 761 inhibits, in a dose-dependent manner, the formation of beta-amyloid-derived diffusible neurotoxic soluble ligands (ADDLs), suggested to be involved in the pathogenesis of Alzheimer's disease.