

Abstracts

Recently Published Abstracts

Effects of ipriflavone on bone loss following a bilateral ovariectomy and menopause: a randomized placebo-controlled study.

Katase K, Kato T, Hirai Y, et al. *Calcif Tissue Int* 2001;69:73-77.

A randomized placebo controlled study was undertaken to evaluate the effect of ipriflavone (IP) against the bone loss in premenopausal ovariectomized women and postmenopausal women. Thirty-seven Japanese women who underwent premenopausal bilateral ovariectomy within 3 months (early stage group) and 52 Japanese women who were ovariectomized or who had undergone menopause more than 3 years before the start of the study (late stage group) were enrolled. The patients were randomly allocated into two groups: those who received IP (600 mg/day) and those who received placebo. The bone mineral density (BMD) of the lumbar vertebrae was measured by dual energy X-ray absorptiometry, and the markers of bone metabolism were measured at the same time that BMD was measured. In the early stage group, the IP group showed a 6.7% decrease in BMD from baseline levels, whereas the placebo group showed a 10.7% decrease ($P < 0.01$) at 12 months of treatment, and 7.1% and 12.6% decrease at 24 months of treatment, respectively ($P < 0.01$). In the late stage group, there was a 0.3% increase in BMD in the IP group and a 2.3% decrease in the placebo group at 6 months of treatment ($P < 0.01$), and similar changes were seen at 18 months (1.4% increase and 3.9% decrease; $P < 0.01$). IP suppressed bone loss compared with placebo, however, did not prevent acute bone loss in the early stage following ovariectomy. The effect of IP alone on bone loss in the early stage is not sufficient to reduce the risk of osteoporosis in later life.

The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity.

Wang Z, Gorski JC, Hamman MA, et al. *Clin Pharmacol Ther* 2001;70:317-326.

BACKGROUND: St John's wort (*Hypericum perforatum*) is a popular over-the-counter dietary supplement and herbal remedy that has been implicated in drug interactions with substrates of several cytochrome P450 (CYP) isozymes. The effect of St John's wort on CYP activity in vivo was examined with a probe drug cocktail. **METHODS:** Twelve healthy subjects (5 female, 7 male) completed this 3-period, open-label, fixed schedule study. Tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A), and intravenous midazolam (hepatic CYP3A) were administered before, with short-term St John's wort dosing (900 mg), and after 2 weeks of intake (300 mg 3 times a day) to determine CYP activities. **RESULTS:** Short-term administration of St John's wort had no effect on CYP activities. Long-term St John's wort administration caused a significant ($P < .05$) increase in oral clearance of midazolam from 121.8 +/- 70.7 to 254.5 +/- 127.8 and a corresponding significant decline in oral bioavailability from 0.28 +/- 0.15 to 0.17 +/- 0.06. In contrast to the >50% decrease in the area under the plasma concentration-time curve (AUC) when midazolam was administered orally, long-term St John's wort administration caused a 20% decrease in AUC when midazolam was given intravenously. There was no change in CYP1A2, CYP2C9, or CYP2D6 activities as a result of St John's wort administration. **CONCLUSION:** Long-term St John's wort administration resulted in a significant and selective induction of CYP3A activity in the intestinal wall. St John's wort did not alter the CYP2C9, CYP1A2, or CYP2D6 activities. Reduced therapeutic efficacy of drugs metabolized by CYP3A should be anticipated during long-term administration of St John's wort.

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Protective effects of dietary phytoestrogens in chronic renal disease.

Ranich T, Bhatena SJ, Velasquez MT. *J Ren Nutr* 2001;1:183-193.

Phytoestrogens are naturally occurring plant compounds that are present primarily in soybeans as isoflavones and in flaxseed as lignans. Because of their structural similarity to endogenous estrogens, phytoestrogens bind to both estrogen receptors (ER)-alpha and beta (but more strongly to ER-beta) and exert estrogen-like effects. There is increasing evidence that dietary phytoestrogens have a beneficial role in chronic renal disease. Nutritional intervention studies have shown that consumption of soy-based protein and flaxseed reduces proteinuria and attenuates renal functional or structural damage in animals and humans with various forms of chronic renal disease. It is not clear which component(s) of the soybean or flaxseed is (are) responsible for the protective effects observed in experimental animals and in limited studies in humans. Vegetable protein has been shown to have a beneficial effect on renal disease in animals and humans. Thus, the role of soy and flaxseed cannot be ruled out. Isoflavones and lignans are readily absorbed from the gut and converted to active metabolites, which may be partly responsible for the beneficial renal effects of soy protein and flaxseed. In addition, an interaction between type of protein and phytoestrogens is also possible. The biological actions of isoflavones and lignans have been well defined in different cell types in vitro and also in vivo, but how these compounds might reduce renal injury remains to be elucidated. Possible mechanisms include inhibition of cell growth and proliferation via ER-mediated mechanisms or non-ER-mediated pathways through inhibition of tyrosine protein kinases, modulation of growth factors involved in extracellular matrix synthesis and fibrogenesis, inhibition of cytokine-induced activation of transcription factors, inhibition of angiogenesis, antioxidative action, suppression of platelet activating factor and platelet aggregation, and immunomodulatory activity. To date, clinical trials in humans are few, of relatively short duration, and involve a small number of patients. Prospective randomized trials are needed to evaluate the long-term safety and effectiveness of dietary phytoestrogens on renal disease progression in patients with chronic renal failure.

Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam.

Akhondzadeh S, Naghavi HR, Vazirian M, et al. *J Clin Pharm Ther* 2001;26:363-367.

Objective: Passionflower (*Passiflora incarnata*) is a folk remedy for anxiety. A double-blind randomized trial compared the efficacy of *Passiflora incarnata* extract with oxazepam in the treatment of generalized anxiety disorder. Methods: The study was performed on 36 out-patients diagnosed with GAD using DSM IV criteria. Patients were allocated in a random fashion: 18 to the *Passiflora* extract 45 drops/day plus placebo tablet group, and 18 to oxazepam 30 mg/day plus placebo drops for a 4-week trial. Results: *Passiflora* extract and oxazepam were effective in the treatment of generalized anxiety disorder. No significant difference was observed between the two protocols at the end of trial. Oxazepam showed a rapid onset of action. On the other hand, significantly more problems relating to impairment of job performance were encountered with subjects on oxazepam. Conclusion: The results suggest that *Passiflora* extract is an effective drug for the management of generalized anxiety disorder, and the low incidence of impairment of job performance with *Passiflora* extract compared to oxazepam is an advantage. A large-scale trial is justified.

The role of phytoestrogens in the prevention and treatment of osteoporosis in ovarian hormone deficiency.

Arjmandi BH. *J Am Coll Nutr* 2001;20:398S-402S.

Ovarian hormone deficiency is a major risk factor for osteoporosis in postmenopausal women. Hormone replacement therapy (HRT) is perhaps the most effective treatment, as it has been demonstrated to both reduce the rate of bone loss and risk of fracture, including hip fracture. However, not all women who may benefit from HRT are willing to initiate this treatment due to fear of cancer and contraindications. Other therapeutic agents currently available are also associated with certain adverse effects. As a result, postmenopausal women are more inclined to use natural remedies to alleviate postmenopausal symptoms and help reduce their risk for chronic diseases such as osteoporosis. Recent reports support the notion that certain bioactive constituents, e.g., phytoestrogens, in plants play a role in maintaining or improving skeletal health. The main consumable plant sources of phytoestrogens include isoflavones and lignans found mainly in soybeans and flaxseed, respectively. Although this paper primarily focuses on the effects of soy protein or its isoflavones on bone, additional statements regarding the role of flaxseed and dried plums, a rich source of polyphenols, with respect to bone will be made.

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Flight microangiopathy in medium- to long-distance flights: prevention of edema and microcirculation alterations with total triterpenic fraction of *Centella asiatica*.

Cesarone MR, Incandela L, De Sanctis MT, et al.
Angiology 2001;52:S33-S37.

The aim of this study was the evaluation of microcirculatory alterations associated with edema in passengers travelling for more than 3 hours and the study of the effects of TTFCA (total triterpenic fraction of *Centella asiatica*) on the development of microcirculation alterations and edema, in a prospective, randomized study. Laser Doppler flowmetry (LDF), transcutaneous PO₂ and PCO₂, rate of ankle swelling (RAS) were used. Subjects were randomized after informed consent into two groups: one control group (no drug or other treatment), and a treatment group (TTFCA 60 mg thrice daily for 2 days before the flight, the day of the flight, and for another day after the flight). Inclusion criteria were age range between 30 and 50, mild-moderate superficial venous disease with varicose veins. Subjects traveled in economy class. In controls there was a progressive increase in CO₂, RAS, and edema score and a progressive decrease in flux (RF) and venoarteriolar response with flying time. The variations in all parameters were milder ($p > 0.05$) in the TTFCA group. RAS and edema were significantly lower in the TTFCA-treated group ($p < 0.025$). The progressive increase in RAS, PCO₂, and the decrease in VAR and O₂ were linearly associated with flight time (up to 10 hours). These results are very interesting and indicate an option for patients prone to edema and microcirculation disturbances during long flights.

Green tea constituent (-)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells.

Berger SJ, Gupta S, Belfi CA, et al. *Biochem Biophys Res Commun* 2001;288:101-105.

DNA topoisomerases I and II are essential for cell survival and play critical roles in DNA metabolism and structure. Inhibitors of topoisomerase constitute a novel family of antitumor agents with demonstrated clinical activity in human malignancies. The clinical use of these agents is limited due to severe toxic effects on normal cells. Therefore, there is a need to develop novel, non-toxic topoisomerase inhibitors that have the ability to spare normal cells. Recent studies have shown that green tea and its major polyphenolic constituent, epigallocatechin-3-gallate (EGCG), impart growth inhibitory responses to cancer cells but not to normal cells. Based on the knowledge that EGCG induces DNA damage, cell cycle arrest, and apoptosis, we considered the possibility of the involvement of topoisomerase in the antiproliferative response of EGCG. Here, for the first time, we show that EGCG inhibits topoisomerase I, but not topoisomerase II in several human colon carcinoma cell lines. Based on this study it is tempting to suggest that combination of EGCG with other conventional topoisomerase inhibitors could be an improved strategy for treatment of colon cancer. The possible role of EGCG as a chemotherapeutic agent needs to be investigated.

Survival and infectious processes in patients with AIDS: analysis according to initial serum vitamin A levels.

Figueiredo JF, Lorenzato MM, Silveira SA, et al. *Rev Soc Bras Med Trop* 2001;34:429-435. [Article in Portuguese]

Patients with AIDS (n = 39) were followed up for a maximum period of 36 weeks, after which the types and topographies of infectious complications presented and patient survival were analyzed and correlated with the vitamin A levels presented by the patients at the beginning of clinical follow-up. Twenty-one (53.8%) patients presented serum retinol levels below 1.6 μ Mol/L, 12 (57%) of whom had values lower than 1.05 μ Mol/L. There was no correlation between low serum vitamin A levels and the types or topographies of the infectious complications that occurred during the follow-up period. Although mean survival at the end of the 36 months follow-up period was similar for the two groups, patients with retinol deficiency presented a lower probability of survival during the first 24 months of follow-up compared to patients without hypovitaminosis A (8.44 x 1.42 months; p = 0.003).

The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults.

Hodson L, Skeaff CM, Chisholm WA. *Eur J Clin Nutr* 2001;55:908-915.

OBJECTIVE: To examine, in free-living adults eating self-selected diets, the effects on plasma cholesterol of substituting saturated fat rich foods with either n-6 polyunsaturated or monounsaturated fat rich foods while at the same time adhering to a total fat intake of 30-33% of dietary energy. **DESIGN:** Two randomised crossover trials. **SETTING:** General community. **SUBJECTS:** Volunteer sample of healthy free-living nutrition students at the University of Otago. Trial I, n=29; and trial II, n=42. **INTERVENTIONS:** In trials I and II participants were asked to follow for 2(1/2) weeks a diet high in saturated fat yet with a total fat content that conformed to nutrition recommendations (30-33% energy). During the 2(1/2) week comparison diet, saturated fat rich foods were replaced with foods rich in n-6 polyunsaturated fats (trial I) whereas in trial II the replacement foods were rich in monounsaturated fats. Participants were asked to maintain a total fat intake of 30-33% of energy on all diets. **MAIN OUTCOME MEASURES:** Energy and nutrient intakes, plasma triglyceride fatty acids, and plasma cholesterol. **RESULTS:** When replacing saturated fat with either n-6 polyunsaturated fat or monounsaturated fat, total fat intakes decreased by 2.9% energy and 5.1% energy, respectively. Replacing saturated fat with n-6 polyunsaturated fat (trial I) lowered plasma total cholesterol by 19% [from 4.87 (0.88) to 3.94 (0.92) mmol/l, mean (s.d.)], low density lipoprotein cholesterol by 22% [from 2.87 (0.75) to 2.24 (0.67) mmol/l], and high density lipoprotein cholesterol by 14% [from 1.39 (0.36) to 1.19 (0.34) mmol/l], whereas replacing saturated fat with monounsaturated fat (trial II) decreased total cholesterol by 12%, low density lipoprotein cholesterol by 15%, and high density lipoprotein cholesterol by 4%, respectively. The change in the ratio of total to high density lipoprotein cholesterol was similar during trial I and trial II. **CONCLUSIONS:** Young adults are very responsive to dietary-induced changes in plasma cholesterol even when an isocaloric replacement of saturated fat with n-6 polyunsaturated or monounsaturated fat is not achieved. Replacing saturated fat with either n-6 polyunsaturated or monounsaturated fat is equally efficacious at reducing the total to high density lipoprotein cholesterol ratio.

Effect of soy isoflavone supplementation on markers of oxidative stress in men and women.

Djuric Z, Chen G, Doerge DR, et al. *Cancer Lett* 2001;172:1-6.

Dietary intake of soy has been linked with decreased cancer risk, and the active compounds in soy that have been identified include the isoflavones genistein and daidzein. Since these compounds have antioxidant properties, we examined levels of oxidative damage in blood of six women and six men before and during soy supplementation using Novasoy tablets. Blood samples were obtained at weekly intervals for 3 weeks from the women taking 50-mg isoflavones once daily and the men taking 50-mg isoflavones twice daily. Plasma levels of genistein and daidzein increased after supplementation with maximal levels occurring at 2 weeks for the women while levels in men kept increasing over the 3 weeks of study. There was wide variation between individuals in the levels of isoflavones achieved. Mean levels of 5-hydroxymethyl-2'-deoxyuridine (5-OHmdU) in DNA from nucleated blood cells decreased after 1 week of supplementation in the women, with a decrease of 47% in mean 5-OHmdU levels after 3 weeks. In men, mean 5-OHmdU levels did not decrease until after 3 weeks of supplementation, at which there was 61% decrease. Mean plasma levels of 8-isoprostanes were not changed appreciably in either men or women. These pilot results suggest that soy isoflavone supplementation decreases levels of oxidative DNA damage in humans, and this may be a mechanism behind the cancer-preventive effects of soy isoflavones.

Allergy development and the intestinal microflora during the first year of life.

Bjorksten B, Sepp E, Julge K, et al. *J Allergy Clin Immunol* 2001;108:516-520.

BACKGROUND: The intestinal microflora is a likely source for the induction of immune deviation in infancy. **OBJECTIVE:** The purpose of this study was to prospectively relate the intestinal microflora to allergy development in 2 countries differing with respect to the prevalence of atopic diseases. **METHODS:** New-born infants were followed prospectively through the first 2 years of life in Estonia (n = 24) and Sweden (n = 20). By that age, 9 Estonian and 9 Swedish infants had developed atopic dermatitis and/or positive skin prick test results. Stool samples were obtained at 5 to 6 days and at 1, 3, 6, and 12 months, and 13 groups of aerobic and anaerobic microorganisms were cultivated through use of standard methods. **RESULTS:** In comparison with healthy infants, babies who developed allergy were less often colonized with enterococci during the first month of life (72% vs 96%; P <.05) and with bifidobacteria during the first year of life (17% to 39% vs 42% to 69%; P <.05). Furthermore, allergic infants had higher counts of clostridia at 3 months (median value, 10.3 vs 7.2 log(10); P <.05). The prevalence of colonization with *Staphylococcus aureus* was also higher at 6 months (61% vs 23%; P <.05), whereas the counts of *Bacteroides* were lower at 12 months (9.9 vs 10.6 log(10); P <.05). **CONCLUSION:** Differences in the composition of the gut flora between infants who will and infants who will not develop allergy are demonstrable before the development of any clinical manifestations of atopy. Because the observations were made in 2 countries with different standards of living, we believe that our findings could indicate a role for the intestinal microflora in the development of and protection from allergy.

Effect of L-arginine, dimercaptosuccinic acid (DMSA) and the association of L-arginine and DMSA on tissue lead mobilization and blood pressure level in plumbism.

Malvezzi CK, Moreira EG, Vassilieff I, et al. *Braz J Med Biol Res* 2001;34:1341-1346.

Lead (Pb)-induced hypertension is characterized by an increase in reactive oxygen species (ROS) and a decrease in nitric oxide (NO). In the present study we evaluated the effect of L-arginine (NO precursor), dimercaptosuccinic acid (DMSA, a chelating agent and ROS scavenger), and the association of L-arginine/DMSA on tissue Pb mobilization and blood pressure levels in plumbism. Tissue Pb levels and blood pressure evolution were evaluated in rats exposed to: 1) Pb (750 ppm, in drinking water, for 70 days), 2) Pb plus water for 30 more days, 3) Pb plus DMSA (50 mg kg⁻¹ day⁻¹, po), L-arginine (0.6%, in drinking water), and the combination of L-arginine/DMSA for 30 more days, and 4) their respective matching controls. Pb exposure increased Pb levels in the blood, liver, femur, kidney and aorta. Pb levels in tissues decreased after cessation of Pb administration, except in the aorta. These levels did not reach those observed in nonintoxicated rats. All treatments mobilized Pb from the kidney, femur and liver. Pb mobilization from the aorta was only effective with the L-arginine/DMSA treatment. Blood Pb concentrations in Pb-treated groups were not different from those of the Pb/water group. Pb increased blood pressure starting from the 5th week. L-arginine and DMSA treatments (4th week) and the combination of L-arginine/DMSA (3rd and 4th weeks) decreased blood pressure levels of intoxicated rats. These levels did not reach those of nonintoxicated rats. Treatment with L-arginine/DMSA was more effective than the isolated treatments in mobilizing Pb from tissues and in reducing the blood pressure of intoxicated rats.

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Molecular aspects of lipoic acid in the prevention of diabetes complications.

Packer L, Kraemer K, Rimbach G. *Nutrition* 2001;17:888-895.

Alpha-Lipoic acid (LA) and its reduced form, dihydrolipoic acid, are powerful antioxidants. LA scavenges hydroxyl radicals, hypochlorous acid, peroxynitrite, and singlet oxygen. Dihydrolipoic acid also scavenges superoxide and peroxy radicals and can regenerate thioredoxin, vitamin C, and glutathione, which in turn can recycle vitamin E. There are several possible sources of oxidative stress in diabetes including glycation reactions, decompartmentalization of transition metals, and a shift in the reduced-oxygen status of the diabetic cells. Diabetics have increased levels of lipid hydroperoxides, DNA adducts, and protein carbonyls. Available data strongly suggest that LA, because of its antioxidant properties, is particularly suited to the prevention and/or treatment of diabetic complications that arise from an overproduction of reactive oxygen and nitrogen species. In addition to its antioxidant properties, LA increases glucose uptake through recruitment of the glucose transporter-4 to plasma membranes, a mechanism that is shared with insulin-stimulated glucose uptake. Further, recent trials have demonstrated that LA improves glucose disposal in patients with type II diabetes. In experimental and clinical studies, LA markedly reduced the symptoms of diabetic pathologies, including cataract formation, vascular damage, and polyneuropathy. To develop a better understanding of the preventative and therapeutic potentials of LA, much of the current interest is focused on elucidating its molecular mechanisms in redox dependent gene expression.

Vitamin C inhibits endothelial cell apoptosis in congestive heart failure.

Rossig L, Hoffmann J, Hugel B, et al. *Circulation* 2001;104:2182-2187.

Background- Proinflammatory cytokines like tumor necrosis factor-alpha and oxidative stress induce apoptotic cell death in endothelial cells (ECs). Systemic inflammation and increased oxidative stress in congestive heart failure (CHF) coincide with enhanced EC apoptosis and the development of endothelial dysfunction. Therefore, we investigated the effects of antioxidative vitamin C therapy on EC apoptosis in CHF patients. Methods and Results- Vitamin C dose dependently suppressed the induction of EC apoptosis by tumor necrosis factor-alpha and angiotensin II in vitro as assessed by DNA fragmentation, DAPI nuclear staining, and MTT viability assay. The antiapoptotic effect of vitamin C was associated with reduced cytochrome C release from mitochondria and the inhibition of caspase-9 activity. To assess EC protection by vitamin C in CHF patients, we prospectively randomized CHF patients in a double-blind trial to vitamin C treatment versus placebo. Vitamin C administration to CHF patients markedly reduced plasma levels of circulating apoptotic microparticles to 32+/-8% of baseline levels, whereas placebo had no effect (87+/-14%, P<0.005). In addition, vitamin C administration suppressed the proapoptotic activity on EC of the serum of CHF patients (P<0.001). Conclusions- Administration of vitamin C to CHF patients suppresses EC apoptosis in vivo, which might contribute to the established functional benefit of vitamin C supplementation on endothelial function.

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A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.

Age-Related Eye Disease Study Research Group. *Arch Ophthalmol* 2001;119:1417-1436.

BACKGROUND: Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss. **OBJECTIVE:** To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity. **DESIGN:** The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo. **MAIN OUTCOME MEASURES:** (1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline ($>$ or $=$ 15 letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring. **RESULTS:** Average follow-up of the 3640 enrolled study participants, aged 55-80 years, was 6.3 years, with 2.4% lost to

follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47-0.91; zinc: OR, 0.71; 99% CI, 0.52-0.99; antioxidants: OR, 0.76; 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations. **CONCLUSIONS:** Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

Anticlastogenic effect of vitamin C on cisplatin induced chromosome aberrations in human lymphocyte cultures.

Nefic H. *Mutat Res* 2001;498:89-98.

Vitamin C (ascorbic acid) is an antioxidant that can scavenge free radicals and protect cellular macromolecules, including DNA, from oxidative damage induced by different agents. The protective effect of Vitamin C on cisplatin induced chromosome aberrations has been determined in the human peripheral lymphocyte chromosome aberration test in vitro. The results of treatments with Vitamin C indicated that it statistically significantly decreases the number of chromosome aberrations and number of metaphases with aberrations induced with cisplatin, but it can not completely protect cells from damage. The test concentrations of Vitamin C (10 and 100µg/ml) had a limited antimutagen effect on cisplatin (0.5µg/ml), which can cause genetic damage through free radical mechanisms. The antimutagen effect included the anticlastogenic effect of Vitamin C and its ability to decrease the number of aneuploid mitoses. Vitamin C showed the most efficient anticlastogenic effect during simultaneous treatment with cisplatin. Also, Vitamin C reduced cell toxicity of cisplatin during simultaneous treatment.

Carnitine as a free radical scavenger in aging.

Juliet Arockia Rani P, Panneerselvam C. *Exp Gerontol* 2001;36:1713-1726.

Carnitine (4-N-trimethylammonium-3-hydroxybutyric acid) plays an important role in the translocation of acetyl moieties from the mitochondria into the cytoplasm for acetylcholine synthesis in the brain. Previous studies in our laboratory have shown that L-carnitine suppresses oxidative damage during aging. This study was carried out to see the effect of L-carnitine on the status of non-enzymatic antioxidants and lipofuscin accumulation in various regions of the aged rat brain. We observed a decrease in the status of ascorbic acid, glutathione and vitamin E in aged rats. Histological work showed that the accumulation of lipofuscin increased as a function of age. The extent of damage varied between the regions we have investigated. Supplementation of L-carnitine to aged rat improved the antioxidant status in a duration dependent manner. The accumulation of lipofuscin was also found to be decreased after L-carnitine administration. The data suggests that decrement of lipofuscin accumulation by L-carnitine may be partially due to its antioxidant promoting action.

Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants.

Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R.
J Perinatol 2001;21:356-362.

INTRODUCTION: With the increased survival of very low birthweight (VLBW) infants, weighing less than 1500 g at birth, the incidence of retinopathy of prematurity (ROP), a significant cause of blindness among children in the United States, is also increasing. Preterm infants with a positive diagnosis of ROP during the perinatal period are at increased risk for ocular abnormalities and for deficits in visual function during later periods of development. Human milk has many antioxidant constituents including inositol, vitamin E, and beta-carotene that may protect against the development of ROP. **OBJECTIVE:** The objective of this study was to examine the effect of human milk feedings on the incidence of ROP among VLBW infants. **STUDY DESIGN:** Observational cohort study. **PARTICIPANTS:** We identified 283 VLBW infants admitted to the Georgetown University Medical Center Neonatal Intensive Care Unit (NICU) from January 1992 through September 1993. All infants surviving to receive enteral feeding and ophthalmologic examinations for ROP (n=174) were included in the analysis. **METHODS:** Type of feeding (human milk versus exclusive formula), presence of ROP, and potential confounding variables were abstracted retrospectively from medical records. ROP was present if any stage of ROP was diagnosed at any age during the initial NICU hospitalization; each case was counted once based on the worse severity of ROP in either eye. Multiple logistic regression was used to control for confounders. **MAIN OUTCOME MEASURE:** ROP. **RESULTS:** Major predictors of ROP were similar in both feeding groups including gestational age, days on mechanical ventilation, and total number of days on supplemental oxygen. The incidence of ROP differed significantly by type of feeding (human milk - 41.0% vs. formula -63.5%, p=0.005). Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.42, 95% CI: 0.19 to 0.93) (p=0.03), controlling for gestational age, duration of supplemental oxygen therapy, 5-minute Apgar score, and race. Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.46, 95% CI: 0.18 to 0.91) (p=0.03), controlling for birthweight, duration of supplemental oxygen therapy, 5-minute Apgar score, and race. **CONCLUSION:** Human milk feeding among VLBW infants was associated with a lower incidence of ROP compared to exclusively formula-fed VLBW infants after adjusting for confounding variables.

Increased apoptosis in a variety of tissues of zinc-deficient rats.

Nodera M, Yanagisawa H, Wada O. *Life Sci* 2001;69:1639-1649.

Zinc deficient rats were prepared to investigate histopathological changes in thymus, testis, skin, esophagus, kidney and liver and the relationship between these changes and apoptosis. Seven-week-old male SD rats were given a Zn deficient diet (0% Zn diet) or a standard diet (0.02% Zn diet). The above-mentioned organs were excised 1, 2, 3, 4, 5, 10, 13, and 34 weeks after initiating diet administration. Then, these organs were examined morphologically, and apoptotic changes were analyzed by either the TdT-mediated dUTP - biotin nick end labeling (TUNEL) or electrophoresis. Significant morphological changes were seen only in rats on the 0% Zn diet. After 4 weeks, atrophy of the thymus was seen. After 5 weeks, oligospermia was observed, and after 10 weeks, testicular atrophy accompanied by the loss of sperm cells and spermatocytes was confirmed. In addition, after 10 weeks, thickening of epithelia was seen in the skin and esophagus of rats on the 0% diet. During the observation period, no marked morphological changes were observed in the liver or kidney. In the thymus and testis of rats on the 0% Zn diet, prior to detecting any morphological changes, increases in apoptosis were confirmed at 1 and 3 weeks after initiating diet administration, respectively. In the kidney and liver, TUNEL positive cells appeared after 13 and 34 weeks, respectively. These observations suggest that the functional and morphological changes in the thymus and testis of rats on the 0% Zn diet are caused by increased apoptosis, and that even when the supply of Zn is terminated for only a short period of time, immunocytes and germ cells can not survive or regenerate sufficiently. Again, the fact that even in the liver and kidney, apoptosis was observed when administration of the 0% Zn diet was prolonged suggests that the appearance of apoptosis is dependent on the amount of Zn in tissues. In addition, the fact that increases in apoptosis were confirmed in the skin of rats on the 0% Zn diet, but not in the esophagus of these rats suggests that apoptosis does not directly cause thickening of stratified squamous epithelium in Zn deficient rats.

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Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines.

Malsch U, Kieser M.
Psychopharmacology
2001;157:277-283.

A 5-week randomized, placebo-controlled, double-blind study was carried out to investigate the efficacy of kava-kava special extract WS(R)1490 in non-psychotic nervous anxiety, tension and restlessness states. During the first treatment week, the study dose drug was increased from 50 mg to 300 mg per day and pretreatment with benzodiazepines was tapered off over 2 weeks. These dosage adjustments were followed by 3 weeks of monotherapy with WS(R)1490 or placebo. Outcome measures were the differences between baseline and end of treatment on the Hamilton Anxiety Scale (HAMA) and on a subjective well-being scale (Bf-S), as well as the benzodiazepine withdrawal symptoms. Changes in the Erlanger Anxiety, Tension and Aggression Scale (EAAS) and Clinical Global Impressions (CGI) were analyzed as secondary measures. Treatment safety was checked by interviews, adverse event reports and laboratory investigations. Forty patients (2x20) were included into the study. WS(R)1490 was superior to placebo regarding the HAMA (P=0.01) and Bf-S (P=0.002) total scores and all secondary efficacy measures. The tolerance of WS(R)1490 was not inferior to placebo. The study confirms the anxiolytic efficacy and good tolerance of WS(R)1490 and shows that a further symptom reduction is possible after a change-over from benzodiazepine treatment.

Influence of plasma glutathione levels on radiation mucositis.

Wardman P, Folkes LK, Bentzen SM, et al. *Int J Radiat Oncol Biol Phys* 2001;51:460-464.

PURPOSE: To test the hypothesis that there is a link between plasma glutathione (GSH) or other antioxidants (uric acid, ascorbate) and the severity of radiation mucositis following radiation treatment of tumors of the head and neck. **PATIENTS AND METHODS:** Patients with carcinomas of the head-and-neck region were treated with the continuous hyperfractionated accelerated radiotherapy (CHART) regimen (54 Gy in 36 fractions over 12 days). Samples of blood plasma were analyzed for GSH, cysteine, urate, and ascorbate by high-pressure liquid chromatography. Patients were graded for dysphagia and requirement for analgesics. The areas under the curves of scores over 2-6 weeks following treatment were computed, and Spearman's rank-correlation coefficient was used to test for an association between plasma GSH levels (or those of other antioxidants) and mucositis. **RESULTS:** The pretreatment plasma GSH level in 18 patients scored in the study was 1.0 +/- 0.7 M. Analysis of these and the dysphagia scores produced a correlation coefficient of 0.22 (confidence interval -0.28, 0.61; p = 0.39). No correlation was seen between mucositis severity and other measures of plasma antioxidants: cysteine (7.6 +/- 1.7 M), cysteine + GSH (8.6 +/- 1.9 M), uric acid (317 +/- 86 M), ascorbate (29 +/- 20 M), or whole-blood GSH concentrations (1,010 +/- 239 M). **CONCLUSION:** The measurements of approximately micromolar levels of plasma GSH, or about 10 M cysteine + GSH (almost all of the total nonprotein thiols), are consistent with most other published data for either healthy adults or cancer patients; however, the values reported in an earlier study, suggesting a link between GSH and mucositis, are much higher. The hypothesis of a possible link between radiation mucositis and plasma-free (nonprotein) thiols was not supported.

Abstracts

Recently Published Abstracts

Effect of glutathione depletion on antitumor drug toxicity (apoptosis and necrosis) in U-937 human promonocytic cells: The role of intracellular oxidation.

Troyano A, Fernandez C, Sancho P, et al. *J Biol Chem* 2001; [epub ahead of print].

Treatment with the DNA topoisomerase inhibitors etoposide, doxorubicin and camptothecin, and with the alkylating agents cisplatin and melphalan, caused peroxide accumulation and apoptosis in U-937 human promonocytic cells. Pre-incubation with the GSH synthesis inhibitor L-buthionine-[S,R]-sulfoximine always potentiated peroxide accumulation. However, while GSH depletion potentiated the toxicity of cisplatin and melphalan, occasionally switching the mode of death from apoptosis to necrosis, it did not affect the toxicity of the other antitumor drugs. Hypoxia or pre-incubation with antioxidant agents attenuated death induction, apoptotic and necrotic, by alkylating drugs. The generation of necrosis by cisplatin could not be mimicked by addition of exogenous H₂O₂ instead of BSO, and was not adequately explained by caspase inactivation nor by a selective fall in ATP content. Treatment with cisplatin and melphalan caused a late decrease in mitochondrial transmembrane potential ($\Delta\psi$), which was much greater during necrosis than during apoptosis. The administration of the antioxidant agents N-acetyl-L-cysteine and butylated hydroxyanisole after pulse-treatment with cisplatin or melphalan did not affect apoptosis, but attenuated necrosis. Under these conditions, both antioxidants attenuated the necrosis-associated $\Delta\psi$ decrease. These results indicate that oxidation-mediated alterations in mitochondrial function regulate the selection between apoptosis and necrosis in alkylating drug-treated human promonocytic cells.

Diagnosis of Helicobacter pylori infection by stool antigen test in southern Taiwan.

Yu FJ, Wu DC, Kuo CH, et al. *Kaohsiung J Med Sci* 2001;17:344-350.

Helicobacter pylori (*H. pylori*) has been found to be associated with various gastrointestinal diseases. Confirmation of *H. pylori* infection includes invasive and non-invasive methods. There has been increasing interest in noninvasive tests recently. However, the geographical differences among *H. pylori* strains have been emphasized recently and the *H. pylori* strain in Taiwan showed a high *cagA* positive result and different *vacA* subtype when compared with those of Western countries. The aim of this study is to access and compare the reliability and the diagnostic accuracy of the stool *H. pylori* antigen tests by spectrophotometry and by the visual method, especially in Southern Taiwan. Thirty-two patients (18 men and 14 women; age range: 23-91 y/o, mean: 50.5 y/o) who underwent gastroendoscopy at Kaohsiung Medical University Hospital were enrolled in this study. *H. pylori* infection status was confirmed by culture or two positive test results on CLO test, histology and ¹³C-urea breath test (¹³C-UBT). The exclusion criteria included previous gastrointestinal tract surgery, use of antibiotics, proton pump inhibitor or compounds containing bismuth within 1 month of the study. Among them, 14 patients were with duodenal ulcer (DU), 4 with gastric ulcer (GU), 12 with non-ulcer dyspepsia, and 2 with GU and DU. Those patients had their stool collected for ELISA tests of *H. pylori* stool antigen (HpSA). The HpSA tests were positive in 16 of 18 patients diagnosed as *H. pylori* positive, and negative in 13 of 14 patients as *H. pylori* negative. The sensitivity and specificity were 88.9% and 92.9% respectively. The positive and negative predictive values were 94.1% and 86.7% respectively. The concordance of HpSA accessed by spectrophotometry and visual method is 100%, which makes this test even easier and cheaper. We concluded that stool HpSA test is a noninvasive, accurate, reliable, rapid and easy way to diagnose *H. pylori* infection in Southern Taiwan, either by spectrophotometry or by visual assessment.

Abstracts

Recently Published Abstracts

Bromelain: biochemistry, pharmacology and medical use.

Maurer HR. *Cell Mol Life Sci* 2001;58:1234-1245.

Bromelain is a crude extract from the pineapple that contains, among other components, various closely related proteinases, demonstrating, in vitro and in vivo, antiedematous, antiinflammatory, antithrombotic and fibrinolytic activities. The active factors involved are biochemically characterized only in part. Due to its efficacy after oral administration, its safety and lack of undesired side effects, bromelain has earned growing acceptance and compliance among patients as a phytotherapeutic drug. A wide range of therapeutic benefits has been claimed for bromelain, such as reversible inhibition of platelet aggregation, angina pectoris, bronchitis, sinusitis, surgical traumas, thrombophlebitis, pyelonephritis and enhanced absorption of drugs, particularly of antibiotics. Biochemical experiments indicate that these pharmacological properties depend on the proteolytic activity only partly, suggesting the presence of nonprotein factors in bromelain. Recent results from preclinical and pharmacological studies recommend bromelain as an orally given drug for complementary tumor therapy: bromelain acts as an immunomodulator by raising the impaired immunocytotoxicity of monocytes against tumor cells from patients and by inducing the production of distinct cytokines such as tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, and IL-8. In a recent clinical study with mammary tumor patients, these findings could be partially confirmed. Especially promising are reports on animal experiments claiming an antimetastatic efficacy and inhibition of metastasis-associated platelet aggregation as well as inhibition of growth and invasiveness of tumor cells. Apparently, the antiinvasive activity does not depend on the proteolytic activity. This is also true for bromelain effects on the modulation of immune functions, its potential to eliminate burn debris and to accelerate wound healing. Whether bromelain will gain wide acceptance as a drug that inhibits platelet aggregation, is antimetastatic and facilitates skin debridement, among other indications, will be determined by further clinical trials. The claim that bromelain cannot be effective after oral administration is definitely refuted at this time.

Quercetin and tamoxifen sensitize human melanoma cells to hyperthermia.

Piantelli M, Tatone D, Castrilli G, et al. *Melanoma Res* 2001;11:469-476.

Hyperthermia produces regression of human cancer. Because hyperthermia has produced only limited results, attention has focused on searching for substances able to sensitize tumour cells to the effects of hyperthermia. The flavonoid quercetin has been reported to be a hyperthermic sensitizer in ovarian and uterine cervical tumours and in leukaemia. Quercetin and tamoxifen inhibit melanoma cell growth. We therefore investigated whether quercetin and tamoxifen can sensitize M10, M14 and MNT1 human melanoma cells to hyperthermia. We observed that both quercetin and tamoxifen synergize with hyperthermia (42.5 degrees C) in reducing the clonogenic activity of M14 and MNT1 and in inducing apoptotic cell death in all three cell lines. As revealed by flow cytometric and Northern blot analyses, quercetin and tamoxifen reduced heat shock protein-70 expression at both protein and mRNA levels. Our results suggest that quercetin and tamoxifen can be usefully combined with hyperthermia in the therapy of recurrent and/or metastatic melanoma.

Ginkgo biloba extract EGb 761 or pentoxifylline for the treatment of sudden deafness: a randomized, reference-controlled, double-blind study.

Reisser CH, Weidauer H. *Acta Otolaryngol* 2001;121:579-584.

In a randomized, prospective, double-blind study involving 72 patients, the therapeutic efficacy of ginkgo extract EGb 761 (n = 37) was compared to that of pentoxifylline (n = 35) for the treatment of sudden deafness. The two therapeutic schedules were equally well tolerated and showed a statistically significant equivalence in improvement or in return to normal of the auditory thresholds in the two patient groups. Furthermore, no differences were found between the treatment groups with regard to the criteria for a return to normal of speech discrimination and reduction of the tinnitus which arose at the same time as the sudden hearing loss. The patient's subjective assessment of the treatment with regard to improvement in hearing and reduction in tinnitus suggested that Ginkgo biloba extract was more beneficial than pentoxifylline. In summary, it was shown that treatment of sudden deafness with ginkgo special extract EGb 761 was as effective as treatment with pentoxifylline.

Effects of melatonin on doxorubicin cytotoxicity in sensitive and pleiotropically resistant tumor cells.

Granzotto M, Rapozzi V,
Decorti G, Giraldi T. *J
Pineal Res* 2001;31:206-213.

Melatonin has been reported to attenuate the oxidative damage caused by doxorubicin on kidney, brain, heart and bone marrow, whereas the in vivo antitumor effects of doxorubicin were not attenuated. The effects of melatonin on doxorubicin cytotoxicity have, therefore, been examined on human normal mammary epithelium HBL-100, on mammary adenocarcinoma MCF-7, on colon carcinoma LoVo, and on mouse P388 leukemia cell lines, and on tumor cell sublines pleiotropically resistant to anthracyclines. Melatonin in the concentration range 10-2000 pg/mL causes an inhibition of the growth of the human cell lines examined which is not clearly dose-dependent and less than 25% when significant. Melatonin similarly causes minor effects on doxorubicin cytotoxicity either on the parental human cell lines or on their resistant sublines. On the contrary, 200-1000 pg/mL melatonin cause a significant and dose-dependent partial sensitization to doxorubicin of resistant P388 mouse leukemia (P388/ADR), which occurs also in vivo, as indicated by a significant increase in survival time of the hosts. Doxorubicin intracellular concentrations in P388/ADR cells are increased by melatonin, suggesting that melatonin might inhibit P-glycoprotein-mediated doxorubicin efflux from the cells. These results indicate that the use of melatonin in clinical cancer treatment should not pose the risk of an attenuation of the effectiveness of doxorubicin, and encourage the further examination of the possible reduction by melatonin of the host toxicity of antitumor chemotherapy.

Redox-mediated effects of selenium on apoptosis and cell cycle in the LNCaP human prostate cancer cell line.

Zhong W, Oberley TD.
Cancer Res 2001;61:7071-7078.

The effects of selenium exposure were studied in LNCaP human prostate cancer cells, and this same cell line adapted to selenium over 6 months to compare acute versus chronic effects of sodium selenite, the latter most closely resembling human clinical trials on the effects of selenium in cancer prevention and therapy. Our results demonstrated that oxidative stress was induced by sodium selenite at high concentrations in both acute and chronic treatments, but outcomes were different. After acute exposure to selenite, cells exhibited mitochondrial injury and cell death, mainly apoptosis. After chronic exposure to selenite, cells showed growth inhibition caused by cell cycle arrest, increased numbers of mitochondria and levels of mitochondrial enzymes, and only minimal induction of apoptosis. Immunoblotting analysis revealed that multiple proteins were up-regulated by chronic exposure to selenite. Among them, only up-regulation of manganese superoxide dismutase and the cyclin-dependent kinase inhibitor p21(Waf1/Cip1), proteins known to be redox sensitive and to have cell cycle regulatory functions, correlated with cell growth inhibition. Our results in selenite-adapted cells suggest that selenium may exert its effects in human prostate cancer cells by altering intracellular redox state, which subsequently results in cell cycle block.

Abstracts

Recently Published Abstracts

Antioxidants and viral infections: host immune response and viral pathogenicity.

Beck MA. *J Am Coll Nutr* 2001;20:384S-388S.

Malnutrition has long been associated with increased susceptibility to infectious disease. The increase in severity from and susceptibility to infectious disease in malnourished hosts is thought to be the result of an impaired immune response. For example, malnutrition could influence the immune response by inducing a less effective ability to manage the challenge of an infectious disease. Work in our laboratory has demonstrated that not only is the host affected by the nutritional deficiency, but the invading pathogen is as well. Using a deficiency in selenium (Se) as a model system, mice deficient in Se were more susceptible to infection with coxsackievirus, as well as with influenza virus. Se-deficient mice develop myocarditis when infected with a normally benign strain of coxsackievirus. They also develop severe pneumonitis when infected with a mild strain of influenza virus. The immune system was altered in the Se-deficient animals, as was the viral pathogen itself. Sequencing of viral isolates recovered from Se-deficient mice demonstrated mutations in the viral genome of both coxsackievirus and influenza virus. These changes in the viral genome are associated with the increased pathogenesis of the virus. The antioxidant selenoenzyme, glutathione peroxidase-1, was found to be critically important, as glutathione peroxidase knockout mice developed myocarditis, similar to the Se-deficient mice, when infected with the benign strain of myocarditis. This work points to the importance of host nutrition in not only optimizing the host immune response, but also in preventing viral mutations which could increase the viral pathogenicity.