

Estrogenicity of black cohosh (*Cimicifuga racemosa*) and its effect on estrogen receptor level in MCF-7 cells. [Article in Chinese]

Liu Z, Yang Z, Zhu M, Huo J. *Wei Sheng Yan Jiu* 2001;30:77-80.

The estrogenicity of Black Cohosh (*Cimicifuga racemosa*, CR) was tested in vivo and in vitro and its effect on estrogen receptor (ER) level of human breast cancer MCF-7 cells were investigated. Based on the body weight of animals, 75, 150 and 300 mg/kg of CR were administered by tube feeding to immature female mice for 14 days. Estrus was observed and the uterine and ovary weights of mice were measured. The optimal dose of CR for the growth of MCF-7 cells was screened by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assay. Subsequently, Growth curves of MCF-7 cells in blank control, 4.75 micrograms/L of CR and 0.3 nmol/L of 17 beta-estradiol groups were observed for 5 days. ER level in MCF-7 cells was analyzed by indirect immunofluorescence assay in flow cytometry. The results showed that uterine weight increased with the increasing dosage of CR and the days of estrus was significantly prolonged in the 300 mg/kg group ($P < 0.05$). The concentration of CR at 4.75 micrograms/L showed the strongest enhancement effects (64.7%). The doubling time (TD) of cell growth in CR group and 17 beta-estradiol group were 32.1 h and 31.7 h respectively, which were shorter than that of blank control (TD = 35.3 h). Additionally, 4.75 micrograms/L of CR significantly increased ER levels compared with the blank control ($P < 0.01$). Taking all the results together, CR has an estrogen-like action. The enhancing effect of CR on ER level is one of the potential mechanisms involved with its therapeutic role in climacteric syndrome.

(+)-Catechin inhibits intestinal tumor formation and suppresses focal adhesion kinase activation in the min/+ mouse.

Weyant MJ, Carothers AM, Dannenberg AJ, Bertagnolli MM. *Cancer Res* 2001;61:118-125.

Colorectal cancer is sensitive to dietary influences. Epidemiological data linking high intake of fruits and vegetables to decreased cancer risk have prompted the search for specific plant constituents implicated in tumor prevention. This task is difficult because of the complex chemical composition of plant foods and the multifactorial nature of carcinogenesis. Researchers are aided in this effort by the C57BL/6J-Min/+ (Min/+) mouse, an animal bearing a germline defect in Apc that is similar to the initiating genetic event in the majority of human colorectal cancers. In this study, we treated Min/+ mice with (+)-catechin, a phenolic antioxidant abundant in certain fruits. Administration of (+)-catechin in an AIN-76A diet at doses of 0.1 and 1% decreased the intestinal tumor number by 75 and 71%, respectively. Mechanistic studies linked this effect to (+)-catechin-induced changes in integrin-mediated intestinal cell-survival signaling, including structural alteration of the actin cytoskeleton and decreased focal adhesion kinase (FAK) tyrosine phosphorylation. Immunoblot analysis of small intestine scrapings from Min/+ mice and Apc+/+ wild-type C57BL/6J littermates together with excised Min/+ adenomas showed increased expression of phosphorylated FAK in the macroscopically normal enterocytes of untreated Min/+ mice and adenomas. Confirming the relevance of this signaling pathway, treatment of Min/+ mice with (+)-catechin reduced the expression of phosphorylated FAK to a level similar to the wild-type littermate controls. Thus, the natural abundance and favorable bioavailability of (+)-catechin make it a promising addition to the list of potential colorectal

Incidence and clinical relevance of the interactions and side effects of Hypericum preparations.

Schulz V. *Phytomedicine* 2001;8:152-160.

Observational studies with preparations of St. John's wort have recorded an incidence of adverse events (AE) among those treated of between 1 and 3%. This is some ten times less than with synthetic antidepressants. The most common adverse events (1 per 300000 treated cases) among the spontaneous reports in the official register concern reactions of the skin exposed to light. Investigations in volunteers have shown that the threshold dose for an increased risk of photosensitisation is about 2-4 g/day of a usual commercial extract (equivalent to approximately 5-10 mg of the hypericin that causes the phenomenon). In view of the newly observed side effects and interactions, the following additional restrictions on use appear justified: as with all preparations in this group of indications, hypericum preparations must not be taken at the same time as other antidepressants. If co-medication with coumarin-type anticoagulants is unavoidable, it must only be undertaken provided the physician closely monitors clotting parameters. Co-medication with ciclosporin and indinavir, and for the time being, other protease inhibitors used in anti-HIV treatment, is absolutely contraindicated. Without exception, all preparations of St. John's wort must only be available through pharmacies.

Ginger for nausea and vomiting in pregnancy: Randomized, double-masked, placebo-controlled trial.

Vutyavanich T, Kraissarin T, Ruangsri R. *Obstet Gynecol* 2001;97:577-582.

Objective: To determine the effectiveness of ginger for the treatment of nausea and vomiting of pregnancy. **Methods:** Women with nausea and vomiting of pregnancy, who first attended an antenatal clinic at or before 17 weeks' gestation, were invited to participate in the study. During a 5-month period, 70 eligible women gave consent and were randomized in a double-masked design to receive either oral ginger 1 g per day or an identical placebo for 4 days. Subjects graded the severity of their nausea using visual analog scales and recorded the number of vomiting episodes in the previous 24 hours before treatment, and again during 4 consecutive days while taking treatment. At a follow-up visit 7 days later, five-item Likert scales were used to assess the severity of their symptoms. **Results:** All participants except three in the placebo group remained in the study. The visual analog scores of posttherapy minus baseline nausea decreased significantly in the ginger group (2.1 +/- 1.9) compared with the placebo group (0.9 +/- 2.2, P = .014). The number of vomiting episodes also decreased significantly in the ginger group (1.4 +/- 1.3) compared with the placebo group (0.3 +/- 1.1, P Y.001). Likert scales showed that 28 of 32 in the ginger group had improvement in nausea symptoms compared with 10 of 35 in the placebo group (P <.001). No adverse effect of ginger on pregnancy outcome was detected. **Conclusion:** Ginger is effective for relieving the severity of nausea and vomiting of pregnancy.

Indian medicinal plants as antiradicals and DNA cleavage protectors.

Russo A, Izzo AA, Cardile V, et al. *Phytomedicine* 2001;8:125-132.

Celastrus paniculatus L. (Celastraceae) (CP), Picrorhiza kurroa L. (Scrophulariaceae) (PK) and Withania somnifera L. (Solanaceae) (WS) are Indian medicinal plants having a remarkable reputation, as a factor of health care, among the indigenous medical practitioners. The plants exhibit varying degrees of therapeutic value some of which useful in the treatment of cognitive dysfunction, epilepsy, insomnia, rheumatism, gout, dyspepsia. In this work, we have investigated the free radical scavenging capacity of methanolic extracts from CP, PK, WS and the effect on DNA cleavage induced by H₂O₂ UV-photolysis. In addition, we investigated whether these plant extracts are capable of reducing the hydrogen peroxide-induced cytotoxicity and DNA damage in human non-immortalized fibroblasts. These extracts showed a dose-dependent free radical scavenging capacity and a protective effect on DNA cleavage; methanolic extracts from PK was more active than extracts from CP and WS. These results were confirmed by a significant protective effect on H₂O₂-induced cytotoxicity and DNA damage in human non-immortalized fibroblasts. These antioxidant effects of active principle of CP, PK and WS may explain, at least in part, the reported anti-stress, immunomodulatory, cognition-facilitating, anti-inflammatory and antiaging effects produced by them in experimental animal and in clinical situations and may justify the further investigation of their other beneficial biological properties.

Abstracts

Recently Published Abstracts

Antimutagenic potential of extracts isolated from Terminalia arjuna.

Kaur S, Grover IS, Kumar S.
J Environ Pathol Toxicol Oncol 2001;20:9-14.

Terminalia arjuna is an important medicinal plants widely used in the preparation of Ayurvedic formulations used against several ailments. The present investigation was aimed at the fractionation of crude extracts from the bark of *T. arjuna* in order to isolate and purify the antimutagenic factors present. The antimutagenicity assay was performed to check the modulatory effect of these fractions against NPD, sodium azide, and 2AF, using the Ames Salmonella his+ reversion assay. Most of the phenolic fractions exhibited mutagen specificity against direct-acting mutagens, being effective in suppressing the frameshift mutagen NPD but failing to inhibit sodium azide (base pair substitution)-induced his+ revertants. ET-1 fraction triterpenoid diglycoside showed a marked effect against sodium azide but was ineffective against NPD. In the case of the indirect-acting mutagen 2AF, all the fractions were found to be quite potent in modulating its mutagenicity in both TA98 and TA100 tester strains of Salmonella typhimurium. The results indicate that the bark of *T. arjuna* harbors constituents with promising antimutagenic/anticarcinogenic potential that should be investigated further.

Undecylenic Acid Inhibits Morphogenesis of Candida albicans.

McLain N, Ascanio R, Baker C, et al. *Antimicrob Agents Chemother* 2000;44:2873–2875.

Resilient liners are frequently used to treat denture stomatitis, a condition often associated with *Candida albicans* infections. Of 10 liners tested, 2 were found to inhibit the switch from the yeast form to hyphae and a third was found to stimulate this switch. The inhibitor was determined to be undecylenic acid.

American ginseng (*Panax quinquefolius* L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals.

Vuksan V, Sievenpiper JL, Wong J, et al. *Am J Clin Nutr* 2001;73:753-758.

BACKGROUND: We previously showed that 3 g American ginseng administered 40 minutes before an oral glucose challenge significantly reduces postprandial glycemia in subjects without diabetes. Whether this effect can be replicated with doses <3 g and administration times closer to the oral glucose challenge is unclear. **OBJECTIVE:** Our objective was to study the dosing and timing effects of American ginseng on postprandial glycemia. **DESIGN:** In a random crossover design, 12 healthy individuals [X \pm SEM age: 42 \pm 7 y; body mass index (BMI; in kg/m²): 24.1 \pm 1.1] received 16 treatments: 0 (placebo), 1, 2, or 3 g American ginseng at 40, 20, 10, or 0 min before a 25-g oral glucose challenge. Capillary blood was collected before administration and at 0, 15, 30, 45, 60, and 90 min after the start of the glucose challenge. **RESULTS:** Two-way analysis of variance showed that the main effects of treatment and administration time were significant ($P < 0.05$). Glycemia was lower over the last 45 min of the test after doses of 1, 2, or 3 g ginseng than after placebo ($P < 0.05$); there were no significant differences between doses. The reductions in the areas under the curve for these 3 doses were 14.4 \pm 6.5%, 10.6 \pm 4.0%, and 9.1 \pm 6%, respectively. Glycemia in the last hour of the test and area under the curve were significantly lower when ginseng was administered 40 min before the challenge than when it was administered 20, 10, or 0 min before the challenge ($P < 0.05$). **CONCLUSIONS:** American ginseng reduced postprandial glycemia in subjects without diabetes. These reductions were time dependent but not dose dependent: an effect was seen only when the ginseng was administered 40 min before the challenge. Doses within the range of 1-3 g were equally effective.

Abstracts

Recently Published Abstracts

Combined administration of a chelating agent and an antioxidant in the prevention and treatment of acute lead intoxication in rats.

Pande M, Mehta A, Pant BP, Flora SJ. *Environ Toxicol Pharmacol* 2001;9:173-184.

The administration of chelating agents, meso 2,3-dimercaptosuccinic acid (DMSA), monoisoamyl DMSA (MiADMSA) either individually or in combination with an antioxidant, n-acetylcysteine (NAC) in the prevention and treatment of acute lead intoxication in rats, was investigated. The results suggest that concomitant oral supplementation of DMSA with lead was most effective in preventing the inhibition of lead sensitive blood delta-aminolevulinic acid dehydratase (ALAD) activity in blood, elevation of zinc protoporphyrin level and the alterations in hepatic reduced and oxidized glutathione (GSH and GSSG) contents. A number of other biochemical variables either remained insensitive to lead exposure or responded moderately to chelation treatment. Combined administrations of NAC plus DMSA was most effective when given during lead exposure or post exposure, followed by DMSA and MiADMSA alone or NAC plus MiADMSA treatment, in reducing the accumulation of lead in blood and liver. Administration of NAC alone was only mildly effective in preventing lead absorption in the blood and tissues. The results suggest that combined administration of DMSA and NAC could be a more effective treatment protocol for acute lead toxicity, keeping in view its beneficial effect on oxidative injury.

Effects of gamma-linolenic acid and oleic acid on paclitaxel cytotoxicity in human breast cancer cells.

Menendez JA, del Mar Barbacid M, Montero S, et al. *Eur J Cancer* 2001;37:402-413.

It has been suggested that dietary interventions may improve the effectiveness of cancer chemotherapy. We have examined the combined in vitro cytotoxicity of paclitaxel and the fatty acids gamma-linolenic acid (GLA, 18:3n-6) and oleic acid (OA, 18:1n-9) in human breast carcinoma MDA-MB-231 cells. The effect of fatty acids on paclitaxel chemosensitivity was determined by comparing IC(50) and IC(70) (50 and 70% inhibitory concentrations, respectively) obtained when the cells were exposed to IC(50) and IC(70) levels of paclitaxel alone and fatty acids were supplemented either before or during the exposure to paclitaxel. The 3-4,5-dimethylthiazol-2-yl-2,5-diphenyl-tetrazolium bromide (MTT) assay was used to determine cell growth inhibition. GLA by itself showed antiproliferative effects, and a possible GLA-paclitaxel interaction at the cellular level was assessed by the isobologram and the combination-index (CI) methods.

Isobole analysis at the isoeffect levels of 50 and 70% revealed that drug interaction was predominantly synergistic when GLA and paclitaxel were added concurrently for 24 h to the cell cultures. Interaction assessment using the median-effect principle and the combination-index (CI) method showed that exposure of MDA-MB-231 cells to an equimolar combination of concurrent GLA plus paclitaxel for 24 h resulted in a moderate synergism at all effect levels, consistent with the results of the isobologram analysis. When exposure to GLA (24 h) was followed sequentially by paclitaxel (24 h) only an additive effect was observed. The GLA-mediated increase in paclitaxel chemosensitivity was only partially abolished by Vitamin E, a lipid peroxidation inhibitor, suggesting a limited influence of the oxidative status of GLA in achieving potentiation of paclitaxel toxicity. When OA (a non-peroxidisable fatty acid) was combined with paclitaxel, an enhancement of chemosensitivity was found when OA was used concurrently with paclitaxel, although less markedly than with GLA. Pretreatment of MDA-MB-231 cells with OA for 24 h prior to a 24 h paclitaxel exposure produced greater enhancement of paclitaxel sensitivity at high OA concentrations than the concurrent exposure to OA and paclitaxel. The OA-induced sensitisation to paclitaxel was not due to the cytotoxicity of the fatty acid itself. When these observations were extended to three additional breast carcinoma cell lines (SK-Br3, T47D and MCF-7), simultaneous exposure to GLA and paclitaxel also resulted in synergism. GLA preincubation followed by paclitaxel resulted in additivity for all cell lines. Simultaneous exposure to paclitaxel and OA enhanced paclitaxel cytotoxicity in T47D and MCF-7 cells, but not in SK-Br3 cells, whereas preincubation with OA failed to increase paclitaxel effectiveness in all three cell lines. For comparison, the effects of other fatty acids on paclitaxel chemosensitivity were examined: GLA was the most potent at enhancing paclitaxel cytotoxicity, followed by alpha-linolenic acid (ALA; 18:3n.3), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), whereas linoleic acid (LA; 18:2n-6) did not increase paclitaxel toxicity. These findings provide experimental support for the use of fatty acids as modulators of tumour cell chemosensitivity in paclitaxel-based therapy.

Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine-deficient diet.

Son HY, Nishikawa A, Ikeda T, et al. *Jpn J Cancer Res* 2001;92:103-108.

We have reported a dramatic synergism between soy intake and iodine deficiency regarding induction of thyroid hyperplasia in rats. Because isoflavones are active constituents of soybeans, in the present study, their possible contribution was examined. Female F344 rats were divided into 8 groups, exposed to diet containing a 0.2% soy isoflavone mixture (SI), 0.2% SI + iodine deficiency (ID), 0.04% SI, 0.04% SI + ID, 20% defatted soybean (DS) alone, 20% DS + ID, ID alone or basal diet alone for 5 weeks. Thyroid weight was not influenced by SI, but was increased by the ID and DS diets with a further significant increment in the DS + ID group ($P < 0.01$). Compared to the control value, serum T(4) was significantly ($P < 0.01$) increased by 20% DS alone and decreased in all groups given the ID treatment ($P < 0.001$). Serum thyroid stimulating hormone (TSH) level was increased by ID, and further enhanced by DS ($P < 0.01$) but not SI. Histopathologically, diffuse hypertrophy and / or hyperplasia of thyroid follicles were observed in the ID-treated groups, the severity being enhanced by DS but not SI. Proliferating cell nuclear antigen labeling indices (%) were elevated in the ID diet groups and again enhanced by DS, but not SI. These results thus suggest that isoflavones may not be involved in the mechanisms underlying the synergistic goitrogenic effect of soybean with iodine deficiency.

Correlates of serum alpha- and gamma-tocopherol in the Women's Health Initiative.

White E, Kristal AR, Shikany JM, et al. *Ann Epidemiol* 2001;11:136-144.

PURPOSE: There is increasing evidence that vitamin E (primarily alpha- and gamma-tocopherol) may reduce the risk of cardiovascular disease and some cancers, therefore it is important to understand factors that influence blood levels. **METHODS:** The correlates of serum alpha- and gamma-tocopherol were investigated among participants in the Women's Health Initiative (WHI), a 40-site disease prevention trial. Subjects were 1047 postmenopausal women aged 50-79 years, who provided fasting blood specimens and detailed information on diet, supplement use, and other factors at entry to the study (1994-96). **RESULTS:** Total serum cholesterol and triglycerides were highly correlated with serum alpha- and gamma-tocopherol concentrations and were controlled for in all analyses along with age, ethnicity and body mass index (BMI). Alpha and gamma-tocopherol were strongly negatively correlated (partial $r = -0.69$). The strongest predictor of serum tocopherols was average daily intake of vitamin E from supplements (partial $r = 0.60$ for alpha, $r = -0.54$ for gamma). Other factors associated with increased alpha- and/or decreased gamma-tocopherol concentrations were serum retinol and carotenoids, supplemental vitamin C, alpha-tocopherol intake from food, dietary fiber, and Hispanic ethnicity. Factors associated with lower alpha- and/or higher gamma-tocopherol concentrations included gamma-tocopherol intake from food, total fat intake, and BMI. Age, income, hormone use, and geographic location were "spuriously" associated with serum tocopherol levels through their association with supplement use, i.e., there was no such association among the subset of women not taking supplements. **CONCLUSIONS:** Vitamin E intake from supplements and BMI are the major independent predictors of serum tocopherol levels in women, whereas dietary factors only play a small role.

Low-dose vitamin B-6 effectively lowers fasting plasma homocysteine in healthy elderly persons who are folate and riboflavin replete.

McKinley MC, McNulty H, McPartlin J, et al. *Am J Clin Nutr* 2001;73:759-764.

BACKGROUND: Current data suggest that physiologic doses of vitamin B-6 have no significant homocysteine-lowering effect. It is possible that an effect of vitamin B-6 was missed in previous trials because of a much greater effect of folic acid, vitamin B-12, or both. **OBJECTIVE:** The aim of this study was to investigate the effect of low-dose vitamin B-6 supplementation on fasting total homocysteine (tHcy) concentrations in healthy elderly persons who were made replete with folate and riboflavin. **DESIGN:** Twenty-two healthy elderly persons aged 63-80 y were supplemented with a low dose of vitamin B-6 (1.6 mg/d) for 12 wk in a randomized, double-blind, placebo-controlled trial after repletion with folic acid (400 microg/d for 6 wk) and riboflavin (1.6 mg/d for 18 wk); none of the subjects had a vitamin B-12 deficiency. **RESULTS:** Folic acid supplementation lowered fasting tHcy by 19.6% ($P < 0.001$). After folic acid supplementation, baseline tHcy concentrations ranged from 6.22 to 23.52 micromol/L and 10 subjects had suboptimal vitamin B-6 status (plasma pyridoxal-P < 20 nmol/L). Two-way analysis of variance showed that the significant improvement in vitamin B-6 status in response to vitamin B-6 supplementation (on the basis of both pyridoxal-P: and the erythrocyte aspartate aminotransferase activation coefficient) was reflected in a significant reduction in plasma tHcy of 7.5%. **CONCLUSIONS:** Low-dose vitamin B-6 effectively lowers fasting plasma tHcy in healthy subjects who are both folate and riboflavin replete. This suggests that any program aimed at the treatment or prevention of hyperhomocysteinemia should include vitamin B-6 supplementation.

Petasites hybridus (butterbur root) extract is effective in the prophylaxis of migraines. Results of a randomized; double-blind trial.

Mauskop A, Grossman WM, Schmidramsl H. *Headache* 2000;40:420.

This study examined the efficacy and tolerability of an extract of *Petasites hybridus* compared to placebo in a double-blind parallel group trial of patients suffering from headaches with and without aura, as classified by the IHS. After a 4-week run-in observation phase without any trial medication, 60 such patients received randomly either the *Petasites* preparation (50 mg BID) or placebo for 12 weeks. A total of 33 patients were allocated to the drug group and 27 patients to the placebo group. In all, 58 patients completed the study. The efficacy was evaluated by means of a headache diary in which the frequency, duration and intensity of migraine headache were assessed. The frequency of migraine attacks per 4 weeks from patient diaries was defined as the primary efficacy variable. In addition, migraine-associated symptoms, use of analgesics, global assessment of efficacy as well as the occurrence of events were assessed. Compared to placebo, *Petasites hybridus* significantly reduced the frequency of migraine attacks and days with migraine per month as well as the frequency of accompanying symptoms (p less than 0.05). Global assessment of efficacy was also significantly better for the active group (p less than 0.01). The duration and intensity of pain were also diminished, but these results were not statistically significant. Compared to baseline, *Petasites hybridus* reduced the frequency of attacks by 46% after 4 weeks, 60% after 8 weeks and 50% after 12 weeks of treatment (placebo group: 24%, 17% and 10%, respectively). No adverse drug reactions were reported in either the drug or placebo group. The efficacy and excellent tolerability of the *Petasites hybridus* extract observed in this study suggest that this plant preparation can be of clinical benefit to migraine patients.

Abstracts

Recently Published Abstracts

Retinal glutamate in diabetes and effect of antioxidants.

Kowluru RA, Engerman RL, Case GL, Kern TS.

Neurochem Int 2001;38:385-390.

Diabetes results in various biochemical abnormalities in the retina, but which of these abnormalities are critical in the development of retinopathy is not known. The aim of this study is to examine the effect of antioxidant supplementation on diabetes-induced alterations of retinal glutamate, and to explore the inter-relationship between alterations of retinal glutamate, oxidative stress, and nitric oxide (NO) in diabetes. Glutamate was measured in the retina at 2 months of diabetes in rats receiving diets supplemented with or without a mixture of antioxidants containing ascorbic acid, Trolox, DL alpha-tocopherol acetate, N-acetyl cysteine, beta-carotene and selenium. The relationship between glutamate, oxidative stress and NO was evaluated using both bovine retinal endothelial cells and normal rat retina. In diabetes, retinal glutamate was elevated by 40, thiobarbituric acid-reactive substances (TBARS) by 100, and NO by 70%, respectively. Administration of antioxidants inhibited the diabetes-induced increases in glutamate, TBARS and NO. Incubation of bovine retinal endothelial cells or normal rat retina with glutamate significantly increased TBARS and NO, and addition of either antioxidant (N-acetyl cysteine) or a NO synthase inhibitor prevented the glutamate-induced elevation in oxidative stress and NO. Incubation of retina with a glutamate agonist, likewise elevated oxidative stress and NO, and memantine inhibited such elevations. Thus, the alterations of retinal glutamate, oxidative stress and NO appear to be inter-related in diabetes, and antioxidant therapy may be a suitable approach to determine the roles of these abnormalities in the development of diabetic retinopathy.

Colorectal adenomas and diet: a case-control study. Colorectal Adenoma Study Group.

Breuer-Katschinski B, Nemes K, Marr A, et al. *Dig Dis Sci* 2001;46:86-95.

It has been postulated that high intakes of animal fat and protein and low intakes of fiber, calcium, and antioxidants increase the risk of colorectal cancer. Whether specific types of protein such as that from red meat are important, and whether vegetables might be key protective factors will also be considered in this study. Dietary intake over the past year was studied according to the diet history method by means of a case-control study in 184 cases and matched controls. After adjustment for energy, relative weight, and social class, no associations were found for fat or protein in comparison with either control group. Unexpectedly, carbohydrate intake was inversely related with adenoma risk, the RR being 0.29 (0.10-0.81) for quintile 5 versus 1 in comparison with hospital controls. None of the antioxidants showed a significant protective effect except beta-carotene intake in comparison with hospital controls, the RR being 0.24 (0.11-0.50) for the highest versus the lowest quintile. There was, however, a statistically significant positive association between adenomas and meat consumption with the RR for the highest versus the lowest quintile. There was, however, a statistically significant positive association between adenomas and meat consumption with the RR for the highest versus the lowest quintile of intake being 3.6 (1.7-7.5) in comparison with hospital controls and 4.4 (1.6-12.1) in comparison with population controls. Our data support the protective role for carbohydrate intake and of beta-carotene intake in the etiology of colorectal adenomas and show a strong increased risk for developing adenomas in those with high meat intake.

Thyroid hypofunction in Down's syndrome: is it related to oxidative stress?

Kanavin OJ, Aaseth J, Birketvedt GS. *Biol Trace Elem Res* 2000;78:35-42.

Oxidative stress affecting the thyroxin biosynthesis might explain the proneness of patients with Down's syndrome (DS) (trisomia 21) to develop hypothyroidism. Thyroideal cells are exposed to endogenous H₂O₂ that acts as a cofactor for the iodination of thyroxin precursors. The gland has high levels of selenium-containing proteins, including peroxide-detoxifying enzyme proteins. The object of the present study was to explore the hypothesis of a role of an imbalance between toxic oxygen production and protective metalloenzymes during the development of thyroid hypofunction in DS patients. We analyzed serum levels of thyroid hormones and trace metals in 38 institutionalized adults with DS, using mentally retarded subjects matched for age, sex, and behavioral function as controls. The DS patients had significantly lower mean values of free thyroxin (fT₄) and increased TSH (thyroid stimulating hormone), as compared to the controls. They had lower serum selenium than the controls. A positive correlation was observed between serum concentrations of fT₄ and selenium in the DS patients ($r = 0.393$, $p < 0.05$). No significant differences were found between the fT₄ or the TSH concentrations in the patients with and without circulating anti-thyroid autoantibodies. Our results support the suggestion that thyroid hypofunction in patients with Down's syndrome in some way is linked to the low serum levels of selenium found in these patients. It is suggested that selenium-containing proteins are involved in thyroid hormonal synthesis, by protecting biosynthetic processes against the toxicity of free oxygen radicals.

New evidence for antioxidant properties of vitamin C.

Vojdani A, Bazargan M, Vojdani E, Wright J. *Cancer Detect Prev* 2000;24:508-523.

This study was designed to examine the effect of 500 to 5,000 mg of ascorbic acid on DNA adducts, natural killer (NK) cell activity, programmed cell death, and cell cycle analysis of human peripheral blood leukocytes. According to our hypothesis, if ascorbic acid is a pro-oxidant, doses between 500 and 5,000 mg should enhance DNA adduct formation, decrease immune function, change the cell cycle progression, and increase the rate of apoptosis. Twenty healthy volunteers were divided into four groups and given either placebo or daily doses of 500, 1,000 or 5,000 mg of ascorbic acid for a period of 2 weeks. On days 0, 1, 7, 15, and 21, blood was drawn from them, and the leukocytes were separated and examined for intracellular levels of ascorbic acid, the level of 8-hydroxyguanosine, NK cell activity, cell cycle progression, and apoptosis. Depending on the subjects, between a 0% and a 40% increase in cellular absorption of ascorbic acid was observed when daily doses of 500 mg were used. At doses greater than 500 mg, this cellular absorption was not increased further, and all doses produced equivalent increases in ascorbic acid on days 1 to 15. This increase in cellular concentration of ascorbic acid resulted in no statistically meaningful changes in the level of 8-hydroxyguanosine, increased NK cytotoxic activity, a reduced percentage of cells undergoing apoptosis, and switched cell cycle phases from S and G2/M to G0/G1. After a period of 1 week, with no placebo or vitamin washout, ascorbic acid levels along with functional assays returned to the baseline and became equivalent to placebos. In comparison with baseline values, no change (not more than daily assays variation) was seen in ascorbate concentrations or other assays during oral placebo treatment. We concluded that ascorbic acid is an antioxidant and that doses up to 5,000 mg neither induce mutagenic lesions nor have negative effects on NK cell activity, apoptosis, or cell cycle. Publication Types:

Why oral calcium supplements may reduce renal stone disease: report of a clinical pilot study.

Williams CP, Child DF, Hudson PR, et al. *J Clin Pathol* 2001;54:54-62.

AIMS: To investigate whether increasing the daily baseline of gut calcium can cause a gradual downregulation of the active intestinal transport of calcium via reduced parathyroid hormone (PTH) mediated activation of vitamin D, and to discuss why such a mechanism might prevent calcium oxalate rich stones. To demonstrate the importance of seasonal effects upon the evaluation of such data. **METHODS:** Within an intensive 24 hour urine collection regimen, daily calcium supplementation (500 mg) was given to five stone formers for a 10 week period during a six month crossover study. In a further population of patients on follow up for previous renal stone disease, observations were made on 1066 24 hour urine samples collected over five years in respect of seasonal effects relevant to the interpretation of the study. **RESULTS:** In the group of patients on calcium supplements the following results were found. During calcium supplementation, the proportion of urine calcium to oxalate was higher (increased calcium to oxalate molar ratio), the 24 hour urine product of calcium and oxalate did not rise, and urine oxalate was lower during the first six weeks of supplementation. Twenty four hour urine calcium was 10.2% higher than baseline in the final four weeks of the 10 weeks of supplementation. Twenty four hour

urine phosphate was 11.4% lower during the first six weeks of supplementation, but then rose while the patients were still on supplementation; renal tubular reabsorption of phosphate (TmP/GFR) mirrored the urine phosphate changes inversely. PTH was higher after stopping supplementation, but 1,25-(OH)₂-cholecalciferol changes were not detected. In the 1066 urine samples collected over five years the following results were found. Calcium and oxalate excretion correlated positively and not inversely. Urine calcium and phosphate excretion were 5.5% and 2.5% higher, respectively, in “light” months of the year compared with “dark” months. A post summer decline in both urine calcium and urine phosphate was relevant to the interpretation of the study. **CONCLUSIONS:** Regular calcium supplementation does not raise the product of calcium and oxalate in urine and the proportion of oxalate to calcium is reduced. The underlying mechanisms of the changes seen in phosphate, calcium, and PTH and the observations on 1,25-(OH)₂-cholecalciferol are not clear. Observed changes in phosphate could possibly be part of a calcium regulating feedback loop operating over a period of weeks. In evaluating these mechanisms background seasonal effects are important. It is possible that “programming” of the gut mucosa in terms of calcium transport is a major determinant of the relation between calcium and oxalate concentrations in urine and their relative abundance. Increased oral calcium, in association with a reduction of the relative proportion absorbed, may be pertinent to the prevention of calcium oxalate rich stones.

Antioxidant treatment in hereditary pancreatitis. A pilot study on three young patients.

Uomo G, Talamini G, Rabitti PG. *Dig Liver Dis* 2001;33:58-62.

BACKGROUND: Abdominal pain is the most challenging symptom of hereditary pancreatitis. No specific and proven therapy is yet available; analgesics, often in large doses, are required also in children and young patients. **PATIENTS AND METHODS:** We performed an open-label, pilot study on three young patients, coming from the same kindred, with hereditary pancreatitis. The study period lasted two years (July 1997-July 1999) and was divided into four sub-periods of six months each. In the first and third period the patients took only oral analgesics, if necessary; in the second and fourth period, an antioxidant regimen per os was added. This treatment consisted of sulphadenosyl-methionine (800 mg per day), Vitamin C (180 mg per day), Vitamin E (30 mg per day), Vitamin A (2,400 microg per day), and selenium (75 microg per day). **RESULTS:** Compliance of patients to the treatment schedule was satisfactory and no important side-effects were observed. Antioxidant treatment led to a significant reduction ($p < 0.05$) in the number of days with abdominal pain experienced by the three patients and this was verified for both periods of treatment. Albeit, consumption of analgesics was lower in the antioxidant treatment periods. **CONCLUSIONS:** Oxidative stress may be one of the principle contributors to pain in hereditary pancreatitis and orally administered antioxidant treatment appears to be effective for control of the condition, in young patients, suffering from this rare disease.

Whey protein concentrate (WPC) and glutathione modulation in cancer treatment.

Bounous G. *Anticancer Res* 2000;20:4785-4792.

The glutathione (GSH) antioxidant system is foremost among the cellular protective mechanisms. Depletion of this small molecule is a common consequence of increased formation of reactive oxygen species during increased cellular activities. This phenomenon can occur in the lymphocytes during the development of the immune response and in the muscular cells during strenuous exercise. It is not surprising that so much research has been done, and is still being done on this small tripeptide molecule. Whey protein concentrate has been shown to represent an effective and safe cysteine donor for GSH replenishment during GSH depletion in immune deficiency states. Cysteine is the crucial limiting amino acid for intracellular GSH synthesis. Animal experiments showed that the concentrates of whey proteins also exhibit anti-carcinogenesis and anticancer activity. They do this via their effect on increasing GSH concentration in relevant tissues, and may have anti-tumor effect on low volume of tumor via stimulation of immunity through the GSH pathway. It is considered that oxygen radical generation is frequently a critical step in carcinogenesis, hence the effect of GSH on free radicals as well as carcinogen detoxification, could be important in inhibiting carcinogenesis induced by a number of different mechanisms. Case reports are presented which strongly suggest an anti-tumor effect of a whey protein dietary supplement in some urogenital cancers. This non toxic dietary intervention, which is not based on the principles of current cancer chemotherapy, will hopefully attract the attention of laboratory and clinical oncologists.

Glutamine.

Labow BI, Souba WW.

World J Surg 2000;24:1503-1513.

Relatively little was known about glutamine metabolism until the 1930s, when Sir Hans Krebs first demonstrated glutamine hydrolysis and biosynthesis in the kidney. Subsequent studies by Rose in 1938 demonstrated that glutamine is a nonessential (dispensable) amino acid, as it can be readily synthesized de novo in virtually all tissues in the body. Because the body has the capacity to synthesize considerable quantities of glutamine, it has been assumed that glutamine is not required in the diet. However, this amino acid becomes quite depleted during the course of a catabolic insult such as injury or infection, indicating that the ability of glutamine production to meet demands during a variety of surgical illnesses is impaired. In states of health, the assumption that glutamine is not required in the diet is probably valid, although it is difficult to test the hypothesis, as glutamine is present in virtually all dietary proteins. Most naturally occurring food proteins contain 4% to 8% of their amino acid residues as glutamine; therefore less than 10 g of dietary glutamine is likely to be consumed daily by the average person. In contrast to this usual dietary availability, studies in stressed patients indicate that considerably larger amounts of glutamine (20-40 g/day) may be necessary to maintain glutamine homeostasis. Thus from a nutritional standpoint, glutamine may be thought of as a drug as well as a nutrient. This paper reviews the physiology and biochemistry of glutamine with an emphasis on its metabolism in surgical illnesses and its role as a conditionally essential amino acid.

Abstracts

Recently Published Abstracts

Melatonin and its relation to the immune system and inflammation.

Reiter RJ, Calvo JR, Karbownik M, et al. *Ann NY Acad Sci* 2000;917:376-386.

Melatonin (N-acetyl-5-methoxytryptamine) was initially thought to be produced exclusively in the pineal gland. Subsequently its synthesis was demonstrated in other organs, for example, the retinas, and very high concentrations of melatonin are found at other sites, for example, bone marrow cells and bile. The origin of the high level of melatonin in these locations has not been definitively established, but it is likely not exclusively of pineal origin. Melatonin has been shown to possess anti-inflammatory effects, among a number of actions. Melatonin reduces tissue destruction during inflammatory reactions by a number of means. Thus melatonin, by virtue of its ability to directly scavenge toxic free radicals, reduces macromolecular damage in all organs. The free radicals and reactive oxygen and nitrogen species known to be scavenged by melatonin include the highly toxic hydroxyl radical (.OH), peroxy nitrite anion (ONOO-), and hypochlorous acid (HOCl), among others. These agents all contribute to the inflammatory response and associated tissue destruction. Additionally, melatonin has other means to lower the damage resulting from inflammation. Thus, it prevents the translocation of nuclear factor-kappa B (NF-kappa B) to the nucleus and its binding to DNA, thereby reducing the upregulation of a variety of proinflammatory cytokines, for example, interleukins and tumor necrosis factor-alpha. Finally, there is indirect evidence that melatonin inhibits the production of adhesion molecules that promote the sticking of leukocytes to endothelial cells. By this means melatonin attenuates transendothelial cell migration and edema, which contribute to tissue damage.

Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women.

Cagnacci A, Arangino S, Renzi A, et al. *Clin Endocrinol* 2001;54:339-346.

OBJECTIVE: The effect of melatonin on human carbohydrate metabolism is not yet clear. We investigated whether melatonin influences glucose tolerance and insulin sensitivity in aged women. **PATIENTS:** Twenty-two postmenopausal women of whom 14 were on hormone replacement therapy. **DESIGN:** After an overnight fast, at 0800 hours on two nonconsecutive days, placebo or melatonin (1 mg) were administered randomly and in a double blind fashion. Forty-five minutes later, an oral glucose tolerance test (75 g; OGTT) was performed in 13 women. In another nine women insulin-dependent (Si) and -independent (Sg) glucose utilization was tested by a frequently sampled intravenous glucose tolerance test (FSIGT). **RESULTS:** Areas under the response curve to OGTT (AUC) for glucose (1420 +/- 59 vs. 1250 +/- 55 mmol x min/l; P < 0.01), and C-peptide (420980 +/- 45320 vs. 33528 +/- 15779 pmol x min/l; P < 0.02) were higher following melatonin than placebo, while Si values were lower (2.6 +/- 0.28 units vs. 3.49 +/- 0.4 units; P < 0.03). Si modifications induced by melatonin were inversely related to Si values of the placebo day (r2 = 0.538; P = 0.025). **CONCLUSIONS:** The present results indicate that in aged women administration of 1 mg of melatonin reduces glucose tolerance and insulin sensitivity. The present data may have both physiological and clinical implications.

Abstracts

Recently Published Abstracts

Effect of dimethylglycine on gastric ulcers in rats.

Hariganesh K, Prathiba J. *J Pharm Pharmacol* 2000;52:1519-1522.

Dimethylglycine is an anti-stress nutrient with antioxidant properties. Recently, studies have implicated the generation of oxygen-derived free radicals and lipid peroxidation as one of the mechanisms in the pathogenesis of gastric ulcer. Hence, we evaluated the antiulcer activity of dimethylglycine in various rat models of ulcer and also investigated the probable antioxidant mechanism of the anti-ulcer effect. Dimethylglycine at a dose of 25 and 35 mg kg⁻¹ significantly reduced ulcer number, ulcer size and ulcer index in pyloric-ligation-, ibuprofen- and stress-induced ulcers. The 35 mg kg⁻¹ dose was more effective than 25 mg kg⁻¹ and was comparable to famotidine. Dimethylglycine did not produce any significant change in acid secretion, unlike famotidine. There was a significant increase in plasma and tissue malondialdehyde levels in pyloric-ligated rats but these levels fell following dimethylglycine treatment. Also, there was a significant reduction in glutathione levels after dimethylglycine treatment. The results suggest that the gastroprotective effect of dimethylglycine could be mediated by its free radical scavenging activity and cytoprotection of gastric mucosa.