Annual Bibliography of Significant Advances in Dietary Supplement Research 2000

To raise the level of knowledge on scientific developments of dietary supplements as they relate to health promotion, health maintenance, and disease prevention.

OFFICE OF DIETARY SUPPLEMENTS
National Institutes of Health

CHPA
Consumer Healthcare Products Association

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We are proud to bring you the second issue of the *Annual Bibliography of Significant Advances in Dietary Supplement Research,* which highlights important research that appeared in scientific journals in 2000. The purpose of this bibliography is to help develop an overall perspective on the science being conducted in the dietary supplement field, as well as to provide well-deserved recognition to investigators.

As with the first issue of the bibliography, we asked editors of peer-reviewed journals to nominate "flagship" original research papers that appeared in their respective journals in 2000. For this issue, we expanded our request to include more journals that publish papers on botanicals. This expansion resulted in the selection of over 450 papers, which is more than twice the number we received for the 1999 issue. These papers were then forwarded to leading scientists in the United States and Europe for review and to identify the top 25 scientific papers. These 25 papers were then annotated and compiled into this bibliography.

The bibliography represents the combined efforts of several individuals. They include the editors of the journals; the numerous scientists who reviewed the papers; and staff at the Office of Dietary Supplements, the Consumer Healthcare Products Association, and the National Agricultural Library in the US Department of Agriculture. These individuals are recognized in the acknowledgment section of this publication. We would especially like to recognize the efforts of Michelle Dell'Orto who worked diligently in obtaining the papers for this bibliography and in coordinating the review process.

This bibliography is a joint effort of the Office of Dietary Supplements and the Consumer Healthcare Products Association. Please contact either organization if you want copies of this publication or if you have questions regarding this project. The contact details are provided on the back cover of this publication.

Sincerely,

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ANNOTATIONS OF 25 SELECTED SCIENTIFIC PAPERS

About the Office of Dietary Supplements (ODS)

ODS was established by the Dietary Supplement Health and Education Act of 1994 (DSHEA, Public Law 103-417)[1]. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the US population.

About the Consumer Healthcare Products Association (CHPA)

CHPA is the 120-year-old trade organization representing the manufacturers and distributors of national and store brand dietary supplements and nonprescription medicines. CHPA's membership includes over 200 companies involved in the manufacture and distribution of these self-care products and their affiliated services, such as raw material suppliers, research testing companies, contract manufacturing companies, and advertising agencies.

[1] *Dietary supplements according to the Act are defined as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (a) a vitamin; (b) a mineral; (c) an herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (a), (b), (c), (d), or (e).*

Night blindness during pregnancy and subsequent mortality among women in Nepal: Effects of vitamin A and β-carotene supplementation.

P Christian, KP West Jr, SK Khatry, E Kimbrough-Pradhan, SC LeClerq, J Katz, SR Shrestha, SM Dali, and A Sommer.
American Journal of Epidemiology **(Am J Epidemiol) 2000 152:542-547.**

Night blindness, commonly caused by vitamin A deficiency, has been associated with negative health and nutritional outcomes during pregnancy. This makes night blindness a potential indicator of maternal health and risk of dying. This study analyzed data from a large intervention trial in Nepal that examined the effects of weekly supplementation with vitamin A and β-carotene on maternal, fetal, and infant mortality. Women in the trial, aged 13-45 years, were supplemented weekly with 7,000 μg retinal equivalents of vitamin A, 42 mg of β-carotene, or a placebo for $3^1/_2$ years. The four groups compared in this analysis were: 1) women with night blindness who received vitamin A or β-carotene supplements; 2) women without night blindness who received vitamin A or β-carotene supplements; 3) women with night blindness who received placebos; and 4) women without night blindness who received placebos. The results of this analysis indicate that night-blind women are five times more likely to die from infections than their non-night blind counterparts. However, the risk of dying was reduced in night-blind women who received vitamin A or β-carotene supplements. Not being night-blind and receiving supplementation were associated with a lower risk of dying. This analysis demonstrates that vitamin A and β-carotene supplementation may reduce the risk of dying in night-blind mothers who may be deficient in these vitamins.

Funding: Johns Hopkins University and US Agency for International Development.

EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer.

N von Zandwijk, O Dalesio, U Pastorino, N de Vries, and H van Tinteren. ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2000 92:977-986.**

Retinoids and N-acetylcysteine, a precursor of cysteine and glutathione, have chemopreventive properties which make them potentially useful in the delay or prevention of cancers of the head, neck, or lungs. The European Study on Chemoprevention with Vitamin A and N-Acetylcysteine (EUROSCAN) is a large randomized intervention study that examined the effect of vitamin A (retinyl palmitate) and N-acetylcysteine on second primary tumors in patients treated for head and neck or lung cancer. A secondary primary tumor is a new tumor growth believed to be unrelated to this first tumor. In the study, the 2,592 patients from 15 countries received one of four treatments for two years: retinyl palmitate alone (300,000 IU daily in year one and 150,000 IU daily in year two), N-acetylcysteine alone (600 mg daily for two years), a combination treatment (retinyl palmitate 300,000 IU daily in year one and 150,000 IU daily in year two with 600 mg N-acetylcysteine daily for two years), or no intervention. After a median 49-month follow-up, 916 patients presented with a recurrence of their cancer, a second primary tumor, or death. There were no differences in overall survival or event-free survival between patients receiving retinyl palmitate and those who did not, or between patients receiving N-acetylcysteine and those who did not. A comparison of all four groups showed no difference in either overall survival or event-free survival. The no intervention group had a non-significant, lower incidence of second primary tumors when compared with the other three groups. These findings suggest that retinyl palmitate and N-acetylcysteine may not be beneficial to the survival, event-free survival, or prevention of second primary tumors in patients with head and neck or lung cancer.

Funding: European Organization for Research and Treatment of Cancer (EORTC), European Commission, and The Netherlands Cancer Institute.

Improved vascular endothelial function after oral B-vitamins: An effect mediated through reduced concentrations of free plasma homocysteine.

JC Chambers, PM Ueland, OA Obeid, J Wrigley, H Refsum, and JS Kooner. ***Circulation*** **2000 102:2479-2483.**

Elevated blood homocysteine levels are considered an independent risk factor for coronary heart disease as they may negatively affect the inner lining of blood vessels or endothelium. This study examined the effects of folic acid and vitamin B_{12} supplementation on vascular endothelial function in 89 men aged 39-67 years with coronary heart disease. The relationships between vascular endothelial function and levels of total, protein-bound, and plasma homocysteine were examined. The men received either an oral dose of 5 mg of folic acid and 1 mg of vitamin B_{12} or a placebo daily for a period of eight weeks. Flow-mediated dilation was used to measure endothelial function. Folic acid and vitamin B_{12} supplementation increased serum folate and vitamin B_{12} levels, which resulted in improved vascular endothelial function and decreased levels of total, protein-bound, and free plasma homocysteine. The study demonstrated that folic acid and vitamin B_{12} supplementation improve vascular endothelial function in patients with coronary heart disease, possibly as a result of reduced blood levels of homocysteine. Overall, this study supports the theory that folic acid and vitamin B_{12} supplementation may reduce the risk for cardiovascular disease in patients with coronary heart disease.

Funding: European Union Commission.

Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet.

DL McKay, G Perrone, H Rasmussen, G Dallal, and JB Blumberg. ***The Journal of Nutrition*** **(J Nutr) 2000 130:3090-3096.**

Low dietary intakes resulting in poor nutrient status of the B-vitamins folate, B_{12}, and B_6 can lead to elevated blood homocysteine levels, an independent risk factor for cardiovascular disease. The added effects of an effervescent multivitamin and mineral supplement on B-vitamin status and homocysteine levels was evaluated in a double-blind, placebo-controlled, clinical trial in 80 men and women aged 50-87 years consuming a folate-fortified diet. The participants received daily for 56 days a multivitamin and mineral supplement containing 100 percent of the daily value for most nutrients, including folic acid (400 µg), B_{12} (6 µg), and B_6 (2 mg) or a placebo. Dietary intakes were determined with a Willett food frequency questionnaire. Plasma levels of folate, B_{12}, and pyridoxal phosphate were used to determine folate, vitamin B_{12}, and vitamin B_6 status respectively. The multivitamin and mineral supplement resulted in improved folate, vitamin B_{12}, and vitamin B_6 status, and decreased total plasma homocysteine levels. By improving B-vitamin status and reducing blood homocysteine levels, multivitamin and mineral supplements appear to provide older adults with additional benefits over those obtained from a folate-fortified diet alone. Older healthy adults with increased plasma homocysteine concentration and low B-vitamin status would benefit from taking a daily multivitamin and mineral supplement that provides 100 percent of the recommended levels of folate, vitamin B_{12}, and vitamin B_6.

Funding: Agricultural Research Service, US Department of Agriculture; and Pharmavite Corporation, California.

Effect of calcium or 25OH vitamin D_3 dietary supplementation on bone loss at the hip in men and women over the age of 60.

Low intakes of calcium and vitamin D may contribute to a loss of bone strength in older adults, which can result in age-related hip fractures. Researchers examined the effects of daily supplementation of calcium or vitamin D on bone mass and structure at the hip and on bone turnover. A total of 316 women and 122 men over the age of 60 participated in a four-year randomized, double-blind, placebo-controlled study. Participants received daily oral supplements containing 750 mg of calcium as calcium citrate malate, 15 µg of 25-hydroxy (OH) vitamin D_3, or a placebo. Bone mass was measured using dual energy x-ray absorptiometry, and bone structure was measured by radiographs. Food frequency questionnaires were used to calculate dietary intakes of calcium and vitamin D. Calcium supplementation, which resulted in a total daily intake of about 1,200 mg, led to decreased bone loss. The supplemental calcium slowed the reduction of bone mineral density and decreased the rate of bone turnover. Effects of the vitamin D supplements were less marked and were most beneficial to those with low vitamin D and calcium intakes. This study demonstrates that calcium intakes at the upper end of the normal range might be beneficial in maintaining bone strength and preventing bone loss at the hip, while vitamin D may be more beneficial in the reversal of calcium insufficiency. Efforts need to be made to educate older individuals to consume calcium and vitamin D at the currently recommended levels.

Funding: National Institute on Aging and National Center for Research Resources, NIH.

M Peacock, G Liu, M Carey, R McClintock, W Ambrosius, S Hui, and CC Johnston. ***The Journal of Clinical Endocrinology and Metabolism*** **(J Clin Endocrinol Metab) 2000 85:3011-3019.**

Lack of hemoglobin response to iron supplementation in anemic Mexican preschoolers with multiple micronutrient deficiencies.

Iron deficiency can result in low hemoglobin levels in individuals, which is an indicator of anemia. However, other nutrient deficiencies that occur with iron deficiency may elevate the risk of anemia and thus limit the hematologic response to iron supplementation. Researchers tested the effects of a 12-month supplementation with iron, zinc, and iron plus zinc on growth and morbidity in 219 children in Mexico, aged 18-36 months. This analysis examined the hematologic response to supplementation and its association with other micronutrient deficiencies, antropometric measurements, morbidity, and usual dietary intake. The children received oral supplements that contained 20 mg of ferrous sulfate, 20 mg of zinc methionine, a combination of 20 mg each of iron plus zinc, or a placebo. After one year, 31 percent of the children who received the iron and iron plus zinc supplements were identified as anemic, however, their iron levels indicated that they were not iron deficient. The hemoglobin response to iron supplementation was predicted by poor diet quality, low growth rates, and low levels of vitamin B_{12} in the diet, all of which are considered indicators of undernutrition. These findings show that among undernourished Mexican children, chronic undernutrition and micronutrient deficiencies are associated with a lack of hemoglobin response to iron supplementation. Future programs need to evaluate the total nutritional status of children before embarking on programs of supplementation with a single nutrient such as iron.

Funding: US Department of Agriculture.

LH Allen, JL Rosado, JE Casterline, P López, E Muñoz, OP Garcia, and H Martinez. ***The American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2000 71:1485-1494.**

Oral magnesium therapy improves endothelial function in patients with coronary artery disease.

M Shechter, M Sharir, MJP Labrador, J Forrester, B Silver, and CNB Merz. ***Circulation*** **2000 102:2353-2358.**

Epidemiological evidence suggests an association between magnesium deficiency and an increased risk of coronary artery disease. Magnesium blocks the physiological actions of calcium and promotes vasodilation possibly through interactions with the inner lining of blood vessels or endothelium. This study examined the effects of an oral magnesium supplement on brachial artery endothelial function and exercise tolerance in patients with coronary artery disease. Fifty patients with stable coronary artery disease were enrolled in a six-month randomized, double-blind, placebo-controlled study and received either 15 mmol (365 mg) of a magnesium formulation or a placebo twice daily. Response to magnesium supplementation was determined by measuring endothelium-dependent vasodilation and independent (nitroglycerin-mediated) vasodilation. This study shows that oral magnesium supplementation results in a significant increase in intracellular magnesium levels and significant improvement in brachial artery endothelial function. Exercise stress testing revealed that patients on the oral magnesium therapy had less electrocardiograph changes, an indicator of myocardial ischemia. Overall, this study demonstrates that oral magnesium supplementation can improve brachial artery endothelial function, suggesting that it may be useful as an inexpensive and adjuvant therapy for patients with coronary artery disease.

Funding: Save A Heart Foundation, California and Asta Medica Company, Inc, Austria.

Prospective study of serum selenium levels and incident esophageal and gastric cancers.

SD Mark, Y-L Qiao, SM Dawsey, Y-P Wu, H Katki, EW Gunter, JF Fraumeni Jr, WJ Blot, Z-W Dong, and PR Taylor. ***The Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2000 2:1753-1763.**

Selenium, an essential trace mineral, functions as an antioxidant that protects cells from free radical damage associated with cancer. Recent prospective cohort studies and randomized intervention trials have determined that a link may exist between selenium levels and the development of cancer in humans. The General Population Trial, conducted in Linxian, China, was a five-year prospective study in adults aged 40-69 that examined whether vitamin-mineral supplementation would decrease overall death rates, and the incidence of and death resulting from esophageal and gastric cardia cancers. Four different vitamin-mineral combinations were tested in this trial. Selenium was provided in the D combination, which contained 50 μg of yeast selenium, 15 mg of β-carotene, and 50 mg of α-tocopherol. This analysis studied the relationship between serum selenium levels and the number of cases of squamous esophageal cancer, gastric cardia cancer, and gastric non-cardia cancer in a region with inherently poor nutrition and elevated cancer prevalence. Incidences of cancer and serum selenium levels were compared between cases and randomly chosen control subjects for 590 cases of squamous esophageal cancer, 402 cases of gastric cardia cancer, and 87 cases of gastric non-cardia cancer. The results of this analysis show an inverse association between serum selenium levels and the incidence of esophageal and gastric cardia cancers. There was no association between serum selenium levels and occurrence of gastric non-cardia cancer. This study supports previous findings of an inverse relationship between selenium levels and the incidence of some, but not all, types of cancers.

Funding: National Cancer Institute, NIH.

Effect of docosahexaenoic acid supplementation of lactating women on the fatty acid composition of breast milk lipids and maternal and infant plasma phospholipids.

Docosahexaenoic acid (DHA) is an important component of lipids in the brain and retinal cell membranes of the eye. It is present in breast milk but is not routinely added to infant formulas, as full-term infants are not considered a group at high risk for DHA deficiency. This study looked at the effects of DHA supplementation on breast milk DHA levels, breast milk fatty acids, and on maternal and infant plasma phospholipids. From two until eight weeks postpartum, 24 women were given one of four supplement regimens consisting of triacylglycerol high in DHA produced by algae, eggs high in DHA, low-EPA (eicosapentaenoic) high-DHA fish oil, or regular eggs (control group). Maternal blood and milk samples as well as infant blood samples were collected to determine fatty acid composition before and during supplementation. DHA supplementation was found to increase plasma and breast milk DHA concentrations in lactating women in all three supplemented groups when compared to the control group. Higher DHA concentrations in the mothers resulted in higher plasma phospholipid DHA concentrations in the infants. Supplementing lactating women with DHA, therefore, may be a suitable method for increasing breast milk DHA. Although the outcome of this study was positive, further research is needed to determine whether increasing breast milk DHA concentrations yields long-term functional benefits for full-term, breast-fed infants.

Funding: Agricultural Research Service, US Department of Agriculture; National Eye Institute, NIH; Mead-Johnson; The Foundation Fighting Blindness; Research to Prevent Blindness; and Retina Research Foundation.

CL Jensen, M Maude, RE Anderson, and WC Heird. ***The American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2000 71(suppl):292-299S.**

Supplementation of postmenopausal women with fish oil rich in eicosapentaenoic acid and docosahexaenoic acid is not associated with greater *in vivo* lipid peroxidation compared with oils rich in oleate and linoleate as assessed by plasma malondialdehyde and F_2-isoprostanes.

Cardiovascular disease remains the leading cause of death and disability in postmenopausal women. Changes during menopause result in altered serum lipids and lipoprotein levels that increase the risk for developing cardiovascular disease. Presently it is unclear as to whether replacing dietary saturated fatty acids with polyunsaturated fatty acids from fish oils as opposed to vegetable oils will increase lipid peroxidation, and potentially increase the risk of cardiovascular disease. This theory was tested in 16 postmenopausal women (aged 50-75 years) who were enrolled in a blinded-crossover study with three treatment periods. The women received dietary oil supplements rich in a monounsaturated fatty acid (sunflower oil rich in oleate), a polyunsaturated fatty acid (safflower oil rich in linoleate), and a fish oil containing eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Several *in vivo* (within the body) lipid peroxidation tests (measured by F_2-isoprostanes, malondialdehyde, and TBARS) were performed on blood samples collected before and at the end of each treatment period. With fish oil supplementation there was no evidence of increased lipid peroxidation as determined by changes in concentrations of plasma F_2-isoprostanes and malondialdehyde. These findings demonstrate that consuming a diet rich in polyunsaturated fatty acids from fish oil as opposed to vegetable oils may not alter the risk for cardiovascular disease in postmenopausal women.

Funding: US Department of Agriculture; National Institute of Diabetes and Digestive and Kidney Diseases, National Cancer Institute, and National Institute of General Medical Science, NIH; and Burroughs Wellcome Fund.

JV Higdon, J Liu, S-H Du, JD Morrow, BN Ames, and RC Wander. ***The American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2000 72:714-722.**

Highly unsaturated (n-3) fatty acids, but not α-linolenic, conjugated linoleic or γ-linolenic acids, reduce tumorgenesis in $Apc^{Min/+}$ mice.

MBH Petrik, MF McEntee, BT Johnson, MG Obukowicz, and J Whelan. ***The Journal of Nutrition*** **(J Nutr) 2000 130:2434-2443.**

Epidemiologic studies show that consumption of fish and fish oil correlates with a reduced risk of colorectal cancer. This study compared the anti-tumorigenic effect of a number of dietary polyunsaturated fatty acids (alpha-linolenic, stearidonic, eicosapentaenoic, docosahexaenoic, conjugated linoleic, and gamma-linolenic acids) to a monounsaturated oil, oleic acid, which served as the control. The investigators fed mice ($Apc^{Min/+}$ mouse) 3 g of the test oils per 100 g of diet for approximately seven weeks. This mouse model is designed to study the effects of nutritional intervention on small intestine and colon tumorgenesis. Mice were sacrificed, and tumor number, size, and location were determined as well as intestinal tissue fatty acid composition and prostaglandin levels. The most pronounced effects of feeding (decreased tumorgenesis) were seen in mice fed the n-3 fatty acids, stearidonic and eicosapentaenoic acids. Stearidonic acid was more effective, resulting in fewer tumors in both the colon and small intestine and in smaller tumors in the small intestine. Both stearidonic and eicosapentaenoic acid resulted in 50 percent fewer intestinal tumors. The other fatty acids were ineffective at the dose tested. Stearidonic acid and eicosapentaenoic acid were associated with the lowest prostaglandin levels. The results of this study show that stearidonic and eicosapentaenoic acids are anti-tumorigenic and that these effects are most likely related to alterations in tissue arachidonic acid content and prostaglandin levels. These findings indicate that not all polyunsaturated fats have the same cancer preventive effects, and that recommendations to increase polyunsaturated fat intake should be specific as to the source of that fat.

Funding: Monsanto Company.

Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner.

MA Hallikainen, ES Sarkkinen, and MIJ Uusitupa. ***The Journal of Nutrition*** **(J Nutr) 2000 130:767-776.**

Recently, plant stanols have been endorsed as a therapeutic option to enhance low-density lipoprotein (LDL) cholesterol lowering, however, the optimal dose has not been identified. This single-blind, dose-response study was designed to characterize the effect of different doses of plant stanol esters on lipid profiles in 22 men and women with elevated cholesterol. Each of the subjects consumed a standardized diet for four weeks including five different doses of plant stanol esters (0, 0.8, 1.6, 2.4, and 3.2 g) incorporated into a rapeseed oil-based margarine. Results show that serum total and LDL cholesterol levels were significantly reduced at a 1.6 g dose of plant stanol esters. Although higher doses resulted in slightly greater cholesterol reductions, the effects tended to level off and did not provide clinically significant additional effects beyond the 1.6 g dose. None of the doses significantly affected serum high-density lipoprotein (HDL) cholesterol or total triglyceride concentrations. Since plant stanol esters may interfere with the absorption of fat-soluble vitamins and carotenoids, serum measurements of these nutrients also were determined. Consumption of plant stanol esters were found to reduce serum levels of some but not all fat-soluble vitamins and carotenoids. These results indicate that consumption of 1.6 g plant stanols per day may be beneficial in reducing serum total and LDL cholesterol levels.

Funding: Raisio Benecol Ltd, Finland.

Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats.

CM Gallaher, J Munion, R Hesslink Jr, J Wise, and DD Gallaher. ***The Journal of Nutrition*** **(J Nutr) 2000 130:2753-2759.**

Glucomannan and chitosan, supplements with dietary fiber properties, have been shown in animal studies to reduce blood cholesterol levels. However, the mechanisms by which they do so have not been identified. The purpose of this study was to determine how these products lower cholesterol using an animal model. Male Wistar rats were randomly divided into four treatment groups. Each group was fed a diet containing cholesterol plus chitosan, glucomannan, chitosan plus glucomannan, or cellulose (control) for 18 days. Results show that both glucomannan and chitosan lower cholesterol levels in rats, although chitosan was more effective. This reduction possibly occurred through reduced cholesterol absorption. Bile acids and fat excretion was higher with chitosan. Although the mechanism of cholesterol reduction was different between the two materials tested, the results confirm that both glucomannan and chitosan reduce cholesterol levels. Additionally, both supplements reduced food intake, which resulted in reduced growth rate in rats. Human studies are needed to confirm these results of cholesterol reduction, increased fat excretion, and reduced growth rate.

Funding: Natural Alternatives, Inc, California.

Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women.

D Lee Alekel, A St Germain, CT Peterson, KB Hanson, JW Stewart, and T Toda. ***The American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2000 72:844-852.**

Many older women experience bone loss that may lead to osteoporosis due to reduced estrogen levels following menopause. Estrogen and other hormone-replacement therapies can be used to help prevent bone loss, but may have undesirable side effects such as increased breast and endometrial cancer risk. Soy contains isoflavones, which are structurally similar to estrogen and may be a potential alternative to hormone-replacement therapy. This 24-week, double-blind clinical trial examined the effects of soy protein consumption on bone loss in women during menopausal transition. Sixty-nine perimenopausal women, randomly assigned to one of three treatment groups, received daily soy protein with isoflavones (80.4 mg aglycone components), soy protein without isoflavones (4.4 mg aglycone components), or whey protein (control). Bone loss was determined by measuring bone mineral density and bone mineral content of the lumbar spine, while bone resorption was determined by measuring levels of two biochemical markers. The results indicate that soy with isoflavones attenuate spinal bone loss, while the soy without isoflavones and the control did not affect spinal bone loss. None of the treatments affected bone resorption. These findings suggest that soy isoflavones may help decrease the rate of bone loss during menopause and may serve as an alternative or adjuvant therapy in the prevention of osteoporosis.

Funding: Hatch Act and State of Iowa funds, US Department of Agriculture, and Iowa State University.

Soy consumption alters endogenous estrogen metabolism in postmenopausal women.

X Xu, AM Duncan, KE Wangen, and MS Kurzer. ***Cancer Epidemiology, Biomarkers, and Prevention*** **(Cancer Epidemiol Biomark Prev) 2000 9:781-786.**

Isoflavones, an active component in soy, are hypothesized to have estrogen-like actions on hormone sensitive tissues in the body. The risk of breast cancer may be reduced in postmenopausal women, as soy isoflavones may produce fewer potentially carcinogenic estrogen metabolites. This theory was tested in this randomized, cross-over design trial of 18 postmenopausal women. These women consumed a soy protein isolate which provided an average of 7 mg (control diet), 65 mg (low-isoflavone diet), or 132 mg (high-isoflavone diet) of soy isoflavones a day in addition to their usual diets. Between each 93-day diet period there was a 26-day washout period. Results show that production of the estrogen metabolite 4-hydroxyestrone, a proposed carcinogenic metabolite, was reduced during the high-isoflavone and low-isoflavone diet periods compared with control and baseline (before study) diet periods. All three diets shifted estrogen metabolism toward the 2-hydroxylation pathway, which is proposed to produce benign and weak estrogen metabolites. These findings suggest that diets rich in isoflavones alter estrogen metabolism in a favorable manner and thus may help protect against breast cancer in postmenopausal women. Additional studies are needed to confirm the mechanism of action by which soy supplements may reduce the risk of breast cancer.

Funding: National Center for Research Resources, NIH; and Minnesota Agricultural Experimental Station.

BOTANICALS

Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*).

JL Nortier, M-CM Martinez, HH Schmeiser, VM Arlt, CA Bieler, M Petein, MF Depierreux, L De Pauw, D Abramowicz, P Vereerstraeten, and J-L Vanherweghem. ***The New England Journal of Medicine*** **(N Engl J Med) 2000 342:1686-1692.**

Aristolochic acid, a contaminant found in some herbal products, causes severe neurotoxic and carcinogenic effects. Early reported cases in Belgium and France linked adverse events among individuals who took herbal weight-loss products with aristolochic acid. Due to manufacturing errors, the herb *Stephania tetrandra* was replaced by *Aristolochia fangchi*. The purpose of this study was to examine the prevalence of urothelial carcinoma among individuals who took herbal supplements contaminated with aristolochic acid. Among the 39 patients from the original Belgian cohort with end-stage renal failure there were 18 cases of urothelial carcinoma. Tissue samples from each kidney and ureters were removed and tested for DNA adducts formed as a result of aristolochic acid. All tissue samples analyzed contained aristolochic acid-related DNA adducts. The authors concluded that the aristolochia toxins (aristolochic acids and possibly other derivatives) cause renal disease and urothelial cancer. This study further validated an earlier FDA action that banned the importation of any botanical dietary ingredients either labeled as or confused with *Aristolochia fangchi*.

Funding: Source not identified.

Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids.

CA Haller and NL Benowitz. ***The New England Journal of Medicine*** **(N Engl J Med) 2000 343:1833-1838.**

Ephedra or ma huang is used in traditional Chinese medicine for the treatment of respiratory track infections. However, in the United States, its popular use is in weight-loss products. At the request of the US Food and Drug Administration (FDA), the authors conducted a systematic review of 140 adverse events that were reported to the Agency (between June 1, 1997 and March 31, 1999) related to the use of ephedra. Events were ranked according to the probability that ephedra was responsible for the adverse event. Events were listed as definitely or probably related, possibly related, or unrelated to the use of supplements containing ephedra. Forty-seven percent of the adverse events were associated with cardiovascular symptoms. Eighteen percent of related and possibly related adverse events involved the central nervous system. Twenty-six percent of the definite, probable, and possible cases resulted in death (10 events) or permanent impairment (13 events). Studying the adverse event reports and making the risk assessments was complicated by several factors including the practice of combining ephedra with other stimulants such as caffeine, by the variability in the levels of pharmacologically active chemicals in the products, by pre-existing medical conditions, or by individual sensitivities to supplements or drugs. The authors concluded that the use of products containing ephedra might pose a health risk to some persons. This study points to the need for future studies that delineate ephedra's mechanism(s) of action and to identify individuals who may be at high risk for these products.

Funding: FDA and the National Institute on Drug Abuse, NIH.

American ginseng (*Panax quinquefolis L*) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus.

V Vuksan, JL Sievenpiper, VYY Koo, T Francis, U Beljan-Zdravhovic, Z Xu, and E Vidgen. ***Archives of Internal Medicine*** **(Arch Intern Med) 2000 160:1009-1013.**

Ginseng, a widely used botanical, is hypothesized to play a role in carbohydrate metabolism and diabetes. Researchers in this study examined the effect of American ginseng on glucose levels in the blood in 10 individuals (6 male and 4 female) without diabetes and nine individuals (5 male and 4 female) with type 2 diabetes. These individuals consumed in random order, on four separate occasions, a gelatin capsule (3 g of ginseng) or a cornflower placebo capsule, either 40 minutes before or together with a 25 g oral glucose challenge. The 25 g oral glucose challenge simulated the effect of a meal. The 3 g dose of ginseng was based on levels used in traditional Asian medical practices. Among nondiabetic individuals, there was no difference in postprandial glycemia between the ginseng and placebo capsules when taken with 25 g of glucose. However, post-meal glucose levels were reduced when ginseng was administered 40 minutes before ingesting 25 g of glucose. In the type 2 diabetic individuals, ginseng effectively lowered blood glucose when taken 40 minutes before or with the oral glucose challenge. This study supports the traditional Asian medical practice of consuming ginseng in the fasted state or between meals. However, in individuals without diabetes, it may be better to consume ginseng with meals to prevent unintended hypoglycemia. As this was an acute study, long-term studies examining the consumption of American ginseng among individuals with and without diabetes need to be undertaken.

Funding: Chai-Na-To Corp, Ontario Ministry of Agriculture, Agriculture and Agri-Food, Canada.

St John's wort induces hepatic drug metabolism through activation of the pregnane X receptor.

LB Moore, B Goodwin, SA Jones, GB Wisely, CJ Serabjit-Singh, TM Wilson, JL Collins, and SA Kilewer. ***Proceedings of the National Academy of Sciences*** **(PNAS) 2000 97:7500-7502.**

St John's wort (*Hypericum perforatum*) is an ancient herbal remedy that has gained popularity because of its effectiveness as an antidepressant. The clinical effects of St John's wort on depression correlate with its hyperforin content. However, studies have shown that hyperforin increases the metabolism of some drugs such as oral contraceptives, cyclosporin, and indinavir. It is thought that St John's wort may interact with such drugs by acting as a ligand for the pregnane X receptor (PXR), a nuclear receptor that regulates cytocrome P450 (CYP) 3A4 monoxygenase expression, resulting in supplement-drug interactions. CYP3A4 is an enzyme that plays a central role in the metabolism of over 50 percent of all drugs in the liver. The objective of this *in vitro* (in cell culture) study, using primary human liver cells, was to examine the mechanism(s) by which St John's wort interacts with prescription drugs. The researchers confirmed that St John's wort activates the pregnane X receptor, which in turn regulates the expression of CYP3A4. The study identified hyperforin to be the single constituent that contributed to the therapeutic benefits as well as side effects of the herb. The authors concluded that as St John's wort induces the expression of CYP3A4, it is likely to interact with many more drugs than previously realized. They also suggest that it may be possible to identify and develop safer hyperforin analogs that retain antidepressant activity but do not activate the pregnane X receptor and thus alter drug metabolism. This study provides valuable insights into the mechanism of action by which St John's wort interacts with prescription drugs.

Funding: Glaxo Wellcome Research and Development.

Comparison of St John's wort and imipramine for treating depression: randomized controlled trial.

H Woelk for the Remotiv/Imipramine Study Group. ***British Medical Journal*** **(BMJ) 2000, 321:536-539.**

St John's wort (*Hypericum perforatum*) has been shown in previous studies to be effective in the management of depression. Despite the positive outcomes of many of these trials, they have been criticized because of their methodology and statistical analyses. At the time when this study was planned, it was designed to be the largest controlled trial of the efficacy of St John's wort for treating depression with particular care toward design and methodology in light of previous criticisms. Forty psychiatric outpatient clinics from medical practices in Germany were selected for this trial. The 324 participants, with mild to moderate depression, from these clinics received either a hypericum extract (standardized to 0.2 percent hypericin) in a 250 mg tablet or 75 mg imipramine tablet twice daily for six weeks. Hypericum, the constituent thought to be the active component in St John's wort was used in this trial, however, some studies have identified hyperforin as the active constituent, as well. The main outcome measures used to test the effect of hypericum and imipramine were the Hamilton depression rating scale, the clinical global impressions scale, and the patients' global impression scale. The results of this study support the conclusion that the two treatments are therapeutically equivalent. Although there were no differences in any of the measures of efficacy, there was some evidence to suggest that hypercium may be better at relieving anxiety associated with depression. These results add to the body of knowledge on the value of St John's wort in the management of mild to moderate depression.

Funding: Bayer AG and Beromed, Germany.

The Andro Project. Physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program.

Androstenedione is a prohormone involved in the synthesis of testosterone. It is marketed with androstenediol to improve sexual performance, reduce body fat levels, and increase muscle mass. To study the hormonal and physiological effects of androstenedione and androstenediol 50 men, aged 35-65 years, were enrolled in a double-blind study while participating in a 12-week, high-intensity resistance training program. Twice a day these men received 100 mg of androstenedione, 100 mg of androstenediol, or a placebo. Serum sex hormone and blood lipid profiles as well as body composition and muscular strength assessment were determined. Androstenedione and androstenediol supplementation increased estrogen-related compounds, altered male hormone profiles, and adversely affected high-density lipoprotein (HDL) cholesterol levels, however, total and free testosterone and serum hormone-binding protein were unchanged. Within one month of androstenedione use, the synthesis of testosterone was decreased. Compared with the placebo, neither supplement enhanced the adaptation to resistance training for body composition or muscular strength. Overall any benefits derived from consuming the testosterone precusor supplements are outweighed by their negative side effects on blood lipid and hormone profiles.

Funding: Metabolic Response Modifiers, California; SmithKline Beecham; several US-based hospitals; Bodystat Ltd, England; and Valhalla Medical Products, California.

CE Broeder, J Quindry, K Brittingham, L Panton, J Thomson, S Appakondu, K Breuel, R Byrd, J Douglas, C Earnest, C Mitchell, M Olson, T Roy, and C Yarlagadda. ***Archives of Internal Medicine*** **(Arch Intern Med) 2000 160:3093-3104.**

Dietary coenzyme Q10 supplement renders swine hearts resistant to ischemia-reperfusion injury.

Coenzyme Q10 (CoQ10), also called ubiquinone, is an essential component of the energy-producing system present in mitochondria of cells. CoQ10 appears to be involved in maintaining the balance between oxidative stress and antioxidant capacity of heart tissue. The purpose of this study was to examine whether CoQ10 can reduce myocardial injury that results from reperfusion of previously damaged tissues. A group of 24 male Yorkshire swine were fed either a regular diet with CoQ10 (5 mg/kg per day) or a regular diet without CoQ10 for 30 days. The results show that CoQ10 supplementation increased levels of CoQ10 in the myocardium. After ischemia and reperfusion insults, the average myocardial CoQ10 content in the treatment group was still higher than in the control group. CoQ10 feeding also resulted in such benefits as higher indices of post-ischemic ventricular function and ventricular recovery, lower creatine kinase (a marker of myocardial damage) release from hearts, and reduced infarct size. This study demonstrates that long-term administration of CoQ10 might enable hearts to increase their CoQ10 content, which may be beneficial in protecting the heart from ischemia-reperfusion injury. Future studies are needed to examine whether the effects of CoQ10 on ischemia-reperfusion injury are reproducible in humans.

Funding: National Heart, Lung, and Blood Institute, NIH; and the American Heart Association.

N Maulik, T Yoshida, RM Engelman, D Bagchi, H Otani, and DK Das. ***The American Journal of Physiology; Heart and Circulatory Physiology*** **(Am J Physiol Heart Circ Physiol) 2000 278:H1084-H1090.**

Glucosamine and chondroitin for treatment of osteoarthritis. A systematic quality assessment and meta-analysis.

TE McAlindon, MP LaValley, JP Gulin, and DT Felson. ***Journal of the American Medical Association*** **(JAMA) 2000 283:1469-1475.**

Dietary supplements containing glucosamine or chondroitin have gained popularity in the management of osteoarthritis, a debilitating condition that affects many individuals in the United States. Despite modest results, these supplements may be useful in the treatment of this disease because of their safety profile. However, due to the quality of existing clinical trials, concerns remain about the effectiveness of these compounds. Using meta-analysis techniques, the quality of evidence from 15 randomized, double-blind, placebo-controlled, clinical trials, on the effects of glucosamine or chondroitin on osteoarthritis was examined. Only trials using oral or parental glucosamine sulfate, glucosamine hydrochloride, or chondroitin sulfate were included. All 15 trials were at least four weeks long and examined osteoarthritis of the knee or hip. These trials were analyzed for the quality of their methodology and results. The results of this meta-analysis revealed that the 15 studies reviewed contain methodological flaws and biases, leading to over-inflated estimates of the effects of glucosamine or chondroitin on osteoarthritis. Despite these shortcomings, glucosamine and chondroitin were still found to be moderately effective in treating osteoarthritis and are considered safe. This paper points to the need for a large well-designed study to confirm and quantify the effects of glucosamine and chondroitin on osteoarthritis.

Funding: National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

Enhancement of natural and acquired immunity by *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (HN017), and *Bifidobacterium lactis* (HN019).

HS Gill, KJ Rutherfurd, J Prasad, and PK Gopal. ***British Journal of Nutrition*** **(Br J Nutr) 2000 83:167-176.**

It has been suggested that lactic acid bacteria stimulate the immune system, and as a result, provide increased resistance to illness and cancers. This animal study was conducted to examine the effects of consumption of three strains of lactic acid bacteria on immune function *in vivo* (within the body) and *in vitro* (in cell culture). Healthy mice were fed oral doses of *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (HN017), *Bifidobacterium lactis* (HN019), or skimmed milk (control). Their immune function was determined on day 10 or day 28 using several indices of natural and acquired immunity, including phagocytic activity of macrophages and peripheral blood leukocytes, antibody responses, natural killer cell activity, and interferon-γ production. Results show that indices of immunity were enhanced in the mice given *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, or *Bifidobacterium lactis*. While additional research in humans is needed, these findings suggest immune function can be enhanced through lactic acid bacteria supplementation.

Funding: Massey University and New Zealand Dairy Research Institute, New Zealand.

Entrainment of free-running circadian rhythms by melatonin in blind people.

RL Sack, RW Brandes, AR Kendall, and AJ Lewy. ***The New England Journal of Medicine*** **(N Engl J Med) 2000 343:1070-1077.**

Melatonin, a hormone secreted by the brain, controls the body's internal clock and has been used to help restore sleep patterns in the elderly, the blind, and individuals who travel across multiple time zones. In totally blind people, disturbances of circadian rhythms are common due to an inability to process important environmental time cues, such as the daily light-dark cycle. Due to this inability, typical 24-hour circadian rhythms are replaced with free-running circadian rhythms predisposing blind persons to periodic symptoms of insomnia and daytime sleepiness. In order to reset, or entrain, their circadian rhythm to a normal 24-hour cycle, seven totally blind subjects with free-running circadian rhythms were given, over a period of three to nine weeks, 10 mg of melatonin or placebo one hour before their preferred bedtime. Baseline circadian rhythm cycles at the start of the study averaged 24.5 hours (range 24.2 to 24.9). The melatonin treatment resulted in six of the seven blind subjects experiencing rhythms that were entrained to a 24.0 hour cycle. Once entrained, the dose of melatonin was gradually reduced without loss of entrainment. The blind subjects spent less time awake after the initial onset of sleep and their efficiency of sleep was higher. This study shows that free-running circadian rhythms in blind people can be entrained to a 24-hour cycle with a daily dose of melatonin. Additionally, melatonin may prove to be a safe and effective way to treat sleep disturbances in blind people. While melatonin has orphan drug status for treating this condition in blind people, the study results provide additional information to support the use of melatonin as a dietary supplement to restore sleep patterns.

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List of Journals and Journal Editors

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- **The American Journal of Clinical Nutrition,** Charles H Halsted, MD
- **American Journal of Epidemiology,** Moyses Szklo, MD, DrPh
- **American Journal of Physiology,** Kim E Barrett, PhD
- **The Annals of Pharmacotherapy,** Harvey AK Witney Jr, MSPharm
- **Archives of Internal Medicine,** James E Dalen, MD, MPH
- **The British Journal of Nutrition,** Professor Paul Trayhurn
- **British Medical Journal,** Richard Smith
- **Cancer Epidemiology, Biomarkers, and Prevention,** Frederick P Li, MD
- **Circulation,** James T Willierson, MD
- **Clinical Pharmacology and Therapeutics,** Marcus M Reidenberg, MD
- **Fitoterapia,** Romano Vitali
- **International Journal for Research and Investigation on Atherosclerosis and Related Diseases,** Professor James Shepherd
- **Journal of Agricultural and Food Chemistry,** James Seiber, PhD
- **The Journal of Alternative and Complementary Medicine,** Kim A Jobst, DM, MRCP, MFHom
- **Journal of the American College of Nutrition,** David M Klurfeld, PhD
- **Journal of the American Dietetic Association,** Elaine R Monsen, PhD, RD
- **The Journal of the American Medical Association,** Catherine D DeAngelis, MD, MPH
- **Journal of the American Pharmaceutical Association,** Ron Teeter, PhD
- **The Journal of Clinical Endocrinology and Metabolism,** John P Bilezikian, MD
- **Journal of Herbs, Spices, and Medicinal Plants,** Lyle E Craker, MA
- **Journal of the National Cancer Institute,** Barnett S Kramer, MD MPH
- **Journal of Natural Products,** A Douglas Kinghorn, PhD, DSc
- **The Journal of Nutrition,** John W Suttie, PhD
- **The Lancet,** Richard Horton, MB
- **Life Sciences,** Rubin Bressler, MD
- **Medicine and Science in Sports and Exercise,** Kent B Pandolf, PhD, MPH
- **Mutation Research,** John S Wassom, PhD
- **The New England Journal of Medicine,** Jeffery M Drazen, MD
- **Pharmaceutical Biology,** John M Pezzuto, PhD
- **Phytochemistry,** Norman G Lewis, PhD
- **Phytomedicine,** Norman R Farnsworth, PhD
- **Phytotherapy Research,** Elizabeth M Williamson, PhD, MRPharmS, FLS
- **Planta Medica,** Adolf Nahrstedt, PhD
- **Proceedings of National Academy of Sciences,** Nicholas Cozzarelli, PhD
- **The Prostate,** John T Isaacs, PhD
- **Science Magazine,** Katrina Kelner, PhD

List of Scientific Reviewers

The Office of Dietary Supplements and the Consumer Healthcare Products Association commend the following scientists for reviewing and scoring the nominated papers. These individuals were selected as reviewers based on their scientific expertise.

- **John JB Anderson, PhD,** The University of North Carolina at Chapel Hill
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