Annual Bibliography of Significant Advances in Dietary Supplement Research 2002

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

OFFICE OF DIETARY SUPPLEMENTS
National Institutes of Health

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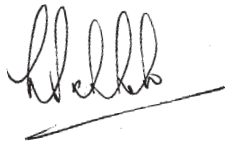
The Office of Dietary Supplements at the National Institutes of Health is pleased to provide you with the 2002 *Annual Bibliography of Significant Advances in Dietary Supplement Research*. This issue contains 25 original research papers on dietary supplements that appeared in scientific journals in 2002. The criteria for selecting papers are the same as those used in the previous four years.

A rigorous multistep process was used to select the top 25 papers. The first step was a comprehensive literature search that identified peer-reviewed journals publishing original research on dietary supplements in 2002. Editors of these journals were asked to nominate a maximum of 24 original research papers that appeared in their journals for that year. Our scientific reviewers were also invited to elect noteworthy papers and through this process, over 350 papers were nominated for this issue. These papers were forwarded to internationally recognized scientists for evaluation and scoring. The top 25 papers were then annotated and compiled into the annual bibliography. To help you track research developments in the field of dietary supplements, citations of papers that appeared in previous issues of the bibliography are listed in the appendix section.

This project is the result of the continued efforts of many individuals, whose outstanding contributions and combined efforts make it possible for us to bring you this publication annually. Please join us in thanking these individuals, who include the journal editors, scientific reviewers, staff at the Office of Dietary Supplements and the National Agricultural Library in the US Department of Agriculture. Specific individuals are identified in acknowledgements.

Please contact us if you have questions, or if you need multiple copies of this or past issues to distribute to your students, in your practice, or in your workplace. Current and previous issues of the *Annual Bibliography of Significant Advances in Dietary Supplement Research* can be downloaded from the Office of Dietary Supplements website http://ods.od.nih.gov. We welcome your comments on this publication.

Sincerely,



Rebecca B Costello, PhD, FACN
Deputy Director
Office of Dietary Supplements
National Institutes of Health

Leila G Saldanha, PhD, RD, FACN
Office of Dietary Supplements
National Institutes of Health

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ANNOTATIONS OF 25 SELECTED PAPERS PUBLISHED IN 2002

About the Office of Dietary Supplements (ODS) at the National Institutes of Health:

ODS was established by the Dietary Supplements Health and Education Act of 1994 (DSHEA, Public Law 103-417). The mission of ODS is to strengthen knowledge and understanding of dietary supplements[1] 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 U.S. population.

[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).*

Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: The Vitamin E Atherosclerosis Prevention Study (VEAPS).

HN Hodis, WJ Mack, L LaBree, PR Mahrer, A Sevanian, C Liu, C Liu, J Hwang, RH Selzer, SP Azen; for the VEAPS Research Group.
Circulation **(Circulation) 2002 106:1453-1459.**

Large observational studies have associated regular intakes of vitamin E with a decreased risk for atherosclerosis and cardiac events. However, intervention studies examining the effects of vitamin E on atherosclerosis progression and cardiovascular disease (CVD) events are not conclusive. The Vitamin E Atherosclerosis Prevention Study (VEAPS) was designed to look at the effects of supplementary vitamin E as DL-α-tocopherol on subclinical atherosclerosis in healthy individuals at low-risk for CVD. Men and women aged 40 years and over with borderline high, low-density lipoprotein (LDL) cholesterol levels (≥3.37 mmol/L or 130 mg/dL) and no clinical signs or symptoms of CVD consumed 400 IU of vitamin E or placebo daily for three years. When compared with the placebo, vitamin E raised serum vitamin E levels, reduced LDL cholesterol levels, and reduced LDL oxidative susceptibility. Progression of atherosclerosis, as determined by measuring carotid artery intima-media thickness, did not differ between the vitamin E and placebo groups. These data show that although vitamin E was effective in altering the lipid profile over a three-year period, it was not effective in altering the progression of atherosclerosis in low-risk healthy individuals. VEAPS suggests that well-nourished, healthy individuals at low-risk for CVD may not benefit from a daily routine that includes a vitamin E supplement.

Funding: National Institute on Aging, NIH; Hoffmann-La Roche, Inc.

Low-density lipoprotein level reduction by the 3-hydroxy-3-methylglutaryl coenzyme-A inhibitor simvastatin is accompanied by a related reduction of F_2-isoprostane formation in hypercholesterolemic subjects: No further effect of vitamin E.

R De Caterina, F Cipollone, FP Filardo, M Zimarino, W Bernini, G Lazzerini, T Bucciarelli, A Falco, P Marchesani, R Muraro, A Mezzetti, and G Cibattoni.
Circulation **(Circulation) 2002 106:2543-2549.**

Statins, which are HMG-CoA reductase inhibitors, reduce the risk of coronary heart disease by lowering low-density lipoprotein (LDL) cholesterol levels. Statins may also reduce oxidative stress by increasing LDL cholesterol's resistance to oxidation. Similarly, vitamin E functions as an antioxidant and may lower the risk of cardiovascular disease. This intervention study evaluated the combined effect of simvastatin and vitamin E on lipid peroxidation. Forty-three hypercholesterolemic patients were given either simvastatin alone or with vitamin E (600 mg/day) for two months, then crossed-over and given the alternative treatment for another two months. Plasma lipid and vitamin E levels and urinary excretion of the prostaglandin isoprostane 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$, an indicator of oxidative stress) were measured at baseline and every 30 days. Simvastatin lowered total and LDL cholesterol, triglycerides, prostaglandin 8-iso-$PGF_{2\alpha}$, and oxidized plasma LDL levels. Adding vitamin E did not result in a further reduction of these levels. This study suggests that in individuals with elevated cholesterol levels who are taking statins, vitamin E supplementation does not provide additional benefit in reducing the risk factors for cardiovascular disease.

Funding: Merck Sharp & Dohome Co; the Center of Excellence on Aging at the University of Chieti, Italy.

MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: A randomised placebo-controlled trial.

Heart Protection Study Collaborative Group. ***The Lancet*** **(Lancet) 2002 360: 23-33.**

The UK Heart Protection Study was designed to study the effect of antioxidants on the outcomes of vascular disease, cancer, and other adverse health conditions in a high-risk population. An antioxidant vitamin supplement or a matching placebo was given daily to 20,536 adults aged 40-80 years with coronary heart disease, other occlusive arterial diseases, or diabetes. The supplement contained 600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene. On average, 83% of participants were compliant to the protocol over a five-year period. Primary outcomes measured were major coronary events or non-fatal vascular events. Although blood vitamin concentrations increased substantially in the antioxidant supplemented group, the incidence in all-cause mortality and deaths due to vascular or non-vascular events were similar to the placebo group. As a result of these findings, the researchers were unable to justify the routine use of these vitamins, but they did conclude that the antioxidant vitamins studied were safe. This study provides additional data on the role of antioxidant vitamins in the management of chronic disease.

Funding: UK Medical Research Council; the British Heart Foundation; Merck & Co; Roche Vitamins.

Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: A randomized controlled trial.

DD Waters, El Alderman, J Hsia, BV Howard, FR Cobb, WJ Rogers, P Ouyang, P Thompson, JC Tardif, L Higginson, V Bittner, M Steffes, DJ Gordon, M Proschan, N Younes, and JI Verter. ***Journal of the American Medical Association*** **(JAMA) 2002 288: 2432-2440.**

Hormone replacement therapy (HRT) and antioxidant vitamin supplements are frequently used by postmenopausal women to reduce the risk of coronary heart disease (CHD); however, there are no intervention trials supporting this use. The Women's Angiographic Vitamin and Estrogen (WAVE) Trial examined the effects of HRT and antioxidant vitamin supplements on CHD in 423 postmenopausal women. Women were assigned to one of four groups and received 400 IU of vitamin E and 500 mg of vitamin C daily with or without HRT over a 6.8-year period. Women who had a hysterectomy took Premarin (0.625 mg conjugated equine estrogen); other women took Prempro (0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone acetate) daily. Each arm had a matching placebo group. The primary end-point of the trial was defined as coronary angiographic change with the worst ranks imputed to women who died or experienced myocardial infarction. The risk associated with HRT was statistically significant, and the risk associated with the antioxidant vitamin supplements was of borderline significance. Total and cardiovascular mortality was higher in women taking the antioxidant vitamin supplements compared with the vitamin placebo. The relative risk of myocardial infarction or CHD was higher in the HRT group in the first two years of treatment. On the basis of these findings, the routine use of HRT or high doses of vitamins E and C by postmenopausal women with coronary disease may worsen the outcomes of this disease.

Funding: National Heart Lung and Blood Institute and General Clinical Research Center, NIH.

Vitamin E oxidation in human atherosclerotic lesions.

Oxidation of low-density lipoproteins (LDL) is an important process in the development of atherosclerotic lesions. Antioxidants are potential antiatherogenic agents that can inhibit LDL oxidation. While there is interest in vitamin E's role in this process, evidence supporting this role is limited. This study was designed to determine the mechanism by which vitamin E (α-tocopherol) affects the oxidation of LDL in vessel walls, as it is the major lipid-soluble antioxidant in LDL. Levels of vitamin E and its oxidation products α-tocopherylquinone (primary product) and 2,3- and 5,6-epoxy-α-tocopherylquinones (secondary products) were determined in human aortic tissues representing four distinct stages of atherosclerosis. The study found that vitamin E remains essentially intact in artery wall lesions as atherosclerosis develops. The single electron or radical oxidants, which are found at higher concentrations in the early stages of atherogenesis, oxidized a small fraction of the vitamin E. Vitamin E did not appear to inhibit lipid oxidation caused by two-electron oxidants, a process that occurs in the later stages of atherogenesis. These results also showed that two-electron oxidants are primarily responsible for LDL oxidation in the artery wall and that vitamin E is not effective in limiting this oxidative process. These findings provide insight into why some vitamin E supplementation studies have not had positive results. The findings also suggest that antioxidants that scavenge two-electron oxidants may be more appropriate in preventing LDL oxidation and thus the formation of atherosclerotic lesions than vitamin E, which is a single-oxidant scavenger.

Funding: National Heart Foundation; National Health and Medical Research Council of Australia; the National Cancer Institute, NIH.

AC Terentis, SR Thomas, JA Burr, DC Liebler, and R Stocker. ***Circulation Research*** **(Circ Res) 2002 90:333-339.**

Glutathione prevents inhibition of fibroblast-mediated collagen gel contraction by cigarette smoke.

A balance between oxidants and antioxidants is important in maintaining normal lung function. Chronic obstructive pulmonary disease or emphysema can result if this balance is not maintained. Glutathione helps to maintain this balance by functioning as an antioxidant and protecting the lungs from oxidative injury caused by substances such as cigarette smoke. The investigators hypothesized that cigarette smoke inhibits the body's repair system by altering the ratio of oxidants to antioxidants in favor of oxidants. To test this theory, they incubated fibroblast cells derived from human lungs in the presence or absence of a cigarette smoke extract. Compounds that increase (*N*-acetyl-L-cysteine) or decrease (buthioninesulfoximine) glutathione production were also added to the collagen gel in which the cells were grown. Neither agent acted alone or directly on smoke, but together they altered levels of glutathione and thus the cells' response to smoke. This study provides important insights on how cigarette smoke affects glutathione levels in the lungs, which is useful information in helping to protect against the adverse effects of cigarette smoke.

Funding: Larson Endowment, University of Nebraska Medical Center.

HJ Kim, X Liu, H Wang, T Kohyama, T Kobayashi, F-Q Wen, DJ Romberger, S Abe, W MacNee, I Rahman, and SI Rennard. ***American Journal of Physiology Lung, Cell Molecular Physiology*** **(Amer J of Physiol Lung Cell Mol Physiol) 2002 283:L409-L417.**

Excentric cleavage products of β-carotene inhibit estrogen receptor positive and negative breast tumor cell growth in vitro and inhibit activator protein-1 mediated transcriptional activation.

EC Tibaduiza, JC Fleet, RM Russell, and NI Krinsky. *Journal of Nutrition* (J Nutr) 2002 132:1368-1375.

Retinoids and carotenoids are potential cancer preventive agents, as they can control the replication and differentiation of cells. However, concern exists about the potential toxicity of retinoids and their synthetic analogs in humans. In this study, the researchers examined mechanisms by which these compounds limit breast tumor cell growth. In a series of tests, they examined the impact of a number of synthetically derived breakdown products of β-carotene and all-*trans* retinoic acid on the growth of human breast tumor cells. Estrogen receptor-positive and -negative human breast tumor cell lines that express retinoic acid receptors and estrogen receptors were evaluated. Three different concentrations of four cleavage products of β-carotene and all-trans retinoic acid were used. Synthetically derived breakdown products of β-carotene were effective inhibitors of estrogen-positive and -negative breast tumor cell growth, but the degree of inhibition varied between products. The study showed that the breakdown product, apo-β-carotenoic acids, regulates breast tumor cell growth independent of its conversion to all-*trans*-retinoic acid and thereby induced fewer side effects than retinoids. This finding is important, given the current debate on the role of retinoic acid versus β-carotene supplementation in the development of cancer.

Funding: US Department of Agriculture

Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: A 3-y prospective study.

MK Lehtonen-Veromaa, TT Möttönen, IO Nuotio, KM Irjala, AE Leino, and JS Viikari. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2002 76:1446-1453.

Achieving peak bone mass during childhood and adolescence is important in preventing the early onset of osteoporosis. Currently, knowledge about the association between vitamin D status and bone development in adolescence is limited. This study examined the association between serum 25-hydroxyvitamin D [25(OH)D, a measure of vitamin D status] and bone development, as well as the association between serum 25(OH)D and biochemical markers of bone metabolism. During the winter months, 171 healthy Finnish girls aged 9-15 years were given vitamin D daily: 10 μg in the first two years and 20 μg in the third year. The dose was increased in the third year because 10 μg/day did not adequately increase blood levels of 25(OH)D. A 500 mg/day calcium supplement was given to girls who consumed <1000 mg/day calcium. Bone mineral density at the spine and neck were measured and bone mineral apparent density values were calculated from these measurements. Baseline levels of serum 25(OH)D and the change in bone mineral density at the spine and the neck were significantly correlated. None of the girls with >50 nmol/L of serum 25(OH)D lost bone at the spine. The results also showed that dietary intakes of vitamin D were inadequate to maintain optimal vitamin D status in winter. Since poor vitamin D status may put girls at risk of not developing peak bone mass, these findings suggest that supplementation with vitamin D should be considered during the winter. In areas where exposure to sunlight is restricted, 20 μg/day may be an appropriate level of supplementation to ensure adequate vitamin D status in adolescent girls.

Funding: Yrjö Jahnsson Foundation; the Medical Research Foundation of the Turku University Central Hospital; the Finnish Medical Foundation, Finland.

Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons. A randomized controlled trial.

Aging is associated with a decline in the body's immune function and some studies show that this decline can be arrested by vitamin and mineral supplementation. This study compared the effects of vitamin E with a daily multivitamin and mineral preparation on the incidence and severity of acute respiratory tract infections in elderly subjects. Six hundred fifty-two well-nourished, free-living older individuals, aged 60 years and older, received one of four treatments for 15 months: 1) a daily multivitamin-mineral supplement that contained 20 mg vitamin E, 2) 200 mg vitamin E, 3) a combination of both multivitamin-mineral and vitamin E supplements, or 4) a placebo. The incidence and severity of acute respiratory tract infections was assessed through a self-reported survey, which was conducted by a nurse via the telephone or a home visit. The severity of infections was assessed by total duration of the illness, the number of symptoms, and body temperature or fever. Supplementation with multivitamins and minerals, vitamin E, or both did not decrease the incidence of infection. The multivitamin-mineral supplement did not change the severity of infection, but the severity of infection was worse for subjects who received the vitamin E supplement and experienced an infection. Given these negative findings, additional studies are needed to confirm whether vitamin E exacerbates respiratory tract infections in the elderly and to determine the mechanism by which it does so.

Funding: Netherlands Organization for Health Research and Development.

JM Graat, EG Schouten, and FJ Kok. ***Journal of the American Medical Association*** **(JAMA) 2002 288:715-721.**

Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease.

Alzheimer's disease and other age-related disease states may result from DNA damage caused by folic acid deficiency and elevated homocysteine levels. Alzheimer's disease is also facilitated by nerve cell death in the brain, which results in the increased production and accumulation of amyloid β-peptide, a protein toxic to cells. This study tested the theory that folic acid deficiency and elevated homocysteine levels alter DNA repair in neurons and increase their susceptibility to death from amyloid β-peptide. Cell cultures, as well as mutant and normal mice, were used to test this theory. Brain cells were grown in a cell culture that had added folic acid, methotrexate (an inhibitor of folic acid metabolism), or homocysteine. Growing brain cells in a medium deficient in folic acid and in the presence of methotrexate or homocysteine promoted cell death and rendered nerve cells susceptible to death from amyloid β-peptide. Mutant mice on the folic acid-deficient diet experienced increased DNA damage and damage to neurons in the hippocampus. These early findings suggest that individuals with or at risk for Alzheimer's disease may benefit from folic acid supplementation, as folic acid deficiency results in damage to DNA and nerve cells.

Funding: Source not identified.

II Kruman, TS Kumaravel, A Lohani, WA Pedersen, RG Cutler, Y Kruman, N Haughey, J Lee, M Evans, and MP Mattson. ***The Journal of Neuroscience*** **(J Neurosci) 2002 22:1752-1762.**

Calcium intake and risk of colon cancer in women and men.

K Wu, WC Willett, CS Fuchs, GA Colditz, and EL Giovannucci. ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2002 94:437-446.**

In some epidemiologic studies, higher intakes of calcium are associated with a reduced risk of colon cancer. However, intervention studies do not consistently confirm these findings. In this analysis, data from two prospective epidemiologic studies — the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) — were examined to determine the relationship between dietary calcium from foods and supplements and the risk of colon cancer at multiple sites. The NHS population included 87,998 women who had been followed from 1980 to 1996 and the HPFS included 47,344 men followed from 1986 to 1996. During the follow-up period, 1,025 cases of colon cancer were identified; 626 in women and 399 in men. Regression analysis was used to estimate relative risks for the diagnosis of cancer. As compared with dietary calcium intakes of <500 mg/day, intakes >1240 mg/day were inversely associated with distal colon cancer in nonusers of aspirin only, with the reduction in risk greater for men than for women. No protective association with calcium could be demonstrated for proximal colon cancer in men or women. Calcium from supplements was associated with a lower risk of distal colon cancer among participants with low calcium intake from foods. Among participants with dietary calcium intakes of >700 mg/day, risks were similar for both supplement users and nonusers. These data suggest that relatively moderate calcium intakes of 700 mg/day may decrease the risk of distal colon cancer and that intakes above 1240 mg/day may not offer additional benefit in risk reduction.

Funding: National Cancer Institute, NIH.

Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations.

R Gärtner, BCH Gasnier, JW Dietrich, B Krebs, and MWA Angstwurm. ***The Journal of Clinical Endocrinology & Metabolism*** **(J Clin Endo Metab) 2002 87:1687-1691.**

Chronic autoimmune thyroiditis is a relatively common disease in the United States, affecting 10% of females and 2% of males. There are several explanations for the development of this disease. Previous research showed that selenium deficiency can induce the destruction of thyroid cells and decrease immune function. The aim of this study was to determine whether supplementation with selenium affects concentrations of antibodies in patients with hypothyroidism. Seventy female patients with hypothyroidism and mild selenium deficiency received 200 μg sodium selenite or a placebo daily for 90 days. Plasma selenium was determined by atomic absorption spectrometry. The primary endpoint of the study was changes in the levels of thyroid peroxidase antibodies. Selenium supplementation reduced concentrations of thyroid peroxidase antibodies from 100% to 63.6%; no change occurred in the placebo group. These results suggest that selenium supplementation may be beneficial by decreasing inflammatory activity in patients with autoimmune thyroid disease and mild selenium deficiency. Research is needed to confirm these findings and to extend the use of selenium supplementation to the investigation of other autoimmune diseases.

Funding: Source not identified.

Effects of coenzyme Q_{10} in early Parkinson Disease: Evidence of slowing of the functional decline.

Parkinson disease is a degenerative neurological condition characterized by resting tremor, muscular rigidity, and slowness of movement. It affects about 1% of Americans over 65. Although the cause of Parkinson disease is not known, a decline in mitochondrial function is associated with the disease. This study examined whether coenzyme Q_{10} could decrease the rate of functional decline in patients with early Parkinson disease. Eighty individuals with early Parkinson disease, who were not being treated with the prescription medicine levodopa, were given a range of doses of coenzyme Q_{10} or a placebo four times daily. The three-dose levels of coenzyme Q_{10} (300, 600, and 1200 mg/day) were delivered in the form of a wafer that also contained 300 IU vitamin E. The wafers were consumed for 16 months or until standard therapy with levodopa was required. The Unified Parkinson Disease Rating Scale (UPDRS) score was used to monitor changes in functional decline between the baseline and final visits. A significant positive association was observed between the coenzyme Q_{10} dosage level and the mean change in the UPDRS score. A significant difference was also observed in UPDRS scores between the groups receiving 1200 mg/day and a placebo. This study shows that coenzyme Q_{10} appears to be well tolerated in doses of 300-1200 mg/day and is effective in reducing the development of functional disability in patients in the early stages of Parkinson disease. Although these results are promising, larger studies are needed to confirm these findings on the role of coenzyme Q_{10} in the management of Parkinson disease.

Funding: National Institute of Neurological Disorders and Stroke, NIH.

CW Shults, D Oakes, K Kieburtz, MF Beal, R Haas, S Plumb, JL Juncos, J Nutt, I Shoulson, J Carter, K Kompoliti, JS Perlmutter, S Reich, M Stern, RL Watts, R Kurlan, E Molho, M Harrison, M Lew, and the Parkinson Study Group. *Archives of Neurology* (Arch Neurol) 2002 59:1541-1550.

Supplementation with conjugated linoleic acid causes isomer-dependent oxidative stress and elevated C-reactive protein: A potential link to fatty acid-induced insulin resistance.

Conjugated linoleic acids (CLAs) are a group of fatty acids that have been shown to have antiobesity, antiatherogenic, and antidiabetic effects in animals. As the effects of CLAs in obese individuals are not known, this study evaluated its effects on insulin resistance and oxidative stress or inflammatory biomarkers. Sixty obese men (mean body mass index >30) with metabolic disease were randomly assigned to receive a CLA isomer (*trans*10*cis*12CLA), a CLA mixture, or a placebo for 12 weeks. Several markers of oxidative stress and inflammatory disease were measured. The CLA isomer increased markers of oxidative stress and inflammatory disease in the obese men. The oxidative stress was closely related to insulin induced resistance, suggesting a link between the fatty acid-induced lipid peroxidation and insulin resistance. This study demonstrates that the CLA isomer (*trans*10*cis*12CLA) increases oxidative stress and inflammation in men, which places them at increased risk for cardiovascular disease and diabetes. Until further studies confirm these findings, it seems prudent that obese individuals avoid the use of dietary supplements containing CLA isomers.

Funding: Swedish Medical Research Council; Swedish National Fund for Industrial and Technical Development; Swedish National Association against Heart and Lung Disease; Swedish Diabetes Foundation.

U Risérus, S Basu, S Jovinge, GN Fredrikson, J Ärnlöv, and B Vessby. *Circulation* (Circulation) 2002 106:1925-1929.

Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension.

RJ Woodman, TA Mori, V Burke, IB Puddey, GF Watts, and LJ Beilin. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2002 76:1007-1015.**

Patients with type 2 diabetes have an increased risk of cardiovascular disease, and fish oils or omega-3 fatty acids are associated with a reduced risk for this disease. This study examined the effects of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on glycemic control, blood pressure, heart rate, and lipid metabolism. Thirty nine men and 12 postmenopausal women with type 2 diabetes and treated hypertension, received 4 g EPA, 4 g DHA, or an olive oil placebo daily for six weeks. Blood samples of serum glucose, insulin, C-peptide, lipids, and lipoproteins were collected at baseline and the end of the study. Fasting glucose levels increased in the EPA and DHA groups compared with the olive oil group. Neither EPA nor DHA altered 24-hour blood pressures, glycated hemoglobin, fasting insulin, C-peptide, or insulin sensitivity or secretion (as measured by a low-dose insulin and glucose infusion test). Although serum triglyceride levels decreased in the EPA and DHA groups, total, low-density lipoprotein, and high-density lipoprotein cholesterol levels did not change. The investigators concluded that EPA and DHA had similar beneficial effects on lipids but noted the short-term adverse effects of worsening glycemic control in these patients. Longer-term studies are needed to confirm these observations before routine use of purified EPA or DHA supplements can be recommended for individuals with type 2 diabetes.

Funding: National Health and Medical Research Council of Australia.

Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress.

T M Hagen, J Liu, J Lykkesfeldt, CM Wehr, RT Ingersoll, V Vinarsky, JC Bartholomew, and BN Ames. ***Proceedings of the National Academy of Sciences*** **(PNAS) 2002 99:1870-1875.**

Mitochondrial decay and increased oxidative stress play an important role in the aging process. This study theorized that supplementation with acetyl-L-carnitine and the antioxidant lipoic acid will reverse age-related metabolic decline. Acetyl-L-carnitine is a mitochondrial metabolite of carnitine and reverses the age-related decline of carnitine levels in tissues. Lipoic acid is a cofactor for enzymes found in mitochondria. Young and old male rats were supplemented with acetyl-L-carnitine, lipoic acid, a combination of both substances, or given an unsupplemented control diet daily for one month. Compared with young rats, old rats fed the combination acetyl-L-carnitine and lipoic acid diet demonstrated significant increases in metabolic activity. In response to oxidative stress, the combination acetyl-L-carnitine and lipoic acid diet reversed markers of lipid peroxidation in the older rats to levels comparable with levels in the young untreated animals. These observed effects were greater than with either acetyl-L-carnitine or lipoic acid alone. This short-term animal study suggests that a combination of acetyl-L-carnitine and lipoic acid appears to increase metabolic activity and lower oxidative stress in old animals. These preliminary findings should be confirmed because of the potential of these findings in managing the aging process.

Funding: National Institute on Aging and National Institute of Environmental Health Sciences, NIH; Ellison Medical Foundation; Department of Energy; Bruce and Giovanna Ames Foundation.

Analysis of thirteen populations of Black cohosh for formononetin.

Black cohosh *(Actaea racemosa)* is used to manage various women's health conditions associated with menopause, such as a reduction of hot flashes. Estrogen-like action of this botanical has been attributed to presence of the isoflavonone formononetin; however, some researchers have been unable to confirm the presence of this compound in black cohosh. As a result of these contradictory findings, an extensive chemical investigation of black cohosh was conducted. Thirteen extracts of black cohosh roots and rhizomes, and two commercially available products were examined for formononetin using thin-layer chromatography, high-performance liquid chromatography, and liquid chromatography-electrospray ionization mass spectrometry analytical techniques. The roots and rhizomes of black cohosh were obtained from 13 locations in the eastern United States. Formononetin was not detected in any of the 15 samples, leading the researchers to conclude that if there is estrogen-like activity in this botanical, it is due to compounds other than formononetin. These findings point to the need for additional research to identify the active compound or compounds responsible for the activity of black cohosh.

Funding: National Center for Complementary and Alternative Medicine, NIH.

EJ Kennelly, S Baggett, P Nuntanakorn, AL Ososki, SA Mori, J Duke, M Coleton, and F Kronenberg. *Phytomedicine* (Phytomedicine) 2002 9:461-467.

A natural product that lowers cholesterol as an antagonist ligand for FXR.

Guggul, an extract from the resin of the mukul myrrh tree *(Commiphora mukul)*, has been used since 600 BC in Ayurvedic medicine to treat obesity and lipid disorders. Guggulipid, an ethyl acetate extract of this resin, is used to treat hyperlipidemia in India and is also available in the US. This study evaluated the mechanisms by which two compounds present in guggulipid, E- and Z-gugglusterone, decrease hepatic cholesterol levels. Several tests were carried out in cell cultures and in mice. The resin extracts were evaluated for their effects on the activity of the bile acid receptor FXR because this receptor plays an important role in bile acid and cholesterol metabolism. Guggulsterone decreased the expression of the FXR receptor, indicating that it was an effective antagonist of this receptor. Guggulsterone did not directly affect DNA binding to FXR but did interact with and inhibit the FXR ligand-binding domain. To determine whether the FXR antagonist property of guggulsterone is required for its cholesterol-lowering effects, normal and FXR-deficient mice were fed a normal diet or a high-cholesterol diet supplemented with guggulsterone for one week. The cholesterol diet increased liver cholesterol levels in both the normal and FXR-deficient mice. Guggulsterone deceased liver cholesterol levels in normal mice fed a high-cholesterol diet but had no effect in normal mice fed a normal diet or in FXR-deficient mice. These findings suggest that guggulsterone lowers cholesterol levels by acting as an antagonist of the FXR bile acid receptor important in the metabolism of cholesterol.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of General Medical Sciences, NIH; US Department of Agriculture; Howard Hughes Medical Institute; the Robert A Welch Foundation.

NL Urizar, AB Liverman, DT Dodds, FV Silva, P Ordentlich, Y Yan, FJ Gonzalez, RA Heyman, DJ Mangelsdorf, and DD Moore. *Science* (Science) 2002 296:1703-1706.

Novel polyphenol molecule isolated from licorice root *(Glycrrhiza glabra)* induces apoptosis, G2/M cell cycle arrest, and Bcl-2 phosphorylation in tumor cell lines.

MM Rafi, BC Vastano, N Zhu, C-T Ho, G Ghai, RT Rosen, MA Gallo, and RS DiPaola. *Journal of Agricultural and Food Chemistry* (J Agri Food Chem) 2002 50: 677-684.

Licorice root is a botanical found in Chinese medicines, such as PC-SPES, used to manage cancers. In previous studies the antiprostate cancer activity of PC-SPES was attributed to phyto-estrogens contained in licorice root that decreased circulating testosterone levels in men and decreased expression of the antiapoptotic protein Bcl-2. Substances that decrease Bcl-2 expression or inactivate Bcl-2 induce apoptosis. In this cell culture study, an extract of licorice root was assessed for its effects on Bcl-2 expression and cell cycle arrest at G2/M phase of cell division in breast cancer and leukemia cells. These researchers demonstrated that licorice root affects Bcl-2 activity, G2/M cell-cycle arrest, and apoptosis in a manner similar to that seen with some prescription products. These preliminary findings suggest that licorice root contains novel compounds that could be used to derive novel anticancer agents. Although PC-SPES has been recalled from the US market because of contamination issues, additional research to confirm these findings are warranted as licorice root is contained in several herbal medicines.

Funding: National Cancer Institute and National Institute of Environmental Health Sciences, NIH; CaPCure; New Jersey Commission on Cancer Research.

Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of *Helicobacter pylori* and prevents benzo[a]pyrene-induced stomach tumors.

JW Fahey, X Haristoy, PM Dolan, TW Kensler, I Scholtus, KK Stephenson, P Talalay, and A Lozniewski. *Proceedings of the National Academy of Sciences* (PNAS) 2002 99:7610-7615.

Gastric infection with *Helicobacter pylori* bacteria in developing countries is a common cause of gastric and peptic ulcers, and can result in gastric cancer. Since many strains of *H pylori* have acquired resistance to conventional antibiotics, these researchers investigated whether sulforaphane is effective in killing strains of *H pylori*. Sulforaphane is an isothiocyanate abundant in cruciferous vegetables, such as broccoli and brussel sprouts. In this cell culture study, the bacteriostatic effects and antibiotic resistance activity of sulforaphane were compared with the known antibiotics amoxicillin, clarithromycin, and metronidazole. Sulforaphane was extracted from broccoli seeds, and three reference strains of *H pylori* were used. *H pylori* penetrates gastric epithelium, and both extracellular and intracellular forms exist; sulforaphane effectively killed both forms. These findings are encouraging because the researchers identified a compound abundant in cruciferous vegetables to potentially treat an antibiotic-resistant gastric infection that can result in gastric cancer. Clinical studies are needed to confirm these findings because of their potential global health benefits.

Funding: Lewis B and Dorothy Cullman Foundation; Barbara Lubin Goldsmith Foundation; McMullan Family Fund; National Cancer Institute, NIH.

Effect of tamarind ingestion on fluoride excretion in humans.

Hydrofluorosis is a condition resulting from drinking water that naturally contains a high level of fluoride. This condition results in the mottling or discoloration of teeth and bone abnormalities, and is endemic in certain areas of the world, such as south India. Since drugs to specifically treat hydrofluorosis are not readily available and because attempts to remove fluoride from drinking water have failed, hydrofluorosis remains a major health problem. Tamarind is a brown pulp extracted from the bean pod of the tamarind tree *(Tamarindus indica)*. It is used extensively as a souring agent in south Asian cooking. In animal studies, tamarind had a beneficial effect on fluoride toxicity. On the basis of these preliminary findings, these researchers designed a study to examine the effects of tamarind consumption in preventing hydrofluorosis in humans. In this crossover design study, healthy boys around 10 years of age consumed 10 g tamarind with lunch for 18 days. Eighteen boys completed the study. Tamarind increased urinary excretion of fluoride. These results indicate that tamarind ingestion may be effective in preventing hydrofluorosis. Given the potential public health significance of these findings, a more rigorous clinical trial is needed.

Funding: National Institute of Nutrition, India.

AL Khandare, GS Rao, and N Lakshmaiah. ***European Journal of Clinical Nutrition*** **(Eur J Clin Nutr) 2002 56: 82-85.**

Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: A randomized controlled trial.

Hypericum perforatum, commonly known as St John's wort, is used to treat depression. In the United States, St John's wort is regulated as a dietary supplement. This study was designed to investigate the efficacy of St John's wort on major depressive disorders because its effectiveness in the management of these disorders had not been conclusively demonstrated. St John's wort was compared with the prescription product sertraline, which also served as the known active control. Three hundred-forty individuals with major depression were randomly assigned to receive one of three treatments daily for eight weeks: 900-1500 mg St John's wort (standardized to 0.12-0.28% hypericin), 50-100 mg sertraline, or a matching placebo. Hamilton Depression Scale and Clinical Global Impression scores were used to measure effectiveness. When compared with the matched placebo, neither St John's wort nor sertraline had a significant effect on these scores. These results suggest that neither product is effective in treating moderately severe major depression. The findings suggest that either St John's wort should not be used to treat major depressive disorders or that the study design was not appropriate for determining the efficacy of this product. Findings from this study should be considered when designing new studies on the effectiveness of St John's wort in managing depression.

Funding: National Center for Complementary and Alternative Medicine and National Institute for Mental Health, NIH.

Hypericum Depression Trial Study Group. ***Journal of the American Medical Association*** **(JAMA) 2002 287:1807-1814.**

Dietary soy isoflavones and bone mineral density: Results from the Study of Women's Health Across the Nation.

GA Greendale, G FitzGerald, M-H Huang, B Sternfeld, E Gold, T Seeman, S Sherman, and MF Sowers. *American Journal of Epidemiology* (Am J Epidemiol) 2002 155:746-754.

Isoflavones found in soy foods have been theorized to have protective effects in bone due to their estrogen-like actions. This study examined the association between soy isoflavone intake and bone mineral density in a cohort of women from the Study of Women's Health Across the Nation. Subjects included 497 African-American, 1,003 Caucasian, 200 Chinese, and 227 Japanese women aged 42-52 years. Dietary intakes of two isoflavones, genistein and daidzein, were assessed by using a food frequency questionnaire. Because genistein and daidzein intakes were highly correlated, only genistein intake was used in the analyses. Median genistein intakes were 7,151 μg/day for Japanese women and 3,511 μg/day for Chinese women compared with 3.9 μg/day for Caucasian women and 1.7 μg/day for African-American women. For premenopausal Japanese women, higher intakes of genistein were associated with higher bone mineral density at the spine and femoral neck. However, there were no associations between genistein intake and bone mineral density for Chinese women or perimenopausal Japanese women. Because isoflavone intakes of African-American and Caucasian women were very low, the researchers did not evaluate data for these women. The results suggest that women may have different bone mineral density responses to isoflavone intake based on ethnicity, menopausal status, and different dietary sources of isoflavones. Research in nutrigenomics (the science of understanding gene-nutrient interactions) is required to explain how these ethnic differences influence the effects of soy isoflavones on bone mineral density in women.

Funding: National Institute on Aging, National Institute of Nursing Research, Office of Research on Women's Health, National Institute of Mental Health, National Institute on Child Health and Human Development, National Center for Complementary and Alternative Medicine, the Office of AIDS Research, NIH.

Clinical characteristics and pharmacokinetics of purified soy isoflavones: Single-dose administration to healthy men.

MG Busby, AR Jeffcoat, LT Bloedon, MA Koch, T Black, KJ Dix, WD Heizer, BF Thomas, JM Hill, JA Crowell, and SH Zeisel. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2002 75:126-136.

Studies suggest that soy isoflavones may have chemoprotective effects, but little is known about the safety of large doses of isoflavones. This study analyzed the absorption, metabolism, and safety of single high doses of purified isoflavones extracted from soy. Thirty healthy men, aged 40-69 years, were given one of five doses of isoflavones containing genistein, daidzein, and glycitein (1, 2, 4, 8, or 16 mg/kg body weight). Within each dose group, half of the men received one isoflavone preparation and half received another preparation. Laboratory analyses were conducted on the day the dose was administered and on days 3, 6, 14, and 30 after administration. No estrogenic or antiestrogenic symptoms were observed in the men. Several adverse events were reported but were not associated with any clinical toxicity. In addition, no other clinically significant physical or behavioral changes were observed. Genistein and daidzein cleared rapidly from the plasma and were excreted in the urine. The findings from this study show that single doses of isoflavones, many times higher than normal dietary intakes, are rapidly eliminated from the body and result in minimal clinical toxicity in men. Additional research is required to understand the effects in women and the safety of chronic doses of isoflavones in men and women.

Funding: National Cancer Institute, NIH.

Soy protein isolate prevents chemically-induced rat mammary tumors.

AL Constantinou, LAM Lucas, D Lantvit, M Hawthorne, X Xu, CW Nho, EH Jeffery, K Christov, RB van Breemen, and JM Pezzuto.
***Pharmaceutical Biology* (Pharma Bio) 2002 40(supplement):24-34.**

Soy consumption is associated with a decreased risk of mammary cancer, but it is unclear as to which components in soy are responsible for this health benefit. To identify the active components in soy, these researchers compared the antitumor effects of soy protein isolate with its isoflavones genistein and daidzein in Sprague-Dawley rats. Mammary carcinomas were induced with the carcinogen, 7,12-dimethylbenz[a]anthracene. The rats were fed a standard diet supplemented per kilogram diet with 1) 200 mg purified genistein, 2) 200 mg purified daidzein, 3) 200 mg genistein plus daidzein, 4) soy protein enriched with isoflavones, 5) soy protein depleted of isoflavones, or 6) an unsupplemented standard or control diet for 120 days. After 120 days there were no differences in tumor incidence or survival among the six groups. Compared with the control group, tumor multiplicity was significantly reduced in the groups that received daidzein, soy protein enriched with isoflavones, and soy proteins depleted of isoflavones. The most significant reduction was observed in the group that received soy protein depleted of isoflavones. The two soy protein groups had up-regulated transcriptional expression of three antioxidant enzymes. These results point to the need for additional research to identify components responsible for the antitumor effects of soy because the antitumor effects of soy protein isolate were not due to genistein or daidzein.

Funding: United Soybean Board; Raymond Cole Memorial Foundation.

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APPENDIX

Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2001*

Supplementation of atherogenic diet with B-vitamins does not prevent atherosclerosis or vascular dysfunction in monkeys. SR Lentz, DJ Piegors, MR Malinow, and DD Heistad. *Circulation* (Circulation) 2001 103:1006-1011.

Low-dose vitamin B_6 effectively lowers fasting plasma homocysteine in healthy elderly persons who are folate and riboflavin replete. MC McKinley, H McNulty, J McPartlin, JJ Strain, K Pentieva, M Ward, DG Weir, and JM Scott. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2001 73:759-764.

Folic acid fortification increases red blood cell folate concentrations in the Framingham Study. SF Choumenkovitch, PF Jacques, MR Nadeau, PWF Wilson, IH Rosenberg, and J Selhub. *Journal of Nutrition* (J Nutr) 2001 131:3277-3280.

Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease. JA Tice, E Ross, PG Coxson, I Rosenberg, MC Weinstein, MGM Hunink, PA Goldman, L Williams, and L Goldman. *Journal of the American Medical Association* (JAMA) 2001 286:936-943.

Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. BG Brown, X-Q Zhao, A Chait, LD Fisher, MC Cheung, JS Morse, AA Dowdy, EK Marino, EL Bolson, P Alaupovic, J Frohlich, and JJ Albers. *New England Journal of Medicine* (N Engl J Med) 2001 345:1583-1592.

Serum carotenoids and breast cancer. P Toniolo, AL Van Kappel, A Akhmedkhanov, P Ferrari, I Kato, RE Shore, and E Riboli. *American Journal of Epidemiology* (Am J Epidemiol) 2001 153:1142-1147.

Effects of a short-term vitamin D_3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. M Pfeifer, B Begerow, HW Minne, D Nachtigall, and C Hansen. *The Journal of Clinical Endocrinology and Metabolism* (J Clin Endocrinol Metab) 2001 86:1633-1637.

Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. D Manzella, M Barbieri, E Ragno, and G Paolisso. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2001 73:1052-1057.

A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. ME Keith, KN Jeejeebhoy, A Langer, R Kurian, A Barr, B O'Kelly, and MJ Sole. *The American Journal of Clinical Nutrition* (Am J Clin Nutr) 2001 73:219-224.

Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Collaborative Groups of the Primary Prevention Project (PPP). *The Lancet* (Lancet) 2001 357:89-95.

Elevated iron status increases bacterial invasion and survival and alters cytokine/chemokine mRNA expression in Caco-2 human intestinal cells. SL Foster, SH Richardson, and ML Failla. *Journal of Nutrition* (J Nutr) 2001 131:1452-1458.

Effect of zinc supplementation on malaria and other causes of morbidity in West African children: randomised double blind placebo controlled trial. O Müller, H Becher, A B van Zweeden, Y Ye, DA Diallo, AT Konate, A Gbangou, B Kouyate, and M Garenne. *British Medical Journal* (BMJ) 2001 322:1-6.

Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double-blind controlled trial. MM Rahman, SH Vermund, MA Wahed, GJ Fuchs, AH Baqui, and JO Alvarez. *British Medical Journal* (BMJ) 2001 323:314-318.

The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccarides: a human volunteer study. KM Tuohy, S Kolida, AM Lustenberger, and GR Gibson. *British Journal of Nutrition* (Br J Nutr) 2001 86:341-348.

Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens. TB Clarkson, MS Anthony, and TM Morgan. *The Journal of Clinical Endocrinology and Metabolism* (J Clin Endocrinol Metab) 2001 86:41-47.

Dietary soy has both beneficial and potentially adverse cardiovascular effects: a placebo-controlled study in men and postmenopausal women. HJ Teede, FS Dalais, D Kotsopoulos, Y-L Liang, S Davis, and BP McGrath. *The Journal of Clinical Endocrinology and Metabolism* (J Clin Endocrinol Metab) 2001 86:3053-3060.

High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women. J Mei, SSC Yeung, and AWC Kung. *The Journal of Clinical Endocrinology and Metabolism* (J Clin Endocrinol Metab) 2001 86:5217-5221.

Endothelium-dependent vasodilation is independent of the plasma L-arginine/ADMA ratio in men with stable angina. HA Walker, E McGing, I Fisher, RH Böger, SM Bode-Böger, G Jackson, JM Ritter, and PJ Chowienczyk. *Journal of the American College of Cardiology.* (J Am Coll Cardiol) 2001 38:499-505.

Dietary supplementation with γ-linolenic acid or fish oil decreases T lymphocyte proliferation in healthy older humans. F Thies, G Nebe-von-Caron, JR Powell, P Yaqoob, EA Newsholme, and PC Calder. *Journal of Nutrition* (J Nutr) 2001 131:1918-1927.

Treatment for the premenstrual syndrome with agnus castus extract: prospective, randomised, placebo-controlled study. R Schellenburg for the study group. *British Medical Journal* (BMJ) 2001 322:134-137

Determination of ephedrine-type alkaloids in dietary supplements by LC/MS using a stable-isotope labeled internal standard. ML Gay, KD White, WR Obermeyer, JM Betz, and SM Musser. *Journal of AOAC INTERNATIONAL* (J AOAC Int) 2001 84:761-769.

Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. T Vutyavanich, T Kraisarin, and R-A Ruangsri. *Obstetrics and Gynecology* (Obstet Gynecol) 2001 97:577-582.

Caffeine intake increases the rate of bone loss in elderly women and interacts with vitamin D receptor genotypes. PB Rapuri, JC Gallagner, HK Kinyamu, and KL Ryschon. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2001 74:694-700.

Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. JY Reginster, R Deroisy, LC Rovati, RL Lee, E Lejeune, O Bruyere, G Giacovelli, Y Henrotin, JE Dacre, and C Gossett. *The Lancet* (Lancet) 2001 357:251-256.

Melatonin treatment for age-related insomnia. IV Zhdanova, RJ Wurtman, MM Regan, JA Taylor, JP Shi, and OU Leclair. *The Journal of Clinical Endocrinology and Metabolism* (J Clin Endocrinol Metab) 2001 86:4727-4730.

Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2000*

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.

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.

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* (Circulation) 2000 102:2479-2483.

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.

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. 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. 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* (Circulation) 2000 102:2353-2358.

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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. 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.

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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.

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.

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.

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.

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* (Proc Natl Acad Sci USA) 2000 97:7500-7502.

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.

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. 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 Q_{10} supplement renders swine hearts resistant to ischemia-reperfusion injury. 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. TE McAlindon, MP LaValley, JP Gulin, and DT Felson. *Journal of the American Medical Association* (JAMA) 2000 283:1469-1475.

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.

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.

Acknowledgements

2002 List of Journals and Journal Editors

The Office of Dietary Supplements thanks the following journal editors for their contributions in nominating scientific papers that appeared in their journals in 2002.

- **The American Journal of Clinical Nutrition,** Charles H Halsted, MD
- **American Journal of Epidemiology,** Moyses Szklo, MD, DrPh
- **American Journal of Physiology,** Margaret Reich, BA
- **Archives of Internal Medicine,** James E Dalen, MD, MPH
- **Atherosclerosis,** James Shepherd, PhD
- **The British Journal of Nutrition,** Paul Trayhurn, DSc
- **British Medical Journal,** Richard Smith, CBE, BSc, MB, ChB
- **Cancer, Epidemiology, Biomarkers and Prevention,** Frederick P Li, MD
- **Circulation,** James T Willerson, MD
- **Clinical Pharmacology and Therapeutics,** C Michael Stein, MD
- **European Journal of Clinical Nutrition,** Professor Jaap C Seidell
- **Journal of AOAC International,** Robert Rathbone, PhD
- **Journal of Agricultural and Food Chemistry,** James Seiber, PhD
- **The Journal of Alternative and Complementary Medicine,** Kim A Jobst, DM, MRCP
- **Journal of the American College of Cardiology,** Anthony N DeMaria, MD, MACC
- **Journal of the American College of Nutrition,** David M Klurfeld, PhD
- **Journal of the American Dietetic Association,** Linda Van Horn, 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 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
- **The New England Journal of Medicine,** Jeffery M Drazen, MD
- **Medicine and Science in Sports and Exercise,** Kent B Pandolf, PhD, MPH
- **Nutrition and Cancer,** Leonard A. Cohen, PhD
- **Nutrition Research,** RK Chandra, MB, FRCP, MACP
- **Obstetrics and Gynecology,** James R Scott, MD
- **Pharmaceutical Biology,** John M Pezzuto, PhD
- **Phytomedicine,** Norman R Farnsworth, PhD
- **Planta Medica,** Professor Dr Adolf Nahrstedt
- **Proceedings of National Academy of Sciences,** Nicholas Cozzarelli, PhD
- **Science Magazine,** Katrina Kelner, PhD

2002 List of Scientific Reviewers

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- **Bruce A Watkins, PhD,** Purdue University
- **Gary M Williams, MD,** New York Medical College
- **Richard J Wood, PhD,** Jean Mayer USDA Human Nutrition Research Center, Tufts University
- **Andrew Young, PhD,** US Army Research Institute of Environmental Medicine at Natick

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For more information, please contact:

Office of Dietary Supplements
6100 Executive Blvd
Rm 3B01, MSC 7517
Bethesda, MD 20892-7517
Tel: (301) 435-2920
Fax: (301) 480-1845
E-mail: ods@nih.gov
Web site: http://ods.od.nih.gov

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