# Annual Bibliography of Significant Advances in Dietary Supplement Research 2003

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 fifth *Annual Bibliography of Significant Advances in Dietary Supplement Research*. Each year, over the past five years, the Office has engaged in a process of identifying exemplary papers on dietary supplements and disseminating this information to researchers, health professionals, and consumers.

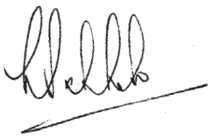
This issue contains 25 original research papers on dietary supplements that appeared in scientific journals in 2003. The criteria for selecting papers are the same as those used in previous years. The first step, in this rigorous multistep process, is a comprehensive literature search that identifies peer-reviewed journals publishing original research concerning dietary supplements. Editors of these journals are then asked to nominate a maximum of 18 original research papers that appeared in their journals. Additionally, our scientific reviewers are invited to elect noteworthy papers and through these efforts over 300 papers were nominated for the 2003 issue. The papers are then forwarded to internationally recognized scientists for evaluation and scoring, and the top 25 papers are 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 the 2002 and 2001 issues of the bibliography are listed in the appendix.

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 at the US Department of Agriculture. Specific individuals are identified in the 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. Copies of the current and previous issues of the *Annual Bibliography of Significant Advances in Dietary Supplement Research* are available online 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**
*Editor and Deputy Director*
Office of Dietary Supplements
National Institutes of Health



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**ANNOTATIONS OF 25 SELECTED PAPERS PUBLISHED IN 2003**

**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 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.

[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).*

## Effect of four monthly oral vitamin $D_3$ (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomized double blind controlled trial.

**DP Trivedi, R Doll, and KT Khaw. *British Medical Journal* (BMJ) 2003 326: 469-475.**

Cost effective measures for the primary prevention of osteoporotic fractures are needed in older men and women, as projected costs for treatment of these types of fractures are expected to increase worldwide. Vitamin D and calcium supplements are commonly prescribed as primary prevention measures. In this randomized controlled trial, researchers in Britain provided 2,686 physicians (2,037 men, 649 women) aged 65-85 years with either a vitamin D supplement (100,000 IU) or placebo capsule once every four months for five years. The goal was to determine the ability of vitamin D supplementation, administered in a feasible yet safe manner, to prevent fractures and reduce mortality. Capsules were mailed to participants every four months along with a questionnaire to determine the occurrence of fracture, cardiovascular disease, and cancer. The physicians were asked to consume the capsule immediately on receipt. After five years, the vitamin D treatment group had a 22 percent lower rate for first fracture at any site and a 33 percent lower rate for a fracture occurring in the hip, wrist or forearm, or vertebrae. Incidence of fracture was ascertained through the self-reported questionnaire. There were no significant effects of vitamin D on total mortality or incidence of cancer or cardiovascular disease. This study provides evidence of a safe and cost effective community intervention for preventing fractures. Future studies should continue to determine the most efficacious dose and frequency of intake of vitamin D required to prevent fractures.

*Funding: Medical Research Council, UK*

## Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol.

**RP Heaney, KM Davies, TC Chen, MF Holick, and MJ Barger-Lux. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2003 77: 204-210.**

Serum 25-hydroxycholecalciferol [25(OH)D], the bioactive form of vitamin $D_3$ is an established marker for vitamin D status. However, the amount of cholecalciferol (vitamin $D_3$) needed per day to meet and maintain specified levels of serum 25(OH)D remains unclear. This study was designed to evaluate the change in serum 25(OH)D levels to different doses of vitamin D and to estimate what proportion of vitamin D requirements are met from body stores during the winter. Sixty-seven men were randomized to receive daily one of four doses (0, 25, 125, or 250 µg) of vitamin D during the winter months of October through early March over two consecutive years. Serum cholecalciferol, serum 25(OH)D, total serum calcium and serum parathyroid hormone (PTH) were measured monthly for the lower dose (0, 25 µg) groups and at 1, 3, 6, 10 and 20 weeks for the higher does groups (125, 250 µg). The total amount of vitamin D needed to sustain baseline 25(OH)D concentrations throughout winter was estimated at around 96 µg per day; 12.5 µg from food or supplements and the remaining 78-82 µg from body stores. Therefore, without adequate vitamin D stores or sunlight exposure, the current vitamin D recommendations of five µg per day for healthy adult men may be insufficient to sustain serum 25(OH)D levels during the winter months. This study provides important information about dietary vitamin D requirements needed to sustain 25(OH)D levels during winter and the potential inadequacy of current dietary recommendations to meet these requirements.

*Funding: Health Future Foundation, Omaha, Nebraska.*

## Prediction of bone mass density variation by bone remodeling markers in postmenopausal women with vitamin D insufficiency treated with calcium and vitamin D supplementation.

**F Grados, M Brazier, S Kamel, M Mathieu, N Hurtebize, M Maamer, M Garabédian, JL Sebert, and P Fardellone.** ***The Journal of Clinical Endocrinology & Metabolism*** **(J Clin Endocrinol Metab) 2003 88:5175-5179.**

Calcium and vitamin D supplementation have been shown to improve bone mineral density (BMD) and bone turnover. However, short-term methods do not exist to evaluate changes in BMD in response to treatment with drugs or supplements. This study examined the ability to predict changes in BMD based on changes in bone resorption markers after supplementation with vitamin D and calcium. One hundred and ninety-two postmenopausal women, aged 65 years and over, with serum 25(OH)D levels below 12 ng/ml were enrolled in the study. These women were considered to be at high risk for vitamin D insufficiency by their physicians. They were randomized to receive a calcium carbonate (500 mg elemental calcium) and vitamin D (400 IU cholecalciferol) supplement or a placebo twice daily for one year. Blood and urine samples were taken to assess calcium homeostasis and bone remodeling markers at baseline, 3, 6, 9 and 12 months of treatment. BMD was assessed by dual energy x-ray absorptiometry at baseline and 12 months. Calcium and vitamin D supplementation significantly improved BMD, calcium homeostasis and several bone remodeling markers. Baseline and three month levels of bone remodeling markers were significantly correlated with one year changes in BMD in the calcium and vitamin D group. These results are promising, as they indicate that short-term changes in bone resorption markers can predict long-term variations in BMD in postmenopausal women taking calcium and vitamin D supplements, who were previously at high risk for vitamin D insufficiency.

*Funding: Laboratoires Innothera, France.*

## The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: Effects on menopause symptoms and bone markers.

**W Wuttke, D Seidlová-Wuttke, and C Gorkow.** ***Maturitas*** **(Maturitas) 2003 44:S67-S77.**

Researchers are currently seeking alternatives to conventional hormone replacement therapy (HRT) in women because of recent research indicating increased health risks with HRT. As black cohosh (*Cimicifuga racemosa*) has selective estrogen receptor modular-like activity, it may potentially benefit postmenopausal women. The aim of this study was to determine if black cohosh affects menopausal complaints (such as hot flashes) and bone metabolism, and promotes positive vaginal effects without untoward side effects such as uterotrophic activity. Sixty-two postmenopausal women were randomized to receive either 40 mg of a black cohosh extract (BNO 1055; Klimadynon®/Menofem®), 0.6 mg conjugated estrogens (HRT), or a placebo for three months. The primary outcome was the assessment of menopausal symptoms using a menopause rating scale. Using this scale, black cohosh was as effective as HRT in reducing menopausal complaints. When the menopause rating scale scores were separated into three categories: 1) hot flashes, 2) psyche, and 3) atrophy, black cohosh scores were lower only for atrophy as compared with the placebo. However, this factor is the least likely to have a placebo effect. A significant increase was seen in bone-specific alkaline phosphatase but not in levels of CrossLaps (marker of bone degradation) indicating possible increased bone formation with black cohosh. Endometrial thickness and vaginal cytology were also evaluated and shown to remain unchanged with black cohosh. These findings suggest that black cohosh may exert selective estrogen receptor modulation-like properties without causing adverse estrogenic effects in the uterus and therefore may provide an alternative therapy to HRT for postmenopausal women.

*Funding: EUROSTERONE; German Research Society.*

## Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: A comprehensive meta-analysis.

**F Richy, O Bruyere, O Ethgen, M Cucherat, Y Henrotin, and JY Reginster.** ***Archives of Internal Medicine*** **(Arch Intern Med) 2003 163: 1514-1522.**

Osteoarthritis is a common cause of disability in aging adults. Ingestion of glucosamine and chondroitin sulfate (compounds found in healthy cartilage), could be potential alternatives to non-steroidal anti-inflammatory drugs for those who are unable to take these medications. This meta-analysis included 15 randomized, controlled trials with a total of 1,775 patients: 1,020 on glucosamine and 755 on chondroitin. The data were pooled to reevaluate the structural efficacy of glucosamine and the symptomatic effects of glucosamine and chondroitin supplements on knee and hip osteoarthritis. Outcome measures that determine efficacy of current drug treatments for osteoarthritis were evaluated, including joint space narrowing, response to treatment as assessed by physicians, report of adverse events, and assessment of pain and mobility. Structural efficacy (reduction in joint space narrowing) was demonstrated in patients taking glucosamine (1,500 mg/day for 3 years) but not with placebos. Glucosamine or chondroitin treated patients experienced significant decreases in symptoms (decreased pain, increased mobility) compared with placebos. Both supplements were safe and well tolerated at doses used in the studies, i.e. 750-1,500 mg/day glucosamine sulfate and 200-2,000 mg/day chondroitin sulfate. These results indicate that glucosamine can be a symptomatic and structural modifying agent, and chondroitin may potentially mitigate symptoms of knee osteoarthritis. The current NIH-funded Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) has been designed to test this theory.

*Funding: Source not identified.*

**SUPPLEMENTS AND CANCER**

## Neoplastic and anti-neoplastic effects of β-carotene on colorectal adenoma recurrence: Results of a randomized trial.

**JA Baron, BF Cole, L Mott, R Haile, M Grau, TR Church, GJ Beck, and ER Greenberg.** ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2003 95: 717-722.**

Studies suggest that β-carotene supplementation may increase the risk of lung cancer, especially among smokers. This randomized controlled study (Antioxidant Polyp Prevention Study) was designed to determine if cigarette smoking and alcohol consumption altered the effect of β-carotene on carcinogenesis at sites other than the lung. A total of 864 subjects (over 75 percent male) who had an adenoma removed and were polyp-free were randomly assigned to receive daily, in a factorial design, either β-carotene (25 mg) or placebo, and/or combination vitamin C and E (1,000 mg, 400 mg α-tocopherol) or placebo. A questionnaire to obtain medical history and lifestyle habits regarding alcohol consumption and cigarette use was administered to men and women in this study. Subjects received follow-up endoscopy screenings one year and four years after the initial endoscopy. In subjects who did not smoke or consume alcohol a slight decrease in adenoma recurrence was observed. β-carotene correlated with a slight increase in the risk of one or more recurrent adenomas in subjects who smoked or consumed alcohol. Subjects who were regular smokers and consumed more than one alcoholic drink per day doubled their risk of adenoma recurrence. This study suggests that while β-carotene may be beneficial in preventing colorectal adenoma recurrence in individuals who abstain from cigarettes or alcohol, β-carotene supplementation may have a pro-neoplastic effect in individuals who smoke and/or consume alcohol. As the results of this study suggest that alcohol intake and cigarette smoking may modify the effect of β-carotene supplementation on the risk of colorectal adenoma recurrence, high-risk individuals should consult their physicians before taking these supplements.

*Funding: National Cancer Institute, NIH*

## Vitamin D, calcium supplementation, and colorectal adenomas: Results of a randomized trial.

**MV Grau, JA Baron, RS Sandler, RW Haile, ML Beach, TR Church, and D Heber.** ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2003 95:1765-1771.**

Calcium and vitamin D play a role in inhibiting the development, spread, and growth of abnormal cells that could potentially lead to colorectal polyps. The Calcium Polyp Prevention Study was a four year randomized controlled trial, designed to study the interaction between calcium supplement and vitamin D status on adenoma recurrence in 803 individuals of average age 61 years. The primary focus was the recurrence of adenomas during the four year treatment period. Subjects received daily calcium (3 g calcium carbonate, or 1,200 mg of elemental calcium) or a placebo. Polymorphisms in the vitamin D receptor gene (VDR) were analyzed using polymerase chain reaction techniques. Polymorphism is a genetic variant that appears in at least one percent of a population. No association was observed between calcium supplementation and adenoma recurrence in subjects with baseline 25(OH) vitamin D levels at or below median levels. In individuals above the median levels, there was an association between calcium supplementation and a reduced relative risk of adenoma. Serum 25(OH) vitamin D levels were associated with a reduced relative risk of adenoma recurrence in individuals given calcium supplementation. VDR polymorphisms did not reduce the risk of adenoma recurrence. While it appears that calcium and vitamin D act together to reduce the relative risk of colorectal adenoma recurrence, the VDR genotype does not appear to have a significant effect. Future studies should focus on determining optimal intakes of calcium and vitamin D needed for the prevention of abnormal cell growth that may develop into colorectal polyps.

*Funding: National Cancer Institute, NIH; and UCLA Clinical Nutrition Research Unit Grant*

## Incidence of cancer and mortality following α-tocopherol and β-carotene supplementation: A postintervention follow-up.

**ATBC Study Group.** ***Journal of American Medical Association*** **(JAMA) 2003 290:476-485.**

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized controlled chemoprevention trial designed to determine whether there is a correlation between the incidence of cancer mortality and supplementation with α-tocopherol and β-carotene. The study tracked 29,133 male smokers aged 50 to 69 years. Over a five to eight year period, the men received either α-tocopherol (50 mg), β-carotene (20 mg), both α-tocopherol and β-carotene, or a placebo. This study served as a post-intervention follow-up, examining possible late effects of the antioxidants and providing information on the time required for intervention effects to occur. The cancer incidence and all cause-specific mortality at six years (from May 1, 1993-April 30, 1999) and total mortality at eight years (from May 1, 1993 to April 30, 2001) were determined. Mortality was determined through the Finnish Cancer Registry and the Register of Causes of Death, and by medical record review. By April 30, 2001, 7,261 subjects died during the post-intervention follow-up period. During this period, overall relative risk of lung cancer in subjects taking β-carotene was 1.06. For subjects taking α-tocopherol, the relative risk of prostate cancer was 0.88. The relative risk of mortality among those taking α-tocopherol and β-carotene, as compared with controls, was 1.01 and 1.07 respectively. There was no excess risk for individuals who took β-carotene four to six years after ending the intervention. There were no late preventive effects on any other cancers due to either supplement. As the beneficial and adverse effects of supplemental α-tocopherol and β-carotene disappeared during postintervention follow-up, further research is recommended to confirm if α-tocopherol plays an important role in the prevention of prostate cancer.

*Funding: Source not identified.*

## Selenium supplementation and secondary prevention of non-melanoma skin cancer in a randomized trial.

Dietary selenium is associated with a reduced risk of non-melanoma skin cancer. The Nutritional Prevention of Cancer Trial, a randomized controlled trial, tested whether selenium supplementation can prevent non-melanoma skin cancer in 1,312 patients with a history of one or more squamous cell carcinomas or two or more basal cell carcinomas of the skin. These individuals received daily either 200 µg selenium (as selenized yeast) or a placebo. Preliminary results from September 15 through December 31, 1993, showed no association between selenium and the incidence of basal and squamous cell carcinomas of the skin. This paper analyzed data for the entire blinded period of the study, which ended January 31, 1996. No significant association was observed between selenium supplementation and the risk of basal cell carcinoma. Selenium supplementation did result in an increased risk of squamous cell carcinoma and non-melanoma skin cancer. These results indicate that among high-risk individuals, selenium supplementation does not have an effect on basal cell carcinoma, but appears to increase the risk of developing non-melanoma and squamous cell carcinoma. Further research is needed to account for confounding environmental factors, such as pesticides that may affect the outcomes related to the interaction between selenium supplementation and skin cancer risk.

*Funding: National Cancer Institute, NIH*

**AJ Duffield-Lillico, EH Slate, ME Reid, BW Turnbull, PA Wilkins, GF Combs, Jr., HK Park, EG Gross, GF Graham, MS Stratton, JR Marshall, and LC Clark; For the Nutritional Prevention of Cancer Study Group.** ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2003 95: 1477-1481.**

## Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines.

Green tea has been shown to help prevent cancer in animal studies, and several mechanisms have been proposed to explain this action. The polyphenol (-)-epigallocatechin-3-gallate (EGCG) is believed to be an important active ingredient in green tea responsible for this chemopreventive activity. This *in-vitro* study was undertaken to test mechanisms by which EGCG acts as a chemopreventive agent. Several human cancer cells (esophageal squamous, colon, and prostate) were exposed to varying doses of EGCG. The results of this study show that EGCG inhibits DNA methyltransferase activity and causes CpG demethylation and reactivation of methylation-silenced genes. This finding is significant, as it has not been reported previously for a dietary constituent. Hypermethylation of DNA is a key epigenetic mechanism for silencing many genes, including those for suppressing tumors, DNA repair enzymes, and receptors. In theory, this epigenetic process is reversible if the newly synthesized DNA strands are not methylated. Therefore, inhibitors of DNA methyltransferase activity are being researched as potential cancer therapeutic agents. These observations with the green tea extract EGCG in cancer cells should be confirmed in animal studies.

*Funding: National Cancer Institute, NIH.*

**MZ Fang, Y Wang, N Ai, Z Hou, Y Sun, H Lu, W Welsh, and CS Yang.** ***Cancer Research*** **(Cancer Res) 2003 63: 7563-7570.**

## Ginger as an antiemetic in nausea and vomiting induced by chemotherapy: A randomized, crossover, double blind study.

**S Sontakke, V Thawani, and MS Naik.** ***Indian Journal of Pharmacology*** **(Indian J Pharmacol) 2003 35:32-36.**

Ginger is often used as an antiemetic or an agent to manage nausea and vomiting. It does this by serving as an antagonist of the serotonin receptor, also called 5-HT or 5-hydroxytryptamine receptor. Researchers in this study compared ginger with drugs used to control nausea in patients undergoing chemotherapy. All 60 patients in this study were on 500-1,000 mg intravenous (IV) cyclophosphamide and other chemotherapeutic agents on a scheduled regimen. These patients received the following three antiemetic regimens in a cross-over design study: 1) two capsules (1,000 mg) of ginger powder and two ml of normal saline delivered intravenously (IV) delivered 20 minutes before chemotherapy, and two capsules of ginger powder delivered six hours after chemotherapy, 2) two capsules of lactulose and 20 ml of IV metoclopramide delivered 20 minutes before chemotherapy, and five mg of metoclopramide given orally delivered six hours after chemotherapy, and 3) two capsules of lactulose and 20 mg of IV ondansetron delivered 20 minutes before chemotherapy, and two capsules (4 mg) of ondansetron delivered six hours after chemotherapy. The 1,000 mg ginger dose selected for this study was found to be as effective as the prescription drug metoclopramide, but less effective than the prescription drug ondansetron in managing nausea and vomiting. This study supports the use of ginger as an antiemetic agent in patients undergoing chemotherapy under supervised medical conditions.

*Funding: Source not identified.*

### SUPPLEMENTS AND CARDIOVASCULAR HEALTH

## Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: A randomised controlled trial.

**F Thies, JMC Garry, P Yaqoob, K Rerkasem, J Williams, CP Shearman, PJ Gallagher, PC Calder, and, RF Grimble.** ***The Lancet*** **(Lancet) 2003 361: 477-485.**

Observational and intervention studies have demonstrated decreased cardiovascular events in patients consuming a diet high in n-3 polyunsaturated fatty acids (PUFAs). A number of mechanisms have been postulated for this risk reduction, such as decreased levels of triglycerides, decreased inflammation of the vascular endothelium, and decreases in post-prandial lipid responses. This trial tested whether incorporation of n-3 and n-6 PUFAs into advanced atherosclerotic plaques would alter plaque stability. Patients awaiting surgery for carotid endarterectomy were randomized to take a control oil (80:20 blend of palm and soybean oils, 6 g/day), n-3 PUFA as fish oil (1.4 g/day), or n-6 PUFA as sunflower oil (3.6 g/day). One hundred and sixty-two individuals completed the study with a median duration of intake of 42 days (range 7-189 days). Sunflower oil had little effect on the fatty acid composition of lipid fractions. Patients treated with fish oil had fewer plaques with thin fibrous caps and signs of inflammation, and had more plaques with thick fibrous caps and no signs of inflammation, as compared with plaques in patients from the control and sunflower oil groups. These results suggest that atherosclerotic plaques readily incorporate n-3 PUFAs inducing changes that enhance stability of the plaques, while this does not appear to occur in individuals given n-6 PUFAs. Enhanced plaque stability could explain reductions in non-fatal and fatal cardiovascular events associated with increased intake of omega-3 fatty acids from fish or dietary supplements.

*Funding: Food Standards Agency, UK.*

## Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study.

The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study, a six year randomized clinical trial, tested the efficacy of supplemental doses of vitamin C and E on preventing the progression of carotid artery arteriosclerosis. Smoking and non-smoking, men and women, aged 45-69 years, were supplemented twice daily with meals either 1) 91 mg of d-α-tocopherol, 2) 250 mg slow-release vitamin C, 3) a combination of both d-α-tocopherol and slow release vitamin C in a single tablet, or 4) a placebo during the initial three year double-masked treatment period. During the open treatment period, all supplemented individuals received the combination vitamin supplement. Four hundred and forty individuals concluded the study. After six years, supplementation with α-tocopherol and vitamin C reduced atherosclerotic progression overall by 26 percent; 33 percent in men and by a non-significant 14 percent in women. In both sexes, mean common carotid artery intima media thickness increased by 0.014 mm in the unsupplemented group and by 0.010 mm in the supplemented group. Observed effects were larger in subjects with low baseline plasma vitamin C levels or with common carotid artery plaques. According to the results from this study, a combination of slow-release vitamin C and vitamin E in reasonable doses may reduce the progression of carotid atherosclerosis in healthy hypercholesterolemic men. However, it is not known if these effects will translate into decreased cardiovascular events in these individuals.

*Funding: Academy of Finland*

**RM Salonen, K Nyyssonen, J Kaikkonen, E Porkkala-Sarataho, S Voutilainen, TH Rissanen, TP Tuomainen, VP Valkonen, U Ristonmaa, HM Lakka, M Vanharanta, JT Salonen, and HE Poulsen. *Circulation* (Circulation) 2003 107:947-953.**

## Cholesterol-lowering effect of a theaflavin-enriched green tea extract: A randomized controlled trial.

Epidemiologic studies associate tea consumption with a reduced risk for cardiovascular disease. However, human intervention studies using tea or tea extracts have not shown any effect on lipids or lipoproteins. This randomized controlled trial was designed to examine the effects of a theaflavin-enriched green tea extract on lipid profiles in individuals with mild to moderate hypercholesterolemia. Two hundred and forty men and women in China, aged 18 years or older, were randomized to receive a daily capsule containing either 375 mg theaflavin-enriched green tea extract (75 mg of theaflavins, 150 mg of green tea catechins, and 150 mg of other tea polyphenols) or a placebo for 12 weeks. During the study, all subjects consumed their usual diets. After 12 weeks, subjects receiving the theaflavin-enriched green tea extract exhibited significantly lower total cholesterol, LDL cholesterol and total cholesterol to HDL cholesterol ratios compared with baseline; differences in HDL cholesterol and triglycerides were not significantly different from baseline levels. Subjects receiving placebos exhibited no significant changes in lipids or lipoproteins subfractions compared with baseline. No serious adverse events occurred in either group. The results from this study suggest that a theaflavin-enriched green tea extract is well tolerated and may help reduce total and LDL cholesterol in Chinese adults with mild to moderate hypercholesterolemia. The results of this study should be confirmed in populations consuming western-style diets, which have higher fat content than Chinese diets.

*Funding: Nashai Biotech, LLC.*

**DJ Maron, GP Lu, NS Cai, ZG Wu, YH Li, H Chen, JQ Zhu, XJ Jin, BC Wouters, and J Zhao. *Archives of Internal Medicine* (Arch Intern Med) 2003 163: 1448-1453.**

## Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: A meta-analysis.

**PG Shekelle, ML Hardy, SC Morton, M Maglione, WA Mojica, MJ Suttorp, SL Rhodes, L Jungvig, and J Gagné. *Journal of the American Medical Association* (JAMA) 2003 289:1537-1545.**

Prior to 2004, the traditional Chinese medicine, ephedra, or *Ma Huang* was used in the United States in dietary supplement products for weight loss and athletic performance. A growing number of cardiovascular related adverse events linked to the use of ephedra led several groups to ask the US Food and Drug Administration (FDA) to ban the sale of ephedra-containing products. This paper is a meta-analysis of published and unpublished research designed to assess the efficacy and safety of ephedra and ephedrine. Nine electronic databases were searched for controlled trials on ephedra and ephedrine. For this analysis, low dose was defined as 10-20 mg per day, medium 40-90 mg per day, and high dose as 100-150 mg per day. Of the 530 articles screened, 52 were randomized controlled or clinical trials; eight on athletic performance and 44 on weight loss. Of the 44 weight loss studies, 24 were excluded from the pooled analysis, as the duration of treatment was less than eight weeks or for other reasons. Of the 18,000 case reports screened, 284 underwent detailed review. Ephedra and ephedrine promoted modest short-term weight loss (~0.9 kg/month). There were no data regarding enhancement of athletic performance or long-term weight loss. Ephedra or ephedrine, in combination with caffeine, was associated with increased risk of psychiatric, autonomic, or gastrointestinal symptoms, and heart palpitations. This meta-analysis of existing research on ephedra contributed to the April 12, 2004 action by FDA to prohibit the sale of ephedra-containing dietary supplements and warning to consumers against using these products.

*Funding: Agency for Healthcare Research and Quality (AHRQ), DHHS.*

## Beneficial effects of antioxidants and L-arginine on oxidation-sensitive gene expression and endothelial NO synthase activity at sites of disturbed shear stress.

**F de Nigris, LO Lerman, SW Ignarro, G Sica, A Lerman, W Palinski, LJ Ignarro, and C Napoli. *Proceedings of the National Academy of Sciences* (PNAS) 2003 100:1420-1425.**

Of the many risk factors for atherosclerosis, disturbed or turbulent blood flow in the artery vessel has been linked to increased endothelial damage. Turbulent blood flow alone or associated with other risk factors of atherosclerosis may activate a variety of signal transduction events that in turn may lead to endothelial dysfunction and enhanced atherogenesis. Nitric oxide, L-arginine, and antioxidants play an important role in mediating vasodilatation and endothelial function in animal models, as well as in human studies. These investigators studied whether proatherogenic conditions induced by turbulent shear stress could be modified by antioxidants and/or L-arginine, using a cultured human vascular endothelial cell model system and an *in-vivo* model, using arterial segments from an LDL-receptor knockout mouse model. Mice were fed a proatherogenic diet for six months and then randomized to six different treatment groups. Under conditions of increased shear stress, both model systems showed increased activities of redox-transcription factors and decreased expression of endothelial nitric oxide. In mice, the effect of antioxidants (vitamins C and E) alone, L-arginine alone, or the combination of both was assessed at one and eight weeks. The researchers found that co-treatment with antioxidants and L-arginine reduced levels of transcription factors and increased endothelial nitric oxide expression, attenuating a proatherogenic environment. These findings suggest that supplementation with antioxidants and L-arginine modulate stress-responsive genes and may have important implications for the pathogenesis and prevention of atherogenesis and subsequent cardiovascular disease.

*Funding: Mayo Foundation; and National Heart, Lung, and Blood Institute, NIH.*

## Vitamin C supplementation decreases oxidative stress biomarker $F_2$-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke.

**M Dietrich, G Block, NL Benowitz, JD Morrow, M Hudes, P Jacob III, EP Norkus, and L Packer. *Nutrition and Cancer* (Nutr Cancer) 2003 45: 176-184.**

Oxidative stress has been linked with the development of several chronic diseases, such as cancer and cardiovascular disease. Cigarette smoke can generate oxidative stress and the production of free radicals. These researchers conducted a randomized clinical trial to determine whether antioxidant supplementation in subjects exposed to environmental tobacco smoke can decrease levels of plasma $F_2$-isoprostanes, a marker of *in-vivo* lipid oxidative damage. Plasma $F_2$-isoprostane levels of 67 healthy passive smokers, mean age 46±15 years, were evaluated at baseline and after two months of daily supplementation with either 500 mg vitamin C, a combination antioxidant mixture (vitamin C, a mixture of vitamin E tocopherols, and alpha-lipoic acid) or a placebo. Plasma cotinine levels, a measure of exposure to environmental smoke, and dietary intakes (using a food frequency questionnaire) were also measured during the study. Blood levels of vitamin C and tocopherols increased with supplementation. Compared to the placebo group, levels of $F_2$-isoprostanes decreased in individuals supplemented with vitamin C or the combination antioxidant mixture. These data suggest that levels of oxidative stress observed in passive smokers can be decreased by certain antioxidants. Maintaining a diet high in antioxidants through either foods or supplements may reduce the risk of oxidative stress and oxidative stress linked diseases in individuals exposed to environmental tobacco smoke.

*Funding: University of California Tobacco-Related Disease Research Program.*

## Taurine and vitamin C modify monocyte and endothelial dysfunction in young smokers.

**FM Fennessy, DS Moneley, JH Wang, CJ Kelly, and DJ Bouchier-Hayes. *Circulation* (Circulation) 2003 107:410-415.**

Cigarette smoking interacts adversely with the cardiovascular system at many different sites along the vascular network. Chronic cigarette smoking can modify normal functioning of vascular endothelium by altering monocyte-endothelial interactions and impairing flow-mediated dilatation. These researchers hypothesized that the amino acid taurine or vitamin C could restore normal flow-mediated dilatation response in chronic smokers, through the release of nitric oxide. Fifteen healthy smokers and 15 control nonsmokers were used to test this hypothesis. Smokers were supplemented with 2 g per day of vitamin C or 1.5 g per day taurine for five days in a crossover design study, with a two-week washout period between each treatment. The dose of taurine used is equivalent to that found in 100 g of fresh fish. The researchers found that endothelial-dependent vasodilatation, as measured by ultrasonography, was significantly impaired in smokers as compared to nonsmokers. Supplementation with vitamin C and, more significantly, with taurine attenuated this response. Monocytes, cultured in medium, taken from smokers exposed to an endothelial cell culture system, impaired the release of nitric oxide and increased levels of endothelin-1. Supplementation with taurine returned levels in smokers to those comparable to nonsmokers. These data suggest that taurine has a beneficial effect on macrovascular endothelial function and warrants further investigation in populations with compromised endothelial function or vascular disorders.

*Funding: Royal College of Surgeons, Ireland.*

## Lifespan is prolonged in autoimmune-prone (NZB/NZW) F1 mice fed a diet supplemented with indole-3-carbinol.

**KJ Auborn, M Qi, XJ Yan, S Teichberg, D Chen, MP Madaio, and N Chiorazzi. *The Journal of Nutrition* (J Nutr) 2003 133:3610-3613.**

Systemic lupus erythematosus (lupus) is an autoimmune disorder that requires treatment with high doses of immunosuppressive drugs over long periods. Due to its antiestrogenic effects, indole-3-carbinol, a constituent of cruciferous vegetables, is thought to benefit individuals with lupus. This animal study examined the effects of supplemental indole-3-carbinol in a lupus-prone female strain of mice. At 1.2 months of age, i.e., before onset of lupus (group 1), and at 5 months (group 2) mice were provided a standard lab chow that contained 0.2 g/kg indole-3-carbinol. There were 10 mice in each group; the control groups did not receive indole-3-carbinol in their food. Indole-3-carbinol significantly increased lifespan in both groups of mice. At 12 months of age, 80 percent of the mice that received indole-3-carbinol at weaning (1.2 months) were alive compared with 10 percent of matching controls. When indole-3-carbinol was introduced at five months of age, 100 percent of mice were alive at 12 months as compared with 30 percent of matching controls. Overall, indole-3-carbinol was effective in increasing the lifespan in these lupus-prone mice before onset of the disease and during early stages of the disease. As indole-3-carbinol suppressed an autoimmune inflammatory response, these results suggest that a decreased dose of immunosuppressive drugs may be required to treat lupus in humans. These positive findings on outcomes and survival rates in lupus-prone mice treated with indole-3-carbinol need to be confirmed in human trials.

*Funding: Ryan Caulfield Foundation; Willa and Robert Bernhard Fund; National Cancer Institute, NIH.*

## Differential effects of prostaglandin derived from ω-6 and ω-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion.

**D Bagga, L Wang, R Farias-Eisner, JA Glaspy, and ST Reddy. *Proceedings of the National Academy of Sciences* (PNAS) 2003 100:1751-1756.**

Prostaglandins are bioactive lipids derived from the metabolism of polyunsaturated fatty acids (PUFAs), such as omega-3 (ω-3) and omega-6 (ω-6) fatty acids. Prostaglandins play important roles in a number of biological processes including cell division, immune responses, and wound healing. Omega-6 PUFAs are precursors to a number of key mediators of inflammation, including the prostaglandin 2-series ($E_2$). Omega-3 PUFAs, on the other hand, reduce concentrations of prostaglandin-$E_2$ and increase concentrations of prostaglandin-$E_3$, which are believed to be less inflammatory. Given the growing interest in omega-3 PUFAs from fish oils, the researchers compared consequences of increases in prostaglandin-$E_3$ versus prostaglandin-$E_2$ at a cellular level using NIH 3T3 fibroblasts. They compared the effects of prostaglandin-$E_3$ and prostaglandin-$E_2$ on 1) cell proliferation, 2) expression and transcriptional regulation, and 3) production of an inflammatory cytokine. The researchers showed that increasing the omega-3 content of membrane phospholipids results in a decrease in mitogen-induced prostaglandin-$E_2$ synthesis. These data suggest that successful replacement of omega-6 PUFA with omega-3 PUFA in cell membranes can result in a decreased cellular response to mitogenic and inflammatory stimuli. The results of this study suggest that omega-3 fatty acids could play a beneficial role in a number of inflammatory conditions.

*Funding: Julia and Delfino Fund for Excellence in Breast Cancer Research, University of California, Los Angeles (UCLA); Jonsson Comprehensive Cancer Center; and the Revlon-UCLA Women's Cancer Research Program.*

## Melatonin reduces renal interstitial inflammation and improves hypertension in spontaneously hypertensive rats.

Renal infiltration of immunocompetent cells (cells capable of developing an immune response) is thought to contribute to the development of salt-sensitive hypertension, and in animal models antioxidant supplements improve hypertension. Melatonin is a potent antioxidant. This study was conducted to determine whether improvement in hypertension resulting from melatonin supplementation is associated with a decrease in renal inflammation. Two groups of rats, Wistar-Kyoto (control group) and spontaneously hypertensive rats (SHR, test group), received unsupplemented drinking water. A third group of SHR received 10 mg melatonin per 100 ml in the drinking water. All rats received standard rodent chow that contained four percent sodium chloride for six weeks. Unsupplemented SHR experienced a progressive increase in blood pressure, while melatonin-treated SHR experienced a gradual decrease in blood pressure over the six-week study period. In addition, melatonin reduced oxidative stress, as determined by renal content of malondialdehyde and intracellular superoxide production, and produced a 40 to 60 percent reduction in the renal infiltration of immune cells. These results suggest that melatonin treatment reduces hypertension in SHR and that this effect is associated with a reduction in renal inflammation. Additional research is required to determine whether melatonin can be an effective adjuvant treatment of hypertension in humans.

*Funding: Asociacion de Amigos del Rinon; Fondo Nacional de Ciencia y Techologia, Venezuela.*

**M Nava, Y Quiroz, N Vaziri, and B Rodriguez-Iturbe.** ***The American Journal of Physiology. Renal Physiology*** **(Am J Physiol Renal Physiol) 2003 284: F447-F454.**

**SUPPLEMENTS AND EARLY DEVELOPMENT**

## Maternal iron status influences iron transfer to the fetus during the third trimester of pregnancy.

Iron deficiency anemia can result in compromised iron stores in the offspring or fetus. The aim of this study was to identify techniques to improve iron stores in the fetus. The study was conducted in pregnant Peruvian women, as the prevalence of iron deficiency in this group is 93 percent. From weeks 10-24 up to the final month of their pregnancy, 26 women received either 60 mg iron (as ferrous sulfate) and 250 µg folate with 15 mg zinc (zinc sulfate) (iron and zinc group), or without zinc (iron group). The 15 women in the control group received supplemental iron only during the final month of their pregnancy. During the third trimester (months 6-9) the women were infused with labeled iron ($^{58}$Fe tracer, 0.6 mg as ferrous citrate) over 10 minutes and consumed a 60-90 ml non-ascorbic acid flavored drink containing 10 mg labeled iron ($^{57}$Fe, as ferrous sulfate). Labeled iron and iron status were determined in fetal blood samples taken at delivery through a venous cord sample and a heel stick. A significantly higher amount of labeled iron ($^{57}$Fe) was transferred to the fetus of women in the non-iron supplemented group, as compared to the control, iron, and iron and zinc supplemented groups. The net transfer of iron to the fetus was positively correlated to the percentage of iron absorbed by the mother, and inversely related to iron status during the third trimester of pregnancy. There was no relationship between fetal levels of labeled iron ($^{58}$Fe) and maternal status. Overall, this study demonstrates that maternal iron status plays a role in the transfer of iron to the fetus. However, lack of a positive finding with iron delivered intravenously, suggests that this regulation may occur at the gastric level.

*Funding: Nestle Foundation*

**KO O'Brien, N Zavaleta, SA Abrams, and LE Caulfield.** ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2003 77: 924-930.**

## Iron supplementation during infancy: Effects on expression of iron transporters, iron absorption, and iron utilization in rat pups.

**WI Leong, CL Bowlus, J Tallkvist, and B Lönnerdal.** ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2003 78: 1203-1211.**

The amount of iron a non-breastfed versus a breastfed infant receives may vary as much as 50-60 fold. Despite this, little is known about the mechanisms of iron regulation in infancy. Two iron transporters, divalent metal transporter 1 (DMT1) and ferroportin 1 (FPN1) are critical for intestinal iron absorption and are regulated by body iron stores. Using a rat model, these researchers studied the expression of these two iron transporters on iron absorption and utilization. Two hundred sixty Sprague-Dawley rat pups consumed 25 µL of a 10 percent sucrose solution containing 0, 30 (median) or, 150 (high) µg iron as ferrous sulfate between 2 to 20 days after birth. Intestinal expression of DMT1 and FPN1 were determined in unsupplemented animals from days 1 to 50 after birth, and the effects of iron supplementation on their expression and on iron absorption and utilization during infancy. Intestinal expression of DMT1 and FPN1 was affected by age; increasing dramatically by day 40. On day 10, no significant effect of iron supplementation on DMT1 and FPN1 Gene expression or on iron absorption was observed. By day 20, DMT1 and FPN1 expression and iron absorption had decreased significantly with iron supplementation. This study demonstrates that during early infancy, rat pups are unable to respond to iron supplementation by down-regulating iron absorption and intestinal iron transporters; however, by late infancy down-regulation of these factors can occur. These preliminary findings suggest that newborn and young infants may need to receive controlled amounts of supplemental iron, as they may be unable to regulate iron at this early age.

*Funding: University of California, Davis, and Uppsala Biomedical Center, Uppsala, Sweden.*

## Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: Double blind randomised community trial.

**P Christian, SK Khatry, J Katz, EK Pradhan, SC LeClerq, SR Shrestha, RK Adhikari, A Sommer, and KP West Jr.** ***British Medical Journal*** **(BMJ) 2003 326:571-576.**

Pregnant women are often supplemented with an array of micronutrients, with the conviction that this will optimize maternal and infant health; however, there is limited research supporting this practice. This practice was assessed in 4,926 Nepalese women. These women took one of the following five micronutrient supplements daily: 1) folic acid (400 µg), 2) folic acid-iron (60 mg ferrous fumarate), 3) folic acid-iron-zinc (30 mg zinc sulfate), 4) multivitamin and mineral supplement that provided 100 percent of the RDA for most nutrients, and 5) vitamin A (1,000 µg), which also served as the control. An anthropometrist measured weight, length, and head and chest circumference of infants after a birth was reported; a weight less than 2,500 g was considered low birthweight. The pregnancies resulted in 4,130 live births. The folic acid supplements did not affect birth size. Folic acid-iron and the multivitamin and mineral supplements increased mean birth weight and head and chest circumference, but not length, and decreased the percentage of low birthweight infants. Folic acid-iron-zinc and vitamin A (control group) affected birth size similarly. None of the five supplements reduced the incidence of preterm births. These findings demonstrate that folic-acid-iron supplementation may reduce the risk of low birth weight by a modest amount, and that the inclusion of additional micronutrients does not appear to result in added benefits. These findings suggest that in pregnant women, multivitamin and mineral supplements do not provide additional health benefits beyond that observed with folic acid-iron supplements alone.

*Funding: Office for Health and Nutrition, US Agency for International Development (USAID); UNICEF Country Office, Nepal; Bill and Melinda Gates Foundation.*

## Retinoic acid receptor alpha gene variants, multivitamin use, and liver intake as risk factors for oral clefts: A population-based case-control study in Denmark, 1991-1994.

**LE Mitchell, JC Murray, S O'Brien, and K Christensen.** ***American Journal of Epidemiology*** **(Am J Epidemiol) 2003 158: 69-76.**

High intakes of vitamin A by pregnant women are known to have teratogenic effects on the unborn fetus. Cleft lip and cleft palate are thought to be an outcome of this effect, which may result from an interaction between the retinoic acid receptor alpha (RARA) binding site and vitamin A. This theory was tested in 869 Danish women. Maternal exposure to vitamin A from multivitamins and liver containing foods during the first trimester of pregnancy was assessed by an interview and from birth records. The vitamin A content in multivitamin supplements was estimated at 800 retinol equivalents (RE). DNA samples were obtained from newborn screening blood spots. Results from this study indicate that cleft lip with or without cleft palate are not significantly associated with the RARA genotype. Inadequate intakes of vitamin A were associated with increased risk for cleft palate and cleft lip. These associations were not observed with adequate intakes of this vitamin. On the other hand, higher intakes of vitamin A seemed to protect against cleft palate and cleft lip. Total daily vitamin A intakes by women in this study were well below 7,500 RE, a level thought to be teratogenic, and only a small proportion exceeded 3,030 RE a day. For each increase in total vitamin A exposure of 500 RE per day, the odds of cleft plate and cleft lip decreased by 0.88. Overall, this study demonstrates that multivitamin supplements taken during the first trimester of pregnancy may reduce the risk of cleft lip with or without cleft palate. The results of this study suggest that adequate intakes of vitamin A may be required for normal growth of the palate.

*Funding: The Egmont Foundation, Helsefonden, Laegeforeningens Forskingsfond, Denmark; and, National Institute of Dental and Craniofacial Research, NIH*

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# APPENDIX

## Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2002*

**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-R Liu, C-H Liu, J Hwang, RH Selzer, and SP Azen; for the VEAPS Research Group. *Circulation* (Circulation) 2002 106:1453-1459.

**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 Ciabattoni. *Circulation* (Circulation) 2002 106:2543-2549.

**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.

**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.

**Vitamin E oxidation in human atherosclerotic lesions.** 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.** 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, Cellular and Molecular Physiology* (Amer J 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.

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

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

**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 Endocrinol Metab) 2002 87:1687-1691.

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

**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.

**Analysis of thirteen populations of black cohosh for formononetin.** 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.** 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.

**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.

**Effect of tamarind ingestion on fluoride excretion in humans.** 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 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.

**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.

**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.

## 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 Group 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, AB 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.

# Acknowledgements

## 2003 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 2003.

- **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
- **Biochemical Pharmacology,** Alan C Sartorelli, PhD
- **The British Journal of Nutrition,** Paul Trayhurn, DSc
- **British Medical Journal,** Richard Smith, CBE, BSc, MB, ChB
- **Cancer, Epidemiology, Biomarkers & Prevention,** John D Potter, MD, PhD, David S Alberts, MD
- **Circulation,** James T Willerson, MD
- **Circulation Research,** Eduardo Marban, MD, PhD
- **European Journal of Clinical Nutrition,** Prof dr Jaap C Seidell
- **Indian Journal of Pharmacology,** R. Raveendrau, MD
- **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 Oil Chemists Society,** John P Cherry, 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
- **Journal of Neuroscience,** Gary L Westbrook, MD
- **The Journal of Nutrition,** A Catherine Ross, PhD
- **The Lancet,** Richard Horton, MB
- **Medicine and Science in Sports and Exercise,** Kent B Pandolf, PhD, MPH
- **Mutation Research / Fundamental and Molecular Mechanisms of Mutagenesis,** Peter J Stambrook, PhD
- **The New England Journal of Medicine,** Jeffery M Drazen, MD
- **Nutrition and Cancer,** Leonard A Cohen, PhD
- **Obstetrics and Gynecology,** James R Scott, MD
- **Pharmaceutical Biology,** John M Pezzuto, PhD
- **Phytomedicine,** Norman R Farnsworth, PhD
- **Planta Medica,** Prof dr Adolf Nahrstedt
- **Proceedings of National Academy of Sciences,** Nicholas Cozzarelli, PhD
- **Science Magazine,** Katrina Kelner, PhD

## 2003 List of Scientific Reviewers

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

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- **John JB Anderson, PhD,** University of North Carolina, Chapel Hill
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- **Barbara A Bowman, PhD,** Centers for Disease Control and Prevention, DHHS
- **Francis Brinker, ND,** University of Arizona,Tucson
- **John H Cardellina, PhD,** National Cancer Institute, NIH
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- **Henry C Lukaski, PhD,** Agricultural Research Service at USDA, Grand Forks
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- **Pamela Starke-Reed, PhD,** Division of Nutrition Research Coordination, NIH
- **Katherine L Tucker, PhD,** Jean Mayer USDA Human Nutrition Research Center, Tufts University
- **Valdimir Vuksan, PhD,** University of Toronto St Michael's Hospital, Canada
- **W Allan Walker, MD,** Massachusetts General Hospital-East, Charleston
- **Gary M Williams, MD,** New York Medical College, Valhalla
- **Wayne R Wolf, PhD,** Agricultural Research Service, USDA
- **Richard J Wood, PhD,** Jean Mayer USDA Human Nutrition Research Center, Tufts University
- **Andrew Young, PhD,** US Army Research Institute of Environmental Medicine, Natick, DoD

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