Annual Bibliography of Significant Advances in Dietary Supplement Research 2005

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

Bibliography of Significant Advances in Dietary Supplement Research 2005

The Office of Dietary Supplements is pleased to provide you with this publication for the seventh consecutive year. The Office engages in a process of identifying exemplary papers on dietary supplements and disseminating this information through the *Annual Bibliography of Significant Advances in Dietary Supplement Research* to researchers, health professionals, and other interested individuals.

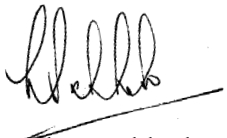
This issue contains 25 original research papers that appeared in scientific journals in 2005. Original research papers are identified through a comprehensive literature search of peer-reviewed journals, requests to editors of these journals, and requests to scientific reviewers of the bibliography. A group of internationally recognized scientists is then asked to evaluate these papers and identify the 25 papers that will be annotated and compiled into this bibliography.

As with previous issues, this bibliography reflects the accumulating scientific evidence on dietary supplements. Included in this issue are several papers examining the effects of nutrients on fractures and the effectiveness of commercially available botanical products. Although study quality appears to be improving, the test materials are often not described sufficiently to enable other researchers to confirm the findings. The National Institutes of Health, through policies and guidelines, is encouraging investigators to better characterize the test materials used in research. You can access these policies and guidelines through the Office of Dietary Supplements website: http://ods.od.nih.gov/research/ProductQualityResources.aspx.

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 scientific reviewers, journal editors, and staff at the Office of Dietary Supplements and the National Agricultural Library at the US Department of Agriculture. These individuals are identified in the acknowledgements section.

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 are available online at 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 & Director of Extramural Activities
Office of Dietary Supplements
National Institutes of Health

Leila G Saldanha, PhD, RD
Co-editor & Scientific Consultant
Office of Dietary Supplements
National Institutes of Health

Contents

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

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

[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 folate and mecobalamin on hip fractures in patients with stroke: A randomized controlled trial.

Y Sato, Y Honda, J Iwamoto, T Kanoko, and K Satoh. ***Journal of the American Medical Association*** **(JAMA) 2005 293:1082-1088.**

Elevated levels of homocysteine are a risk factor for ischemic stroke and osteoporotic fractures in older men and women. A recent epidemiological study found that high blood levels of homocysteine were associated with an increased risk of nonvertebral fractures in older people independent of bone mineral density or recent falls. These researchers theorized that supplementation with folate (as folic acid) and vitamin B_{12} may reduce blood homocysteine levels and thus the incidence of hip fractures in patients with hemiplegia (paralysis of one side of the body) following stroke. In a double-blind, randomized controlled study, 628 elderly Japanese, aged 65 years or older, with residual hemiplegia for at least 1 year received either 5 mg of folate and 1,500 µg of vitamin B_{12}, or a placebo for 2 years. Both groups had high baseline levels of plasma homocysteine and low serum levels of cobalamin and folate. After 2 years, homocysteine levels decreased 38 percent in the treatment group and increased 31 percent in the placebo group. The number of hip fractures per 1,000 patient-years was 10 and 43 for the treatment and placebo groups, respectively. The adjusted relative risk, absolute risk reduction, and number needed to treat for hip fractures in the treatment vs. placebo groups were 0.20 percent, 7.1 percent, and 14 respectively. No adverse effects were reported in the paper. In elderly individuals with a high baseline fracture risk, combined treatment with folate and vitamin B_{12} was safe and effective in reducing the risk of a hip fracture following stroke. It has been theorized that vitamin B_{12} improves bone quality by increasing osteocalcin concentration (a major protein in bone that binds with calcium) and by promoting collagen cross-linking. Additional research is needed to validate these findings in other population groups.

Funding: Source not identified.

Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials.

HA Bischoff-Ferrari, WC Willett, JB Wong, E Giovannucci, T Dietrich, and B Dawson-Hughes. ***Journal of the American Medical Association*** **(JAMA) 2005 293:2257-2264.**

Calcium together with vitamin D is thought to be effective in the prevention of hip and nonvertebral fractures among the aged. This study estimated the effectiveness of vitamin D in preventing such fractures in older persons through a systematic evaluation of published studies. Randomized controlled trials of supplemental vitamin D with or without calcium, calcium alone, or placebo in participants 60 years and over, with at least one fracture, and follow-up of at least one year were pooled and analyzed using meta-analysis techniques. Individual studies were assessed for adequacy of the randomization procedure, treatment concealment and blinding, and withdrawals. Five trials for hip fracture (n=9,294) and 7 trials for nonvertebral fracture risk (n=9,820) met the inclusion criteria. Vitamin D supplementation ranged from 400 to 800 IU/day of cholecalciferol, the active form of vitamin D_3. Calcium intake, from a variety of calcium salts, ranged from 500 to 1,200 mg/day. The higher-dose vitamin D (700-800 IU/day) combined with calcium (500 to 1,200 mg/day) reduced the risk for hip fractures by 26 percent and all nonvertebral fractures by 23 percent. The lower-dose vitamin D (400 IU/day) was not sufficient to prevent fractures. The additional effect of calcium and independent effect of higher-dose vitamin D could not be examined, as the higher-dose vitamin D studies (except for one) provided calcium supplements and the lower-dose studies did not. Future studies should focus on independent and interactive effects of higher doses of vitamin D and calcium in the prevention of primary and secondary fractures.

Funding: Medial Foundation and the James Knox Memorial Foundation.

Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or Vitamin D, RECORD): A randomised placebo-controlled trial.

The RECORD Trial Group. *Lancet* (Lancet) 2005 365:1621-1628.

Vitamin D and calcium are often recommended for prevention of fractures. Elderly people who have experienced a fracture are at higher risk of another. In this study, the effect of supplemental vitamin D_3 and calcium, taken alone or together on the prevention of secondary fractures, was examined. In a factorial-design trial, 5,292 people aged 70 years or older (85 percent female) who had suffered a low-trauma osteoporotic fracture within the past 10 years were randomly assigned to receive either 800 IU vitamin D_3, 1,000 mg calcium (given as calcium carbonate), vitamin D_3 combined with calcium, or a placebo. The individuals were followed up for between 24 and 62 months. The primary outcome was the development of new low-trauma fractures, confirmed by radiography. Thirteen percent of the participants had a new low-trauma fracture, 26 percent of which were of the hip. The groups did not differ in the incidence of all-new fractures, hip fractures, deaths, number of falls, or quality of life. By 24 months, 54·5 percent of the individuals in the study were still taking the supplements and 35·8 percent had stopped taking the supplements but were still providing data for the main outcomes of the study. Of the remaining participants, 8·5 percent had died and 1·1 percent withdrew from the study. This study failed to support previous observations of a benefit of calcium or vitamin D supplementation for the prevention of fractures. The poor compliance rates raise questions about the generalizability of the findings. More studies in elderly people are needed to confirm any benefits from supplemental vitamin D on falls and fracture endpoints.

Funding: Scottish Executive Health Department.

The association of calcium and vitamin D with risk of colorectal adenomas.

TJ Hartman, PS Albert, K Snyder, ML Slattery, B Caan, E Paskett, F Iber, JW Kikendall, J Marshall, M Shike, J Weissfeld, B Brewer, A Schatzkin, E Lanza, and the Polyp Prevention Study Group. *Journal of Nutrition* (J Nutr) 2005 135:252-259.

Research suggests that calcium and vitamin D may reduce the risk for colorectal adenomas, but many studies have not evaluated the combined effects of these two nutrients. The association between calcium and vitamin D intake and the recurrence of adenomatous polyps in the large bowel was determined using data collected from a multicenter, randomized clinical trial that examined the effects of a high-fiber, low-fat diet on polyps. The trial involved 1,905 men and women, primarily Caucasian and male, mean age of 61 years, with one or more confirmed colorectal adenomas. Information on diet and discretionary supplement use was obtained at baseline and at each of four annual visits through a modified Block-National Cancer Institute food frequency questionnaire and 4-day food records. No overall significant associations were found between adenoma recurrence and either dietary calcium or vitamin D intakes when the lowest (<666 mg/day calcium; <3.35 μg/day vitamin D) and highest quintiles (>1,226 mg/day calcium; >11.70 μg/day vitamin D) of intake were compared. However, total vitamin D intakes from food and supplements were weakly associated with adenoma recurrence, as was combined supplemental calcium and vitamin D use. Slightly stronger associations were found for the prevention of multiple recurrences. Overall, these results demonstrate a weakly protective effect of calcium and vitamin D on the risk of recurrence of adenomatous polyps.

Funding: National Cancer Institute, NIH.

Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial.

The HOPE and HOPE-TOO Trial Investigators. ***Journal of the American Medical Association*** **(JAMA) 2005 293:1338-1347.**

Scientific evidence on the association between vitamin E supplementation and a lower risk for cardiovascular disease and some forms of cancer is inconsistent. HOPE (Heart Outcomes Prevention Evaluation) is a randomized, double-blind, placebo-controlled multi-center trial that evaluated the effects of vitamin E (400 IU natural α-tocopherol per day) in 9,541 individuals at high risk for cardiovascular disease. The HOPE-TOO (the ongoing outcomes) study presents an additional 2.6 years of follow-up for 7,030 patients over 55 years of age with vascular disease or diabetes mellitus who previously participated in HOPE. After a mean follow-up of 7.2 years in the 3,994 patients who continued on their assigned interventions, vitamin E did not reduce total cancer incidence, cancer deaths, or cardiovascular events (myocardial infarction, stroke, and death) compared to subjects taking a matched placebo. The vitamin E group had a 13 percent greater incidence of heart failure and a 21 percent increased incidence of hospitalization due to heart failure – adverse outcomes not seen in other studies. The investigators concluded that long-term vitamin E therapy does not prevent cancer or cardiovascular events and may increase the risk of heart failure in individuals with existing disease. The mechanisms for the observed harmful effects of vitamin E in this study are not clear and require further study.

Funding: Medical Research Council of Canada, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Source Vitamin E Association and Negma, Heart and Stroke Foundations of Ontario, and Aventis Pharmaceuticals.

Vitamin E in the primary prevention of cardiovascular disease and cancer. The Women's Health Study: A randomized controlled trial.

I-M Lee, NR Cook, JM Gaziano, D Gordon, PM Ridker, JE Manson, CH Hennekens, and JE Buring. ***Journal of the American Medical Association*** **(JAMA) 2005 294:56-65.**

Observations from basic research and epidemiologic studies support the hypothesis that the antioxidant vitamin E may reduce the risks of developing cardiovascular disease (CV) and cancer, but findings from randomized trials challenge it. The Women's Health Study is the largest randomized clinical trial to investigate the impact of aspirin and vitamin E on the primary prevention of cardiovascular and cancer risk in women at least 45 years old. This paper reports the findings from the vitamin E component of the study. The 39,876 women were randomly assigned to receive either 600 IU vitamin E (as all-natural α-tocopherol) or a placebo every other day. Average follow-up was 10 years. Vitamin E did not significantly reduce the risk of major CV events, cancer, cancer mortality, or total mortality. However, among women aged >65 years there was a 24 percent significant reduction in CV mortality and a significant reduction in major CV events in the vitamin E group. Overall, this study with its large sample size and long duration does not support the use of vitamin E to prevent CV disease or cancer in women. Additional research is needed to determine whether the finding of a protective effect and a reduction in CV mortality with supplemental vitamin E in women aged >65 years can be confirmed.

Funding: National Heart, Lung and Blood Institute and National Cancer Institute, NIH and Natural Source Vitamin E Association.

Lower plasma α-carboxyethyl-hydroxychroman after deuterium-labeled α-tocopherol supplementation suggests decreased vitamin E metabolism in smokers.

RS Bruno, SW Leonard, J Li, TM Bray, and MG Traber. ***American Journal of Clinical Nutrition*****, (Am J Clin Nutr) 2005 81:1052-1059.**

Oxidative stress such as cigarette smoking can deplete blood levels of α-tocopherol, but its effects on α-tocopherol metabolism are not known. These researchers theorized that smoking would reduce available α-tocopherol and thus lower plasma α-carboxyethyl-hydroxychroman (α-CEHC) levels, a measure of α-tocopherol status. Smokers and nonsmokers (10 per group) were supplemented for 6 days with deuterium-labeled α-tocopherol (75 mg each of d_3-RRR-α-tocopheryl acetate and d_6-all-rac-α-tocopheryl acetate). Plasma tocopherols and α-CEHC levels were measured during supplementation and the following 17 days. After 6 days of supplementation, plasma d_3- and d_6-α-tocopherol concentrations did not differ significantly between smokers and nonsmokers. However, smokers had about one-half the plasma total, d_6-, or d_3-α-CEHC concentrations of nonsmokers. Smoking therefore did not increase the disappearance of α-tocopherol through decreased α-CEHC levels. The mechanism of increased α-tocopherol disappearance in smokers likely operates through oxidation pathways, which is consistent with the antioxidant function of α-tocopherols. Alternative pathways may be activated to dispose of excess liver α-tocopherol, as plasma levels of α-CEHC did not remain elevated or continue to rise during the α-tocopherol supplementation phase. This work provides new insights into the molecular mechanisms responsible for tocopherol metabolism and the effect that cigarette smoking has on its regulation.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases, NIH and Oregon State University.

MINERALS

Long-term calcium supplementation does not affect the iron status of 12-14 year-old girls.

C Molgaard, P Kaestel, and KF Michaelsen. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2005 82:98-102.**

Nutrient requirements for iron and calcium are higher in adolescent girls around the time of menarche. Calcium supplementation can compromise long-term iron status, but few data are available for adolescent girls. The aim of this randomized, double-blind, placebo controlled study was to evaluate whether calcium supplementation affected iron status in 113 Dutch girls aged 12-14 years. Subjects took 500 mg calcium (as calcium carbonate) a day or a placebo with the main daily meal for 1 year. Measures of iron status (concentrations of hemoglobin, serum ferritin, and serum transferrin receptors) were collected at baseline and one year along with dietary calcium intake through a food frequency questionnaire. The mean hemoglobin level at baseline was 134 grams/liter. Two groups were selected according to their dietary calcium intake: a medium intake group (1,000-1,304 mg/day; n=60) and a low intake group (<713 mg/day; n=53). Calcium supplementation had no effect on iron status in either group. This study shows that calcium supplementation does not alter iron status in iron-sufficient adolescent girls. Additional research is necessary to understand the effect of long-term calcium supplementation on iron status in iron-deficient adolescents.

Funding: Danish government Food and Technology Research Program and Danish Dairy Research Foundation.

Long-term moderate zinc supplementation increases exchangeable zinc pool masses in late-middle-aged men: The Zenith Study.

Assessing exchangeable zinc pools may be a useful approach to evaluating zinc status and is positively related to dietary zinc intake, daily-absorbed zinc, and excretion of zinc. The aim of this randomized, double-blind, placebo-controlled study conducted in France was to evaluate the effects of zinc supplementation on zinc status in healthy middle-aged men. Men (16 per group) were supplemented daily for 6 months with 15 mg or 30 mg of zinc (as zinc gluconate) or a placebo. Kinetic studies to estimate the distribution and excretion of zinc were performed. After six-months of supplementation, zinc concentrations were measured in plasma, red blood cells, and urine at various time points over a 10-day period. Compared with the control group, the supplemented groups increased exchangeable zinc pool mass regardless of the approach used to estimate these levels. However, the changes in exchangeable zinc pool mass were smaller than the changes in plasma zinc concentration, suggesting that exchangeable zinc pool mass may not be as sensitive as plasma zinc concentrations in assessing zinc status. Based on these findings, the authors concluded that zinc intakes by French men were inadequate and needed to be increased to levels recommended in the United States (11 mg/day). In addition, these data suggest that zinc supplementation is an efficient way of improving zinc status in late-middle-aged men.

Funding: European Commission.

C Feillet-Coudray, N Meunier, M Rambeau, M Brandolini-Bunlon, JC Tressol, M Andriollo, A Mazur, KD Cashman, and C Coudray. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2005 82:103-110.**

BOTANICALS

Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms.

The use of black cohosh (*Actaea racemosa*, formerly *Cimicifuga racemosa*) to treat various gynecological conditions has been studied for decades, although results are not in agreement. A variety of outcome measures may have contributed to the mixed results. A randomized, double-blind, placebo-controlled trial was conducted to determine if a patented black cohosh product (standardized to contain 2.5 mg isopropanolic extract, corresponding to 20 mg of rootstock, per pill) could effectively treat menopause-related symptoms. The 304 postmenopausal women, recruited from gynecologic private practices in Germany, took 2 tablets a day of the supplement or placebo for 12 weeks. These women provided information on the intensity of menopausal symptoms at baseline, 4, and 12 weeks via clinical examinations and interviews using the Menopause Rating Scale (MRS). Compared to placebo, subjects taking the black cohosh product experienced a significant, clinically relevant reduction in their MRS scores, particularly in the subscore evaluating hot flashes, sweating, and sleep disorders. In general, differences in total scores were more pronounced for subjects in their first years after menopause. There were no reported adverse effects related to use of this supplement. These findings suggest that a standardized black cohosh product may help to relieve some menopausal symptoms, particularly in the early postmenopausal years.

Funding: Source not identified.

R Osmers, M Friede, E Liske, J Schnitker, J Freudenstein, and H-H Henneicke-von Zepelin. ***Obstetrics and Gynecology*** **(Obstet Gynecol) 2005 105:1074-1083.**

Comparison of the in vitro estrogenic activities of compounds from hops (*Humulus lupulus*) and red clover (*Trifolium pratense*).

CR Overk, P Yao, LR Chadwick, D Nikolic, Y Sun, MA Cuendet, Y Deng, AS Hedayat, GF Pauli, NR Farnsworth, RB van Breemen, and JL Bolton. ***Journal of Agricultural and Food Chemistry*** **(J Agric Food Chem) 2005 53:6246-6253.**

Currently prescribed hormone replacement therapies for the management of menopausal symptoms are associated with the development of breast and uterine cancers, so alternative therapies such as extracts from red clover (*Trifolium pratense L.*) and hops (*Humulus lupulus L.*) are being considered. The focus of the University of Illinois at Chicago's Center for Botanical Dietary Supplements Research in Women's Health is to identify active constituents that have potential benefits for women's health and to develop standardized preparations. In this study, the ability of hops and red clover extracts, and 8 compounds isolated from these extracts, to bind to the estrogen receptor was evaluated using high-throughput screening techniques and *in-vitro* estrogenic bioassays (measurement of the concentration or potency of a substance by its effect on living cells or tissues). These tests were selected to evaluate estrogenic responses and help predict more accurately the response in women. Based on these preliminary tests, the authors concluded that hops and red clover extracts are attractive ingredients for alleviating menopause-associated symptoms. Additional research is needed to determine the level of estrogenic activity necessary to confer benefits for the management of menopausal symptoms without the side effects that have been associated with hormone replacement therapies, and to standardize botanical extracts based on these findings.

Funding: Office of Dietary Supplements, the National Institute of General Medical Sciences, the Office for Research on Women's Health, and the National Center for Complementary and Alternative Medicine, NIH.

Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: A prospective study and cross-sectional analysis.

Y Song, JE Manson, JE Buring, HD Sesso, and S Liu. ***Journal of the American College of Nutrition*** **(J Am Coll Nutr) 2005 24:376-384.**

It has been theorized that the antioxidant properties of flavonoids may blunt impairments to pancreatic β-cell function and thereby reduce the risk of type 2 diabetes. Investigators prospectively examined the association between dietary intakes of flavonoid-rich plant foods and total flavanols and flavones to the self-reported development of type 2 diabetes in 38,018 female health professionals in the Women's Health Study. Intake was measured in 1993 with a food frequency questionnaire, and the average follow-up was 8.8 years. No significant associations were found between the intake of total flavanols or flavones and the incidence of type 2 diabetes. Any apple consumption was associated with decreased development of the disease. Tea consumption (≥4 cups/day) was also associated with a reduced risk but was of borderline statistical significance. Additionally, in a cross-sectional sub-study of 344 women, no relationship was found between flavonoid intake and indicators of insulin resistance. These results do not support a relationship between flavonoid intake and reduced risk for type 2 diabetes. These findings should be viewed as preliminary, as this is an observational study using self-reported data.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases, National Cancer Institute, and National Heart, Lung, and Blood Institute, NIH.

Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: A randomized, placebo-controlled trial.

T Chow, V Browne, HL Heileson, D Wallace, J Anholm, and SM Green. *Archives of Internal Medicine* (Arch Intern Med) 2005 165:296-301.

Acute mountain sickness occurs when unacclimatized individuals ascend to altitudes above 2,000 meters. The medication acetazolamide and *Ginkgo biloba* are used to manage these symptoms, though the use of *Ginkgo biloba* has not been rigorously studied. This randomized, placebo-controlled trial compared the efficacy of these products in 57 unacclimatized adults who were taken to an elevation of 3,800 meters for 24 hours. Subjects received acetazolamide, a *Ginkgo biloba*-containing product, or a placebo. The *Ginkgo biloba* product contained 120 mg *Ginkgo biloba* extract (Leaf), 125 mg Eleuthero (*Eleutherococcus senticosus*) (Root), and 150 mg Gotu Kola (*Centella asiatica*) (Leaf). Acute mountain sickness symptoms were graded using the Lake Louise Acute Mountain Sickness Scoring System (LLS). Lower scores indicate less severe symptoms. The median LLS scores were 2 in the acetazolamide group (range 0-5), 4 in *Ginkgo biloba* group (range 1-10), and 4 in the placebo group (range 1-13). The incidence of acute mountain sickness was 30 percent in the acetazolamide group, 65 percent in *Ginkgo biloba* group, and 60 percent in the placebo group. The authors concluded that acetazolamide, but not *Ginkgo biloba*, decreased the symptoms of acute mountain sickness and tended toward reducing its incidence. There were several shortcomings to this study: the subjects were not age or gender matched, individuals in the acetazolamide group tended to be younger in age and male, and the *Ginkgo biloba* product contained other botanicals. Additional research is needed to confirm the independent effects of *Ginkgo biloba* on acute mountain sickness.

Funding: Source not identified.

Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: A randomized controlled trial.

GN Predy, V Goel, R Lovlin, A Donner, L Stitt, and TK Basu. *Canadian Medical Association Journal* (CMAJ) 2005 173:1043-1048.

The common cold is a frequent cause of illness throughout the world. North American ginseng (*Panax quinquefolium*) is claimed to have immune enhancing properties that could aid in the management of the common cold. This randomized, double-blind, placebo-controlled trial was conducted to determine if a patented ginseng product (standardized to 80 percent poly-furanosyl-pyranosyl-saccharides and 10 percent protein) could reduce the number of colds and, secondarily, reduce the severity of symptoms and duration of colds. Study subjects were Canadian, 18-65 years of age, and reported having at least 2 colds the previous year. The 279 subjects took 2 capsules a day of the supplement (providing 400 mg ginseng extract) or placebo for 4 months during the influenza season. Subjects kept a daily log of cold-related symptoms and their severity. Compared to those taking placebo, subjects receiving the ginseng product experienced fewer total and recurrent colds, had fewer total symptoms per cold, and suffered fewer days with symptoms. Although fewer subjects in the ginseng group contracted at least one cold compared to the placebo group, the difference was not significant. These findings suggest that North American ginseng may be an attractive natural prophylactic for upper respiratory tract infections. Additional studies are needed to confirm these findings.

Funding: CV Technologies Inc.

Effects of encapsulated green tea and guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men.

S Bérubé-Parent, C Pelletier, J Doré, and A Tremblay. ***British Journal of Nutrition*** **(Br J Nutr) 2005 94:432-436.**

Some research has suggested that green tea stimulates thermogenesis, resulting in increased energy expenditure. This has sparked interest in its possible role in weight management. While some thermogenic effect is attributable to its caffeine content, green tea is also rich in catechins, particularly epigallocatechin-3-gallate (EGCG). This study examined the effect of EGCG (green tea extract) enhanced with caffeine (guarana extract) on energy expenditure and fat oxidation. Fourteen men with a body mass index (BMI) between 20 and 27 participated in this crossover study. On five separate occasions, each person spent 24 hours in a metabolic chamber and ingested in random order, three times daily, before standardized meals, a placebo or capsules containing 200 mg caffeine and a variable dose of EGCG (90, 200, 300, or 400 mg). Twenty-four hour energy expenditure increased a mean of 8 percent with all green tea-guarana mixtures compared to the placebo. Although increasing doses of EGCG were associated with increasing 24-hour energy expenditure, the differences were not significant. No significant effect on fat oxidation was seen. This preliminary work suggests that green tea and guarana extracts may play a role in weight management through increased energy expenditure. However, as a dose-response was not observed with varying levels of green tea extract intake, the observed effects could be from the independent effects of the guarana extract.

Funding: Iovate Health Sciences Research Inc.

Induction of cell-specific apoptosis and protection from Dalton's lymphoma challenge in mice by an active fraction from *Emilia sonchifolia*.

BS Shylesh, SA Nair, and A Subramoniam. ***Indian Journal of Pharmacology*** **(Indian J Pharmacol) 2005 37:232-237.**

Emilia sonchifolia, known by several common names including lilac tassel flower, is a plant found in India and other Asian countries that may have anticancer properties. The aim of this study was to investigate the *in-vitro* and *in-vivo* anticancer activity of extracts from *Emilia sonchifolia*. In the laboratory portion of this study, several extracts were found to be toxic to cells obtained from mice, with the n-hexane fraction showing the most potency. This fraction was toxic to thymocyte and Dalton's lymphoma ascitic (DLA) cells, but not macrophage cells, indicating cell-specific effects. In addition, it inhibited DNA synthesis in both DLA and thymocyte cells. In the animal portion of this study, Swiss albino mice with DLA tumors were divided into 6 groups of 8 each and given one of the following oral treatments for 15 days: n-hexane fraction of *Emilia sonchifolia* at concentrations of 50, 100 or 250 mg/kg body weight; the anticancer agent vincristine at 0.5 or 1 mg/kg; or gum acacia (control). Forty days after being challenged with DLA cells, 4 of 8 mice in both the 250 mg/kg n-hexane fraction and 1 mg/kg vincristine groups were still alive. All other mice had died. The n-hexane fraction showed no apparent toxicity at doses up to 500 mg/kg. These preliminary results suggest that *Emilia sonchifolia* has cell specific toxic effects and warrants further investigation as a cancer prevention product.

Funding: Partially funded by the Council of Scientific and Industrial Research, government of India.

Docosahexaenoic acid: A positive modulator of Akt signaling in neuronal survival.

Docosahexaenoic acid (DHA) is present in phospholipids in membranes of cells in the nervous system. Adequate intakes of this omega-3 polyunsaturated fatty acid (PUFA) during infancy improve mental development, and low levels of DHA in the adult brain are associated with neurodegenerative disorders such as Alzheimer's disease. DHA is critical to the survival of neurons through its effects on phosphatidylinositol-3-kinase (PI3K) and Akt (Protein Kinase B). The PI3K-Akt signaling pathway regulates a variety of biological processes including cell survival, proliferation, growth, motility, and glycogen metabolism. Studying the role of DHA on this pathway may provide a mechanistic basis to support the beneficial effects of DHA in neurodegenerative disorders. In this study, DHA was the preferred substrate to promote phosphatidylserine accumulation in neuronal membranes and thereby facilitate membrane translocation/activation of Akt in mouse neuroblastoma cells (malignant tumor-containing embryonic nerve cells). Concentrations of phosphatidylserine, the major acidic phospholipid in cell membranes, are highly correlated with the DHA content of neurons. In contrast, cells deprived of DHA accumulated docosapentaenoic acid, which was less effective in synthesizing phosphatidylserine, activating Akt, and preventing apoptosis (cell death). In another experiment, embryonic cells from the brain's hippocampus made deficient in DHA showed decreased concentrations of phosphatidylserine and were more susceptible to apoptosis. These preliminary data provide a mechanistic basis for understanding the involvement of DHA in neurodegenerative diseases such as Alzheimer's disease.

Funding: National Institute on Alcohol Abuse and Alcoholism, NIH.

M Akbar, F Calderon, Z Wen, and H-Y Kim. ***Proceedings of the National Academy of Sciences*** **(PNAS) 2005 102:10858-10863.**

Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: A randomized controlled trial.

Findings from studies suggest that the antiarrhythmic properties of omega-3 fatty acids may play a role in reducing sudden cardiac death. This study was a randomized, double-blind, placebo-controlled trial in 200 patients (primarily white males) with an implantable cardioverter defibrillator (ICD), a device used to correct aberrant heart rhythms such as ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients consumed daily either 1.8 grams of fish oil containing 42 percent eicospentaenoic acid and 30 percent docosahexaenoic acid or an olive oil placebo capsule containing 73 percent oleic acid and 12 percent palmitic acid. They were followed for 20 to 828 days (median 718 days). The primary endpoint for the study was the time to the first episode of VT or VF leading to an ICD response. Patients in the fish oil group had significant increases in omega-3 fatty acids in plasma and in red blood cell membranes compared to the placebo group. For all time points measured (6, 12, and 24 months), patients randomized to fish oil experienced a non-significantly higher ICD response rate. In a subset of VT patients, the incidence of VT/VF treated by the ICD was higher in the fish oil group. Recurrent VT/VF events were also more common in patients randomized to fish oil. While the potential benefit of fish oil may depend on the underlying etiology of the heart disease, additional studies are in progress to define which ICD patients may be at risk from supplemental fish oil.

Funding: National Heart, Lung, and Blood Institute and General Clinical Research Centers Program NIH; and Hoffman-LaRoche Inc.

MH Raitt, WE Connor, C Morris, J Kron, B Halperin, SS Chugh, J McClelland, J Cook, K MacMurdy, R Swenson, SL Connor, G Gerhard, DF Kraemer, D Oscran, C Marchant, D Calhoun, R Shnider, and J McAnulty. ***Journal of the American Medical Association*** **(JAMA) 2005 293:2884-2891.**

Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis.

M Arita, M Yoshida, S Hong, E Tjonahen, JN Glickman, NA Petasis, RS Blumberg, and CN Serhan. ***Proceedings of the National Academy of Sciences*** **(PNAS) 2005 102:7671-7676.**

Omega-3 polyunsaturated fatty acids (PUFA) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have beneficial effects in human inflammatory disorders such as inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. Although the mechanisms are not well understood, they appear to involve oxygenated derivatives of omega-3 PUFA, collectively known as resolution phase interaction products (Resolvin), which are potent anti-inflammatory and immunoregulatory lipid mediators. Resolvin E1 in particular is synthesized from EPA in the presence of aspirin during the healing phase of acute inflammation. In experiments conducted in a mouse peritonitis model, administration of EPA and aspirin initiated the endogenous production of Resolvin E1 and resulted in reduced leukocyte infiltration. Similar results were obtained when synthesized Resolvin E1 was introduced. Resolvin E1 also provided substantial protection to the mice from a chemically induced colitis, in part by reducing leukocyte infiltration and down-regulating proinflammatory gene expression. Given the critical role of the proinflammatory cytokine TNF-α in the pathogenesis of human IBD, these results suggest the existence of a potential new target (Resolvin E1 receptors) for therapeutic interventions in this as well as other inflammatory disorders.

Funding: Uehara Memorial Foundation, Crohn's and Colitis Foundation of America, and National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of General Medical Sciences, NIH.

Responsiveness of plasma lipids and lipoproteins to plant stanol esters.

NB Cater, A-B Garcia-Garcia, GL Vega, and SM Grundy. ***American Journal of Cardiology*** **(Am J Cardiol) 2005 96(suppl):23D-28D.**

The National Cholesterol Education Program (NCEP) recommends plant sterols and stanol esters as a therapeutic option to enhance the low-density lipoprotein cholesterol (LDL)-lowering effect of a fat-modified diet. The recommended intake is 2 grams a day. To further delineate the efficacy of plant stanol esters in persons with elevated LDL, these investigators conducted three studies to test whether 1) plant stanols given in amounts greater than the NCEP dose of 2 grams a day provide additional LDL lowering, 2) 3 grams a day of plant sterols added to the diet of postmenopausal women result in lower LDL levels than with diet alone, and 3) patients with elevated above-goal LDL levels despite statin therapy attain further LDL lowering when 3 grams a day of plant sterols are added to their therapy. Each study followed a randomized, placebo-controlled, crossover design with each treatment phase lasting 6-8 weeks. Study 1 had 8 subjects, study 2 had 13 women, and study 3 had 10 men. Plant esters were given in a canola oil-based margarine; the placebo treatment consisted of unenriched margarines. In study 1, maximal LDL lowering (12 percent) was achieved with the 2 grams/day dose; LDL levels were not significantly different on 3 or 4 grams/day doses. In study 2, stanol esters reduced LDL by 13 percent. In study 3, LDL levels were reduced by an additional 15 percent when stanol esters were added to the statin therapy. Although the sample sizes in these studies are small, these results reinforce the guidelines that plant esters are effective in lowering risk in high-risk individuals when used singly or in combination with statin therapy.

Funding: McNeil Nutritionals, Veterans Affairs Medical Center of Dallas, and DW Reynolds Foundation.

Effect of combining psyllium fiber with simvastatin in lowering cholesterol.

AE Moreyra, AC Wilson, and A Koraym. ***Archives of Internal Medicine*** **(Arch Intern Med) 2005 165:1161-1166.**

Elevated levels of low-density lipoprotein cholesterol (LDL) increase the risk for coronary heart disease. Psyllium husk has been shown to lower serum cholesterol levels but has not been evaluated in combination with the cholesterol-lowering drug simvastatin. This randomized double-blind, placebo-controlled parallel study evaluated the effects of simvastatin and psyllium in 68 hyperlipidemic adults aged 18-80 years who met the National Cholesterol Education Program (NCEP) ATP III criteria (http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm). Following a 4-week diet stabilization period, subjects were randomly assigned to one of three 8-week treatments: 1) 20 mg simvastatin plus placebo, 2) 10 mg simvastatin plus placebo, or 3) 10 mg simvastatin plus 15 grams psyllium. All subjects followed a NCEP Step 1 cholesterol-lowering diet. After 8 weeks, the group receiving 10 mg simvastatin plus psyllium had significantly lower LDL, apolipoprotein B and total cholesterol levels than the group receiving 10 mg simvastatin plus placebo. The mean decreases in total cholesterol and LDL levels for the group receiving 10 mg simvastatin plus psyllium were comparable to the group receiving 20 mg simvastatin plus placebo. None of the treatments significantly affected triglycerides or high-density lipoprotein cholesterol (HDL) levels. These results suggest that 10 mg simvastatin with psyllium is as effective in lowering cholesterol as 20 mg of simvastatin alone and highlights the benefit of additional fiber.

Funding: The Procter & Gamble Company.

The effect of soy consumption on the urinary 2:16-hydroxyestrone ratio in postmenopausal women depends on equol production status but is not influenced by probiotic consumption.

JA Nettleton, KA Greany, W Thomas, KE Wangen, H Adlercreutz, and MS Kurzer. ***Journal of Nutrition*** **(J Nutr) 2005 135:603-608.**

Research suggests that soy isoflavones reduce breast cancer risk by shifting estrogen metabolism toward the relatively inactive 2-hydroxyestrogen metabolites versus the active 16 α-hydroxyestrone metabolite. A urinary ratio of these metabolites ($2{:}16OHE_1$) has been used as a marker of breast cancer risk. This study compared the effects of ingestion of soy and probiotic bacteria (involved in the metabolism of soy) on the urinary $2{:}16OHE_1$ ratio in 20 postmenopausal breast cancer survivors and 20 controls. Subjects were given 4 treatments for 6 weeks each in a randomized crossover design: 1) soy protein isolate (26.6 grams protein/day containing 44.4 mg isoflavones), 2) soy protein isolate plus probiotics (*Lactobacillus acidophilus* DDS®+1, *Bifidobacterium longum*), 3) milk protein isolate, and 4) milk protein isolate plus probiotics. At baseline, women with a previous history of breast cancer had lower $2{:}16OHE_1$ ratios than controls, but the differences were not significant. Overall, soy consumption did not affect the $2{:}16OHE_1$ ratio. However, among the breast cancer survivors who produced equol, soy consumption significantly increased urinary 2-hydroxyestrogens and the $2{:}16OHE_1$ ratio. Equol is produced by intestinal bacteria from the isoflavone daidzein in approximately 20-40 percent of the population. The results were not affected by probiotic consumption. These findings suggest that soy favorably alters the $2{:}16OHE_1$ ratio only in women who produce equol. Additional research is required to more fully understand the relationships between soy, estrogen metabolism, equol producer status, and breast cancer risk.

Funding: United States Army Department of Defense; National Center for Research Resources, NIH; and Minnesota Agricultural Experiment Station.

L-citrulline and L-arginine supplementation retards the progression of high-cholesterol-diet-induced atherosclerosis in rabbits.

T Hayashi, PAR Juliet, H Matsui-Hirai, A Miyazaki, A Fukatsu, J Funami, A Iguchi, and LJ Ignarro. *Proceedings of the National Academy of Sciences* (PNAS) 2005 102:13681-13686.

L-arginine may slow the progression of atherosclerosis by increasing the production of nitric oxide, a potent vasodilator. This study tested this theory by examining the effects of orally administered L-arginine, L-citrulline (a precursor of L-arginine) and vitamins C or E on the progression of atherosclerosis in rabbits fed a high cholesterol diet. Rabbits aged 3-4 months were divided into seven groups (six rabbits per group). After 12 weeks, the rabbits were sacrificed. The fatty diet promoted atherosclerosis and impaired endothelium-dependent vasorelaxation and blood flow as well as promoted an increase in oxidative-sensitive gene expression. L-arginine plus L-citrulline, together or combined with the antioxidants, improved endothelium-dependent vasorelaxation, ear blood flow, and regression in atheromatous lesions, and produced a decrease in oxygen free radical production coupled with a decrease in oxidative-sensitive gene expression. These findings suggest that ingestion of L-arginine, L-citrulline, and antioxidants may reverse the progression of atherosclerosis via the nitric oxide pathway and awaits confirmation in human studies.

Funding: Ministry of Education, Science, Sports, and Culture of Japan, and the Japan Society for Promotion of Science.

Chitosan supplementation and fat absorption in men and women.

MD Gades and JS Stern. *Journal of the American Dietetic Association* (J Am Diet Assoc) 2005 105:72-77.

Chitosan is marketed as a supplement that traps fat, resulting in fat malabsorption and weight loss. While there is evidence that large amounts fed to animals produces fecal fat loss, there is little evidence that it promotes weight reduction in humans. These investigators attempted to quantify fecal fat loss among 12 men and 12 women who received 10 capsules a day of a dietary supplement promoted for weight loss. For 12 days, participants ate five meals a day with an energy content set at weight maintenance levels. The chitosan product contained 500 mg chitosan, 200 mg psyllium, 40 mg malic acid and 20 mg aloe vera per two-capsule dose taken before meals on days 6 through 9. Each meal contained at least 10 grams of fat. With the chitosan product, fecal fat excretion increased by 1.8±2.4 grams per day in men and did not change in women. Weight remained stable in both groups during the study. The strengths of this study lie in more complete fecal collection than some previous studies and examination of effects separately for men and women. However, it was not placebo-controlled and, as the product contained several ingredients in addition to chitosan, it did not test for the independent effects of chitosan. The findings from this study are consistent with other studies using chitosan-containing supplements, suggesting that these products are not likely to promote weight loss through dietary fat malabsorption.

Funding: Consumer Justice Center, Laguna Nigel, California; University of California, Davis; and National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Lactobacillus paracasei strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh.

SA Sarker, S Sultana, GJ Fuchs, NH Alam, T Azim, H Brüssow, and L Hammarström. *Pediatrics* (Pediatrics) 2005 116: e221-e228.

The benefits of live bacterial cultures found in fermented milk products on the gastrointestinal tract have been known for centuries. Previous studies have shown that selected strains of lactobacilli can result in a modest reduction in the duration of diarrhea. Stomach virus, bacteria, and parasite infections are common causes of diarrhea in children. However, rotavirus is the most common cause of severe diarrhea in infants and young children in the United States and is a major cause of childhood deaths worldwide. In this trial, using World Health Organization criteria, investigators evaluated the effectiveness of a new probiotic, *Lactobacillus paracasei* strain ST11, in acute childhood diarrhea. In a randomized, double-blind, placebo-controlled clinical trial conducted in Bangladesh, 230 male infants and young children age 4 to 24 months of age, presenting with severe diarrhea of <2 days duration, were hospitalized and fed 10^{10} colony-forming units of lyophilized ST11 or placebo daily for 5 days. Stool output and frequency, oral rehydration solution intake, and excretion of rotavirus were monitored daily. No effect of ST11 treatment on severe rotavirus diarrhea was observed. Compared with those receiving placebo treatments, the probiotic treatment significantly reduced cumulative stool output, stool frequency, and oral rehydration solution intake in children with less-severe nonrotavirus diarrhea. A significantly higher proportion of nonrotavirus-infected children receiving ST11 had their diarrhea resolved within 6 days of therapy (ST11 versus placebo: 76 percent vs. 49 percent). ST11 had a clinically significant benefit in the management of children with nonrotavirus-induced diarrhea, but it was ineffective in those with rotavirus diarrhea. The current trial suggests an effect of ST11 on nonrotavirus diarrhea, but a confirmation of this result with a greater number of children and a better definition of the etiology is needed. Confirmation of these findings might allow the targeted feeding of ST11 to patients who are likely to benefit from this treatment.

Funding: Swedish Agency for Research in Developing Countries (SAREC), the Karolinska Institute Stockholm, Sweden, and Nestlé Research Centre, Lausanne, Switzerland.

Due to copyright laws, full-text articles of the citations listed above cannot be provided. The articles may be obtained from public, university, or medical libraries such as the National Library of Medicine (web address: http://www.nlm.nih.gov). An additional resource is the International Bibliographic Information on Dietary Supplements (IBIDS) database. This database provides access to bibliographic citations and abstracts from the published, international, and scientific literature on dietary supplements (web address: http://ods.od.nih.gov/Health_Information/IBIDS.aspx).

APPENDIX

Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2004*

Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements. The Cache County study. PP Zandi, JC Anthony, AS Khachaturian, SV Stone, D Gustafson, JT Tschanz, MC Norton, KA Welsh-Bohmer, and JCS Breitner; for the Cache County Study Group. *Archives of Neurology* (Arch Neurol) 2004 61:82-88.

The SU.VI.MAX study: A randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. S Hercberg, P Galan, P Preziosi, S Bertrais, L Mennen, D Malvy, A-M Roussel, A Favier, and S Briançon. *Archives of Internal Medicine* (Arch Intern Med) 2004 164:2335-2342.

Antioxidant supplements for prevention of gastrointestinal cancers: A systematic review and meta-analysis. G Bjelakovic, D Nikolova, RG Simonetti, and C Gluud. *The Lancet* (Lancet) 2004 364:1219-1228.

Antioxidants block prostate cancer in Lady transgenic mice. V Venkateswaran, NE Fleshner, LM Sugar, and LH Klotz. *Cancer Research* (Cancer Res) 2004 64:5891-5896.

Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. SM Henning, Y Niu, NH Lee, GD Thames, RR Minutti, H Wang, VLW Go, and D Heber. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 80:1558-1564.

The antiatherogenic potential of oat phenolic compounds. L Liu, L Zubik, FW Collins, M Marko, and M Meydani. *Atherosclerosis* (Atherosclerosis) 2004 175:39-49.

Luteolin inhibits vascular endothelial growth factor-induced angiogenesis: Inhibition of endothelial cell survival and proliferation by targeting phosphatidylinositol 3'-kinase activity. E Bagli, M Stefaniotou, L Morbidelli, M Ziche, K Psillas, C Murphy, and T Fotsis. *Cancer Research* (Cancer Res) 2004 64:7936-7946.

Soy isoflavone intake lowers serum LDL cholesterol: A meta-analysis of 8 randomized controlled trials in humans. XG Zhuo, MK Melby, and S Watanabe. *Journal of Nutrition* (J Nutr) 2004 134:2395-2400.

Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? D-H Lee, AR Folsom, L Harnack, B Halliwell, and DR Jacobs Jr. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 80:1194-1200.

Effect of Vitamin D on falls: A meta-analysis. AH Bischoff-Ferrari, B Dawson-Hughes, WC Willett, HB Staehelin, MG Bazemore, RY Zee, and JB Wong. *Journal of the American Medical Association* (JAMA) 2004 291:1999-2006.

Vitamin E and respiratory tract infections in elderly nursing home residents: A randomized controlled trial. SN Meydani, LS Leka, BC Fine, GE Dallal, GT Keusch, MF Singh, and DH Hamer. *Journal of the American Medical Association* (JAMA) 2004 292:828-836.

Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death. The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JF Toole, MR Malinow, LE Chambless, DJ Spence, LC Pettigrew, VJ Howard, EG Sides, CH Wang, and M Stampfer. *Journal of the American Medical Association* (JAMA) 2004 291:565-575.

Folate therapy and in-stent restenosis after coronary stenting. H Lange, H Suryapranata, G De Luca, C Börner, J Dille, K Kallmayer, MN Pasalary, E Scherer, and JH Dambrink. *New England Journal of Medicine* (N Engl J Med) 2004 350:2673-2681.

A randomized trial of multivitamin supplements and HIV disease progression and mortality. WW Fawzi, GI Msamanga, D Spiegelman, R Wei, S Kapiga, E Villamor, D Mwakagile, F Mugusi, E Hertzmark, M Essex, and DJ Hunter. *New England Journal of Medicine* (New Eng J Med) 2004 351:23-32.

Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. JD Milner, DM Stein, R McCarter, and RY Moon. *Pediatrics* (Pediatrics) 2004 114:27-32.

Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of β-carotene and α–tocopherol in normocholesterolemic humans. M Richelle, M Enslen, C Hager, M Groux, I Tavazzi, J-P Godin, A Berger, S Métairon, S Quaile, C Piguet-Welsch, L Sagalowicz, H Green, and LB Fay. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 80:171-177.

Zinc for severe pneumonia in very young children: Double-blind placebo-controlled trial. WA Brooks, M Yunus, M Santosham, MA Wahed, K Nahar, S Yeasmin, and RE Black. *The Lancet* (Lancet) 2004 363:1683-1688.

Zinc absorption as a function of the dose of zinc sulfate in aqueous solution. CD Tran, LV Miller, NF Krebs, S Lei, and KM Hambidge. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 80:1570-1573.

Selenium and colorectal adenoma: Results of a pooled analysis. ET Jacobs, R Jiang, DS Alberts, RE Greenberg, EW Gunter, MR Karagas, E Lanza, L Ratnasinghe, ME Reid, A Schatzkin, SA Smith-Warner, K Wallace, and ME Martinez. *Journal of the National Cancer Institute* (J Natl Cancer Inst) 2004 96:1669-1675.

Hyperforin content determines the magnitude of the St John's wort-cyclosporine drug interaction. I Mai, S Bauer, ES Perloff, A Johne, B Uehleke, B Frank, K Budde, and I Roots. *Clinical Pharmacology and Therapeutics* (Clin Pharmacol Ther) 2004 76:330-340.

Proteomics analysis of rat brain protein modulations by grape seed extract. J Deshane, L Chaves, KV Sarikonda, S Isbell, L Wilson, M Kirk, C Grubbs, S Barnes, S Meleth, and H Kim. *Journal of Agricultural and Food Chemistry* (J Agric Food Chem) 2004 52:7872-7883.

Conjugated linoleic acid supplementation for 1 y reduces body fat mass in healthy overweight humans. J-M Gaullier, J Halse, K Høye, K Kristiansen, H Fagertun, H Vik, and O Gudmundsen. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 79:1118-1125.

Cognitive aging, childhood intelligence, and the use of food supplements: Possible involvement of n-3 fatty acids. LJ Whalley, HC Fox, KW Wahle, JM Starr, and IJ Deary. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 2004 80:1650-1657.

Effect of DHEA on abdominal fat and insulin action in elderly women and men: A randomized controlled trial. DT Villareal and JO Holloszy. *Journal of the American Medical Association (JAMA)* 2004 292:2243-2248.

Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: Evidence from two 3-year studies. O Bruyere, K Pavelka, LC Rovati, R Deroisy, M Olejarova, J Gatterova, G Giacovelli, and JY Reginster. *Menopause* (Menopause) 2004 11:138-143.

Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2003*

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.

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.

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, J-L Sebert, and P Fardellone. *The Journal of Clinical Endocrinology & Metabolism* (J Clin Endocrinol Metab) 2003 88:5175-5179.

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.

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.

Neoplastic and antineoplastic 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.

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.

Incidence of cancer and mortality following α-tocopherol and β-carotene supplementation: A postintervention follow-up. ATBC Study Group. *Journal of the American Medical Association* (JAMA) 2003 290:476-485.

Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. 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. 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.

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.

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

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.

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.

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.

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.

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.

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

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

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.

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 Epi) 2003 158:69-76.

Acknowledgements

2005 List of Journals and Journal Editors

List of peer-reviewed journals from which original research papers on dietary supplements were identified. The Office of Dietary Supplements thanks the journal editors who assisted with the selection process.

- **American Journal of Cardiology,** William C Roberts, MD
- **American Journal of Clinical Nutrition,** Charles H Halsted, MD
- **American Journal of Health-System Pharmacy,** C Richard Talley
- **American Journal of Physiology,** Margaret Reich
- **Archives of Internal Medicine,** Philip Greenland, MD
- **Atherosclerosis,** James Shepherd, PhD
- **Blood Coagulation & Fibrinolysis,** Richard Marlar, PhD
- **British Journal of Nutrition,** Prof Philip Calder
- **British Medical Journal,** Fiona Godlee, MD
- **Canadian Medical Association Journal,** Noni MacDonald, MD (Acting Editor)
- **Cancer, Epidemiology, Biomarkers & Prevention,** John D Potter, MD, PhD & David S Alberts, MD
- **Cancer Research,** Frank J Rauscher III, PhD
- **Clinical Pharmacology & Therapeutics,** C. Michael Stein, MD
- **Diabetes, Obesity & Metabolism,** Richard Donnelly, PhD
- **European Journal of Clinical Nutrition,** Prof Dr Jaap C Seidell
- **High Altitude Medicine Biology,** John B West, MD, PhD
- **Indian Journal of Pharmacology,** R Raveendran, MD
- **International Journal of Sport Nutrition & Exercise Metabolism,** Emily M Haymes, PhD
- **Journal of Agricultural and Food Chemistry,** James Seiber, PhD
- **Journal of the American College of Nutrition,** John J Cunningham, PhD
- **Journal of the American Dietetic Association,** Linda Van Horn, PhD, RD
- **Journal of the American Medical Association,** Catherine D DeAngelis, MD, MPH
- **Journal of Ethnopharmacology,** Prof Dr R Verpoorte
- **Journal of the National Cancer Institute,** Barnett S Kramer, MD, MPH
- **Journal of Nutrition,** A Catherine Ross, PhD
- **The Lancet,** Richard Horton, MB
- **New England Journal of Medicine,** Jeffery M Drazen, MD
- **Medicine and Science in Sports and Exercise,** Andrew Young, PhD
- **Metabolism,** James B Field, MD
- **Nutrition & Cancer,** Leonard A Cohen, PhD
- **Obstetrics & Gynecology,** James R Scott, MD
- **Pediatrics,** Jerold F Lucey, MD
- **Pharmaceutical Biology,** John M Pezzuto, PhD
- **Phytochemistry,** Norman G Lewis, PhD
- **Phytotherapy Research,** Elizabeth M Williamson, PhD
- **Proceedings of the National Academy of Sciences,** Nicholas Cozzarelli, PhD

2005 List of Scientific Reviewers

The Office of Dietary Supplements commends the following scientists for reviewing and scoring the nominated papers. These individuals were selected based on their scientific expertise. Their evaluation helped identify the 25 articles that were selected for this bibliography.

- **Sanjiv Agarwal, PhD,** Nutrition Center of Excellence, ConAgra Foods
- **John JB Anderson, PhD,** University of North Carolina, Chapel Hill
- **Wendy Applequist, PhD,** Missouri Botanical Garden, St Louis
- **Sujata Archer, PhD,** Northwestern University Medical School, Chicago
- **Margaret B Artz, PhD, RPh,** Ingenix, Eden Prairie, MN
- **E Wayne Askew, PhD,** University of Utah, Salt Lake City
- **Adrianne Bendich, PhD,** GlaxoSmithKline, Parsippany, NJ
- **Robert Alan Bonakdar, MD,** Scripps Center for Integrative Medicine, La Jolla, CA
- **Barbara A Bowman, PhD,** Centers for Disease Control and Prevention, DHHS
- **Joseph Carlson, PhD, RD,** Michigan State University, East Lansing
- **Laura Caulfield, PhD,** Johns Hopkins School of Public Health, Baltimore, MD
- **William T Cefalu, MD,** Pennington Research Center, Baton Rouge, LA
- **Chun-Tao Che, PhD,** Chinese University of Hong Kong, China
- **Gerald Combs, PhD,** USDA/Agricultural Research Service, Grand Forks, ND
- **Sridevi Devaraj, PhD,** University of California Davis Medical Center, Sacramento
- **Luc Djousse, MD, DSc, MPH,** Harvard Medical School, Boston, MA
- **R Curtis Ellison, MD,** School of Medicine, Boston University, MA
- **Daniel Fabricant, PhD,** Natural Products Association, Washington, DC
- **Norman Farnsworth, PhD,** University of Illinois, Chicago
- **Christopher Gardner, PhD,** Stanford School of Medicine, CA
- **Myron Gross, PhD,** University of Minnesota Medical School, Minneapolis
- **William S Harris, PhD,** South Dakota Health Research Foundation, Sioux Falls
- **Sushil K Jain, PhD,** Louisiana State University Health Sciences Center, Shreveport
- **Elizabeth H Jeffery, PhD,** University of Illinois, Urbana-Champaign
- **Leonard Keilson, MD, MPH,** The Cardiovascular Institute, Scarborough, ME
- **David Kiefer, MD,** University of Washington, Seattle
- **William EM Lands, PhD, retd.** NIH, College Park, MD
- **David A Lathrop, PhD,** National Heart, Lung, and Blood Institute, NIH
- **Henry C Lukaski, PhD,** USDA/Agricultural Research Service, Grand Forks, ND
- **Gail B Mahady, PhD,** University of Illinois, Chicago
- **Donald B McCormick, PhD,** Emory University, Atlanta, GA
- **Michael K McIntosh, PhD, RD** University of North Carolina, Greensboro
- **Scott Montain, PhD,** US Army Research Inst. of Environmental Medicine, Natick, MA
- **Phylis B Moser-Veillon, PhD, retd.** University of Maryland, College Park
- **Jerry L Nadler, MD,** University of Virginia Health System, Charlottesville
- **John P. Porter, PhD,** University of the Sciences in Philadelphia, PA
- **Richard Rivlin, MD,** Rockefeller University, New York City, NY
- **Cheryl L Rock, PhD, RD,** University of California at San Diego
- **Sharon Ross, PhD,** National Cancer Institute, NIH
- **Andrew Shao, PhD,** Council for Responsible Nutrition, Washington, DC
- **Neil F Shay, PhD,** WK Kellogg Institute, Battle Creek, MI
- **Cynthia S Smith, PhD,** National Institute of Environmental Health Sciences, NIH
- **Pamela Starke-Reed, PhD,** Division of Nutrition Research Coordination, NIH
- **Cynthia Thomson, PhD, RD,** University of Arizona, Tucson
- **Katherine L Tucker, PhD,** Tufts University, Boston, MA
- **WA van Staveren**, **Prof Dr,** Wageningen University, Netherlands
- **Vladimir Vuksan, PhD,** University of Toronto, Canada
- **W Allan Walker, MD,** Massachusetts General Hospital - East Charleston
- **Gary M Williams, MD,** New York Medical College, Valhalla
- **Susan Z Yanovski, MD,** National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Special recognition and thanks are due to these individuals at the National Institutes of Health and other organizations that helped bring this project to fruition.

We recognize the exemplary efforts of *Judith Chamot, MS, RD* and *Erin Braunscheidel, BS* in administrating this project. In addition, recognition is given to *Carol Haggans, MS, RD, Paul Thomas, EdD, RD,* and *Lora Wilder, DSc, RD* at the Office of Dietary Supplements for their assistance in abstracting the nominated papers, as well as *Donna Allen* and *Leslie Johnson* for their support-staff assistance. We thank *Andrea Lindsey, MS* at the National Agricultural Library, US Department of Agriculture, for the literature searches to identify papers on dietary supplements published in scientific journals in 2005; *Roy Upton, PhD,* Executive Director of the American Herbal Pharmacopoeia, for his nominations of scientific papers published in botanical journals; and *Jean Pennington, PhD, RD* Division of Nutrition Research Coordination, for her editorial review. Finally, we thank *Jan Ehrman, BS*, Office of Communications and Public Liaison, and *Kelli Marciel, MA,* Office of Medical Applications of Research, for their assistance with approvals and promotion of this publication.

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/

U.S. Department of
Health and Human Services
National Institutes of Health

NIH Publication No. 06-6060
September 2006