Annual Bibliography of Significant Advances in Dietary Supplement Research 2004

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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Dietary supplements continue to be widely used by Americans. According to data published in 2004 from the 1999-2000 National Health and Nutrition Examination Survey, 55 percent of American adults took a dietary supplement in the past month and 35 percent of these users took a multivitamin/multimineral supplement. Given this high interest and use of dietary supplements, the Office of Dietary Supplements tracks peer-reviewed publications on dietary supplements every year through the *Annual Bibliography of Significant Advances in Dietary Supplement Research*. The Office is pleased to provide this publication for the sixth consecutive year. As in past years, the Office engages 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 2004. The criteria for selecting papers have not changed. The first step is a comprehensive literature search that identifies peer-reviewed journals publishing original research concerning dietary supplements. Editors of these journals and scientific reviewers are invited to select noteworthy papers that appeared in these and other journals. Through these efforts, 325 papers were nominated for evaluation by internationally recognized scientists to identify the top 25 scoring papers. These papers are then annotated and compiled into the annual bibliography. To help you track research developments in the field of dietary supplements, citations of papers that appeared in the 2003 and 2002 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 scientific reviewers, journal editors, and 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 this 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.

Sincerely,

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ANNOTATIONS OF 25 SELECTED PAPERS PUBLISHED IN 2004

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)[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).*

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.**

Nerve cells are vulnerable to free-radical-mediated damage, which over time may contribute to the pathogenesis of Alzheimer disease. Antioxidant nutrients that scavenge free radicals may protect nerve cells from free-radical-mediated damage and thus delay the onset of Alzheimer disease. This cross-sectional and prospective study in Cache County, Utah examined the relationship between use of antioxidant supplements and Alzheimer disease. Of the 4,740 elderly residents enrolled in the study between 1995-1997 that provided sufficient information to evaluate cognitive status and dietary supplement use, 200 were categorized as having Alzheimer disease. When assessment for Alzheimer disease was conducted again in 1998-2000, 104 cases were identified among the 3,227 survivors. This reduced prevalence and incidence of Alzheimer disease was associated with use of vitamin E (taken alone or in a multivitamin preparation containing at least 400 IU E) and vitamin C (taken alone or in a multivitamin preparation containing at least 500 mg vitamin C). However, there was no evidence of reduction of risk with use of vitamin E or C alone, with multivitamins or with B-complex supplements. Antioxidant supplement users in the study were younger, more educated, and in better general health than nonusers of these supplements. Controlling for these characteristics, however, did not alter the study findings. The results suggest that combination vitamins E and C supplements may protect against Alzheimer disease, a finding that should be confirmed though a randomized prevention trial.

Funding: National Institute on Aging and National Institute of Mental Health, NIH.

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.**

Epidemiologic studies show a strong relationship between intakes of antioxidant nutrients (or foods rich in them) and lowered risks of cancer and cardiovascular disease. However, primary prevention trials in which these antioxidants were taken singly or in combination at high doses over long periods have not confirmed these findings. This randomized, placebo-controlled study investigated whether a cocktail of antioxidants provided at doses that might be achieved with a healthy diet could reduce the incidence of cancer and ischemic cardiovascular disease among individuals free of any risk factors living in France. Over 13,000 adults (7,876 women aged 35-60 years and 5,141 men aged 45-60 years) were randomized to receive either a daily placebo or a capsule containing 120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 µg selenium, and 20 mg zinc. After a median follow-up period of 7.5 years, antioxidant supplementation was associated with a lowered total cancer incidence in men only but had no major effects on cardiovascular disease or all-cause mortality in men or women. One explanation for this finding is that women had better baseline antioxidant status (especially of β-carotene) than men. This hypothesis is supported by the fact that there was an inverse relation between baseline β-carotene concentrations and the incidence of cancer and cardiovascular disease among men receiving the placebo. These results suggest that antioxidant supplementation at recommended dietary intake levels may have protective effects against cancer in men with low or marginal dietary intakes of those nutrients.

Funding: Fruit d'Or Recherche, Lipton, Cereal, Candia, Kellogg Company, CERIN, LU/Danone, Sodexho, L'Oréal, Estée Lauder, Peugeot, Jet Service, RP Scherer, France Telecom, Becton Dickinson, Fould Springer, Boehringer Diagnostic, Seppic Givaudan Lavirotte, Le Grand Canal, Air Liquide, Carboxyque, Klocke, Trophy Radio, Jouan, and Perkin Elmer.

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

The buildup of free radicals in cells causes oxidative stress, which may result in cancer. As antioxidant nutrients are scavengers of free radicals, the aim of this review was to establish whether supplementation with these nutrients could reduce the incidence of gastrointestinal cancer and overall mortality. All randomized trials conducted from 1945 to 2003, comparing antioxidant supplements with placebos for the prevention of gastrointestinal cancers, were analyzed using the Cochrane Collaboration methodology. Fourteen randomized trials were identified with over 170,000 participants. There were 10 different interventions varying in dose and duration (1-12 years) of supplementation with vitamins A, C, E, selenium and β-carotene and 2,100 cancer endpoints, at five sites (esophagus, stomach, large bowel, pancreas, and liver). The 10 interventions and cancer sites were considered individually and in combination. When the 10 interventions were considered individually, there was no evidence of benefit (or harm) in the combined group of five cancers. The design of the trials was also evaluated. When high-quality studies were compared with low-quality studies, there was a harmful effect of antioxidant supplementation on mortality. The exception was selenium. In four trials (three of poor quality), selenium had a beneficial effect on the incidence of gastrointestinal cancer. This review suggests that regular use of antioxidant supplements might not be helpful for prevention of gastrointestinal cancers and may increase overall mortality.

Funding: Knowledge and Research Centre for Alternative Medicine and Centre for Clinical Intervention Research, H:S Rigshospitalet, Denmark.

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.

Epidemiologic studies have shown associations between fat intake, antioxidant supplementation, and the incidence of prostate cancer. Vitamin E, selenium, and lycopene are dietary antioxidants that have been studied for their potential chemopreventive effects. This study examined the effects of antioxidant supplementation on the development of prostate cancer using male, Lady (12T-10) transgenic mice. The mice were divided into four groups of 19 animals each and received one of four dietary treatments starting at five to six weeks of age and continuing to 28 to 32 weeks of age: standard diet; standard diet plus antioxidant supplements; high-fat diet (40 percent of calories from fat); and high-fat diet plus antioxidant supplements. Antioxidant supplements were in proportion to the human equivalent per day of 800 IU vitamin E (α-tocopherol succinate), 200 µg selenium (seleno-DL-methionine), and 50 mg lycopene. Incidence of prostate cancer was reduced by antioxidant supplementation. At the end of the experiment, prostate cancer had developed in 73.7 percent of the mice on the standard and 100 percent on the high-fat diets. In contrast, only 10.5 percent of the mice on the standard and 15.8 percent on the high-fat diets supplemented with antioxidants developed tumors; microscopic analysis of the tissues confirmed this finding. The antioxidant supplements were well tolerated and had no effect on body weight of the mice. The findings from this animal study suggest that vitamin E, selenium, and lycopene show promise as chemopreventive agents for prostate cancer. Human intervention studies are required to confirm these findings before vitamin E, selenium, and lycopene can be routinely recommended for the prevention of prostate cancer.

Funding: Prostate Cancer Research Foundation of Canada; Canadian Prostate Cancer Research Initiative; and Canadian Prostate Cancer BioResearch Network.

Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement.

Polyphenols, in green and black tea leaves, have been studied extensively for their antioxidant activity and as cancer chemopreventive agents. The aim of this study was to compare the rate of absorption and excretion of tea polyphenols eight hours after a bolus consumption of either green tea, black tea, or a green tea extract supplement, and their effect on the antioxidant capacity in the blood. Thirty healthy subjects were randomly assigned to three different sequences of green tea, black tea, or a green tea extract supplement in a crossover design with a one-week washout period between interventions. All three interventions provided similar amounts of the flavanol epigallocatechin-gallate (EGCG), the presumed active ingredient. Flavanol absorption was enhanced when tea polyphenols were administered as a green tea supplement in capsule form, noting a small but significant increase in plasma antioxidant activity compared with tea polyphenols consumed as black tea or green tea. This may be because polyphenols administered as a green tea extract supplement were more bioavailable than as green or black tea. These observations suggest that green tea extract supplement retains the positive benefits of green and black tea and may be a way to administer large doses of tea polyphenols in chemoprevention studies without the side effects of caffeine associated with green and black tea beverages.

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

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.

Avenanthramides A, B, and C, which are major components of the soluble phenolic fractions in oats, may play a role in modulating the inflammatory process associated with the development of atherosclerosis or formation of plaques in arteries. This study examined the potential antiatherogenic activity of avenanthramides from oats on immune and human aortic endothelial cell interactions. Three concentrations (4, 20, and 40 ng/ml) of oat avenanthramide-enriched mixtures were tested, and vitamin E (17 ng/ml) served as the active control. The 17 ng/ml level of vitamin E is the plasma concentration that can be achieved from consuming 200 IU supplemental vitamin E daily. Oat avenanthramides exhibited a high capacity to inhibit adhesive interaction between endothelial cells through inhibition of adhesion molecule expression as well as to inhibit pro-inflammatory cytokines and chemokines, which are important in the recruitment of immune cells and leukocytes to the site of inflammation. These findings were comparable with those observed with vitamin E. Further studies are needed to elucidate the mechanism of avenanthramide action in modulating inflammatory processes associated with the development of atherosclerosis.

Funding: US Department of Agriculture; The Agriculture and Agri-Food Canada Matching Investment Initiative Program; Eastern Cereals and Oilseeds Research Centre, Canada; and The Quaker Oats Company.

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.

Diets rich in plant foods have been shown to reduce the risk of many forms of cancer. Luteolin is a flavonoid found in some plant foods that has been shown to inhibit tumor cell proliferation and angiogenesis, which is the formation of new blood vessels from pre-existing vessels. Angiogenesis plays a key role in tumor growth and is regulated by vascular endothelial growth factor. The effects of luteolin on tumor growth and angiogenesis were evaluated through a series of animal and laboratory experiments. Female immunodeficient mice were inoculated with A-431 tumor cells in the right flank. After one week, mice were treated near the tumor sites with either luteolin or a luteolin-free control. Luteolin significantly reduced tumor volume by approximately 50 percent compared with control. In addition, luteolin-treated tumors exhibited significantly fewer indications of angiogenesis. Using New Zealand White rabbits, the researchers also found that luteolin significantly inhibited vascular endothelial growth factor-induced angiogenesis in the cornea of the eye compared with control. Laboratory experiments examining several signaling pathways emanating from the vascular endothelial growth factor receptor-2 helped shed light on the mechanisms of action of luteolin and other flavonoids. These results add to the body of evidence suggesting luteolin and other flavonoids have chemoprotective effects.

Funding: European Commission and European Nutrigenomics Organization.

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.

Clinical trials suggest that soy protein has cholesterol-lowering effects, and these effects have been attributed to the soy isoflavone compounds, genistein and daidzein. This meta-analysis pooled data from eight randomized-controlled trials published from 1966 to 2003 to examine the effects of high and low intakes of soy isoflavones, independent of soy protein level, on low-density lipoprotein (LDL) cholesterol levels. Subjects in the selected trials included men, premenopausal women, and postmenopausal women with normal and high blood cholesterol levels. Trials used soy protein isolate with intakes ranging from 25 to 100 g/day and isoflavone intakes ranging from three to 132 mg/day for one to three months. Results of the meta-analysis showed that consumption of soy protein isolate with high isoflavone content (mean 96 mg isoflavones/day) significantly lowered serum LDL cholesterol compared with consumption of the same amount of soy protein isolate with low isoflavone content (mean 6 mg isoflavones/day). Reductions in serum LDL cholesterol of 0.14 mmol/L and 0.18 mmol/L were observed in individuals with normal and high blood cholesterol levels, respectively. These results suggest that consumption of 90 mg/day of soy isoflavones, independent of soy protein, can significantly reduce serum LDL cholesterol. A recent evidence-based review of the effects of soy on health outcomes conducted by the Agency for Healthcare Research and Quality concluded that soy products appear to exert a small, but not clinically significant, benefit on LDL and triglycerides in individuals.

Funding: Japanese Ministry of Education, Sports and Culture.

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.**

Vitamin C commonly serves as a powerful and beneficial antioxidant, but, it may also act as a harmful pro-oxidant under certain conditions. This study examined the association between vitamin C supplementation and mortality from cardiovascular disease in a subset of 1,923 postmenopausal women with diabetes but free of coronary artery disease at baseline. The data analyzed were from the Iowa Woman's Health Study Cohort. The survey consisted of a self-administered health questionnaire, a 127-item food-frequency questionnaire, and 24-hour dietary recall interviews. The women were monitored over a period of 15 years or until death, whichever occurred first. Participants were categorized based upon one of three vitamin C exposure indices: total vitamin C from food and supplements, from food alone, and from supplements alone. The study also examined intakes of folate, vitamin E, and beta-carotene and the relative risk of cardiovascular disease mortality across quintiles of total vitamin C intake. The data were adjusted for age, total energy and alcohol intake, smoking status, hypertension history, and waist-hip ratio. Vitamin C from supplements (> 300 mg/day), but not food, was positively associated with cardiovascular disease mortality in diabetic, but not in nondiabetic, postmenopausal women. This observational study suggests that high doses of supplemental vitamin C could be potentially harmful to older women with diabetes.

Funding: National Heart, Lung and Blood Institute and National Cancer Institute, NIH; and Singapore Biomedical Research Council.

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**

Falling occurs in 30 percent of individuals >65 years and 40-50 percent of individuals >80 years every year, which increases the risk of fractures in this population group. The increasing proportion of older individuals and the consequent increase in falls have increased the burden on health care resources. Vitamin D has been shown to decrease the risk of fracture from falls due to its ability to increase bone mineral density as well as increase muscle strength by binding to specific nuclear receptors in muscles. This meta-analysis analyzed data from five randomized control trials conducted from 2002 to 2004, involving 1,237 individuals, that looked at the effect of vitamin D supplementation, with or without calcium, on preventing falls in the elderly population (mean age 60 years and over). The dosage of vitamin D varied as follows: 400 IU/day with 800-1000 mg calcium to 800 IU with 1000-1200 mg calcium; or bolus dose of 100,000 IU vitamin D every four months with no calcium; bolus dose of 300,000 IU vitamin D with or without supplemental calcium. Vitamin D supplementation in this analysis reduced the risk of falling by 22 percent. Dose, duration of therapy, and gender of the participants affected this outcome. The combination of vitamin D and calcium resulted in a nine percent improvement in body sway (balance and stability) compared with calcium alone. Calcium alone or the type of vitamin D had no effect on these outcomes. Further research is needed to confirm these important findings that the risk of fractures among older individuals can be reduced by decreasing the possibility of falling through supplementation with vitamin D.

Funding: Harvard/Harford Foundation, Charles A. King Trust Fellowship Award and Irene and Fredrick Stare Nutrition Education Fund, Swiss Foundation for Nutrition Research, and International Foundation for Promotion of Nutrition Research and Nutrition Education.

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.**

Aging is associated with a decline in the body's immune function. Previous research has shown that vitamin E at doses of 200 IU/day induces a robust improvement in immune function among older individuals, but the clinical implications of these findings are not known. To evaluate the effect of vitamin E supplementation on respiratory tract infections (ranging from the common cold and influenza of the upper respiratory tract to acute bronchitis and pneumonia of the lower tract), 617 elderly subjects were given either 200 IU of vitamin E as DL-α tocopherol or a placebo for one year. A total of 451 subjects completed the study. The investigators prospectively collected data once a week by means of an interview, focused physical examination and chart review to determine the incidence of respiratory tract infections, as well as the number of new antibiotic prescriptions. This study showed that vitamin E had no significant effect on the incidence or number of days with infection for all upper or lower respiratory tract infections or antibiotic use. However, a post-hoc subgroup analysis showed a protective effect of vitamin E supplementation on upper respiratory tract infections regardless of gender or smoking status as evidenced by a lower incidence of common colds. These findings could help address a public health problem, as common colds are frequently associated with increased illness and economic burden for the elderly.

Funding: National Institute on Aging, NIH; U.S. Department of Agriculture; and Hoffman-LaRoche Inc.

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, JD Spence, LC Pettigrew, VJ Howard, EG Sides, CH Wang, and M Stampfer. ***Journal of American Medical Association*** **(JAMA) 2004 291:565-575**

Elevated homocysteine levels are associated with atherosclerosis and increased incidence of stroke. Folate therapy (folate, vitamin B_{12} and vitamin B_6) has been shown to reduce blood homocysteine levels and help reverse endothelial injury caused by high homocysteine levels. This randomized double-blind trial compared the effect of high doses of folic acid, vitamin B_{12}, and vitamin B_6 with low doses of these vitamins on the risk of recurrent stroke. A total of 3,680 patients with non-disabling cerebral infarction were randomly assigned to receive the high-dose formulation (25 mg vitamin B_6, 0.4 mg vitamin B_{12}, 2.5 mg folic acid) or low-dose formulation (200 µg vitamin B_6, 6 µg vitamin B_{12}, 20 µg of folic acid) daily for two years. Baseline homocysteine levels were 8.5 µmol/L in women and 9.5 µmol/L in men. After a two-year follow up period, no differences in the incidence of recurrent stroke, coronary heart disease events (such as myocardial infarction, fatal coronary heart disease, coronary revascularization or cardiac resuscitation) or death were found between the high- and the low-dose groups even though the mean reduction in homocysteine levels were greater in the high-dose group. The study did demonstrate, however, a persistent and graded relationship between baseline homocysteine levels and cardiovascular outcomes, with a lower (but non-significant) risk of stroke, coronary heart disease events, and death in the high-dose versus the low-dose groups. Although this study was unable to demonstrate a benefit of folate therapy on cardiovascular disease outcomes, it did reinforce previous findings of an association between homocysteine levels and these outcomes.

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

Folate therapy and in-stent restenosis after coronary stenting.

Elevated homocysteine levels are associated with increased risk for cardiovascular disease. Recent studies have demonstrated that folate therapy (folate, vitamin B_{12}, and vitamin B_6) is associated with decreased risk of angiographic restenosis after coronary-stent placement. Stenting is the placement of a wire mesh tube in a damaged artery to support the arterial walls and keep them open after angioplasty. This randomized controlled trial analyzed the effect of folate therapy on coronary stenting. A total of 636 patients who had undergone successful coronary stenting were randomly assigned to receive either an intravenous bolus dose of 1 mg of folic acid, 5 mg of vitamin B_6 and 1 mg of vitamin B_{12} followed by daily oral administration of 1.2 mg of folic acid, 48 mg of vitamin B_6 and 60 µg of vitamin B_{12} or a placebo for six months. Patients on folate therapy had greater progression of disease compared with the placebo group. The extent of restenosis was also greater in the treated group. Folate therapy had adverse effects on the risk of restenosis in all sub-groups except for women, individuals with diabetes, and those with high homocysteine levels (>15µmol/L). These data suggest that individuals with coronary artery stents should not use folate therapy routinely to reduce the risk of restenosis.

Funding: Medice, Germany

H Lange, H Suryapranata, G De Luca, C Börner, J Dille, K Kallmayer, MN Pasalary, E Scherer, and J-H E 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.

Micronutrient supplements are thought to suppress progression of HIV disease. This study was conducted from 1995 to 2003, a time when the antiretroviral drugs were not available to most women in Tanzania. The researchers enrolled 1,078 HIV-infected pregnant women. Eligible women were randomly assigned to receive a daily oral dose of one of four regimens: vitamin A alone (30 mg of β-carotene plus 5,000 IU of preformed vitamin A), multivitamins excluding vitamin A (20 mg of vitamin B_1, 20 mg of vitamin B_2, 25 mg of vitamin B_6, 100 mg of niacin, 50 µg of vitamin B_{12}, 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid), multivitamins plus vitamin A in the same doses listed above, or placebo. In all, 18 of 271 women (7 percent) who took multivitamins progressed to stage 4 AIDS during the course of the study, compared with 31 of 267 (12 percent) in the placebo group. Fifty-two of 271 (19 percent) who took multivitamins died, compared with 66 of 267 (25 percent) in the placebo group. The women taking multivitamins had fewer symptoms of later stage HIV infection than did women in the other groups. The HIV virus level in the blood was also modestly but significantly lower in women who received multivitamins. Women who took vitamin A alone did not show any pronounced differences from those in the placebo group, and adding vitamin A to the multivitamin preparation did not appear to offer any added benefit. This study provides evidence that multivitamin supplements keep women with the AIDS virus healthier longer, thus delaying the initiation of treatment with anti-AIDS drugs.

Funding: National Institute of Child Health and Human Development and Fogarty International Center, NIH; and Hoffmann-La Roche, Inc.

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 35:23-32.**

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.**

Environmental exposures during childhood have been suggested to contribute to asthmatic and allergic diseases. As multivitamin use in infants and toddlers is a common practice, this study examined the association between infant exposure to immune-modulating vitamins on the subsequent risk of food allergy and asthma. Data analyzed for health and disease outcomes were obtained from the 1988 National Maternal and Infant Health Survey. This survey collected perinatal, maternal, and child data (from birth to age 3) on >8,000 mothers coupled with data collected from the same cohort in the Longitudinal Follow-up in 1991. All data were collected by written, self-reported questionnaires from the individuals surveyed. The overall incidence of asthma and food allergy was 10.5 percent and 4.9 percent, respectively. Early vitamin use (before the age of 6 months) was more frequent in children who were born to families with a higher annual income and a higher level of maternal education, and it was shown to be a more common practice with premature infants and breastfed infants. More importantly, an increased risk of asthma was shown with early multivitamin intake among black infants. Early multivitamin intake was associated with food allergies in formula-fed infants. In both breastfed and exclusively formula-fed infants, vitamin use at three years of age was associated with an increased risk for food allergies but not for asthma. This complex study tested a hypothesis that multivitamin use in infancy may increase the risk of food allergies and asthma. While only an observational study, it suggests the need for a randomized controlled clinical trial to evaluate the relationship between vitamin intake and the subsequent development of allergy and/or asthma in children.

Funding: Source not identified.

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.**

Sterols from plant foods such as soy reduce absorption of dietary cholesterol in the gut and lower blood concentrations of low-density lipoprotein (LDL) or "bad" cholesterol, a risk factor for heart disease. However, sterols may also decrease absorption of some fat-soluble, health-promoting compounds such as β-carotene and α-tocopherol (vitamin E) and thereby lower their concentrations in blood. This placebo-controlled, double-blind, randomized, crossover study evaluated the extent to which sterols (in both free and ester form) reduced cholesterol absorption and altered the bioavailability of β-carotene and α-tocopherol in 26 young adult men (28-30 years of age) with normal cholesterol levels (less than 200 mg/dl). For three one-week periods, subjects consumed a normal diet along with one of the following three supplements (1) a low fat, milk-based beverage, (2) the beverage supplemented with 2.2 g free (nonesterified) soy-derived sterols, or (3) the beverage supplemented with 2.2 g esterified soy-derived sterols. To measure absorption and bioavailability, subjects also received labeled cholesterol and deuterium-labeled β-carotene and α-tocopherol. The free and esterified sterols reduced cholesterol absorption in the gut by 60 percent, and reduced the bioavailability of β-carotene and α-tocopherol by approximately 50 percent and 20 percent respectively, with the esterified sterols having the greater effect. The biological significance of these findings is not clear, but other evidence suggests that regular consumption of carotenoid-rich foods such as orange and green fruits and vegetables will likely counterbalance the sterol-induced decrease in blood carotenoid concentrations.

Funding: Nestlé Research Center and Nestlé Product Technology, Switzerland.

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.
Lancet **(Lancet) 2004 363:1683-1688.**

Pneumonia is a leading cause of morbidity and mortality in children under the age of five. Previous research suggests that zinc may be effective in the management of pneumonia. The purpose of this study was to determine if a zinc supplement in conjunction with antibiotic treatment would shorten the duration of severe pneumonia and length of hospital stay in children. A total of 270 children (65% male) aged 2-23 months in Bangladesh with severe pneumonia were randomized to receive daily either 20 mg of elemental zinc syrup (as acetate) or placebo in addition to a standard antibiotic treatment. Severe pneumonia was diagnosed using standard measures. When age was controlled, each severe pneumonia indicator was improved in the zinc supplement group versus placebo. Furthermore, duration of severe pneumonia (4 vs. 5 days) and length of hospital stay (5 vs. 6 days) were significantly decreased in the zinc vs. placebo group. The zinc supplement was safe and well tolerated in children as young as two months. Future studies should explore the mechanism of action and application in other populations. These findings could equate to substantial health-care cost savings in developing countries among children with marginal zinc status.

Funding: US Agency for International Development; and International Centre for Diarrhoeal Disease Research, Bangladesh Centre for Health and Population Research.

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.**

Zinc supplements are often used to prevent and treat infections such as diarrhea, common cold, and pneumonia. However, the optimal dosage of supplementation is not known. The purpose of this study was to determine whether absorption of zinc is dose dependent. Labeled zinc (^{67}Zn, ^{68}Zn, ^{70}Zn) was mixed with zinc sulfate solutions in potencies ranging from 2-30 mg. Labeling is a technique used by researchers to track distribution and excretion of ingested minerals. Zinc solutions were randomly administered as pairs (2 and 5, 10 and 15, 20 and 30 mg) to eight healthy young adults (3 men, 5 women) in a post-absorptive state over a 15-week period with a three-week washout between each phase. ^{67}Zn was administered intravenously 1 hour after the first oral zinc dose of each pair. Two daily urine samples were collected during each phase from day 3 to 15 after administering ^{67}Zn. Five additional urine samples were collected over 3 days after completion of the 2nd and 3rd phases to measure residual isotope levels from the previous phase. Absorbed zinc was calculated by multiplying the fraction of zinc absorbed at each dose level. The proportion of zinc absorbed declined steadily when doses were above 10 mg and were marginal when the dose exceeded 20 mg. These findings suggest that there may be limited benefits to consuming zinc supplements in doses exceeding 20 mg. Additional research on optimal doses in young children may be warranted given the increasing use of zinc supplements to prevent and treat infections.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Child Health and Human Development, NIH; and American Australian Association.

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

Selenium, a trace element, is considered to have cancer protective properties by virtue of its ability to induce apoptosis (self-destruction of cells), enhance immune function, and reduce DNA damage. Several observational studies have shown an increased risk of cancer in people living in geographic areas with low selenium in the soil. Epidemiologic studies have also shown an inverse relationship between blood selenium levels and the occurrence of colorectal tumor. Due to the number of participants, precise estimations of the risk reduction in these studies have not been possible. This study analyzed the relationship between blood selenium levels and the risk of recurrence of colorectal adenoma in a pooled sample of 1,763 patients from three large randomized trials: 498 from the Wheat Bran Fiber Trial, 713 from the Polyp Prevention Trial, and 552 from the Polyp Prevention Study. Blood selenium levels were divided into quartiles and compared with adenoma recurrence and median selenium levels in each quartile; median selenium levels by quartile were 113, 125, 136, and 150 ng/ml. There was an inverse relationship between median blood selenium levels and recurrence of adenomas. This finding of an inverse association supports previous observations of a decreased risk of colorectal cancer with optimal selenium status. The study also provides an excellent example of the advantages of pooling data from large trials to help determine dose and biological forms of selenium for chemoprevention trials.

Funding: National Cancer Institute, NIH

BOTANICALS

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.

Botanical dietary supplements, like St. John's wort, can interact with prescription medications such as immunosuppressants. Immunosuppressants are used to keep the body's immune system from rejecting transplanted organs. To illustrate this interaction, this study compared the effects of two St. John's wort extracts with high and low concentration of hyperforin on the metabolism of cyclosporine, an immunosuppressant. Hyperforin is thought to be the active component in St John's wort responsible for its interactions with drugs. In a cross-over trial design separated by a 27-day wash-out phase, ten renal transplant patients who took cyclosporine regularly for at least 2 months received daily for 14 days 900 mg of St. John's wort extract with high (42/mg) and low (0.6/mg) hyperforin content. Patients continued to take cyclosporine for the duration of the study. Blood samples were taken at multiple time points to determine the rate of metabolism of cyclosporine. Kidney function was monitored throughout the study. There was a difference in the metabolism of cyclosporine between the two St. John's wort preparations. The high-hyperforin extract decreased (by 52 percent) blood concentrations of cyclosporine requiring an increased dose of cyclosporine to maintain sufficient immunosuppression. The low-hyperforin extract did not result in reductions in blood concentrations of cyclosporine or alterations in its dosing. These findings demonstrate that the hyperforin content in St. John's wort is a major determinant affecting cyclosporine metabolism and warrants further studies utilizing low hyperforin preparations of St. John's wort.

Funding: Kneipp-Werke, Würzburg, Germany.

Proteomics analysis of rat brain protein modulations by grape seed extract.

Proanthocyanidins (oligomeric polyphenols) in grape seed extracts have been purported to have multiple health benefits. However, a systematic analysis of the cellular basis of these benefits has not been demonstrated. Because the brain is vulnerable to age-related oxidative damage and other insults including inflammation, it was hypothesized that rats ingesting grape seed extract would experience changes in expression or modifications of specific brain proteins that might protect against pathologic events. Ten normal adult female rats were divided into two groups; one group was fed a rat diet (AIN-76A) and the other fed the rat diet supplemented with five percent grape seed extract for six weeks. Novel proteins (identified through proteomics analysis) were expressed in brain cells in the grape seed extract-treated group compared with the non-treated group. Because many of these changes were quantitatively in the opposite direction from previous findings for the same proteins in Alzheimer disease or mouse models of neurodegeneration, the data suggest that these proteins may mediate the neuroprotective actions of grape seed extract. This was the first study that identified and quantified specific proteins in animal tissues altered by grape seed extract as well as indicate a link between these proteins and diseases of the central nervous system. As these findings are promising, additional animal research is warranted.

Funding: National Center for Complementary and Alternative Medicine, National Cancer Institute, and the Office of Dietary Supplements NIH; US Army Medical Research and Materiel Command; and UAB Health Services Foundation General Endowment Fund.

J Deshane, L Chaves, KV Sarikonda, S Isbell, L Wilson, M Kirk, C Grubbs, S Barnes, S Meleth, and H Kim. ***Journal of Agriculture and Food Chemistry*** **(J Agric Food Chem) 2004 52:7872 -7883.**

FATTY ACIDS

Conjugated linoleic acid supplementation for 1 y reduces body fat mass in healthy overweight humans.

Conjugated linoleic acid (CLA) is a naturally occurring free fatty acid found mainly in meat and dairy products. It is sold as a dietary supplement to reduce body fat and increase lean body mass. Because short-term studies in humans have produced mixed results, the purpose of this study was to determine the long-term efficacy and safety of two forms of CLA on total body fat and lean body mass in overweight adults. Healthy, overweight males and females (n=180) ages 18-65 years received one of three capsules containing either 4.5 gm olive oil (placebo), 3.6 gm free CLA isomers, or 3.4 gm conjugated CLA isomers for 12 months. Body fat mass was assessed via dual energy X-ray absorptiometry at 0, 6, 9, and 12 months. Secondary outcome measures included changes in body weight, lean body mass, various blood parameters, and self-reported adverse effects. Body fat mass at 6 and 12 months was lower in both CLA supplemented groups compared to placebo. At 12 months, weight and body mass index were lower in the conjugated CLA group but not in the free CLA group when compared with placebo. The free CLA group, but not the conjugated CLA group, experienced significant increases in lean body mass. There were no differences between groups in adverse events or in the safety parameters measured. This study provides promising evidence for the use CLA supplements in altering body fat in healthy, overweight adults. It also demonstrated that the from of CLA, free versus conjugated, produces different results.

Funding: Natural Ltd and Cognis Nutrition and Health.

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.**

A large proportion of the elderly population take supplements, including fish oil supplements, because of their assumed health benefits that include improvements in vascular health and cognitive performance. This was an observational study of individuals born in 1936 in Scotland. Their cognitive function was tested in 1947 at age ~11 years and again in 2000-2001 at age ~64 years. Information on supplement use (self-reported) and risk factors for vascular disease were assessed in 2000-2001. Within this study population, a nested case-control design was used to examine associations between omega-3 levels of red blood cell membranes and cognitive aging among users (n=60) and non-users (n=60) of fish oil supplements matched by gender and IQ score at age 11. Fatty acid content of red blood cell membranes was measured by gas chromatography for total saturated fatty acids, n-3, n-6, and n-9 polyunsaturated fatty acids. Fish oil supplement users consumed more vegetable and cereal fiber and vitamin C compared to non-supplement users. Although the omega-3 content in red blood cell membranes was higher in fish-oil users versus nonusers, cognitive function was the same. However, improved cognitive function in later life was associated with dietary supplement use, total omega-3 red blood cell content, and the ratio of docosahexaenoic acid (DHA) to arachidonic acid. These findings were independent of initial childhood IQ at age ~11 years. This observational study provides little support for the role of fish oil supplements in improving cognitive performance; however, supplement use was associated with improved cognitive function later in life.

Funding: Wellcome Trust, the Medical Research Council (UK), the Biotechnology and Biological Sciences Research Council (UK), and The Alzheimer's Research Trust.

OTHER

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.**

Metabolic syndrome is a combination of risk factors that place a person at high risk for heart disease. Risk factors include type 2 diabetes, high blood pressure, high levels of fat in the blood, and abdominal obesity. Results from animal studies show that administration of dehydroepiandrosterone (DHEA) reduces abdominal fat and improves insulin resistance. DHEA is a naturally occurring steroid hormone that declines with age in men and women. The purpose of this study was to confirm these findings in human trials. Fifty-six men and women (ages 65-78 years) were randomly assigned to receive either 50 mg/day of DHEA or placebo for six months. Abdominal fat, insulin responses to an oral glucose tolerance test, blood hormone and lipid levels were measured at baseline and at six months. After six months, visceral and subcutaneous fat were lower in the DHEA compared with the placebo group. The insulin area under the curve during the glucose tolerance test was lower in the DHEA versus the placebo group. Despite these positive findings, DHEA increased estradiol levels in men and women and increased testosterone levels in women, warranting caution for long-term use of this compound. Future long-term studies involving DHEA supplementation are needed to assess its safety and to confirm its usefulness as an agent to help manage metabolic syndrome.

Funding: National Institute on Aging, National Center for Research Resources, and National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: Evidence from two 3-year studies.

Osteoarthritis, which is the breakdown of cartilage in joints, results in pain and physical disability in older adults. Research shows that glucosamine has potential as a disease-modifying compound for this condition. This study evaluated the effects of glucosamine sulfate on symptoms and structure modifications in osteoarthritis using data from two 3-year randomized, double-blind, and placebo-controlled prospective studies. Of the 414 individuals randomized in the two studies, 319 were post-menopausal women over 45 years of age, with primary osteoarthritis. These women took 1,500 mg of crystallized glucosamine sulfate or a placebo daily for three years. Minimal joint space width, measured from a standing anteroposterior knee radiograph, and symptoms scored on the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index were evaluated at baseline and three years. After three years, there was no narrowing of joint space in the glucosamine treated group, but there was narrowing of joint space (-0.33 mm) in the placebo group. There was improvement in the WOMAC index in the glucosamine treated group and a worsening trend in the placebo group. These findings suggest that supplementation with glucosamine sulfate is helpful in the management of osteoarthritis in post-menopausal women.

Funding: Source not identified.

O Bruyere, K Pavelka, LC Rovati, R Deroisy, M Olejarova, J Gatterova, G Giacovelli, and JY Reginster. *Menopause* (Menopause) 2004 11:138-143.

APPENDIX

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

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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.

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

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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.

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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.

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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.

Acknowledgements

2004 List of Journals and Journal Editors

List of peer-reviewed journals from which original research papers on dietary supplements were nominated and their editors. The Office of Dietary Supplements thanks the journal editors who assisted in nominating scientific papers that appeared in their journals in 2004.

- **American Journal of Cardiology,** William C Roberts, MD
- **The American Journal of Clinical Nutrition,** Charles H Halsted, MD
- **American Journal of Epidemiology,** Moyses Szklo, MD, DrPh
- **American Journal of Health-System Pharmacy,** C Richard Talley
- **American Journal of Physiology,** Margaret Reich
- **Annals of Neurology,** Richard T Johnson, MD
- **American Journal of Public Health,** Nancy J Johnson, MA
- **Applied Microbiology & Biotechnology,** Prof dr Alexander Steinbüchel
- **Archives of Internal Medicine,** Philip Greenland, MD
- **Archives of Neurology,** Roger N Rosenberg, MD
- **Atherosclerosis,** James Shepherd, PhD
- **Blood & Coagulation Fibrinolysis,** Prof EGD Tuddenham & Richard Marlar, 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
- **Cancer Research,** Frank J Rauscher, III, PhD
- **Circulation,** James T Willerson, MD
- **Diabetes Care,** Mayer B Davidson, MD
- **Diabetes, Obesity & Metabolism,** Prof R Donnelly, Prof A Garber & Prof I Caterson
- **European Journal of Clinical Nutrition,** Prof dr Jaap C Seidell
- **High Altitude Medicine & Biology,** John B West, MD, PhD
- **Indian Journal of Pharmacology,** R Raveendrau, MD
- **International Journal of Obesity,** Richard L Atkinson, MD
- **International Journal of Sports Nutrition & Exercise Metabolism,** Emily M Haymes, 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 Pharmacists Association,** Ron Teeter
- **The Journal of Clinical Endocrinology and Metabolism,** John P Bilezikian, MD
- **Journal of Ethnopharmacology,** Prof R Verpoorte
- **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
- **Journal of Nutrition, Health & Aging,** Bruno Vellas, MD, PhD & Shumei S Sun, PhD
- **The Lancet,** Richard Horton, MB
- **The New England Journal of Medicine,** Jeffery M Drazen, MD
- **Maturitatis,** Peter Kenemans, MD, PhD
- **Medicine and Science in Sports and Exercise,** Kent B Pandolf, PhD, MPH
- **Metabolism,** James B Field, MD
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- **Phytomedicine,** Norman R Farnsworth, PhD
- **Phytotherapy Research,** Elizabeth M Williamson, PhD
- **Proceedings of National Academy of Sciences,** Nicholas Cozzarelli, PhD
- **Proceeding of the Nutrition Society,** Gail R Goldberg
- **Science Magazine,** Katrina Kelner, PhD

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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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- **Susan Z Yanovski, PhD,** National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- **Andrew Young, PhD,** USARIEM, Natick, MA

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