Annual Bibliography of Significant Advances in Dietary Supplement Research 2006

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

OFFICE OF DIETARY SUPPLEMENTS
National Institutes of Health

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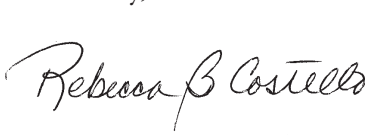
The National Institutes of Health, Office of Dietary Supplements is pleased to offer you the *Annual Bibliography of Significant Advances in Dietary Supplement Research* for the eighth consecutive year. This publication contains annotations of 25 original papers, which were selected from about 300 papers related to dietary supplements that appeared in more than 45 peer-reviewed scientific journals in 2006. The bibliography provides a snapshot of research published on dietary supplements, the quality of the research, funding sources, and journals publishing the findings. The 2006 bibliography highlights new findings on vitamin D, omega-3 fatty acids, black cohosh, *Ginkgo biloba*, and resveratrol.

A multi-step process is used to identify the 25 papers. First, peer-reviewed journals publishing original research concerning dietary supplements are identified. Next, a targeted literature search of each journal is conducted to identify original papers concerning dietary supplements. A group of internationally recognized scientists is then asked to evaluate the papers. Each paper is scored independently based on the quality of the research and implications to public health. The scores received are tallied to identify the top scoring 25 papers[1]. The 25 papers selected through this process are then annotated and sent for internal review before appearing in the final annual bibliography. The annotations are written from information contained in the original papers, related press releases, commentaries, editorials, and reviewer comments.

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 each year. Please join us in thanking these individuals, who include the 53 scientific reviewers, journal editors, and staff at ODS and the National Agricultural Library, USDA. These individuals are identified in the acknowledgements section. We would especially like to recognize the efforts of Cindy Lentino who worked diligently in coordinating this project.

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

Sincerely,



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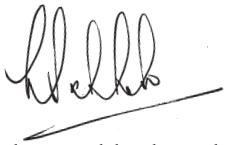

Leila G Saldanha, PhD, RD
Co-editor & Scientific Consultant

[1] NOTE: The papers that appear in the bibliography do not reflect an endorsement by the National Institutes of Health or the Office of Dietary Supplements of the companies, methods, or products cited.

Annual Bibliography of Significant Advances in Dietary Supplement Research 2006

ANNOTATIONS OF 25 SELECTED PAPERS PUBLISHED IN 2006

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

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

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

Effects of black cohosh (*Cimicifuga racemosa*) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: A double-blind, placebo-controlled, and conjugated estrogens-controlled study.

W Wuttke, C Gorkow, and D Seidlová-Wuttke. *Menopause* (Menopause) 2006 13(2):185-196.

Use of hormone therapy has decreased because of a perceived increased risk for breast cancer and cardiovascular disease. As a result, physicians and women are seeking alternatives to estrogens to manage menopause symptoms and maintain bone strength. In this 12-week randomized-controlled study, the effects of *Cimicifuga racemosa* (black cohosh, daily dose corresponding to 40 mg of herbal drug) were compared with conjugated estrogens (0.6 mg/day), or a placebo. The study was conducted between 1998 and 2000 in 62 postmenopausal women, aged 40 to 60 years, in 13 study centers in the Czech Republic. In this secondary analysis, markers of bone turnover (bone-specific alkaline phosphatase, CrossLaps), estradiol, follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin, blood lipids, and routine clinical chemistry parameters were determined from blood samples. Vaginal maturity index was determined from vaginal smears. The analyses of bone turnover markers indicated beneficial effects for black cohosh and conjugated estrogens on bone metabolism. Black cohosh stimulated osteoblast activity (bone formation), whereas conjugated estrogens inhibited osteoclast activity (bone destruction). Conjugated estrogens showed strong estrogenic effects on vaginal mucosa, whereas black cohosh showed weak estrogen-like activity. Black cohosh was well tolerated. These findings suggest that black cohosh has beneficial effects on bone remodeling and weak estrogen-like effects in the vaginal mucosa. As this paper reports a secondary analysis of the data, additional research is needed to confirm these findings.

Funding: European Commission.

Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men.

DM Antoniucci, T Yamashita, and AA Portale. *The Journal of Clinical Endocrinology & Metabolism* (J Clin Endocrinol Metab) 2006 91(8):3144-3149.

The discovery of the fibroblast growth factor, FGF-23 (a circulating factor made by osteocytes in bone) has uncovered primary regulatory pathways and new biology systems governing bone mineralization, vitamin D metabolism, parathyroid gland function, and renal phosphate handling. This dose-response study examined the effect of dietary phosphorous on serum concentrations of FGF-23 and how this in turn alters serum levels of $1,25(OH)_2D$. In this 4-week study, 13 men (28-43 yrs) were supplemented at three time points with a solution of sodium and potassium phosphate (4:1 mixture) to achieve the following intake levels of dietary phosphorous: control (1500 mg/day), supplemented (2300 mg/day), or restricted (625 mg/day). The baseline diet provided 500 mg phosphorous, 200 mg calcium, 100 mg magnesium, and 70 meq sodium per 70 kg body weight. Serum levels of FGF-23, vitamin D, phosphorus, and calcium were determined for each dose level. There was a positive or direct relationship between serum FGF-23 levels and dietary phosphorous levels, and a negative or inverse relationship between $1,25(OH)_2D$ levels and dietary phosphorous levels. There was also an inverse relationship between serum FGF-23 and $1,25(OH)_2D$ levels. Serum calcium levels stayed constant throughout the 4-wk study. This study demonstrates that serum FGF-23 and $1,25(OH)_2D$ levels are sensitive to the level of phosphorous in the diet. The data also suggest that circulating FGF-23 levels mediate production of $1,25(OH)_2D$ by dietary phosphorus. These findings contribute new information on the relationship between dietary phosphorous, blood levels of vitamin D, and bone metabolism.

Funding: Veterans Affairs Research Enhancement Award Program; National Institute of Digestive and Diabetes and Kidney Diseases, NIH; and the David Carmel Trust.

Calcium plus vitamin D supplementation and the risk of fractures.

RD Jackson, AZ LaCroix, and M Gass, for the Women's Health Initiative Investigators. ***New England Journal of Medicine*** **(N Engl J Med) 2006 354(7):669-683.**

The Women's Health Initiative (WHI) Calcium with Vitamin D trial was primarily designed to study the effect of calcium and vitamin D supplementation on preventing hip fractures. Over an average of 7 years, 374 of the 36,282 postmenopausal women ages 50 to 79 years had hip fractures. The supplementation regimen was 500 mg elemental calcium as calcium carbonate and 200 IU of vitamin D_3 or a matching placebo twice daily. Overall, women taking the supplements had 12% fewer hip fractures than those taking placebo. Women taking the supplements also had 4% fewer total fractures (all types of fracture combined). However, this difference was not statistically significant. Among women who took the supplements regularly, 29% had fewer hip fractures compared with those on the placebo. Among women 60 years of age and older, those taking the supplements had a 21% decreased risk of hip fracture compared to those taking the placebo. Further research is needed to understand the differences in findings by age. This study found that calcium plus vitamin D supplements improved hipbone density compared to placebo and lowered the risk of hip fractures in some groups. The study also found a small but significant 1% higher hipbone density for those taking calcium combined with vitamin D compared to those taking placebo. There was, however, a 17% higher risk of kidney stones in the women who took supplements. The findings show that calcium and vitamin D supplementation reduces hip fracture in women, especially among women who take these supplements regularly.

Funding: National Heart, Lung, and Blood Institute and National Center for Research Resources, NIH.

SUPPLEMENTS AND CANCER RISK REDUCTION

Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: Implications for prostate cancer prevention by vitamin D.

L Nonn, L Peng, D Feldman, and DM Peehl. ***Cancer Research*** **(Cancer Res) 2006 66(8):4516-4524**

The active metabolite of vitamin D, calcitriol, and other vitamin D analogs are promising chemopreventive agents that may protect against prostate cancer. The aim of this study was to explore the significance of mitogen-activated protein kinase phosphatase 5 (MKP5 gene) in mediating prostate cancer prevention by vitamin D. Mitogen-activated protein kinases are crucial mediators of many signaling pathways that regulate immune responses. Primary cultures of prostate cells of normal and adenocarcinoma cells from prostatic epithelial cells were used to evaluate MKP5 expression, interleukin-6 (IL-6) and tumor necrosis factor-α expression under treatment with vitamin D (1,25 $(OH)_2D$). Upon incubation with 50 nmol/L of vitamin D, a rapid increase in MKP5 expression was observed which could be abolished by use of small interfering RNA. This suggests that the induction of MKP5 by vitamin D is dependent on the presence of vitamin D receptors and is regulated by vitamin D at the transcription level. To evaluate vitamin D's role in inflammation as mediated by protein kinase p38, cells were pretreated with vitamin D. Protein kinase p38 plays a key role in inflammatory diseases. Both UV irradiation and tumor necrosis factor-α stimulated IL-6 production in normal cells via protein kinase p38 inhibition. Together these results suggest that the ability of vitamin D to inhibit p38 signaling via MKP5 up-regulation may play a significant role in prostate cancer prevention by facilitating p38 inhibition and reducing IL-6 production in prostatic epithelial cells.

Funding: Department of Defense; American Foundation for Urological Disease; and the National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Supplemental and dietary vitamin E, β-carotene, and vitamin C intakes and prostate cancer risk.

Oxidative damage by free radicals may play a role in prostate carcinogenesis. Research suggests the antioxidant nutrients E, C, and β-carotene can neutralize these free radicals. The small number of clinical trials reporting on the effects of supplemental vitamins E, C, and β-carotene on prostate cancer risk show mixed results and raise questions regarding specific patient subgroups. These investigators report on the association between dietary and supplemental vitamin E, vitamin C, or β-carotene intakes and prostate cancer risk among 29,361 men who were randomly assigned to the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. At entry, participants were 55-74 years old with no history of the cancers of interest. A self-administered food frequency questionnaire assessed diet and supplement use. Follow-up averaged 4.2 years during which 1,338 cases of prostate cancer were diagnosed. Overall, there was no association between dietary or supplemental intakes of vitamin E, vitamin C, or β-carotene and prostate cancer risk. However, for current and recent smokers, increasing dose and duration of supplemental vitamin E use was associated with decreasing risk of advanced prostate cancer. Supplemental β-carotene at the dose level of at least 2,000 mcg/day was associated with a reduced prostate cancer risk in men with low dietary β-carotene intakes. Observations from this study suggest that supplementation with antioxidant nutrients vitamin E, vitamin C, or β-carotene for reduction of prostate cancer risk may benefit select populations at risk for advanced prostate cancer.

Funding: National Cancer Institute, NIH.

VA Kirsh, RB Hayes, ST Mayne, N Chatterjee, AF Subar, LB Dixon, D Albanes, GL Andriole, DA Urban, and U Peters; on behalf of the PLCO Trial. ***Journal of the National Cancer Institute*** **(J Natl Cancer Inst) 2006 98(4):245-254.**

Calcium plus vitamin D supplementation and the risk of colorectal cancer.

Observational studies suggest that calcium with vitamin D may be beneficial in preventing colorectal cancer; however, clinical studies to support this observation are lacking. Between 1995 and 2000, the 36,282 participants already enrolled in the Women's Health Initiative (WHI) hormone or dietary studies were invited to join the Calcium and Vitamin D Study. WHI is the largest randomized clinical trial of calcium and vitamin D supplements. The supplementation regimen was 500 mg elemental calcium as calcium carbonate and 200 IU of vitamin D_3 or a matching placebo twice daily. This paper focuses on the findings on colorectal cancer risk outcomes. Over an average of 7 years, 322 women were diagnosed with invasive colorectal cancer; 168 cases in calcium plus vitamin D group and 154 cases in the placebo group. In addition, there were no differences in the number of colon polyps reported by participants assigned to the active supplement group compared to the placebo group. Findings from this study suggest that taking calcium and vitamin D supplements for an average of 7 years will not reduce the risk of colorectal cancer. However, it is not known if taking calcium and vitamin D supplements for a longer period could change these findings.

Funding: National Heart, Lung, and Blood Institute and National Center for Research Resources, NIH.

J Wactawski-Wende, JM Kotchen, and GL Anderson, for the Women's Health Initiative Investigators. ***New England Journal of Medicine*** **(N Engl J Med) 2006 354(7):684-696.**

Melanoma growth is reduced in fat-1 transgenic mice: Impact of omega-6/omega-3 essential fatty acids.

S Xia, Y Lu, J Wang, C He, S Hong, CN Serhan, and JX Kang. ***Proceedings of the National Academy of Sciences of the United States of America*** **(Proc Natl Acad Sci U S A). 2006 103(33):12499-12504.**

The concentration of omega-6 to omega-3 polyunsaturated fatty acids may influence how omega-3 fatty acids inhibit the growth and development of tumors. In this study, fat-1 mice (engineered to produce omega-3 from omega-6 fatty acids and thus have a low ratio of omega-6 to omega-3 fatty acids in their tissues without dietary intervention) and their wildtype littermates (with a substantially higher tissue omega-6:omega-3 ratio) were implanted with mouse melanoma B16 cells. Compared to the wildtype mice, a dramatic reduction in melanoma formation and growth was observed in the fat-1 mice. Fat-1 mice had higher levels of omega-3 fatty acids and the anti-inflammatory prostaglandin E_3 (PGE_3) in the tumor and surrounding tissues as well as up regulation of the PTEN gene. The PTEN gene acts as a tumor suppressor gene, meaning it helps regulate the cycle of cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. Subsequent *in vitro* experiments demonstrated that the addition of EPA (an omega-3 fatty acid) or PGE_3 inhibited the growth of the melanoma cell line and increased PTEN expression, and that inhibiting PGE_3 production attenuated PTEN expression. These exploratory studies demonstrate that omega-3 fatty acids have the potential to protect against melanoma by interacting at the gene level.

Funding: American Cancer Society; American Institute for Cancer Research; National Institute of Dental and Craniofacial Research, and National Institute of General Medical Sciences, NIH.

Soy phytochemicals prevent orthotopic growth and metastasis of bladder cancer in mice by alterations of cancer cell proliferation and apoptosis and tumor angiogenesis.

AV Singh, AA Franke, GL Blackburn, and JR Zhou. ***Cancer Research*** **(Cancer Res) 2006 66(3):1851-1858.**

Soy isoflavones may have anticarcinogenic properties and little is known about their possible effects on bladder cancer risk. The aim of this series of laboratory and animal studies was to investigate the effects of the isoflavones genistein, glycitein, and daidzein on the growth of human bladder cancer cells, as well as the effects of genistin (a form of genistein) and a soy phytochemical concentrate on tumor growth and metastasis in mice. The soy phytochemical concentrate contained 51.9% soy isoflavones by weight (50.8% genistein, 40.5% daidzein, and 8.7% glycitein aglycone equivalents). In the *in vitro* studies, genistein was found to inhibit growth of poorly differentiated 253J B-V human bladder cancer cells in a time- and dose-dependent manner through cell cycle arrest and induction of apoptosis (programmed cell death). Glycitein and daidzein had only limited effects. In female severe combined immune deficient mice, treatment with genistin and the soy protein concentrate for 10 weeks following 253J B-V tumor cell inoculation significantly reduced final tumor weight by 56% and 52% respectively via induction of apoptosis and reduced angiogenesis (growth of new blood vessels). The soy protein concentrate also significantly inhibited lung metastases by 95%. These preliminary results suggest genistein and other soy phytochemicals may inhibit bladder tumor growth and warrant further investigation.

Funding: National Cancer Institute, NIH.

Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial.

Identification of blood selenium biomarkers to monitor compliance to dietary intervention and evaluate toxicity is important. The purpose of this placebo-controlled trial was to evaluate varying forms and doses of selenium on plasma selenium biomarkers and urinary selenium excretion. Three forms of selenium (selenomethionine, high-selenomethionine yeast, and sodium selenite) were fed randomly at three dose levels (200, 400, or 600 mcg/day) to 81 selenium-replete adults for 16 weeks; a tenth group served as a control. Urinary selenium excretion and three plasma biomarkers of selenium status (concentrations of selenium and selenoprotein P and activity of glutathione peroxidase) were measured prior to supplementation and every 4 weeks during the 16-week study. Supplementation with selenomethionine and high-selenomethionine yeast raised plasma selenium levels in a dose-dependent manner, while selenite did not. Selenium absorption as estimated from urinary excretion was highest for selenomethionine, less for high-selenomethionine yeast, and least for selenite. As judged by urinary selenium excretion, selenium as selenomethionine is better absorbed than selenite. The findings from this study indicated that plasma selenium concentrations can be used to monitor compliance and safety of selenium in clinical trials that use selenomethionine but not selenite.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Research Resources, and National Institute of Environmental Health Sciences, NIH.

RF Burk, BK Norsworthy, KE Hill, AK Motley, and DW Byrne. ***Cancer Epidemiology, Biomarkers & Prevention*** **(Cancer Epidemiol Biomarkers Prev) 2006 15(4):804-810.**

SUPPLEMENTS AND CARDIOVASCULAR HEALTH

(n-3) Long-chain polyunsaturated fatty acids prolong survival following myocardial infarction in rats.

Sudden cardiac death from ventricular arrhythmias is a major cause of mortality in patients with coronary artery disease. Several studies have reported that dietary omega-3 fatty acids (n-3) reduce the incidence of sudden cardiac death in these patients. This theory was tested in two separate animal studies focusing on modulation of enzyme phosphorylation activities as one determinant of cardiac electrical activity. Male Wistar rats were subjected to coronary ligation to induce myocardial infarction, and fed a high n-3 fish oil (n-6:n-3 ratio 0.11) or high n-6 corn oil (n-6:n-3 ratio 72.5) fatty acid diet for six months. The high n-3 diet decreased the ratio of n-6:n-3 in the plasma and tissues corresponding to higher levels of EPA and DHA in the plasma and cardiac tissues. Cardiac tissue extracts from both diet groups had a 7-8 fold enrichment of DHA relative to EPA. Rats fed the high n-3 diet survived longer than rats on the high n-6 diet; a 37% improvement in survival at six months. The increased survival with the high n-3 diet was associated with decreased activities of membrane associated protein kinase A, calcium calmodulin-dependent kinase II, and phosphorylation of the ryanodine receptor calcium release channel. These findings provide a possible mechanism for the effect of a high n-3 diet on sudden cardiac death via DHA enrichment of cardiac tissues.

Funding: Showalter Foundation, Indiana.

GP Zaloga, N Ruzmetov, KA Harvey, C Terry, N Patel, W Stillwell, and R Siddiqui. ***Journal of Nutrition*** **(J Nutr) 2006 136(7):1874-1878.**

Resveratrol attenuates TNF-α-induced activation of coronary arterial endothelial cells: Role of NF-κB inhibition.

A Csiszar, K Smith, N Labinskyy, Z Orosz, A Rivera, and Z Ungvari. ***The American Journal of Physiology–Heart and Circulatory Physiology*****. (Am J Physiol Heart Circ Physiol) 2006 291(4): H1694-H1699.**

Resveratrol, a compound found largely in the skins of red grapes, is purported to have cardioprotective effects. However, the mechanisms by which resveratrol exerts these effects are not completely understood. Because tumor necrosis factor (TNF)-α-induced endothelial activation and vascular inflammation play a critical role in vascular aging and atherogenesis, these researchers evaluated whether resveratrol inhibits TNF-α-induced signal transduction in human coronary arterial endothelial cells. In a series of experiments, they were able to demonstrate that pretreatment with resveratrol affected factors that have been implicated in the development of atherosclerotic plagues. In addition, because of the anti-necrosis factor-κB activity of resveratrol it is likely antiatherogenic. These results confirm findings from other laboratories that resveratrol at submicromolar concentrations, which the authors define as nutritionally relevant concentrations, are sufficient to suppress cytokine-induced necrosis factor-κB-dependent cellular responses. This suggests that these anti-inflammatory actions of resveratrol are responsible, at least in part, for its cardioprotective effects. Additional research is needed to elucidate the mechanisms by which resveratrol exerts its vascular-protective effects.

Funding: National Heart, Lung, and Blood Institute, NIH; American Heart Association; Philip Morris USA; and Philip Morris International.

Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial.

SS Schleithoff, A Zittermann, G Tenderich, HK Berthold, P Stehle, and R Koerfer. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2006 83(4):754-759.**

Hypertension, cardiomyopathy, diabetes, coronary artery disease, and defective heart valves are risk factors for congestive heart failure. Vitamin D supplementation may help prevent the development and progression of congestive heart failure as patients with this condition have lower blood levels of vitamin D metabolites than healthy matched controls. The purpose of this clinical study was to evaluate the effect of vitamin D supplementation on the survival rate and select biochemical parameters in 123 men with congestive heart failure. The men were randomized to receive either 50 mcg (2,000 IU) vitamin D_3 with 500 mg calcium, or a placebo with 500 mg calcium daily for nine months; 93 patients completed the study. Vitamin D had no effect on either left ventricular function or 15-month survival rates. However, vitamin D supplementation resulted in decreased serum levels of tumor necrosis factor-α (an inflammatory cytokine) and increased levels of interleukin 10 (an anti-inflammatory cytokine). These changes suggest that vitamin D may have protective effects on the heart itself and on atherosclerosis that may precipitate heart failure. This study is important as it confirms previous evidence that vitamin D supplementation affects immune-modulating cytokines in desirable ways and it points to a higher dose requirement for achieving this in at-risk populations.

Funding: German Heart Foundation.

Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) Randomized Trial.

Findings from animal and human studies suggest that omega-3 fatty acids from fish oil have antiarrhythmic properties and may reduce risk of sudden cardiac death. However, three recent studies of omega-3 fatty acids in patients with implantable cardioverter defibrillators (ICDs) produced inconclusive results with some suggestion of a potential detrimental effect in the subgroup with previous ventricular tachycardia (VT). ICDs correct life-threatening ventricular tachyarrhythmia. This randomized controlled trial involved 546 patients, who had or were about to receive an ICD, with a history of at least one episode of VT or ventricular fibrillation (VF) in the preceding year. Patients received either 2g/day fish oil (464 mg EPA and 335 mg DHA) or placebo (2 g/day high-oleic sunflower oil) in capsules for a median of 273 days. The primary endpoint was either an appropriate ICD intervention for VT or VF or death from any cause. Thirty percent of omega-3 patients vs. 33% of placebo patients experienced a primary endpoint. This difference was not statistically significant. In two pre-specified subgroup analyses of 332 patients with prior MI and 411 patients with a history of VT, there were no significant tendencies toward benefit among those receiving fish oil supplements. These findings do not support a strong protective effect of fish oil in patients with ICD but neither do they show indication of harm. Together with previous findings, this study does not support supplementation with omega-3 fatty acids from fish oil to correct ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators.

Funding: Wageningen Centre for Food Sciences, The Netherlands.

IA Brouwer, PL Zock, AJ Camm, D Böcker, RN Hauer, EF Wever, C Dullemeijer, JE Ronden, MB Katan, A Lubinski, H Buschler, and EG Schouten, for the SOFA Study Group. ***Journal of the American Medical Association*** **(JAMA) 2006 295:2613-2619.**

Homocysteine lowering with folic acid and B vitamins in vascular disease.

Elevated homocysteine levels are associated with increased risk for cardiovascular disease and stroke. Supplementation with B vitamins (folic acid, vitamin B_{12}, and vitamin B_6) has been shown to reduce blood homocysteine levels; however, results from intervention trials have been disappointing. HOPE 2 was a randomized controlled trial involving 5,522 adults with vascular disease or diabetes who received supplements of 2.5 mg folic acid, 50 mg vitamin B_6 and 1 mg vitamin B_{12} or placebo for an average of 5 years. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke. Although mean plasma homocysteine levels decreased 2.4 µmol/L in the treatment group, the treatment did not significantly decrease the risk of death from cardiovascular disease or stroke, though there was a reduction in nonfatal strokes. Additionally, there were no significant differences between groups for total ischemic events or hospitalizations for heart failure and revascularization. Rates for unstable angina, however, were increased in the treatment group (268 vs. 219, p=0.02). These finding are consistent with those of the Norwegian Vitamin (NORVIT) Trial (KH Bonaa, et al., *N Engl J Med* 2006 Apr 354(15):1578-88), which demonstrated a lack of effect with B-vitamin supplementation in a secondary prevention trial of 3,749 men and women with a recent myocardial infarction. Findings from these studies do not support the association between B-vitamin supplementation, reduction in elevated homocysteine levels, and reduced risk for cardiovascular disease in individuals with existing disease.

Funding: Canadian Institutes of Health Research Grant.

The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. ***The New England Journal of Medicine*** **(N Engl J Med) 2006 354(15): 1567-1577.**

Effects of selenium supplementation on cardiovascular disease incidence and mortality: Secondary analyses in a randomized clinical trial.

S Stranges, JR Marshall, M Trevisan, R Natarajan, RP Donahue, GF Combs, E Farinaro, LC Clark, and ME Reid. ***American Journal of Epidemiology*** **(Am J Epidemiol) 2006 163(8):694-699.**

Oxidative damage is thought to play an important role in the initiation and progression of atherosclerosis. Selenium, an essential trace mineral, is a component of selenoproteins that have antioxidant activity. This paper reports on secondary analyses of data from the Nutritional Prevention of Cancer Trial, a randomized placebo-controlled skin cancer prevention trial whose participants (mean age 63.2 years) were recruited from dermatology clinics in low-selenium areas of the eastern US and randomized to receive either 200 mcg/day selenium (as selenized yeast) or a yeast placebo. Subjects for the main analyses were 1,004 trial participants (504 from the selenium group, 500 from the placebo group) who were free of cardiovascular disease at baseline and followed for a mean of 7.6 years. During follow-up, 103 cardiovascular events occurred in the selenium group, including 40 cardiovascular disease deaths, and 96 cardiovascular events occurred in the placebo group, including 31 cardiovascular disease deaths. Selenium supplementation was not significantly associated with overall or specific cardiovascular disease endpoints. Analyses stratified by tertiles of baseline plasma selenium concentrations also produced no significant associations. In a separate analysis among participants with prevalent cardiovascular disease at baseline (n=246) there was no association between selenium supplementation and cardiovascular disease endpoints. The findings from this large clinical trial corroborate those from previous smaller studies of a potential harmful effect of selenium supplementation on cardiovascular outcomes.

Funding: Not indicated.

SUPPLEMENTS AND COGNITIVE HEALTH

Amyloid-ß-induced pathological behaviors are suppressed by *Ginkgo biloba* extract EGb 761 and ginkgolides in transgenic *Caenorhabditis elegans*.

Y Wu, Z Wu, P Butko, Y Christen, MP Lambert, WL Klein, CD Link, and Y Luo. ***The Journal of Neuroscience*** **(J Neurosci) 2006 26(50):13101-13113.**

Amyloid beta (amyloid-ß) toxicity has been postulated to initiate synaptic loss and subsequent neuronal degeneration seen in Alzheimer's disease. Amyloid beta is the main constituent of senile plaques in the brains of Alzheimer's disease patients. In this study, *Ginkgo biloba* extract (EGb 761) and its single constituents were used to associate amyloid-ß species with amyloid-ß-induced pathological behaviors in the roundworm (*Caenorhabditis elegans*). The *Ginkgo biloba* extract and one of its components, ginkgolide A, alleviated amyloid-ß-induced pathological behaviors, including paralysis, and reduced chemotaxis behavior and serotonin hypersensitivity. The *Ginkgo biloba* extract also inhibited amyloid-ß oligomerization and amyloid-ß deposits. The researchers also tested ascorbic acid and found that even though ascorbic acid reduced oxidative stress to the same extent as ginkgo, it was not as effective as ginkgo in suppressing paralysis. The researchers concluded that the mechanism by which the *Ginkgo biloba* extract and ginkgolide A suppressed amyloid-ß-induced paralysis was not through reduction of oxidative stress. The findings suggest that 1) the *Ginkgo biloba* extract (EGb 761) suppresses amyloid-ß-related pathological behaviors, 2) the protection against amyloid-ß toxicity by the *Ginkgo biloba* is mediated primarily by modulating amyloid-ß oligomeric species, and 3) ginkgolide A has therapeutic potential for prevention and treatment of Alzheimer's disease. Two large-scale randomized controlled studies are presently being undertaken (Ginkgo Evaluation of Memory and GuidAge) to test whether *Ginkgo biloba* can prevent or delay the onset of Alzheimer's disease.

Funding: National Center for Complementary and Alternative Medicine, NIH; and Ipsen, Paris, France.

ω-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study.

Preliminary studies have shown a reduced risk of Alzheimer's disease (AD) in people consuming increased amounts of fish in their diets. Many of the health benefits of fish are attributed to the abundance of omega-3 fatty acids contained in fish. In this double-blind, placebo-controlled clinical trial, 244 elderly patients with medically diagnosed Alzheimer's disease were randomized to receive omega-3 either as DHA (1.7 g/day) and EPA (0.6 g/day) or a placebo for 6 months, after which all received the omega-3 supplements for 6 more months. Cognition was measured with the Mini-Mental State Examination and Alzheimer Disease Assessment Scale, and global functioning was assessed using Clinical Dementia Rating Scale. At 6 months, the 174 patients in both groups who completed the trial showed no differences in decline of cognitive function. However, a subgroup of 32 in the treatment group with very mild cognitive dysfunction showed a significant reduction in the decline rate as compared to those taking placebo. When similar individuals in the placebo group were switched to the DHA/EPA supplement for 6 months, they too exhibited a significantly reduced decline in function. The supplements were well tolerated. Currently a large NIH-funded clinical trial (A Randomized Double-Blind Placebo-Controlled Trial of the Effects of Docosahexaenoic Acid (DHA) in Slowing the Progression of Alzheimer's Disease) will test the findings from this and other similar studies.

Funding: Pronova Biocare A/S, Funds of Capio; Gamla Tjänarinnor; Swedish Alzheimer Foundation; Odd Fellow; Swedish Society of Physicians; and Lion's Sweden.

Y Freund-Levi, M Eriksdotter-Jönhagen, T Cederholm, H Basun, G Faxén-Irving, A Garlind, I Vedin, B Vessby, LO Wahlund, and J Palmblad. ***Archives of Neurology*** **(Arch Neurol) 2006 63(10):1402-1408.**

Superior efficacy of St John's wort extract WS® 5570 compared to placebo in patients with major depression: A randomized, double-blind, placebo-controlled, multi-center trial.

St. John's wort (*Hypericum perforatum*) extract is an attractive option for management of mild to moderately severe depression as it is well tolerated. The aim of this double-blind, randomized, placebo-controlled study was to assess the efficacy and safety of St. John's wort (extract WS® 5570) at doses of 600 mg/day in a single dose and 1200 mg/day in two doses. The participants were male and female adult outpatients living in Germany with mild or moderate major depression (single or recurrent events). For the 6-week treatment, 332 patients were randomized to St. John's wort 600 mg/day, St. John's wort 1200 mg/day, or a placebo. An active control was not included. The primary outcome measure was the change in total score on the Hamilton Rating Scale for Depression (HAM-D) between baseline and endpoint. Additional measures included the number of responders, the number of patients in remission, and several other standard rating scales. After 6 weeks of treatment, decreases in HAM-D total scores of 11.6 ± 6.4, 10.8 ± 7.3, and 6.0 ± 8.1 points were observed for the St. John's wort 600 mg/day, 1200 mg/day, and placebo groups, respectively. St. John's wort was consistently more effective than placebo in patients with mild or moderate major depression. The number of patients who experienced remission was higher in the St. John's wort 1200 mg/day group than the St. John's wort 600 mg/day group. Overall, St. John's wort at doses of 600 and 1200 mg/day was found to be more effective than placebo for the management of mild to moderate major depression and both doses were equally efficacious in this short-term study.

Funding: Dr Willmar Schwabe Pharmaceuticals, Germany.

S Kasper, IG Anghelescu, A Szegedi, A Dienel, and M Kieser. ***BioMed Central Medicine*** **(BMC Med) 2006 4(14):1-13.**

Zinc supplementation reduces iron absorption through age-dependent changes in small intestine iron transporter expression in suckling rat pups.

SL Kelleher and B Lönnerdal. ***Journal of Nutrition*** **(J Nutr) 2006 136(5):1185-1191.**

The mechanism by which supplemental zinc decreases iron absorption is not understood. In this study, investigators examined the effects of zinc on intestinal iron transport in suckling rat pups from the 10th day of infancy through weaning at day 20. The rats were randomly assigned to three groups, low (300 mcg/day), high (750 mcg/day) and control (0 mcg/day) zinc from zinc sulfate. Tissue iron distribution, iron absorption, intestinal DMT1 (divalent metal transporter, responsible for absorption of iron), expression of ferroportin-1 and hephaestin (an enzyme that oxidizes iron from the ferrous to ferric form), and localization and liver expression of hepcidin (a proposed communication link between liver iron stores and intestinal iron absorption) were determined. Supplemental zinc was found to reduce iron absorption by increasing retention of iron in the intestine due to reduced levels of hephaestin. However, by the time of weaning, zinc supplements no longer had a significant effect on iron absorption, likely a result of increased iron efflux due to increased hephaestin levels. Because early supplementation with zinc reduces iron absorption through specific changes in the intestinal iron transport machinery in this animal model, the investigators suggest that zinc supplementation in young infants should be approached with caution. The long-term implications of these findings in infants deserve further investigation.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases, NIH; and faculty research grants.

Feeding Infants and Toddlers Study: Do vitamin and mineral supplements contribute to nutrient adequacy or excess among US infants and toddlers?

R Briefel, C Hanson, MK Fox, T Novak, and P Ziegler. ***Journal of the American Dietetic Association*** **(J Am Diet Assoc) 2006 106:S52-S65.**

There is limited information on the use of dietary supplements by infants and toddlers. The 2002 Feeding Infants and Toddlers Study was conducted to expand knowledge about food and nutrient intakes among infants and toddlers in the United States. Subjects included a stratified random national sample of 3,022 children ranging from four to 24 months of age. The parent or primary caregiver completed a household survey and a 24-hour dietary recall for his/her child. A second 24-hour dietary recall was collected in a random sub-sample of 703 respondents. The prevalence of supplement use ranged from 8% among 4-5 month infants to 31% among 12-24-month-old toddlers. Most (97%) took one supplement, which was usually a multivitamin and/or multimineral. Nutrient, energy, and supplement intakes were assessed using the Dietary Reference Intakes (DRIs) for infants from 6-11 months and 12-24 months. Measurements of vitamins A, C, D, E, and B_{12}, folate, calcium, iron, phosphorus, potassium, sodium, zinc, and fiber were compared to current DRIs. Supplement users showed higher intake levels of vitamins and minerals. However, results indicated that infants 6-11 months and 12-24 months both reached most vitamin and mineral recommended levels regardless of supplementation. Toddlers 12 to 24 months demonstrated higher excessive intake levels for vitamin A, folate, and zinc with or without supplementation. Vitamin E was substantially lower in nonusers. This study suggests that nutrient adequacy can be obtained from dietary intakes, and that supplementation with multivitamin and/or multiminerals may not be necessary in infants and toddlers.

Funding: Gerber Products Company, USA.

Vitamins C and E and the risks of preeclampsia and perinatal complications.

There is evidence of oxidative stress in women with established preeclampsia, a condition some women with diabetes or hypertension experience during the late stages of pregnancy. The Australian Collaborative Trial of Supplements (ACTS) was designed to test whether supplementation with vitamin C and vitamin E reduced perinatal complications in women who have never given birth. In this randomized controlled study, 1,877 women (mean age 26 years), between 14 and 22 weeks of gestation received either antioxidant vitamins (1000 mg of vitamin C as ascorbic acid and 400 IU of vitamin E as d-α-tocopherol succinate) or a placebo daily until delivery. Supplementation with the vitamins or placebo did not alter the risk of preeclampsia (6% vs. 5%, respectively), death or serious outcomes in the infant or having an infant of low birth weight (below the 10th percentile for gestational age). A similar large randomized trial conducted in the United Kingdom (L Poston et al., *Lancet*. 2006 367(9517):1145-54) also demonstrated that concomitant supplementation with vitamins C and E did not prevent preeclampsia in high-risk women. The ACTS study represents a cohort of low-risk women more representative of a normal population, whereas, the United Kingdom studied a cohort of women with risk factors for preeclampsia. Together these studies suggest that supplementation with the antioxidant vitamins C and E are not effective in preventing or reducing the risk of preeclampsia in women.

Funding: National Health and Medical Research Council, Australia; Channel 7 Research Foundation, South Australia; and the Discipline of Obstetrics and Gynecology, University of Adelaide, South Australia.

AR Rumbold, CA Crowther, RR Haslam, GA Dekker, and JS Robinson for the ACTS Study Group. ***The New England Journal of Medicine*** **(N Engl J Med) 2006 354(17):1796-1806.**

Chromium activates glucose transporter 4 trafficking and enhances insulin-stimulated glucose transport in 3T3-L1 adipocytes via a cholesterol-dependent mechanism.

Dietary chromium supplementation has been extensively studied for its role in the prevention and reduction of risk for developing type 2 diabetes. This study tested if the beneficial effects of chromium on insulin action result from changes in plasma membrane properties. Pretreatment and incubation of 3T3-L1 adipocytes with 10 μM chromium chloride or 10 μM chromium picolinate for 16 hours demonstrated that chromium elicits an insulin-like accumulation of a specific glucose transporter, GLUT4, at the plasma membrane. GLUT4 membrane content was increased by 44% with chromium chloride and by 35% with chromium picolinate treatment. Additional studies revealed that the chromium-induced accumulation of GLUT4-containing vesicles occurred adjacent to the inner cell surface membrane, which in the presence of insulin became incorporated into the plasma membrane. Further, chromium picolinate reduced plasma membrane cholesterol, which in turn activated GLUT4 translocation. Upon repletion of plasma membrane cholesterol, the enhancement of insulin action by chromium picolinate was rendered ineffective. These data build on earlier *in vitro* studies showing enhanced glucose uptake and membrane fluidity by chromium and suggest a novel mechanism by which chromium may enhance GLUT4 trafficking and insulin-stimulated glucose transport. Additional studies are warranted to elucidate the molecular basis and clinical relevance of chromium supplementation and its role in diabetes.

Funding: National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements, NIH; American Diabetes Association; and American Heart Association Midwest Affiliate.

G Chen, P Liu, GR Pattar, L Tackett, P Bhonagiri, AB Strawbridge, and JS Elmendorf. ***Molecular Endocrinology*** **(Mol Endocrinol) 2006 20(4):857-870.**

Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process.

GL Close, T Ashton, T Cable, D Doran, C Holloway, F McArdle, and DP MacLaren. *British Journal of Nutrition* (Br J Nutr) 2006 95(5):976-981.

Strenuous exercise often results in muscle fatigue and soreness. Delayed onset of muscle soreness is frequently attributed to an increase in reactive oxygen species. Although the relationship between delayed onset of muscle soreness and an increase in reactive oxygen species is uncertain, athletes often use antioxidant nutrients such as ascorbic acid (vitamin C) as therapy for muscle soreness. This randomized controlled trial assessed 20 physically active male subjects with similar aerobic fitness profiles to evaluate post-exercise muscle soreness. Subjects were randomly assigned to receive a lactose placebo (1g) or visually identical ascorbic acid (1g) tablet, which were administered prior to a 30 min downhill run. Blood samples were taken before and after the run at days 1-4, 7, and 14 to assess blood glutathione, malonaldehyde, and plasma ascorbate levels; indicators of oxidative stress. The increased blood ascorbic acid concentration in the vitamin C supplemented group lead to increased malonaldehyde concentrations and consequently reduced levels of reactive oxygen species compared to the placebo group. The vitamin C supplemented group also experienced longer muscle soreness and muscle torque. The findings from this study indicate that reactive oxygen species may be positively involved in the recovery of delayed onset of muscle soreness and suggest that vitamin C supplementation may in fact be detrimental to muscle recovery. The basis for the one gram dose was not justified and it is plausible that a lower dose could produce different results. Additional research is needed to understand the relationship between reactive oxygen species and delayed onset of muscle soreness, and the effect of varying doses of vitamin C on the entire muscle recovery process.

Funding: not indicated

Echinacea in the prevention of induced rhinovirus colds: A meta-analysis.

R Schoop, P Klein, A Suter, and SL Johnston. *Clinical Therapeutics* (Clin Ther) 2006 28(2):174-183

Echinacea is used in popular medicine for the treatment and prevention of colds. However, findings from intervention and observational studies on the efficacy of this botanical product are mixed. This meta-analysis was conducted to determine the reason for the negative results from experimental rhinovirus infection studies on the efficacy of *Echinacea* extracts to prevent symptomatic development of experimentally induced colds. Rhinovirus is the cause of the common cold in an estimated 30 to 35% of all adults. The primary endpoint selected was the development of symptomatic clinical colds, as defined by the authors of the original studies. The secondary outcome was the difference in total symptom severity scores between treatment groups (assessed daily by integrating the severity scores of eight individual cold-related symptoms that were rated on a scale from zero [absent] to four [very severe]). Of the 234 articles identified through the literature search, 231 were excluded as they related to studies of spontaneous common colds, leaving three studies in the final pooled analysis where the common cold was induced. Based on the analysis, the likelihood of experiencing a clinical cold was 55% higher with placebo than with *Echinacea*. The absolute difference in total symptom scores between groups was -1.96. This meta-analysis suggests that standardized extracts of *Echinacea* can prevent symptoms of the common cold after clinical inoculation compared with placebo. Further prospective, appropriately powered clinical studies are required to confirm this finding.

Funding: A Vogel Bioforce AG, Switzerland

Resveratrol improves health and survival of mice on a high-calorie diet.

Resveratrol has been shown to extend lifetime in experimental animal models. In these models, extension of lifespan is dependent on sirtuins, a family of enzymes hypothesized to play a key role in response to stress, such as heat or calorie restriction. This paper describes the results of studies of year-old (middle-aged) mice placed on three different diets for six months: a standard mouse diet (AIN-93G), a high-calorie (modified AIN-93G, providing 60% of calories from fat) diet, and a high-calorie (60% of calories from fat) diet supplemented with resveratrol. Resveratrol was added at two concentrations of ~5.2 and 22.4 mg/kg/day, which the authors state are reasonable daily doses for humans. After six months, the researchers observed a clear trend toward increased survival and improved insulin sensitivity (important for the body's efficient processing of glucose into energy) in the high-calorie diet supplemented with resveratrol at 22.4 mg/kg/day relative to that seen on the high-fat diet without resveratrol supplementation. Findings from resveratrol supplementation at 5.2 mg/kg/day were not reported in the paper. In this study, resveratrol shifted the physiology of middle-aged mice on a high-calorie diet towards that of mice on a standard diet and increased their survival. The findings from this study suggest that overweight aged male mice whose high-calorie (fat) diet was supplemented with resveratrol had better health and survival than aged overweight mice who did not receive resveratrol. It should be noted that the doses reported in the study are high and may not be feasible through usual intake of food or supplements.

Funding: National Institute on Aging, NIH; Ministerio de Ciencia y Tecnología, Spain; and PF Glenn and The Paul F Glenn Laboratories for the Biological Mechanisms of Aging.

JA Baur, KJ Pearson, NL Price, HA Jamieson, C Lerin, A Kalra, VV Prabhu, JS Allard, G Lopez-Lluch, K Lewis, PJ Pistell, S Poosala, KG Becker, O Boss, D Gwinn, M Wang, S Ramaswamy, KW Fishbein, RG Spencer, EG Lakatta, D Le Couteur, RJ Shaw, P Navas, P Puigserver, DK Ingram, R de Cabo, and DA Sinclair. ***Nature*** **(Nature) 2006 444(16):337-342.**

Articles cited 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 published, international, and scientific literature on dietary supplements (web address: http://ods.od.nih.gov/Health_Information/IBIDS.aspx).

http://www.nal.usda.gov/fnic/IBIDS/journals.html

The Office of Dietary Supplements at NIH produces IBIDS.

APPENDIX

Citations of papers that appeared in the *Annual Bibliography of Significant Advances in Dietary Supplement Research 2005*

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.

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Acknowledgements

2006 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 especially thanks the journal chief editors (names bolded and italicized) who assisted with the selection of papers.

- **American Journal of Cardiology,** William C Roberts, MD
- **American Journal of Clinical Nutrition,** ***Charles H Halsted, MD***
- **American Journal of Epidemiology,** Moyses Szklo, MD, DrPH
- **American Journal of Physiology–Heart and Circulatory Physiology,** Alberto Nasjletti, MD
- **American Journal of The Medical Sciences,** David W Ploth, MD
- **Archives of Internal Medicine,** Philip Greenland, MD
- **Archives of Neurology,** Roger N Rosenberg, MD
- **Atherosclerosis,** Ernst J Schaefer, MD, James Shepherd, PhD
- **Biological-Trace-Element-Research,** Gerhard N Schrauzer, PhD
- **BMC Medicine,** Melissa Norton, MD
- **British Journal of Nutrition,** ***Prof Philip Calder***
- **British Medical Journal,** Fiona Godlee, MD
- **Cancer Research,** Frank J Rauscher III, PhD
- **Cancer, Epidemiology, Biomarkers & Prevention,** John D Potter, MD, PhD, David S Alberts, MD
- **Circulation Research,** Eduardo Marbán, MD, PhD
- **Circulation,** Joseph Loscalzo, MD, PhD
- **Clinical Pharmacology & Therapeutics,** C Michael Stein, MD
- **Clinical Therapeutics,** Philip D Walson, MD
- **Diabetes, Obesity & Metabolism,** Ian Caterson, PhD, Richard Donnelly, PhD, Allan Garber, MD
- **European Journal of Clinical Nutrition,** Prof Prakash S Shetty
- **European Journal of Nutrition,** Gerhard Rechkemmer, PhD
- **Indian Journal of Pharmacology,** ***R Raveendran, MD***, Dr Shivprakash
- **Journal of Agricultural and Food Chemistry,** James N Seiber, PhD
- **Journal of Clinical Endocrinology & Metabolism,** Paul W Ladenson, MD
- **Journal of Neuroscience,** Gary L Westbrook, MD
- **Journal of Nutrition,** ***A Catherine Ross, PhD***
- **Journal of the American College of Cardiology,** Anthony N DeMaria, MD
- **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 the National Cancer Institute,** Barnett S Kramer, MD, MPH
- **Maturitas,** Prof Dr Peter Kenemans, MD, PhD
- **Medicine and Science in Sports and Exercise,** Andrew J Young, PhD
- **Menopause,** Isaac Schiff, MD
- **Metabolism,** James B Field, MD
- **Molecular Endocrinology,** John A Cidlowski, PhD
- **Mutation Research,** PJ Stambrook, PhD, LHF Mullenders, PhD, Dr LR Ferguson
- **Nature,** Philip Cambell, PhD
- **New England Journal of Medicine,** Jeffery M Drazen, MD
- **Obstetrics & Gynecology,** James R Scott, MD
- **Pediatrics,** Jerold F Lucey, MD
- **Pharmaceutical Biology,** John M Pezzuto, PhD
- **Phytomedicine,** Hildebert Wagner, Norman R Farnsworth, Yoshinori Asakawa
- **Phytotherapy Research,** Elizabeth M Williamson, PhD
- **Proceedings of National Academy of Sciences,** Randy Schekman, PhD
- **The Canadian Medical Association Journal,** Paul C Hebert, MD
- **The Lancet,** Richard Horton, MB

2006 List of Scientific Reviewers

The Office of Dietary Supplements commends the following scientists for reviewing, scoring, and providing comments on the nominated papers. The comments were beneficial in helping us choose the most significant articles. These individuals were selected based on their scientific expertise.

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- **E Wayne Askew, PhD,** University of Utah, Salt Lake City
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- **Robert Alan Bonakdar, MD,** Scripps Center for Integrative Medicine, La Jolla, CA
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- **Gerald Combs, PhD,** USDA/Agricultural Research Service, Grand Forks, ND
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- **Donald B McCormick, PhD,** Emory University, Atlanta, GA
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- **Mark Messina, PhD,** Nutrition Matters, Inc, Port Townsend, WA
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- **Suzanne P Murphy, PhD, RD,** University of Hawaii, Honolulu
- **Kimberly O'Brien, PhD,** Cornell University, Ithaca, NY
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- **Cheryl L Rock, PhD, RD,** University of California at San Diego
- **Sharon Ross, PhD,** National Cancer Institute, NIH
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- **Cynthia S Smith, PhD,** National Institute of Environmental Health Sciences, Research Triangle Park, NC
- **Pamela Starke-Reed, PhD,** Division of Nutrition Research Coordination, NIH
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- **J Michael Wyss, PhD,** University of Alabama, Birmingham
- **Susan Z Yanovski, MD,** National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- **Paula Ziegler, PhD, RD,** Wyeth Consumer Healthcare, Madison, NJ

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For more information, please contact:

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

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