Annual Bibliography of Significant Advances in Dietary Supplement Research 2007

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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For the ninth consecutive year, the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) is pleased to offer you the *Annual Bibliography of Significant Advances in Dietary Supplement Research*. This publication contains annotations of 25 original papers[1] selected from over 400 related to dietary supplements that appeared in more than 80 scientific publications in 2007. The bibliography provides a snapshot of basic, observational, clinical, and translational research published on dietary supplements, citations where these papers appeared, and funding sources. Among the findings reported in the 2007 bibliography are the role of vitamins in the management of risk for venous thromboembolism, folic acid on hearing loss in adults, omega-3 fatty acids in the management of risk for type 1 diabetes, genistein on bone mineral density, and botanicals in the management of risk factors for diabetes.

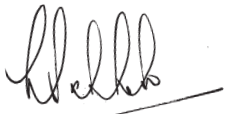
A multi-step process was used to identify the 25 papers. First, peer-reviewed journals publishing original research concerning dietary supplements are identified. Next, colleagues at the National Agricultural Library, U.S. Department of Agriculture (USDA) conducted a targeted literature search of each journal to identify original papers concerning dietary supplements. A search of press releases, news stories, and recommendations from scientific reviewers were also used to identify original papers. For 2007, this process yielded 437 papers from 83 journals. These studies were then manually reviewed before identifying the 223 papers that were sent to an external team of internationally recognized scientists for evaluation. At least two scientists scored each paper independently. Scientists were provided with scoring sheets to ensure uniform scoring. The scores received were tallied to identify the top scoring 25 papers. The 25 papers selected through this process were annotated and sent for internal review and clearance 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 contributions and combined efforts make it possible for us to bring you this publication each year. These individuals include the scientific reviewers, journal editors, and staff at ODS and the National Agricultural Library, USDA. These individuals are identified in the acknowledgements section.

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

Sincerely,

Rebecca B Costello, PhD, FACN
Co-editor & Director of Extramural Activities



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

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[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 that are cited in the studies.*

Contents

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

ODS was established by the Dietary Supplement Health and Education Act of 1994 (DSHEA, Public Law 103-417)[1]. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the 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 the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: A randomized trial.

H Marini, L Minutoli, F Polito, A Bitto, D Altavilla, M Atteritano, A Gaudio, S Mazzaferro, A Frisina, N Frisina, C Lubrano, M Bonaiuto, R D'Anna, ML Cannata, F Corrado, EB Adamo, S Wilson, and F Squadrito.
Annals of Internal Medicine (Ann Intern Med) 2007 146(12):839-847.

Menopause is associated with reductions in estrogen levels, an increased rate of bone loss, and therefore a greater risk for osteoporosis. Genistein, a phytoestrogen in soybeans, has been shown to reduce bone loss in postmenopausal women, but the evidence is not conclusive. In addition, genistein is associated with increased risk for developing certain cancers in some studies. However, soy phytoestrogens continue to be attractive options for women, given the published side effects of estrogen-replacement therapies. In this randomized controlled trial, the effects of genistein on bone metabolism were tested in 389 women in Italy, aged 49-67 years, with decreased bone density. The women were supplemented with either 54 mg/day of genistein (equivalent to amounts found in Asian vegetarian diets) or a placebo for two years. Both supplements also contained 500 mg calcium (as calcium carbonate) and 400 IU vitamin D. Compared to the placebo group, women taking genistein had decreased levels of bone resorption markers, increased levels of markers of new bone formation and increases in lumbar spine and femoral neck bone mineral density. The genistein group also experienced more gastrointestinal side effects. In another 2007 publication by the same research group, genistein had favorable effects on blood-sugar control and some cardiovascular risk factors (M Atteritano, et al., *J Clin Endocrinol Metab* 2007 92:3068-3075). Overall, the findings from these studies suggest that long-term intake of genistein has favorable effects on bone mineral density and some cardiovascular risk factors in older women.

Funding: Italian Ministry of Education, University, and Research; and the University of Messina, Messina, Italy.

Soluble dietary fibre fraction of *Trigonella foenum-graecum* (fenugreek) seed improves glucose homeostasis in animal models of type 1 and type 2 diabetes by delaying carbohydrate digestion and absorption, and enhancing insulin action.

JMA Hannan, L Ali, B Rokeya, J Khaleque, M Akhter, PR Flatt, and YHA Abdel-Wahab.
British Journal of Nutrition (Br J Nutr) 2007 97(3):514-521.

Fenugreek seeds (*Trigonella foenum-graecum*) have a long history of medical use in Ayurvedic and Chinese medicine. In India, they are used in cooking and are consumed by people suffering from diabetes. The antidiabetic effect of fenugreek seeds has been demonstrated in experimentally induced diabetes in dogs, rats, and mice. In this study, the antidiabetic properties of a soluble dietary fiber fraction of fenugreek seeds were evaluated in Long-Evans male rats made diabetic with streptozotocin. Administration of the fiber fraction (0.5 g/kg body weight) to normal, type 1 or type 2 diabetic rats improved oral glucose tolerance. Total remaining unabsorbed sucrose in the gastrointestinal tract following oral sucrose loading was increased with the fiber fraction. The fiber fraction suppressed the elevation of blood glucose after oral sucrose ingestion in both non-diabetic and type 2 diabetic rats. Intestinal disaccharidase activity and glucose absorption were decreased and gastrointestinal motility increased by the fiber fraction. Further, twice-daily oral administration of the fiber to type 2 diabetic rats for 28 days decreased serum glucose, increased liver glycogen content and enhanced total antioxidant status. Serum insulin and insulin secretion were not affected by the fiber fraction. These results indicate that the soluble dietary fiber fraction of fenugreek seeds exerts antidiabetic effects mediated through inhibition of carbohydrate digestion and absorption, and enhancement of peripheral insulin action. These findings are important and deserve further investigation as diabetes is one of the leading causes of death and disability worldwide.

Funding: University of Ulster Research Strategy Fund, Northern Ireland; and Biomedical Research Group, BIRDEM, Dhaka, Bangladesh.

Extract of *Salacia oblonga* lowers acute glycemia in patients with type 2 diabetes.

JA Williams, YS Choe, MJ Noss, CJ Baumgartner, and VA Mustad. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2007 86(1):124-130.**

According to surveys conducted by Centers for Disease Control and Prevention, an estimated 23.6 million people (7.8 percent) of the U.S. population had diabetes in 2007. The *Salacia* plant has been used as part of the traditional Ayurvedic system of Indian medicine to treat diseases such as diabetes. The aim of this randomized controlled trial was to evaluate the effect of a root extract of *Salacia oblonga* on blood glucose and insulin levels in individuals with type 2 diabetes after ingestion of a high-carbohydrate meal. In a fasted state, 82 individuals with diabetes received one of the following three meals: control (510 g chocolate Ensure) or control with 240 or 480 mg *Salacia oblonga* extract. Serum glucose and insulin samples were measured at baseline and at postprandial intervals up to 180 minutes. Compared to the control meal, both doses of the *Salacia* extract significantly lowered the postprandial positive area under the glucose curve (14 percent for 240 mg and 22 percent for 480 mg extracts), and the adjusted peak glucose response (19 percent for 240 mg and 27 percent for 480 mg extracts). In addition, both doses of the herbal extract decreased the postprandial insulin response, significantly lowering both the positive area under the insulin curve and the adjusted peak insulin response (14 percent and 9 percent, respectively, for the 240 mg and 19 percent and 12 percent, respectively, for the 480 mg extracts). The results from this study suggest that *Salacia* may be beneficial to individuals with type 2 diabetes for postprandial glucose control. These findings deserve further investigation, given the financial burden of diabetes in medical expenditures, disability, and lost productivity in the United States.

Funding: Abbott Laboratories, USA.

Hydrogen sulfide mediates the vasoactivity of garlic.

GA Benavides, GL Squadrito, RW Mills, HD Patel, TS Isbell, RP Patel, VM Darley-Usmar, JE Doeller, and DW Kraus. ***Proceedings of the National Academy of Sciences*** **(Proc Natl Acad Sci) 2007 104(46):17977-17982.**

Studies suggest that regular garlic intake is associated with reduction in the risk factors for cardiovascular disease, such as, high blood pressure, high cholesterol, platelet aggregation, and blood coagulation. However, the constituents in garlic and the mechanisms by which they confer such protection are not well understood. When garlic is crushed, allicin, the major organosulfur compound, is decomposed to organic polysulfides by the enzyme allinase. Through a series of *in vitro* experiments with human erythrocytes and isolated aorta segments from rats, it was shown that these polysulfides are metabolized and increase the production of hydrogen sulfide in blood vessels. Hydrogen sulfide is a cell-signaling molecule produced in vascular smooth muscle cells and erythrocytes that diffuses through plasma membranes and induces smooth muscle cell relaxation. In a series of studies, the vasoactivity of various garlic polysulfides was directly associated with their yields of hydrogen sulfide. These experiments provide a mechanism by which garlic works to lower cardiovascular risk. They also suggest that the potency of garlic supplements could be standardized based on their ability to produce hydrogen sulfide in relevant blood cells and tissues.

Funding: National Heart, Lung, and Blood Institute, NIH; and the American Heart Association.

Effect of raw garlic vs. commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: A randomized control trial.

Despite promising results from animal studies indicating that various garlic preparations have cholesterol-lowering effects, clinical trial evidence is inconsistent. Differences in the bioavailabilities of allicin among garlic preparations could explain the inconsistent findings. This study evaluated the effects of raw garlic and two commercially available supplements in 192 adults aged 30-65 years with low-density lipoprotein (LDL) cholesterol concentrations between 130 and 190 mg/dL. In this well-controlled feeding study, individuals were randomized to receive garlic in three forms equivalent to four-grams garlic clove: raw garlic cloves, a powdered garlic supplement (four Garlicin™ tablets), an aged garlic extract supplement (six Kyolic™ tablets), or a placebo six days a week for six months. This dosage was substantially higher than the manufacturers' recommended amounts. The stability of the commercial garlic preparations and formation of allicin were tested using recognized methodology. Although the study design and attention to quality of test materials exemplify botanical research methodology, neither the raw garlic nor the garlic supplements had clinically significant effects on plasma lipid concentrations in adults with moderate hypercholesterolemia.

Funding: National Center for Complementary and Alternative Medicine, National Center for Research Resources, and the Office of Dietary Supplements, NIH; and the National Science Foundation, USA.

CD Gardner, LD Lawson, E Block, LM Chatterjee, A Kiazand, RR Balise, and HC Kraemer. ***Archives of Internal Medicine*** **(Arch Intern Med) 2007 167(4):346-353.**

Activation of FOXO3a by the green tea polyphenol epigallocatechin-3-gallate induces estrogen receptor α expression reversing invasive phenotype of breast cancer cells.

Green tea is rich in the polyphenol epigallocatechin-3 gallate (EGCG), which has antioxidant properties. Many epidemiologic studies have shown an inverse association between green tea intake and breast cancer risk. Forkhead box O3a or FOXO3a is a human gene that triggers apoptosis through expression of genes necessary for cell death. In this study, researchers tested the hypothesis that activation of FOXO3a by EGCG plays an important role in the observed reversal of an invasive phenotype of breast cancer cells that are low in estrogen receptor α. Reduced estrogen receptor α activity in breast tumors is frequently associated with a switch from an epithelial architecture to induction of invasive growth. When tumor cells lose their polarized epithelial phenotype, they acquire an invasive phenotype and metastasize to other organs in the body. Using gene expression profiling, these researchers were able to show that EGCG treatment of a human epidermal growth factor receptor-driven mammary tumor cells alters the expression of key regulators in the epithelial to mesenchymal transition (EMT) pathway, reducing the invasive phenotype. Specifically, a set of genes that control cell-to-cell contact and generally inhibit tumorigenesis as well as the estrogen receptor α were up-regulated by EGCG, whereas the proinvasive snail gene, that is critical to mesoderm development in the embryo, was down-regulated. These results identify, for the first time, a role for FOXO3a in the inhibition of an invasive phenotype in breast cancer cells with active estrogen receptor α signaling and elucidate a novel mechanism whereby EGCG represses EMT of breast cancer cells. This study offers new molecular understanding of the observed anticarcinogenic effect of green tea.

Funding: National Institute of Environmental Health Sciences, NIH; and the Avon Foundation, USA.

K Belguise, S Guo, and GE Sonenshein. ***Cancer Research*** **(Cancer Res) 2007 67(12):5763-5770.**

Effectiveness of an early supplementation scheme of high-dose vitamin A versus standard WHO protocol in Gambian mothers and infants: A randomised controlled trial.

MK Darboe, DI Thurnham, G Morgan, RA Adegbola, O Secka, JA Solon, SJ Jackson, C Northrop-Clewes, TJ Fulford, CP Doherty, and AM Prentice. ***Lancet*** **(Lancet) 2007 369(9579): 2088–2096.**

Vitamin A deficiency is a major nutritional problem that threatens the survival and health of millions of children worldwide. The aim of this study was to compare the effectiveness of the 2002 International Vitamin A Consultative Group (IVACG) with the standard 1997 World Health Organization (WHO) protocols for maternal and infant plasma vitamin A. The WHO recommendation is 200,000 IU to mothers early postpartum, 100,000 IU to infants at nine months, and 200,000 IU to infants at four-six month intervals thereafter. The IVACG recommendation is a higher dosing schedule of two 200,000 IU doses to mothers early postpartum and 50,000 IU to infants at their 6-, 10-, and 14-week immunization visits. The study was conducted in rural Gambia with mothers who had moderate vitamin A deficiency and their infants. There were no adverse events at dosing. No differences were observed in the primary outcomes between IVACG and WHO protocols. Vitamin A status, measured by plasma retinol concentrations, improved during supplementation and was similar in the IVACG and WHO groups. Other scientists have raised concerns about the IVACG protocol that include potentially negative interactions on immunization vaccines and increased exposure to toxic vitamin A metabolites that may result in the generation of reactive oxygen species and increased oxidative stress. These observations do not support increasing existing WHO vitamin A dosing schedules in areas with moderate vitamin A deficiency.

Funding: Hoffman La Roche, Switzerland and BASF, Germany.

Effect of folic acid supplementation on hearing in older adults: A randomized controlled study.

J Durga, P Verhoef, LJC Anteunis, E Schouten, and FJ Kok. ***Annals of Internal Medicine*** **(Ann Intern Med) 2007 146(1):1-9.**

Elevated blood homocysteine levels are associated with increased risk of cardiovascular disease and have been hypothesized to also play a role in age-related hearing loss. Folic acid supplementations can reduce blood homocysteine levels but its effects on hearing loss are not clear. The Folic Acid and Carotid Intima-Media Thickness (FACIT) trial was a randomized controlled trial in the Netherlands involving 819 adults, 50 to 70 years of age. The primary goal was to determine if folic acid supplementation could slow atherosclerotic progression. Additional measurements were age-related decline in cognitive function and hearing. Individuals with homocysteine levels between 13 and 26 umol/L received either 800 mcg of folic acid or a placebo daily for three years. Hearing thresholds were assessed in both ears at low and high frequencies at baseline and at the end of the study. The difference in hearing loss between the two groups was small. Folic acid slowed the decline in hearing at the low frequencies by 0.7 dB, but did not affect hearing thresholds at the high frequencies. Subjects with low baseline folate status showed a stronger treatment effect. In another study published in 2007, 800 mcg folic acid taken for three-years improved performance on information-processing speed and memory in subjects with elevated homocysteine concentrations (J Durga et al., *Lancet* 2007 369(9557):208-216). These findings of a positive benefit of folic acid on hearing and cognition in the elderly are promising. However, as folic acid fortification was not mandatory in the Netherlands at the time of this study, baseline blood levels were about half of those found in the United States and thus limits extrapolation of the results to the United States.

Funding: Netherlands Organisation for Health Research and Development, Wageningen University and Wageningen Centre for Food Science, The Netherlands.

Folic acid supplementation lowers blood arsenic.

Arsenic-contaminated water, estimated to affect more than 100 million people worldwide, can increase risk for arsenic-induced illnesses, including some cancers. Inorganic arsenic detoxification via hepatic methylation to monomethylarsonic (MMAs) and dimethylarsinic (DMAs) acids, which are subsequently excreted in urine, requires folate. Marginal folate status and arsenic-contaminated drinking water are documented problems in areas of Bangladesh. The National Influences on Arsenic Toxicity (NIAT) study, in collaboration with the Health Effects of Arsenic Longitudinal Study, investigated effects of folic acid supplementation on blood arsenic levels. Adults in Bangladesh (n=130) were randomized to receive either 400 mcg folic acid or a placebo daily for 12 weeks. Changes in blood MMAs and blood and urine DMAs were the primary outcome measures. Consistent with a beneficial effect of folic acid supplementation on blood levels, MMAs were lowered and urinary DMAs were increased in the supplemented group compared to the placebo group. In addition, total blood arsenic was reduced by 13.6 percent in the supplemented group and by 2.5 percent in the placebo group. This study may provide an important contribution to the prevention of arsenic-induced illnesses in individuals with low folate status. It also has important public health implications in countries with high exposure to arsenic and poor folate nutriture. Additional research is necessary to understand the effects of varying doses and forms of folate on arsenic-induced illnesses.

Funding: National Institute of Environmental Health Sciences, NIH.

MV Gamble, X Liu, V Slavkovich, JR Pilsner, V Ilievski, P Factor-Litvak, D Levy, S Alam, M Islam, F Parvez, H Ahsan, and JH Graziano. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2007 86(4):1202-1209.**

Folic acid for the prevention of colorectal adenomas: A randomized clinical trial.

Although epidemiologic studies suggest diets higher in folate may help prevent colorectal polyps and cancer, the findings from clinical trials are less convincing. In the 1994-2004 Aspirin/Folate Polyp Prevention Study, 1021 participants with a history of colorectal lesions but not overt colon cancer were randomized to 1000 mcg folic acid or a placebo daily, with subsequent randomization to aspirin or placebo. The occurrence of at least one colorectal adenoma, advanced lesions, multiple adenomas, or adverse events were determined through colonoscopic examination at two intervals at three years (n=957) and at three to five years later (n=607). Folic acid supplementation did not reduce the risk of adenoma occurrence at either follow-up cycle. However, at the second follow-up, supplementation was associated with an increased risk for advanced lesions with the presence of three or more adenomas and with the presence of non-colorectal cancers, primarily prostate. This study raises the concern that folic acid supplementation may increase the risk for colorectal cancer in those with a history of adenomas and highlights the need for more research on how dose, duration, and timing of folic acid supplementation affects the growth of early lesions and tumors, including other forms of cancer.

Funding: National Cancer Institute, NIH; and Wyeth Consumer Health Care, USA.

BF Cole, JA Baron, RS Sandler, RW Haile, DJ Ahnen, RS Bresalier, G McKeown-Eyssen, RW Summers, RI Rothstein, CA Burke, DC Snover, TR Church, JI Allen, DJ Robertson, GJ Beck, JH Bond, T Byers, JS Mandel, LA Mott, LH Pearson, EL Barry, JR Rees, N Marcon, F Saibil, PM Ueland, and ER Greenberg for the Polyp Prevention Study Group. ***Journal of the American Medical Association*** **(JAMA) 2007 297(21): 2351-2359.**

Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: Report from the Women's Health Study.

RJ Glynn, PM Ridker, SZ Goldhaber, RY Zee, and JE Buring. ***Circulation*** **(Circulation) 2007 116(13):1497-1503.**

A secondary analysis of the Women's Health Study was conducted to evaluate whether vitamin E supplementation reduced the risk of venous thromboembolism. According to a 2008 U.S. Surgeon General's report, at least 100,000 deaths in the United States result from deep vein thrombosis and pulmonary embolism induced by venous thromboembolism. Women 45 years and older (n=39,876) were randomized to 600 IU vitamin E (α-tocopherol) or a placebo every other day. Genotyping for coagulation disorders (factor V Leiden, G20210A prothrombin, and 677C>T MTHFR polymorphisms) was completed for 26,779 participants. Documented cases of venous thromboembolism, including unprovoked venous thromboembolism (occurrence in absence of trauma, surgery, or malignancy) were the primary outcome measures. There were 482 cases (213 supplemented and 269 placebo) of venous thromboembolism. Vitamin E supplementation was associated with a 21 percent reduction of venous thromboembolism, a 27 percent reduction of unprovoked venous thromboembolism, and a 28 percent reduction of pulmonary embolism. In participants with a history of venous thromboembolism or with factor V Leiden or prothrombin mutation, supplementation was associated with a 40-49 percent risk reduction. Adverse coagulation effects, such as hemorrhagic stroke or hematuria (the presence of red blood cells in the urine), did not differ between groups. Although additional confirmation studies are needed, this study supports the benefits of vitamin E supplementation in the prevention of venous thromboembolism, especially in those with prior history or genetic predisposition.

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

Homocysteine-lowering therapy and risk of venous thromboembolism: A randomized trial.

JG Ray, C Kearon, Q Yi, P Sheridan, and E Lonn for the Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. ***Annals of Internal Medicine*** **(Ann Intern Med) 2007 146(11):761-767.**

Raised blood levels of homocysteine can damage the surface of arteries and veins promoting the formation of blood clots (thromboembolism). These clots can block blood flow and can cause pain, swelling, and skin discoloration. Supplementation with B-vitamins (folic acid, vitamin B_{12}, and vitamin B_6) has been shown to reduce blood homocysteine levels. The Heart Outcomes Prevention Evaluation 2 (HOPE-2) was a prospective randomized controlled trial involving 5522 adults from 13 countries with vascular disease or diabetes. Subjects received a B-vitamin supplement containing 2.5 mg folic acid, 50 mg vitamin B_6, and 1 mg vitamin B_{12} or a placebo for an average of five years. This secondary data analysis of the HOPE-2 study evaluated individuals at high risk for atherosclerosis. The primary outcome measure was symptomatic venous thromboembolism inducing deep venous thrombosis, pulmonary embolism, or both. There was no difference in the incidence of venous thromboembolism between the B-vitamin supplemented group vs. placebo, even though the B-vitamins lowered plasma homocysteine levels. Additionally, supplementation did not decrease venous thromboembolism in middle-aged or older adults independent of their demographic location, folic acid food fortification, or baseline plasma homocysteine levels. Findings from this study suggest that B-vitamin supplementation is not an effective regimen for the prevention of first or recurrent episodes of venous thromboembolism.

Funding: Canadian Institutes of Health Research and Jamieson Laboratories, Ontario, Canada.

Effect of supplemental dietary zinc on the mammalian target of rapamycin (mTOR) signaling pathway in skeletal muscle and liver from post-absorptive mice.

JP McClung, TN Tarr, BR Barnes, AG Scrimgeour, and AJ Young. *Biological Trace Element Research* **(Biol Trace Elem Res) 2007 118(1):65–76.**

Zinc is an essential trace element that functions in cellular signaling, including the initiation of protein synthesis, which occurs through the phosphorylation of proteins in the mammalian target of rapamycin (mTOR) signaling pathway. The stimulation of the mTOR pathway by nutrients and insulin has been characterized in cell culture models, although animal studies have not assessed the *in vivo* contribution of single nutrients, including zinc, in the molecular regulation of this pathway. As such, the objective of this study was to determine whether supplemental dietary zinc could stimulate phosphorylation of the mTOR pathway in an animal model. Thirty mice (C57BL/6J) were fed diets marginal in zinc (5 mg/kg) for four weeks, followed by fasting and/or refeeding with zinc-marginal or zinc-supplemented (300 mg/kg) diets for three or six hours. Multiplex analysis and traditional Western blotting techniques were used to determine protein phosphorylation in skeletal muscle and liver after fasting/refeeding. The results indicate that zinc supplementation may promote the phosphorylation of proteins implicated in mTOR signaling in both skeletal muscle and liver. The use of multiplex analysis coupled with Western blotting techniques represents a novel approach to the determination of protein phosphorylation levels in response to micronutrient supplementation in an animal model. Furthermore, the findings of this study indicate that the role of dietary zinc in growth and the accretion of lean body mass may occur through stimulation of the mTOR pathway.

Funding: US Army Medical Research and Materiel Command, Department of Defense.

Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: A randomized controlled trial.

BE Hurwitz, JR Klaus, MM Llabre, A Gonzalez, PJ Lawrence, KJ Maher, JM Greeson, MK Baum, G Shor-Posner, JS Skyler, and N Schneiderman. *Archives of Internal Medicine* **(Arch Intern Med) 2007 167(2):148-154.**

Immune dysfunction is observed in regions where the soil is selenium-deficient. Selenium deficiency is associated with human immunodeficiency virus (HIV) spectrum disease, but the effects of selenium supplementation on this disease are not known. The Miami Selenium for Heart and Immune Health Trial was a placebo-controlled trial consisting of a pretreatment phase followed by an 18-month treatment protocol. Of the 450 HIV-1 positive men and women who underwent screening, 174 completed the nine-month follow-up assessment; 91 received daily selenium supplements (200-mcg capsules of high-selenium yeast) and 83 a placebo. Demographic characteristics, including use of antiretroviral therapy, were not significantly different between treatment groups. After nine months of treatment, selenium supplementation significantly increased serum selenium concentrations compared with placebo. The increased selenium levels were associated with decreased HIV-1 viral loads, which were in turn associated with increased CD4 count, a measure of immunity. Selenium supplementation caused no adverse events. The results from this study suggest that selenium supplementation suppresses the progression of HIV-1 viral load and indirectly improves CD4 count in HIV-positive adults. The findings from this study suggest that selenium supplementation may be an inexpensive and safe adjunct therapy in HIV spectrum disease.

Funding: National Institute on Drug Abuse, National Center for Research Resources, National Heart, Lung, and Blood Institute, and National Institute of Mental Health, NIH; and Nutrition 21, USA.

Six months supplementation with conjugated linoleic acid induces regional-specific fat mass decreases in overweight and obese.

J-M Gaullier, J Halse, HO Høivik, K Høye, C Syvertsen, M Nurminiemi, C Hassfeld, A Einerhand, M O'Shea, and O Gudmundsen. ***British Journal of Nutrition*** **(Br J Nutr) 2007 97(3):550–560.**

Conjugated linoleic acid (CLA) is a collective term for the isomers of linoleic acid that have two conjugated double bonds. Research suggests that CLA may reduce body fat mass in humans. The cis-9,trans-11 CLA isomer is the primary form of CLA in dairy products. This study examined the effects of this isomer on regional fat distribution in overweight and obese adults (body mass index of 28-32 kg/m^2). Participants (n=118) were randomized to receive 3.4 grams CLA (a 1:1 mix of cis-9,trans-11 and trans-10,cis-12 isomers) or an olive oil placebo daily for six months; 84 women and 21 men were included in the main analysis. Body composition was determined by dual-energy X-ray absorptiometry. At six months, weight and lean body mass were similar between groups. However, body fat mass was significantly reduced with CLA (-1.0 kg) compared with placebo (-0.1 kg). Regionally, leg fat mass was significantly reduced by CLA compared with placebo (-0.5 kg vs. +0.3 kg), but arm and abdominal fat mass were not. Waist, hip, and waist-hip ratio were reduced with CLA, but not with the placebo. In subgroup analysis, leg fat mass reductions were significant for women (-1.3 kg), but not for men (-0.7 kg); however, the number of men was small. Body composition changes were independent of reported diet and physical activity. These findings suggest that CLA decreases fat mass in certain regions of the body and may have beneficial effects on lipid, inflammatory and diabetogenic biomarkers. Larger, long-term investigations into these effects and their implications are warranted.

Funding: Loders Croklaan, The Netherlands.

Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes.

JM Norris, X Yin, MM Lamb, K Barriga, J Seifert, M Hoffman, HD Orton, AE Barón, M Clare-Salzler, HP Chase, NJ Szabo, H Erlich, GS Eisenbarth, and M Rewers. ***Journal of the American Medical Association*** **(JAMA) 2007 298(12):1420-1428.**

Preliminary research supports the theory that omega-3 fatty acids may reduce the risk of type I diabetes in children. Type 1 diabetes is an autoimmune disease in which the insulin-producing pancreatic cells are destroyed. The objective of the Diabetes Autoimmunity Study in the Young (DAISY) was to determine if the intake of omega-3 and omega-6 fatty acids was associated with the development of islet autoimmunity in children. DAISY tracked two groups of young patients at risk for diabetes: one group consisted of unaffected first-degree relatives of individuals with type 1 diabetes, and the other consisted of children determined to be at genetic risk for diabetes. Between 1994 and 2006, 1770 children (≤ 8 years) were identified as at risk for type 1 diabetes. With an average follow-up of 6.2 years, 58 of the 1770 children, or 3.3 percent, developed diabetes. After adjusting for risk of inheriting the disease (HLA genotype), family history, caloric intake, and total omega-6 fatty acid intake, omega-3 fatty acid intake was inversely associated with a 55 percent reduced risk for developing islet autoimmunity. Omega-6 intake was not associated with a reduction in risk. In an analysis of fatty acid content of erythrocyte membranes from 244 children, omega-3 fatty acid content was inversely associated with the risk of developing islet autoimmunity. Overall, these findings suggest that consumption of omega-3 fatty acids during childhood may decrease the risk of islet autoimmunity. A current NIH-funded study, Nutritional Intervention to Prevent Type 1 Diabetes, will determine if supplementation with omega-3 fatty acids during the last trimester of a mother's pregnancy and/or the first three years of life for children who are at higher risk of type 1 diabetes will prevent the development of islet autoimmunity. The outcome from this trial could help determine if a supplementation protocol for children at risk for type 1 diabetes is warranted.

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

Cardiac proinflammatory pathways are altered with different dietary n-6 linoleic to n-3 α-linoleic acid ratios in normal, fat-fed pigs.

S Ghosh, EM Novak, and SM Innis. ***American Journal of Physiology and Heart Circulation Physiology*** **(Am J Physiol Heart Circ Physiol) 2007 293(5):H2919-H2927.**

Dietary fatty acids play a key role in modulating the risk factors for cardiovascular disease. This study sought to evaluate the interactions between dietary fatty acids and inflammatory and oxidative stress biomarkers to understand the role of fatty acids on initiating or preventing cardiovascular disease. Piglets from postnatal day one to 30 were fed one of three diets that contained as a percentage of energy: 1) low linoleic acid (n-6) (1.2 percent) plus low α-linolenic acid (n-3) (0.06 percent), 2) low linoleic acid (1.4 percent) plus high α-linolenic acid (1.2 percent), and 3) high linoleic acid (11.6 percent) and high α-linolenic acid (1.2 percent). These experimental diets were designed to mimic total fat content and diets typically consumed by humans, but differing in n-6 and n-3 polyunsaturated fatty acids. Membrane phospholipid fatty acids, proinflammatory enzymes, and measures of nitrosative stress and lipid peroxidation were determined in the pig hearts. The diet high in both linoleic acid and α-linolenic acid significantly increased indicators of cardiac oxidative stress, including nitrotyrosine levels. Lowering the dietary linoleic acid to α-linolenic acid ratio closer to 1:1 decreased proinflammatory enzyme activation and reduced lipid peroxidation and nitrotyrosine production in the heart. These findings suggest that diets differing in ratios of linoleic acid to α-linolenic acid influence cardiac proinflammatory pathways and that the cardiovascular benefits of dietary α-linolenic acid is only achieved when dietary linoleic acid is low.

Funding: Canadian Institute for Heart Research and Bristol Myers Squibb Foundation Award.

α-Lipoic acid attenuates LPS-induced inflammatory responses by activating the phosphoinositide 3-kinase/Akt signaling pathway.

WJ Zhang, H Wei, T Hagen, and B Frei. ***Proceedings of the National Academy of Sciences*** **(PNAS) 2007 104(10):4077-4082.**

Acute inflammation triggers an immunological response resulting in the release of proinflammatory mediators that cause endothelial injury and dysfunction of blood vessel walls. Oxidative stress often accompanies these inflammatory changes; however, intracellular antioxidants, such as α-lipoic acid, may slow the response of endothelial cells to this stress. In a series of studies, the investigators sought to identify the mechanisms and signaling pathways by which α-lipoic acid reduces monocyte white blood cell activation and acute inflammatory response induced by the bacterial endotoxin, lipoprotein polysaccharide. Results indicated that α-lipoic acid activates the P13K/Akt cell-signaling pathway. The P13K/Akt pathway is a family of enzymes that are involved in regulating cell division and cell death. In addition, P13K plays a critical role in inhibiting lipoprotein polysaccharide-induced inflammation by partially inhibiting pathways that turn on proinflammatory mediators in monocytes. Alpha-lipoic acid improved survival of septic mice and inhibition of P13K with a known inhibitor, which blocked the protective effect of α-lipoic acid. Given these findings, the authors concluded that α-lipoic acid might be helpful in the prevention of sepsis and inflammatory vascular diseases.

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

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis.

M Yokoyama, H Origasa, M Matsuzaki, Y Matsuzawa, Y Saito, Y Ishikawa, S Oikawa, J Sasaki, H Hishida, H Itakura, T Kita, A Kitabatake, N Nakaya, T Sakata, K Shimada, K Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators. ***Lancet*** **(Lancet) 2007 369(9567):1090-1098.**

Research suggests that consumption of omega-3 fatty acids from fish or supplemental fish oils can protect against coronary heart disease (CHD) and reduce the risk of cardiovascular mortality; however, large-scale studies, particularly those using supplemental fish oil have been lacking. Eicosapentaenoic acid (EPA) is the precursor of anti-inflammatory eicosanoids and is the primary omega-3 fatty acid in cold-water fatty fish. In this large randomized study, 5859 men and 12,786 postmenopausal women in Japan with high cholesterol levels, and either with CHD (secondary prevention) or without CHD (primary prevention), received 600 mg EPA ethyl ester three times/day after meals plus statins (a cholesterol-lowering drug) or statins only. The primary endpoint was any major adverse coronary event; secondary endpoints included all-cause mortality, stroke, peripheral artery disease, and cancer. After 4.6 years there was a 19 percent significant reduction in major adverse coronary events in the EPA-treated individuals; however, this effect was only significant in those with CHD. EPA had no significant effects on coronary death or myocardial infarction. Both groups experienced a 25 percent reduction in LDL-cholesterol, while triglyceride levels were reduced significantly more in the EPA group than in the statins-only group (nine percent vs. four percent). As there was no difference in LDL- or HDL-cholesterol levels between the two groups during follow-up, the benefits associated with EPA treatment, beyond statin therapy alone, appear to be mediated through cholesterol-independent mechanisms. There were more, but mostly mild, adverse events in the EPA group. For individuals with diets high in natural sources of EPA, supplemental high-dose EPA resulted in a reduction in non-fatal coronary events, but had no effect on cardiac death. Because Japanese diets are high in fish, the benefit of supplemental EPA might not be as evident as in countries where less fish is eaten.

Funding: Mochida Pharmaceutical Co. Ltd, Tokyo, Japan.

L-arginine supplementation in peripheral arterial disease: No benefit and possible harm.

AM Wilson, R Harada, N Nair, N Balasubramanian, and JP Cooke. ***Circulation*** **(Circ) 2007 116(2):188-195.**

Supplementation with L-arginine has been shown to have beneficial effects by improving vasodilation and increasing vascular nitric oxide synthesis in animal models of cardiovascular disease and in subjects with peripheral arterial disease. The Nitric Oxide in Peripheral Arterial Insufficiency (NO-PAIN) randomized clinical trial tested the benefits and safety of L-arginine in 133 patients with intermittent claudication, a symptom of peripheral arterial disease. Because atherosclerosis decreases blood supply to the legs, people with intermittent claudication experience leg or calf pain after walking a certain distance. After baseline testing, individuals received either L-arginine (three g/day) or a placebo for six months. The primary outcome measure was walking distance as assessed by the Skinner-Gardner treadmill protocol. Secondary outcome measures were nitric oxide availability, including flow-mediated vasodilation, vascular compliance, plasma and urinary nitrogen oxides, and plasma citrulline formation. L-arginine supplementation increased plasma L-arginine levels but did not reduce or improve measures of nitric oxide availability. Although absolute claudication distance (onset of maximal walking distance) improved in both L-arginine and placebo-treated patients, absolute claudication distance was actually worsened in the L-arginine group compared to placebo. The authors speculate that the long-term administration of L-arginine may partially explain these negative findings, given that short-term L-arginine administration has shown beneficial effects in other trials. Basic mechanistic research may be necessary to explain the differences in findings between short and long-term administration L-arginine in regulating nitric oxide production.

Funding: National Heart, Lung, and Blood Institute, NIH; and Ajinomoto Inc.

Inhibition of tumorigenesis in $Apc^{Min/+}$ mice by a combination of (–)-epigallocatechin-3-gallate and fish oil.

M Bose, X Hao, J Ju, A Husain, S Park, JD Lambert, and CS Yang. *Journal of Agricultural and Food Chemistry* (J Agric Food Chem) 2007 55(19):7695-7700.

Studies suggest that consumption of green tea polyphenols and omega-3 fatty acids may reduce colon cancer risk. In a series of experiments, the effects of epigallocatechin-3-gallate (EGCG) and fish (menhaden) oil alone and in combination on intestinal tumorigenesis were tested in mice ($Apc^{Min/+}$) fed a high-fat diet. The control high-fat diet was formulated to represent the fat composition of the average American diet. The fish oil contained about 1.7 percent α-linolenic acid, 13 percent eicosapentaenoic acid (EPA), and 12 percent docosahexaenoic acid (DHA). EGCG was given at 0.16 percent concentration in drinking water. Compared with controls, EGCG combined with fish oil reduced the number of tumors by 53 percent; however, EGCG or fish oil alone had no effect. There was a decrease in cell proliferation in the EGCG group and the combination group, but not in the fish oil alone group. Apoptosis (programmed cell death) was increased in all treatment groups. EGCG combined with fish oil, but not alone, inhibited tumor formation and size in mice fed a high-fat diet. These results indicate that a combination of EGCG and fish oil can inhibit tumor multiplicity in mice. The dose of EGCG used in these studies corresponds to five or six cups of green tea a day. Although the dose of fish oil used in the present study converts to a rather high daily intake of 16 grams omega-3, this dose of fish oil is the lowest reported dose that has been shown to inhibit intestinal tumorigenesis in animals. Future studies are needed to determine whether lower doses of fish oil, appropriate for human intake, are also effective against tumorigenesis.

Funding: National Cancer Institute, NIH; and New Jersey Commission for Cancer Research, USA.

Calcium and vitamin D intake and risk of colorectal cancer: The multiethnic cohort study.

SY Park, SP Murphy, LR Wilkens, AM Nomura, BE Henderson, and LN Kolonel. *American Journal of Epidemiology* (Am J Epidemiol) 2007 165(7):784-793.

Although vitamin D and calcium have been proposed to reduce colorectal cancer risk, the results from observational studies and clinical trials are inconclusive. This large, multiethnic cohort study examined associations between intakes of calcium and vitamin D from food and supplements and colorectal cancer risk in 85,903 men and 105,108 women, 45 to 75 years of age, living in Hawaii and California. Between 1993 and 1996, subjects completed a detailed quantitative food frequency questionnaire that included questions on vitamin and mineral supplement use. During an average follow-up period of 7.3 years, 2110 incident cases of colorectal cancer were identified. Total calcium intake from food and supplements was inversely associated with colorectal cancer risk in both men and women. Compared with those in the lowest quartile of calcium intake (<288 mg/1000 kcal/day), men and women in the highest quartile (≥611 mg/1000 kcal/day) had a 30 percent and 36 percent lower risk of developing colorectal cancer, respectively. Total vitamin D intake was inversely associated with risk of colorectal cancer in men, but not in women. Men in the highest quartile of vitamin D intake (≥276 IU/1000 kcal/day) had a 28 percent lower risk of developing colorectal cancer compared with men in the lowest quartile of intake (<39 IU/1000 kcal/day). These observational data support protective roles of calcium and vitamin D in reducing colorectal cancer risk.

Funding: National Cancer Institute, NIH.

Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial.

JM Lappe, D Travers-Gustafson, KM Davies, RR Recker, and RP Heaney. ***American Journal of Clinical Nutrition*** **(Am J Clin Nutr) 2007 85(6):1586-1591.**

Animal and observational data suggest that vitamin D status could affect cancer risk, but supporting clinical trial data are lacking. In this four-year, population-based, randomized, controlled clinical trial, the effects of calcium and vitamin D supplementation were examined in 1179 postmenopausal women over 55 years of age living in a rural area of Nebraska. The primary outcome was fracture incidence and the secondary outcome was all-cancers incidence. Individuals were randomly assigned to one of three supplement combinations daily: 1) 1400 mg calcium as calcium citrate or 1500 mg calcium as calcium carbonate and vitamin D placebo; 2) calcium and 1000 IU vitamin D3; or 3) calcium and vitamin D placebo tablets. Measures of calcium and vitamin D status were determined in blood samples at baseline and annually. During the course of the study, 50 women developed cancers at various sites. Overall, women in the calcium and vitamin D group had a 60 percent lower risk of developing all cancers than those in the placebo group. When cancers diagnosed during the first year of the study were not included (in an attempt to exclude cancers that were present but undetected on entry), women in the calcium and vitamin D group had a 77 percent lower risk of developing cancer than those in the placebo group. Vitamin D and serum 25-hydroxy vitamin D (a measure of vitamin D status) were independent predictors of cancer. Women receiving calcium only had somewhat lower risk of cancer compared with the placebo group, but this effect did not reach statistical significance. The results from this study suggest that increasing the intake of vitamin D, alone and with calcium, significantly reduces cancer risk in postmenopausal women. However, these findings should be viewed as preliminary as the study was not powered to answer the question of whether or not vitamin D reduces all-cancer risk.

Funding: National Institute on Aging, NIH.

A randomized factorial trial of vitamins C and E and beta-carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study.

NR Cook, CM Albert, JM Gaziano, E Zaharris, J MacFadyen, E Danielson, JE Buring, and JE Manson. ***Archives of Internal Medicine*** **(Arch Intern Med) 2007 167(15):1610-1618.**

Although observational studies associate diets rich in antioxidant food components from fruits and vegetables with reduced risk for cardiovascular disease, the findings from intervention trials are inconsistent, tending to show a lack of benefit. In the Women's Antioxidant Cardiovascular Study, the independent effects and interactions between vitamin C (500 mg ascorbic acid), vitamin E (600 IU *d*-α tocopherol acetate), and beta-carotene (560 mg) on cardiovascular disease were examined in 8171 female health professionals over 10 years. Women enrolled were 40 years or older with three risk factors for cardiovascular disease. A total of 1450 women experienced one or more cardiovascular disease outcomes. There were no combined or independent effects of vitamin C, vitamin E, or beta-carotene on the primary combined endpoint of vascular disease or on the individual secondary outcomes of myocardial infarction, stroke, coronary revascularization, or death from cardiovascular disease. However, there were fewer observed strokes among those taking vitamin C and vitamin E. Overall, there was no observed benefit or harm from the antioxidants tested alone or in combination. This study does not support the regular use of antioxidants in reducing the risk of cardiovascular disease outcomes among women with risk factors for cardiovascular disease.

Funding: National Heart, Lung, and Blood Institute, NIH; Cognis Corporation; and BASF Corporation.

Multivitamin supplementation improves hematologic status in HIV-infected women and their children in Tanzania.

WW Fawzi, GI Msamanga, R Kupka, D Spiegelman, E Villamor, F Mugusi, R Wei, and D Hunter.
American Journal of Clinical Nutrition **(Am J Clin Nutr) 2007 85(5):1335-1343.**

Anemia, which is common during pregnancy, is a frequent complication of HIV infection and leads to more rapid disease progression and mortality. In this randomized clinical trial, investigators examined the effects of multivitamin supplementation on hemoglobin concentrations and risk of anemia in 1078 HIV-infected pregnant women living in Tanzania. Women (mean age 24.7 years, 20.3 weeks gestation) were randomly assigned to one of four daily treatments: 1) 30 mg beta-carotene and 5000 IU vitamin A; 2) multivitamins with no beta-carotene or vitamin A; 3) multivitamins and 30 mg beta-carotene and 5000 IU vitamin A; and 4) placebo. The multivitamin contained 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 0.8 mg folic acid, 25 mg vitamin B_6, 50 mcg vitamin B_{12}, 500 mg vitamin C, and 30 mg vitamin E. All women also received antenatal supplements of 120 mg iron and 5 mg folic acid. During the first two years after enrollment, women who received multivitamins only had hemoglobin concentrations 0.59 g/dL higher than women receiving the placebo. No treatment significantly affected the risk of maternal anemia. Children of women receiving multivitamins had hemoglobin concentrations 0.18 g/dL higher and reduced risk of anemia, including a 40 percent lower risk of severe iron-deficiency anemia than children of mothers who did not receive multivitamins. Results from a similar trial involving HIV-negative pregnant women in Tanzania indicated that multivitamin supplementation significantly reduced the risks of low birth weight and small for gestational age births, but not prematurity or fetal death (WW Fawzi et al., *N Engl J Med* 2007 356(14):1423-1431). Collectively, these findings indicate that multivitamin supplementation improves hematologic status and some perinatal outcomes among pregnant, HIV-infected women and their children in Tanzania. Multivitamin supplementation for pregnant women in developing countries could significantly benefit maternal and child health.

Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.

Research papers cited in this bibliography may be obtained from public, university, or medical libraries such as the National Library of Medicine (web address: http://www.nlm.nih.gov/). The International Bibliographic Information on Dietary Supplements (IBIDS) database is an additional resource for bibliographic citations and abstracts from published, national and international, scientific literature on dietary supplements (web address: http://ods.od.nih.gov/Health_Information/IBIDS.aspx). The Office of Dietary Supplements produces IBIDS.

APPENDIX

Citations of papers that appeared in the *2006 Annual Bibliography of Significant Advances in Dietary Supplement Research*

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.

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***Lactobacillus paracasei* strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh.** SA Sarker, S Sultana, GJ Fuchs, NH Alam, T Azim, H Brüssow, and L Hammarström. *Pediatrics* (Pediatrics) 2005 116:e221-e228.

Acknowledgements

2007 List of Journals and Journal Editors

The following is a list of peer-reviewed journals containing the 223 research papers that were sent for external review. The journal chief editors who assisted with the selection of papers from their respective journals are bolded and italicized. The Office of Dietary Supplements especially thanks these journal chief editors for their contribution to this project. A complete list of the 83 journals is available on request.

- **American Journal of Cardiology,** William C Roberts, MD
- **American Journal of Clinical Nutrition,** ***Dennis M Bier, MD***, *editor-in-chief* and ***D'Ann Finley, PhD,*** *assistant editor*
- **American Journal of Epidemiology,** Moyses Szklo, MD, DrPH
- **American Journal of Physiology–Heart and Circulatory Physiology,** Alberto Nasjletti, MD
- **Annals of Internal Medicine,** Harold C Sox, MD
- **Archives of Internal Medicine,** Philip Greenland, MD
- **Archives of Neurology,** Roger N Rosenberg, MD
- **Asia Pacific Journal of Clinical Nutrition,** Mark Wahlqvist, MD
- **Atherosclerosis,** Prof Steve Humphries
- **Biological-Trace-Element-Research,** Gerhard N Schrauzer, PhD
- **British Journal of Nutrition,** ***Prof Philip Calder***
- **British Medical Journal,** Fiona Godlee, MD
- **Canadian Medical Association Journal,** Paul C Hebert, MD, MHSc
- **Cancer Research,** Frank J Rauscher III, PhD
- **Cancer, Epidemiology, Biomarkers & Prevention,** Timothy R Rebbeck, PhD
- **Circulation,** Joseph Loscalzo, MD, PhD
- **Clinical Pharmacology & Therapeutics,** Scott Waldman, MD, PhD
- **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,** Dr Shiv Prakash
- **International Journal of Sports Nutrition & Exercise Metabolism,** *Co-Editors:* Emily M Haymes, Ronald J Maughan, Louise Burke
- **Journal of Agricultural and Food Chemistry,** James N Seiber, PhD
- **Journal of Alternative and Complementary Medicine,** Kim A Jobst, MA, DM
- **Journal of Clinical Endocrinology & Metabolism,** Paul W Ladenson, MD
- **Journal of Nutrition,** ***A Catherine Ross, PhD***
- **Journal of the American College of Nutrition,** John J Cunningham, PhD
- **Journal of the American Dietetic Association,** Linda Van Horn, PhD, RD
- **Journal of the American Medical Association,** Catherine D DeAngelis, MD, MPH
- **Journal of the National Cancer Institute,** Barnett S Kramer, MD, MPH
- **The Lancet,** Richard Horton, MB
- **Maturitas,** Peter Kenemans, MD, PhD
- **Medicine and Science in Sports and Exercise,** Andrew J Young, PhD
- **Menopause,** Isaac Schiff, MD
- **Metabolism,** James B Field, MD
- **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, PhD (*Co-Editors:* Norman R Farnsworth, Yoshinori Asakawa, Gudrun Ulrich-Merzenich, Dennis VC Awang)
- **Phytotherapy Research,** Elizabeth M Williamson, PhD
- **Proceedings of National Academy of Sciences,** Randy Schekman, PhD
- **Science,** Bruce Alberts, PhD

2007 External Team of Scientific Reviewers

The Office of Dietary Supplements thanks the following scientists, who were selected based on their scientific expertise, for their time in reviewing, scoring, and providing valuable comments on the nominated papers.

- **Sanjiv Agarwal, PhD,** Sara Lee: Food and Beverage, Downers Grove, Illinois
- **Wendy Applequist, PhD,** Missouri Botanical Garden, St Louis, Missouri
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- **Adrianne Bendich, PhD,** GlaxoSmithKline, Parsippany, New Jersey
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Special recognition is due to the following individuals with the National Institutes of Health and the U.S. Department of Agriculture for helping to bring this project to fruition.

With the Office of Dietary Supplements, *Cindy Lentino, BA* for her exemplary efforts in administrating this project; *Carol Haggans, MS, RD, Joyce Merkel, MS, RD, Paul Thomas, EdD, RD*, and *Lora Wilder, ScD, RD* for their assistance in abstracting the nominated papers; and *Donna Allen* and *Leslie Johnson* for their support staff assistance. With the U.S. Department of Agriculture, *Andrea Lindsey, MS* at the National Agricultural Library for the literature searches to identify papers published in scientific journals on dietary supplements. With the National Institutes of Health, *Jean Pennington, PhD, RD* Division of Nutrition Research Coordination for her editorial review; *Claudia Faigen, BS* Office of Dietary Supplements, *Jan Ehrman, BS* Office of Communications and Public Liaison, and *Kelli Marciel, MA* Office of Medical Applications of Research for their assistance with the approvals and promotion of this publication.

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

NIH Publication No. 08-6456
September 2008