

# Annual Bibliography of Significant Advances in Dietary Supplement Research **1999**

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



# Annual Bibliography of Significant Advances in Dietary Supplement Research 1999

We are proud to bring you the first issue of the *Annual Bibliography of Significant Advances in Dietary Supplement Research*. The purpose of this bibliography is to help develop an overall perspective on how the dietary supplement field is advancing through quality research, as well as to provide well-deserved peer recognition to investigators.

Today, dietary supplements are a multi-billion dollar industry in the United States. About half of the adult American population use these products. Consumers frequently cite general health maintenance – or “wellness” – and the desire to decrease susceptibility to health problems such as stress, colds, heart attacks, and cancer as motivating reasons for dietary supplement use. As more consumers use these products to “feel better,” the work performed by researchers contributing to the science on dietary supplements becomes ever more important and noteworthy.

To develop this bibliography, we asked editors of peer-reviewed journals to nominate “flagship” original research papers that appeared in their respective journals in 1999. This request resulted in over 200 nominations, which then were forwarded to leading scientists in the United States for review to identify the top 25 scientific papers. These 25 papers were annotated by staff at the Office of Dietary Supplements and the Consumer Healthcare Products Association, and compiled into this bibliography. Please note this is a first edition and may not be all-encompassing. We welcome your suggestions for future editions.

This bibliography is a joint effort of the Office of Dietary Supplements at the National Institutes of Health and the Consumer Healthcare Products Association. Please contact either organization should you have questions regarding this project. The contact details are provided on the back cover of this publication.



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## Fortification with low amounts of folic acid makes a significant difference in folate status in young women: implications for the prevention of neural tube defects.

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It is well established that adequate folate intake during pregnancy protects against the occurrence of neural tube defects in infants. This study examined the effect of foods fortified with low amounts of folic acid (a synthetic form of folate) on folate status in 51 non-pregnant women (17 to 40 years). Changes in dietary folate intakes, and red blood cell and serum concentrations of folate were monitored in response to removing folic acid-fortified foods from the diet for 12 weeks. The investigators found that women who consumed folic acid-fortified food at least once a week had higher total folate intakes and higher concentrations of red blood cell folate compared with women who did not. Additionally, significant reductions in red blood cell folate concentrations were observed in response to removing folic acid-fortified foods from the diet. This study reinforces the need for women of childbearing age to consume folic acid-fortified foods regularly.

GJ Cuskelly, H McNulty, and JM Scott. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 1999 70:234-239.

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## The effect of folic acid fortification on plasma folate and total homocysteine concentrations.

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Adequate folate status through diet, fortified foods, or supplements has been associated with improved birth outcomes and reductions in blood levels of the amino acid homocysteine. High levels of homocysteine have been associated with an increased risk for cardiovascular disease. This study assessed the effect of B vitamin supplements among participants in the Framingham Offspring Study who were seen before and after implementation of the U.S. FDA's 1996 folic acid-fortification regulation. Exposure to folic acid-fortified foods significantly increased blood folate and reduced blood homocysteine concentrations. Although this apparent effect of folic acid fortification was striking, individuals who also took B vitamin supplements that contained folic acid demonstrated significantly higher blood concentrations of folate and significantly lower concentrations of homocysteine. There were no significant changes in the concentrations of folate and homocysteine in individuals who did not consume supplements or fortified foods. These findings suggest that among individuals exposed to folic acid-fortified foods there may be an added benefit of taking B vitamin supplements that contain folic acid, although this benefit has not been quantified.

PF Jacques, J Selhub, AG Bostom, PWF Wilson, and IH Rosenberg. *The New England Journal of Medicine* (N Engl J Med) 1999 340:1449-1454.

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## Antioxidant supplementation effects on low-density lipoprotein oxidation for individuals with type 2 diabetes mellitus.

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JW Anderson, MS Gowri, J Turner, L Nichols, VA Diwadkar, CK Chow, and PR Oeltgen. *Journal of the American College of Nutrition* (J Am Coll Nutr) 1999 18:451-461.

Oxidation of low-density lipoprotein (LDL) cholesterol is a risk factor for coronary heart disease. The effects of antioxidant supplementation on LDL oxidation were studied in 20 men with type 2 diabetes and 20 men without diabetes. The antioxidant supplement contained 24 mg of  $\beta$ -carotene, 1000 mg of ascorbate, and 800 IU of  $\alpha$ -tocopherol and was administered for 12 weeks. The extent of LDL oxidation, measured four different ways, was compared before and after treatment in these individuals. The results indicated that LDL from men with type 2 diabetes was more susceptible to oxidation than LDL from men without diabetes. In addition, antioxidant supplementation significantly decreased LDL oxidation in the diabetic men. The results of this study suggest that antioxidant supplementation may decrease the risk of coronary heart disease in men with type 2 diabetes.

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## Antioxidants, but not B-group vitamins, increase the resistance of low-density lipoprotein to oxidation: a randomized, factorial design, placebo-controlled trial.

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JV Woodside, IS Young, JWG Yarnell, HE Roxborough, D McMaster, EE McCrum, KF Gey, and A Evans. *Atherosclerosis* 1999 144:419-427.

Increased blood homocysteine levels and oxidation of low-density lipoprotein (LDL) cholesterol may play a significant role in coronary heart disease. The role of antioxidants in protecting LDL from oxidative damage and its clinical significance has received considerable attention. This study assessed the effects of antioxidants and B-group vitamins on the oxidation of LDL and plasma homocysteine levels. One hundred and thirty-two men who qualified to enter this eight-week trial received one of four treatments: B-group vitamins alone (1 mg folic acid, 7.2 mg B<sub>6</sub>, 0.02 mg B<sub>12</sub>), antioxidant vitamins (150 mg vitamin C, 67 mg  $\alpha$ -tocopherol, 9 mg  $\beta$ -carotene), B-group vitamins with antioxidant vitamins, or placebo. The study found that the lag time of LDL oxidative damage was increased in the two groups receiving the antioxidants, both with and without the B-group vitamins. While the B-group vitamins alone lowered plasma homocysteine levels, they had no effect on the susceptibility of LDL to oxidation. Further, homocysteine concentrations were not correlated with LDL lag time nor found to influence LDL oxidation. These results suggest that B-group vitamins and antioxidants appear to have separate and independent effects in reducing cardiovascular risk. While the measurement of oxidative processing of LDL is complicated, this study shows that the resistance of LDL to oxidation can be increased by supplementation with moderate doses of antioxidants.

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## Effect of long-term beta-carotene and vitamin A on serum cholesterol and triglyceride levels among participants in the Carotene and Retinol Efficacy Trial (CARET).

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CARET was a multicenter randomized cancer chemoprevention trial that evaluated the combined effects of supplemental  $\beta$ -carotene and vitamin A on the incidence of cancer and heart disease. CARET was halted when a 46 percent increase in lung cancer and 25 percent increase in cardiovascular deaths were observed in the supplemented group. The investigators conducted this analysis to evaluate reasons for these incidences of increased deaths in the CARET trial. Specifically, the effects of long-term supplementation with  $\beta$ -carotene and vitamin A on serum triglyceride and cholesterol lipoprotein levels were evaluated in 52 CARET participants during the five-year intervention period and the 10 months following termination of the trial. After a mean of five years on the intervention, there was a small but nonsignificant increase in serum triglyceride levels in the supplemented group and no difference in high-density lipoprotein (HDL) or low-density lipoprotein (LDL) levels. Once the intervention was stopped, triglyceride levels decreased but HDL and LDL levels remained unchanged. Although an increased incidence of cardiovascular deaths was observed in the CARET trial, this study suggests that this increase was not due to changes in serum lipid and lipoprotein levels. As this analysis was conducted in a subgroup of the CARET population, it is difficult to generalize the results to other groups. Additional research is needed to confirm the effects of long-term use of  $\beta$ -carotene and vitamin A on cardiovascular disease.

CA Redlich, JS Chung,  
MR Cullen, WS Blaner,  
AM Van Bennekum,  
and L Berglund.  
*Atherosclerosis* 1999  
143:427-434.

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## Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D.

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Blood levels of vitamin D are known to decline as part of the aging process. This study examined the effects of age on the absorption and metabolism of orally ingested vitamin D in men. Nine younger men (22 to 28 years) and nine older men (65 to 73 years) received either 1800 IU/day of vitamin D<sub>2</sub> or no supplement for three weeks. In both age groups, the supplemented men had higher plasma levels of the storage forms of vitamin D, 25-hydroxyvitamin D<sub>2</sub>, and total 25-hydroxyvitamin D compared to the men who did not receive vitamin D<sub>2</sub>. In addition, younger men who received supplements of vitamin D<sub>2</sub> had higher plasma levels of 25-hydroxyvitamin D<sub>2</sub> and total 25-hydroxyvitamin D than older men who received supplements. The results of this study suggest that the absorption or metabolism of orally ingested vitamin D declines with age. Therefore, vitamin D requirements for older men may be higher than those for younger men.

SS Harris, B Dawson-  
Hughes, and GA  
Perrone. *Journal of the  
American College of  
Nutrition* (J Am Coll  
Nutr) 1999 18:470-474.

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## Moderate supplementation with natural $\alpha$ -tocopherol decreases platelet aggregation and low-density lipoprotein oxidation.

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L Mabile, KR  
Bruckdorfer, and  
C Rice-Evans.  
*Atherosclerosis* 1999  
147:177-185.

Increased blood platelet activity and oxidation of low-density lipoprotein (LDL) cholesterol are risk factors for cardiovascular disease. In this study, the effects of supplementation with oral  $\alpha$ -tocopherol (vitamin E) on the above parameters were examined in 22 healthy, non-smoking men and women between the ages of 23 and 50. All subjects received  $\alpha$ -tocopherol supplements at the following doses for three consecutive two-week periods: 75 IU/day, 200 IU/day, and 400 IU/day. Supplementation with 75 IU  $\alpha$ -tocopherol for two weeks resulted in a significant decrease in platelet activity and moderate protection of LDL against oxidation. The higher doses of  $\alpha$ -tocopherol gradually increased these protective effects. These findings suggest that daily supplementation with as little as 75 IU  $\alpha$ -tocopherol may be protective against cardiovascular disease.

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## Vitamin E improves arterial compliance in middle-aged men and women.

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P Mottram, H Shige, and  
P Nestel. *Atherosclerosis*  
1999 145:99-404.

One of the emerging risk factors for cardiovascular disease is loss of elasticity in large arteries. The effect of 400 IU vitamin E on arterial elasticity was examined in 28 men and women between the ages of 43 and 69. Arterial elasticity was significantly increased in the group receiving the vitamin E supplements for eight weeks compared to the group that did not receive these supplements. These findings suggest that short-term vitamin E supplementation may have beneficial effects on arterial elasticity that may in turn reduce the risk for cardiovascular disease.

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## Effect of dietary supplementation with black currant seed oil on the immune response of healthy elderly subjects.

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A decline in immune function with age is well documented. Nutritional supplements, such as certain fats, can alter the fatty acid composition of cell membranes, thereby modifying the immune response of cells. This study tested whether black currant seed oil rich in  $\gamma$ -linolenic and  $\alpha$ -linolenic acids, can improve the immune response in healthy elderly individuals. Compared with individuals given soybean oil, individuals given black currant seed oil experienced a moderate immune-enhancing effect attributable to reduced prostaglandin E<sub>2</sub> production. Although the researchers hypothesized that black current seed oil exerts its effect by altering cell membrane fluidity, this effect was not observed. This study concludes that black currant seed oil did not adversely affect the immune response of healthy elderly subjects and may have a moderate immune-enhancing effect.

D Wu, M Meydani, L Leka, Z Nightingale, GJ Handelman, JB Blumberg, and SN Meydani. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 1999 70:536-543.

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## Conjugated linoleic acid-enriched butter fat alters mammary gland morphogenesis and reduces cancer risk in rats.

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Conjugated linoleic acid (CLA) found naturally in some animal fats has been shown to be a cancer preventive agent in animal models. This study determined whether butter fat with higher levels of CLA, produced by adding sunflower oil to the diets of Holstein cows, has the same biological activity as synthetically prepared CLA. In rats fed the CLA butter fat during pubescent mammary gland development, there was a decrease in the rate of morphologic maturation of the mammary epithelial tissue; this in turn reduced the risk of mammary cancer. This result was similar to those observed in rats fed the synthetic CLA. However, rats fed CLA butter fat accumulated more CLA in their tissues. The authors note this is the first time that a naturally occurring conjugated linoleic acid in a food form has been shown to have biological activity.

C Ip, S Banni, E Angioni, G Carta, J McGinley, HJ Thompson, D Barbano, and D Bauman. *Journal of Nutrition* (J Nutr) 1999 129:2135-2142.



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## Dietary conjugated linoleic acid influences the immune response of young and old C57BL/6NCrIBR mice.

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MG Hayek, SN Han,  
D Wu, BA Watkins,  
M Meydani, JL Dorsey,  
DE Smith, and  
SN Meydani. *Journal of  
Nutrition (J Nutr)* 1999  
129:32-38.

The aging process is associated with altered regulation of the immune system. Conjugated linoleic acid (CLA), a naturally occurring substance in foods, is hypothesized to have an impact on the immune response during aging. This study examined whether supplementation with CLA would enhance the immune response in aged mice. Forty young and 40 old mice consumed diets containing zero or one gram of CLA per 100 grams for eight weeks. The authors found that CLA enhanced T cell function *in vitro* (in cell culture) but had no effect on T cell-mediated function *in vivo* (within the animal). The immunostimulatory effect was more pronounced in younger versus older mice, and was not mediated through a change in prostaglandin E<sub>2</sub> or interleukin-2 production. Although this study suggests that CLA may have beneficial effects on the immune system, further research is needed to determine its mechanism of action on specific immune parameters.

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## Fish oil supplementation prevents diabetes-induced nerve conduction velocity and neuroanatomical changes in rats.

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A Gerbi, J-M Maixent,  
J-L Ansaldi, M Pierlovisi,  
T Coste, J-F Pelissier,  
P Vague, and D Raccah.  
*Journal of Nutrition (J  
Nutr)* 1999 129:207-213.

Diabetic neuropathy is a serious and common complication of diabetes, a disease that affects over 16 million Americans. Diabetic neuropathy has been associated with a decrease in nerve conduction velocity, enzyme activity, and damage of the sciatic nerve. This eight-week study evaluated the effect of fish oil supplementation on nerve conduction velocity and neuroanatomical lesions in diabetic rats. Diabetic animals were fed a non-purified diet supplemented with either olive oil or fish oil and were compared to a control group. Nerve conduction velocity as well as enzyme (Na, K-ATPase) activity were improved with the fish oil treatment. Fish oil also had a preventative effect on nerve histological damage. These results show a beneficial effect of fish oil supplementation on diabetes-induced abnormalities of the sciatic nerve and suggest fish oil may be effective in the prevention of diabetic neuropathy.

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## Long-term effects of fish oil on lipoprotein subfractions and low-density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyceridemia.

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Non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes) is frequently associated with abnormal triglyceride metabolism leading to an increase in small dense low-density lipoprotein (LDL) cholesterol. This abnormality may explain the higher cardiovascular risk in these patients. The effects of long-term fish oil supplementation on very low-density lipoprotein (VLDL), LDL subfractions, and LDL particle size were evaluated in 16 NIDDM patients with hypertriglyceridemia for six months. LDL particle size and three VLDL and LDL subfractions were measured at various time points during the study. The study found that fish oil did not induce a significant change in either VLDL subfraction distribution or composition. Fish oil supplementation did produce a significant reduction (approximately 45 percent) in triglycerides with no significant change in either the distribution of LDL sub-fractions or LDL particle size. This study indicates for the first time that fish oil is effective in lowering total VLDL without altering the distribution of the VLDL subfraction. These findings suggest that fish oil supplements may be of benefit to NIDDM patients with hypertriglyceridemia.

L Patti, A Maffettone,  
C Lovine, L Di Marino,  
G Annuzzi, G Riccardi,  
and AA Rivellesse.  
*Atherosclerosis* 1999  
146:361-367.

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### MINERALS

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## Calcium supplements for the prevention of colorectal adenomas.

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There is currently a lack of scientific agreement about the association between the intake of dairy products, calcium, and the risk of colorectal cancer. This clinical trial evaluated the effect of calcium supplementation on the recurrence of colorectal adenomas in 930 men and women. These individuals received either 1200 mg of calcium (as calcium carbonate) or placebo. Follow-up colonoscopy procedures were conducted at one and four years. The study found that the calcium-supplemented subjects had a significantly lower risk of recurrent adenomas, and that this result was not affected by the baseline intakes of either dietary fat or calcium. These results suggest that calcium supplementation may have chemopreventive activity against colorectal cancers. While these findings are consistent with many epidemiological and experimental studies, additional research is needed before public health recommendations are made on the use of calcium as a colorectal cancer preventative agent.

JA Baron, M Beach, JS  
Mandel, RU van Stolk,  
RW Haile, RS Sandler, R  
Rothstein, RW Summers,  
DC Snover, GJ Beck, JH  
Bond, and ER Greenberg,  
for the Calcium Polyp  
Prevention Study Group.  
*The New England Journal  
of Medicine* (N Engl J  
Med) 1999 340:101-107.

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## A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children.

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TD Thacher, PR Fischer, JM Pettifor, JO Lawson, CO Isichei, JC Reading, and GM Chan. *The New England Journal of Medicine* (N Engl J Med) 1999 341:563-568.

Nutritional rickets can cause disability among children. In North America and Western Europe fortification with vitamin D has virtually eliminated rickets; however, it remains prevalent in other parts of the world. This study evaluated the effect of supplements containing calcium alone or with vitamin D for 24 weeks in 123 Nigerian children with rickets and low calcium intakes. The median age of these children was 46 months. Treatments consisted of: vitamin D (600,000 U) given intramuscularly at the start of the study and at 12 weeks, 1,000 mg calcium as calcium carbonate given orally daily, or a combination calcium supplement with vitamin D injections. To assess the response to treatment at 24 weeks, serum calcium and alkaline phosphatase (a marker for bone metabolism), and a 10-point radiographic score were obtained. This study found that the vitamin D treatment group had a smaller increase in serum calcium levels compared with the calcium treatment group or the combination treatment group. Calcium alone and the combination of calcium and vitamin D were more effective than vitamin D alone in treating rickets. This study shows that calcium alone or with vitamin D can be used to treat rickets in young children who consume a low calcium diet.

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## Influence of prenatal iron and zinc supplements on supplemental iron absorption, red blood cell iron incorporation, and iron status in pregnant Peruvian women.

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KO O'Brien, N Zavaleta, LE Caulfield, D-X Yang, and SA Abrams. *American Journal of Clinical Nutrition* (Am J Clin Nutr) 1999 69:509-515.

Iron deficiency is believed to be the most prevalent nutrient deficiency in the world, with an estimated 60 percent of pregnant women worldwide considered anemic. In this study, pregnant Peruvian women with a high prevalence of anemia consumed prenatal supplements containing both 60 mg iron and 250 µg folate, with or without 15 mg of zinc. A third group received no supplements. Women in the first two groups consumed the supplements from week 10 to week 24 of gestation until delivery. Iron status indicators and blood samples using stable isotopes of iron were measured. Prenatal supplements containing iron and folate significantly improved the iron and folate status of these women. A negative outcome among women receiving only the iron/folate supplements was lower serum zinc concentrations. While prenatal iron supplements are important in meeting iron requirements in pregnancy, the negative effect of these supplements on zinc status deserves further investigation.

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## Behavioral and hematologic consequences of marginal iron-zinc nutrition in adolescent monkeys and the effect of a powdered beef supplement.

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As early adolescence is a time of nutritional stress, there is greater risk for developing iron and zinc deficiencies. This study evaluated the effects of a mildly restricted iron and zinc deficient diet in 24 healthy adolescent monkeys. The diet was designed to produce a marginal-to-moderate iron and zinc deficient state. After three months, half the monkeys on the low iron-zinc diet were given a beef supplement in tablet form to replete their iron and zinc stores. Although growth and blood parameters were not affected significantly by iron-zinc deprivation, this diet did affect the monkeys' participation in behavioral tests. They responded more slowly and were less active than monkeys that were not on the low iron-zinc diet. The beef supplements reversed the behavioral and blood abnormalities in monkeys on the low iron-zinc diet. Although blood indicators of iron-zinc deficiency were not significantly affected in this study, the results suggest that marginal iron-zinc deficiency may negatively affect behavioral outcomes.

MS Golub, CL Keen,  
and ME Gershwin.  
*American Journal of  
Clinical Nutrition*  
(Am J Clin Nutr)  
1999 70:1059-1068.

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## The chemical form of selenium influences 3,2'-dimethyl-4-aminobiphenyl-DNA adduct formation in rat colon.

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Epidemiological and animal studies suggest that adequate selenium intake may reduce the risk of cancer. Studies also suggest that dietary selenium can alter the ability of cells to metabolize carcinogenic compounds. This study was designed to examine whether selenite, selenate, or selenomethionine is protective against chemically induced cancerous growth in rat colons and livers, and to define the mechanism for the protective effects of these different chemical forms of selenium. In selenium-deficient rats, supplementation with selenite or selenate, but not selenomethionine, resulted in significantly lower C8-3,2'-dimethyl-4-aminobiphenyl (DMABP)-DNA (a measure of potential carcinogenesis) in the colons but not in the livers of these rats. However, the selenomethionine-supplemented rats had greater plasma and liver selenium concentrations and glutathione peroxidase activity, and more DMABP-DNA adducts. These results show that the protective effects of selenite and selenate may be related to differences in metabolism of the different forms of selenium, and not to changes in plasma and liver selenium concentrations or enzyme activity. Further, the study suggests that different dietary forms of selenium produce different responses in animal models, thus complicating recommendations regarding selenium and cancer prevention.

CD Davis, Y Feng,  
DW Hein, and JW Finley.  
*Journal of Nutrition*  
(J Nutr) 1999 129:63-69.

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## Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients.

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F Girodon, P Galan, A-L Monget, M-C Boutron-Ruault, P Brunet-Lecomte, P Preziosi, J Arnaud, J-C Manuguerra, S Herberg, and the MIN.VIT.AOX. geriatric network. *Archives of Internal Medicine* (Arch Intern Med) 1999 159:748-754.

Existing science suggests that aging is associated with altered regulation of the immune system. Antioxidant supplementation is thought to improve immunity and thereby reduce the burden of infectious disease. This study examined the effects of long-term daily supplementation with trace minerals and vitamins on the immune status and incidence of infections in 725 institutionalized elderly subjects in France. These subjects received one of four supplement regimes daily for two years: trace minerals containing zinc (20 mg) and selenium (100 µg); vitamins containing β-carotene (6 mg=1000 retinol equivalents), ascorbic acid (120 mg), and α-tocopherol (15 mg); trace minerals plus vitamins; or placebo. The supplements in this study corrected existing nutrient deficiencies but did not affect the delayed hypersensitivity skin response test (a measure of allergic response). Antibody titers after an influenza vaccine (a measure of immune response) were higher in groups that received the trace minerals alone or with vitamins, while lower antibody titers were observed in the vitamin-only group. Subjects who received trace minerals tended to have fewer respiratory tract infections during the study. These results suggest a beneficial effect of trace minerals when combined with antioxidant vitamins on immune status and resistance to infection in older individuals.

### BOTANICALS

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## Effect of ascorbic acid and green tea on endogenous formation of N-nitrosodimethylamine and N-nitrosopiperidine in humans.

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ITM Vermeer, EJC Moonen, JW Dallinga, JCS Kleinjans, and JMS van Maanen. *Mutation Research* (Mutat Res) 1999 428:353-361.

Exposure to N-nitroso compounds is related to an increased risk of gastric, esophageal, nasopharyngeal, and bladder cancers in humans. Dietary substances, such as vitamins C and E, and polyphenols may inhibit the formation of these carcinogenic compounds in the body. This study evaluated the effects of ascorbic acid and green tea on the urinary excretion of two breakdown products of N-nitroso compounds, N-nitrosodimethylamine and N-nitrosopiperidine, in 25 healthy females. The women served as their own controls. Along with consuming fish-based meals and drinking water containing nitrate compounds, the women consumed the following supplements daily for one week over a six-week period: two different doses of ascorbic acid (250 mg or one gram) or two different doses of green tea (4 or 8 cups). An increased intake of nitrate compounds resulted in increased urinary excretion of N-nitrosodimethylamine. Levels of N-nitrosopiperidine in the urine were not affected by the amount of nitrate in the diet. The intake of 250 mg or one gram ascorbic acid per day resulted in a significant decrease in urinary N-nitrosodimethylamine excretion. In addition, consumption of four cups of green tea per day, but not eight cups, decreased excretion of N-nitrosodimethylamine. Urinary excretion of N-nitrosopiperidine was not related to nitrate intake or composition of the diet. This study shows that ascorbic acid and moderate amounts of green tea can reduce the formation of N-nitroso compounds in the body, which may potentially reduce the risk of certain forms of cancer.

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## Heating garlic inhibits its ability to suppress 7,12-dimethylbenz(a)anthracene-induced DNA adduct formation in rat mammary tissue.

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Epidemiological and controlled trials suggest that garlic consumption may have a protective effect against some chronic diseases. Currently, the evidence for garlic is strongest for heart disease. This study examined the effect of heating garlic on its anticarcinogenic potential in experimentally induced tumors in rats. It was found that crushed garlic reduced the quantity of chemically induced DNA adducts (a measure of potential carcinogenesis) present in mammary epithelial cells of rats. Microwave heating for 60 seconds, but not 30 seconds, decreased the protective effect of garlic against chemically induced adduct formation. However, allowing the crushed garlic to stand for 10 minutes before microwave heating for 60 seconds significantly restored its anticarcinogenic activity. Heating the garlic in a convection oven blocked its anticarcinogenic activity. These series of experiments provide evidence that the methods of processing garlic can influence its effectiveness in blocking chemically induced carcinogenesis. In addition, they suggest that time is an important factor for the formation of chemoprotective compounds such as allyl sulfur compounds. These studies point to the importance of how garlic is processed and consumed when evaluating its anticancer properties in humans.

**K Song and JA Milner.**  
*Journal of Nutrition (J Nutr)* 1999 129:657-661.

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## Daidzein and genistein glucuronides in vitro are weakly estrogenic and activate human natural killer cells at nutritionally relevant concentrations.

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Epidemiological and experimental studies suggest that soybean isoflavones may have cancer-protective effects. The content and forms of isoflavones in soy foods differ and so do their biological activities. This study used a rat model to evaluate the estrogen receptor binding ability and the natural killer cell activation activity (an important measure of immune function) of two soy isoflavones, daidzein and genistein, and their respective active metabolic glucuronides. Glucuronides are formed in the body from dietary isoflavones. This study showed that genistein, daidzein and genistein glucuronides are not toxic to natural killer cells at normal physiological levels. Genistein glucuronides were found more active over a wider concentration range than the parent isoflavone genistein in activating natural killer cells, which may increase the body's immune defenses against cancer. The results of this study suggest that glucuronides may compete with endogenous estrogen and thus may inhibit estrogen-dependent cancer cell growth. This study provides additional information regarding how isoflavones may be protective against cancer.

**Y Zhang, TT Song, JE Cunnick, PA Murphy, and S Hendrich.** *Journal of Nutrition (J Nutr)* 1999 129:399-405.

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## Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. A randomized controlled trial.

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DS King, RL Sharp, MD Vukovich, GA Brown, TA Reifenrath, NL Uhl, and KA Parsons. *Journal of the American Medical Association (JAMA)* 1999 281:2020-2028.

Androstenedione is a precursor to testosterone. It is marketed as a dietary supplement to increase testosterone levels and produce anabolic-androgenic effects. This study examined the short- and long-term effects of androstenedione supplementation in 30 young men (19 to 29 years) who were not currently engaged in a resistance-training program. In the short-term study, 10 of the 30 men received a one-time dose of 100 mg androstenedione. For the long-term study, the remaining 20 men performed eight weeks of resistance training and received either 300 mg/day androstenedione or placebo. Neither short-term nor long-term supplementation of androstenedione with resistance training affected serum concentrations of free or total testosterone. In addition, long-term androstenedione supplementation with resistance training did not affect knee extension strength, muscle fiber area, lean body mass, or fat mass compared with placebo. However, compared with baseline, long-term androstenedione supplementation increased serum concentrations of estradiol and estrone and reduced serum concentrations of high-density lipoprotein cholesterol (HDL) at several time points during the eight-week supplementation period. This study suggests that androstenedione supplementation does not increase testosterone levels, nor improve muscle strength, and may produce adverse health consequences in young men.

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## Cholesterol-lowering effects of dietary fiber: a meta-analysis.

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L Brown, B Rosner, WW Willett, and FM Sacks. *American Journal of Clinical Nutrition (Am J Clin Nutr)* 1999 69:30-42.

Increasing dietary fiber intake is a safe and practical approach to managing cholesterol in individuals with hypercholesterolemia. An increase in soluble fiber intake is associated with decreases in total and low-density lipoprotein (LDL) cholesterol in a number of clinical studies. Meta-analysis of 67 controlled trials was used to quantify the cholesterol-lowering effect of four different soluble fibers: pectin, oat bran, guar gum, and psyllium. The results of this statistical analysis showed that 2-10 g/day of soluble fiber were associated with small but significant decreases in total cholesterol and LDL. Although pectin, oat, and psyllium fibers reduced plasma lipids by similar amounts, the effects were not uniform across trials. In addition, the soluble fibers did not significantly alter triglycerides or high-density lipoprotein (HDL) cholesterol levels. These results suggest that various soluble fibers reduce total and LDL cholesterol levels by similar amounts. Further, increasing soluble fiber can make an effective contribution to a dietary regime to lower blood cholesterol levels.

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## Comparison of melatonin products against USP's nutritional supplements standards and other criteria.

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Melatonin, a hormone produced by the human brain, controls the body's internal clock. As a dietary supplement, melatonin is used to help restore sleep patterns in the elderly, the blind, and in individuals who travel across multiple time zones. The United States Pharmacopeia (USP) establishes standards for dietary supplements, although they have not developed a standard for melatonin. This study evaluated 11 immediate-release and controlled-released melatonin products using USP tests and other tests for weight variation, friability, disintegration, dissolution, and hardness. All products met the USP weight variation guideline. Two products exhibited excessive friability. Four out of nine immediate-release products failed to meet the USP disintegration and dissolution guidelines, raising questions about the potential bioavailability of these products. Of the nine products evaluated for hardness, one showed an unusually high variation in hardness. The results of this study indicate that melatonin products on the market vary in quality, making it difficult for consumers and health care practitioners to select a high-quality product.

H Hahm, J Kujawa, and L Augsburger. *Journal of the American Pharmaceutical Association* (J Am Pharm Assoc) 1999 39:27-31.

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## OFFICE OF DIETARY SUPPLEMENTS (ODS) AT THE NATIONAL INSTITUTES OF HEALTH

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

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CHPA is a 119-year-old trade organization representing the manufacturers and distributors of national and store brand dietary supplements and nonprescription medicines. CHPA's membership includes over 200 companies involved in the manufacture and distribution of these self-care products and their affiliated services; *i.e.*, raw material suppliers, research testing companies, contract manufacturing companies, advertising agencies, etc.

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