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Silymarin, Found in the Herb Milk Thistle, Might Help in Insulin Resistance, Cancer

Silymarin, an antioxidant flavonoid complex derived from the herb milk thistle (*Silybum marianum*), has long been used as a liver tonic. Two new studies show that it can reduce insulin resistance (the underpinning of adult-onset diabetes, hypertension, and hypercholesterolemia) and diabetic complications. A third study reports that it may have some anti-cancer benefits as well.

Mario Velussi, MD, and his colleagues at the Monfalcone Hospital, Gorizia, Italy, treated 60 diabetic patients with either 600 mg of silymarin or placebo daily for 12 months. The patients had non-insulin-dependent diabetes (NIDDM), were suffering from alcoholic cirrhosis (alcohol-induced liver damage), and had been receiving insulin therapy for at least two years.

"Insulin resistance is constantly fairly high in patients with NIDDM and hepatic cirrhosis," Velussi wrote in the *Journal of Hepatology* (1997;26:871-9). "This metabolic disorder is partly related to increased blood glucose levels due to reduced glucose uptake by the liver. Hyperglycemia promotes hyperinsulinemia and this, together with the decreased hepatic degradation of the insulin molecule, may lead to insulin resistance in the target tissues."

Velussi used silymarin because research has shown it to be a powerful antioxidant with a long history of use in treating liver disorders.

After 12 months, the results of silymarin therapy were dramatic. Although fasting glucose levels rose slightly during the first month of use, they subsequently showed a progressive and significant decline, going from an average of 190 mg/dl to 174 mg/dl. In addition, average daily glucose levels dropped from 202 mg/dl to 172 mg/dl.

Although such decreases in blood sugar might raise concerns about hypoglycemia, the patients treated with silymarin did not have any increase in the number of mild or severe hypoglycemic episodes, suggesting that silymarin stabilized as well as lowered glucose levels.

The silymarin-treated patients had still other benefits. Their glucosuria (sugar in urine) decreased from an average of 37 grams/day to 22 grams/day. Glycosylated hemoglobin levels decreased significantly, indicating improved overall glucose control. Their average daily insulin requirement also decreased during the study, going from 55 IU to 42 IU daily.

In addition, SGOT and SGPT values declined significantly in the patients taking silymarin, confirming

that liver function improved. There was also a decrease in blood levels of malondialdehyde, a marker of free radical damage, approaching that of healthy subjects. By all measures, the placebo group did not improve.

In a separate cell-culture study, German researchers found that a specific silymarin flavonoid, silybinin, prevented the accumulation of fibronectin protein in kidney cells. Fibronectin is one of the principal causes of kidney damage in diabetics.

Simone Wenzel, PhD, of Justus-Liebig University, Germany, incubated human mesangial cells (HMCs, a type of kidney cell) in a high concentrations of glucose or a combination of glucose and silybinin for eight days.

According to Wenzel's article in the *Journal of Pharmacology and Experimental Therapeutics* (1996;279:1520-6), the silybinin prevented the accumulation of fibronectin. Wenzel believed that silybinin's protective effect was the result of its antioxidant properties. Malondialdehyde, an marker of free radical damage to fats, increased only in cells not treated with silybinin.

Finally, researchers from Case Western Reserve University, Cleveland, reported that silymarin slowed the growth of human cancer cells. In a cell-culture study, Rajesh Agarwal, PhD, and his collaborators determined that silymarin inhibited epidermal growth factor cell receptors, a type of tyrosine kinase receptor that promotes tumor growth.

"Silymarin treatment also resulted in a highly significant inhibition of cell growth and proliferation," Agarwal wrote in the *Journal of Investigative Dermatology* (1997;108:547, #60). "Treatment of cells with other antioxidant-like green tea polyphenols, EGCG [epigallocatechin gallate], quercetin, curcumin and genistein, also resulted in similar inhibitory effects albeit at different levels." □

"Good" Bacteria Inhibit Cancer Cells

Lactobacillus, one of the many types of "good" intestinal bacteria, has long been known to discourage the growth of disease-causing bacteria. They may also protect against the development and proliferation of cancer cells.

In a series of cell-culture experiments, Anna Biffi, PhD, of the Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy, exposed breast cancer cells to milk

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fermented with five types of lactic acid bacteria: *Bifidobacterium infantis*, *Bifidobacterium bifidum*, *Bifidobacterium animalis*, *Lactobacillus acidophilus*, and *Lactobacillus paracasei*.

All of the bacteria slowed the growth of cancer cells. However, *B. infantis* and *L. acidophilus* were the most effective, resulting in an 85 percent inhibition of growth after nine days. Further experiments were conducted with milk products in which the bacteria had been killed. Once again, cancer cell growth was inhibited.

"Our findings suggest that a soluble compound produced by bacteria during the fermentation process and released in the medium is responsible for the antiproliferative effect of fermented milk, since we observed growth inhibition even in the absence of bacteria," Biffi wrote in *Nutrition and Cancer* (1997;28:93-9).

Biffi was not able to identify the anti-tumor compound released by the lactic acid bacteria. Other studies have shown that lactic acid bacteria inhibit the growth of colon cancer. □

Calcium: People Need More to Prevent Osteoporosis

Your dietary requirement for calcium has officially gone up, and supplements can reduce your risk of bone-thinning osteoporosis.

In August, researchers at the National Academy of Sciences released new recommendations for calcium and a handful of other nutrients. Their report, *National Academy of Sciences Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*, was the start of a long process to replace the Recommended Dietary Allowances (RDAs), which were last revised in 1989.

The new Dietary Reference Intake (RDI) for calcium is 1,000 mg daily for people over age 25, increasing to 1,200 mg after age 51. The old RDA was 800 mg. Significantly, the researchers wrote, most people fail to obtain 75 percent of the new RDI for calcium, and only 10 percent of elderly persons get enough calcium. As a consequence, millions of people are at risk of osteoporosis.

As if to underscore the importance of calcium, three weeks later, Bess Dawson-Hughes, MD, of Tufts University, reported that supplements of calcium and vitamin D could halve the number of bone fractures.

Hughes and her colleagues gave either placebos or 500 mg of calcium and 700 IU of vitamin D daily to 389 men and women over age 65. The supplement increased bone density throughout the body after just one year, and the benefits continued to accrue through the third year of the study, according to Dawson-Hughes' article in the *New England Journal of Medicine* (Sept 4, 1997;337:670-6).

Of the 37 people who developed fractures, 26 were taking placebos and 11 were taking calcium and vitamin D supplements. □

Diets High in Vitamin C, Beta-Carotene Keep the Mind Sharp

Long-term consumption of foods rich in vitamin C and beta-carotene are strongly associated with mental performance among the elderly. That's the finding of a study by Walter J. Perrig, PhD, of the Institute for Psychology at the University of Bern, Switzerland.

Perrig and his associates analyzed blood levels of vitamins C and E and beta-carotene in 442 men and women ranging in age from 65 to 94 years. The subjects had originally had their blood nutrient levels measured in 1971. In 1993, Perrig reanalyzed their nutrient levels and gave them a series of cognitive tests.

In the *Journal of the American Geriatrics Society* (June 1997;45:718-24), Perrig noted a remarkable consistency in the subjects' blood levels of beta-carotene and vitamin E, despite the 22-year difference in samples. That supported the idea that people's eating habits remain relatively consistent over long periods.

"Our general hypothesis was that disturbances in memory functions related to aging can be linked to increased oxidative stress with aging," he wrote.

Perrig measured several aspects of memory in the subjects. He found that recall, recognition, and vocabulary were specifically associated with high blood levels of vitamin C and beta-carotene. These nutrients "reflect similar eating habits because both are important constituents of fruits and vegetables," Perrig wrote.

He added, "The effects of antioxidants on memory performance found in our study do not appear to be based on the intake of vitamin supplements because the study was carried out during the spring and summer seasons, when the intake of vitamin supplements is rather low. In our studied cohorts, only about 6 percent of the subjects mentioned vitamin supplementation." □

Aged Garlic Extract Slows Growth of Prostate Cancer Cells

Some of the compounds found in "aged garlic extract" supplements, and similar synthetic compounds, can slow the growth of prostate cancer cells, according to cell-culture experiments conducted at the Memorial Sloan-Kettering Cancer Center and Cornell University Medical Center, New York.

John T. Pinto, PhD, found that the growth of prostate cancer cells was almost completely halted by S-allylmercaptocysteine, one of the compounds found in garlic. Another compound, S-allylcysteine, slowed the growth of prostate cancer cells, but not as much.

Both substances also increased levels of glutathione, the principal antioxidant found in cells.

"These data provide further evidence that nonessential nutrients derived from garlic may modulate

tumor growth," Pinto wrote in the *American Journal of Clinical Nutrition* (Aug 1997;66:398-405).

In an editorial in the same journal (66:425-6), David Heber, MD, of the University of California, Los Angeles, suggested that these nutrients might be essential for health. The reason, he explained, was that humans and their ancestors evolved with and became dependent on such nutrients over millions of years. □

Mix of Dietary Carotenoids Helps Maintain Normal Immune Function

Although beta-carotene is known to enhance the immune system, the immune effects of other carotenoids are not well understood. To tease out the effects of other carotenoids, Tim R. Kramer, PhD, and Betty J. Burri, PhD, of the USDA Agricultural Research Service asked nine women to eat a low-carotene diet—few fruits, vegetables, and juices—for four months. At the same time, five of the women took a low-dose beta-carotene supplement for two months, while the remaining four women were given placebos.

Then, for the third and fourth months, all of the women were given low-dose beta-carotene supplements; and during the last month, all of the women were also given a mixed-carotenoid supplement, containing a higher dose of beta-carotene, plus alpha-carotene, cryptoxanthin, lutein, zeaxanthin, and lycopene. All of these carotenoids are found in a diet of mixed fruits and vegetables.

Kramer and Burri measured the activity of lymphocytes drawn from the blood of the subjects at various times during the study. They found that a low-carotene diet suppressed the immune response, and that this suppression was not corrected with a low-dose beta-carotene supplement.

However, according to their report in the *American Journal of Clinical Nutrition* (1997;65:871-875), the mixed-carotenoid supplement, containing higher amounts of beta-carotene and the related carotenoids, did restore normal lymphocyte activity. □

Diabetics Suffer from Oxidative Stress, Get Fewer Antioxidants

Large numbers of free radicals and relatively low levels of antioxidant vitamins result in oxidative stress, causing or contributing to heart disease, cancer, arthritis, and many other diseases. Oxidative stress is increasingly being viewed as a factor that aggravates many diabetic complications, including an above-average risk of heart disease, blindness, and nerve damage.

Two recent studies confirmed that oxidative stress plays a major role in poor diabetic control and complications.

In one study, reported in the *European Journal of Clinical Nutrition* (1997;27:484-490), a team of British

researchers investigated antioxidant levels in 52 insulin-dependent and noninsulin-dependent diabetics and compared them with healthy subjects.

They found that insulin-dependent diabetics had significantly lower total antioxidant activity, largely attributable to lower vitamin C and urate (an antioxidant made by the body). While the noninsulin-dependent diabetics had higher antioxidant levels, they were still lower than in healthy people. The researchers, led by Dr. S.R.J. Maxwell, wrote, "These results show that diabetic patients have significant defects of antioxidant protection, which may increase vulnerability to oxidative damage and the development of diabetic complications."

In a separate study, British and German researchers found that levels of lipid peroxidation were higher in both insulin-dependent and noninsulin-dependent diabetics, compared with healthy subjects.

"Increased oxidative stress in diabetic patients appears to be related to the underlying metabolic abnormalities in diabetes, rather than to the complications of this disease," Dr. J. Nourooz-Zadeh wrote in *Diabetologia* (1997;40:47-653). □

Geriatrics Editor Weighs In: Good Diet, Exercise, and Vitamin E

Studies have shown that vitamin E supplements decrease the risk of heart attacks, slow the progression of Alzheimer's disease, and increase immunity in the elderly. Although the American Psychiatric Association recently recommended the use of vitamin E to treat Alzheimer's, fewer than one-half of cardiologists take it or recommend it to patients to reduce their risk of heart disease.

In the July issue of *Geriatrics* (1997;52:7-8) editor-in-chief Robert N. Butler, MD, made it clear that he recommends that his patients take a multivitamin supplement with 250 mg of vitamin C and 200 IU of vitamin E. Butler noted that the typical American diet does not provide sufficient vitamin E to achieve documented health benefits. To get 400 IU of vitamin E, he wrote, a person would have to eat 1,000 almonds, which would also provide more than 8,000 calories and more than a pound of fat.

Butler, who acknowledged that his view on vitamin supplements is "not universally shared," also recommended that people eat a well-rounded diet with fruits and vegetables and go for daily walks. □

Lutein Supplements Increase Density of Macular Pigment

There's increasing evidence that macular degeneration results, at least in part, from the inadequate intake of lutein and zeaxanthin. These two nutrients, related to beta-carotene, form the macular pigment in the retina of the eyes.

People who eat diets rich in lutein-containing foods,

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Quick Reviews of Recent Research

• Lycopene better absorbed in cooked tomatoes

Researchers compared the bioavailability of lycopene from tomato paste and fresh tomatoes. Five subjects were given one serving of either tomato paste or fresh tomatoes (containing 23 mg of lycopene) with corn oil. Lycopene levels rose 2.5 times higher after consumption of the tomato paste, compared with fresh tomatoes, supporting the idea that cooking releases more lycopene. Two years ago, researchers reported that regular consumption of tomato products, rich in lycopene, dramatically reduced the risk of prostate cancer. Tomato sauces were more protective than raw tomatoes or tomato juice.

Gärtner C, et al., *American Journal of Clinical Nutrition*, 1997;66:116-22.

• Vitamin C promotes vasodilation

High cholesterol levels impair normal vasodilation (relaxation) of coronary and other blood vessel walls. In a study of men with elevated cholesterol, intravenous vitamin C improved vasodilation in the forearm. Vitamin C is the principal water-soluble antioxidant in blood plasma.

Ting HH, et al., *Circulation*, 1997;95:2617-2622.

• Large number of cardiologists take antioxidants

Forty-four percent of cardiologists responding to a questionnaire acknowledged taking antioxidant supplements, though only 37 percent routinely recommended antioxidants to their patients. Vitamin E was the most commonly taken antioxidant, used by 39 percent of the physicians. Vitamin C was used by 33 percent and beta-carotene by 19 percent.

Mehta J, *American Journal of Cardiology*, 1997;79:1558-60.

• Dietary curcumin inhibits skin cancer

In an experiment, mice were exposed to a compound known to cause skin cancer. Some of the mice were given large amounts of curcumin in their diets—1 percent of their total diets. Mice receiving curcumin, found in turmeric, had fewer and smaller tumors than those on a regular diet.

Limtakul P, et al., *Cancer Letters*, 1997;116:197-203.

• Avocados lower cholesterol and triglycerides

Replacing some dietary fats with an avocado or two daily can dramatically lower cholesterol and triglyceride levels in people with normal and elevated blood fats. In subjects with moderately high cholesterol, total cholesterol levels decreased by an average 17 percent, and low-density lipoproteins and triglycerides each decreased by 22 percent. High-density lipoproteins increased by 11 percent. In healthy individuals, total cholesterol declined by 16 percent. Researchers attributed the improvement to the large amount of monounsaturated fat found in avocados.

Ledesma RL, et al., *Archives of Medical Research*, 1996;27:519-23.

• Chocolate constituents benefit immune function

Chocolate contains a number of antioxidant polyphenols. In experiments, researchers found that cacao liquor polyphenols inhibited the production of hydrogen peroxide and superoxide radicals in human lymphocytes. This finding suggested that cacao liquor polyphenols have "immunoregulatory effects."

Sanbongi C, et al., *Cellular Immunology*, 1997;177:129-36.

• Polyphenol content of berries

Different species of berries vary in their content of flavonoids, ellagic acid, and polyphenolic acids. For example, blueberries and bilberries are rich in antioxidant hydroxycinnamic acids, and cranberries and lingonberries contain large amounts of flavonoids. Strawberries and red raspberries are high in ellagic acid.

Törrönen R, et al., *Cancer Letters*, 1997;191-2.

• N-acetylcysteine counters meningitis symptoms

N-acetylcysteine (NAC) boosts cell levels of glutathione, the principal endogenous antioxidant found in the body's cells. In a study with laboratory rats, researchers found that NAC can correct some of the pathological changes that occur during a pneumococcal meningitis infection. NAC reduced water retention and intracranial pressure in the brain and white blood cell counts in the cerebrospinal fluid.

Koedel U, et al., *Neuroscience*, 1997;225:33-6.

Lutein and Macular Degeneration...

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such as kale and spinach, tend to have thick macular pigments and a low risk of developing macular degeneration. (The body converts some lutein to zeaxanthin.) To determine whether lutein supplements could increase the density of macular pigment, researchers gave 30 mg of lutein daily to two healthy subjects for 140 days.

The macular density in these subjects increased by 39 and 21 percent, according to John T. Landrum, Ph.D., of Florida International University. He wrote in *Experimental Eye Research* (1997;65:57-62) that the greater density resulted in a 30-40 percent decrease in the amount of damaging blue light reaching light receptors in the retina. □

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