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FILE: ■ Red Clover (*Trifolium pratense*)
■ Cardiovascular Disease Risk
■ Perimenopause
■ Isoflavones

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RE: Potential Protective Effects of Isoflavones from Red Clover Against Cardiovascular Disease

Atkinson C, Oosthuizen W, Scollen S, Laktionov A, Day NE, Bingham SA. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with apoE genotype in 49–65 year-old women. *J Nutr.* 2004;134:1759–1764.

It has been known for decades that the substitution of animal protein for soy (*Glycine max*) protein can have beneficial effects on the blood lipid profile. Elevated blood cholesterol concentrations are associated with heart disease, and it has been estimated that for every 1% reduction in blood cholesterol there is a corresponding 2.5% decrease in the incidence of heart disease. Therefore, strategies to decrease blood cholesterol concentrations could result in a substantial reduction in the incidence of heart disease. The results of some studies suggest that soy protein, an important source of isoflavones, may have lipid-lowering effects and thus reduce the risk of cardiovascular disease. The contribution of isoflavones to the lipid-lowering effect of soy protein is questionable, however, because studies have been conflicting. The objective of this study was to examine the effects of isoflavones derived from red clover (*Trifolium pratense*) on some risk factors of cardiovascular disease.

Two hundred five women aged 49–65 years were recruited from the Breast Screening Unit of Addenbrooke Hospital (Cambridge, United Kingdom) and randomly assigned in a double-blind controlled trial to receive either one Promensil (Novogen; North Ryde, Australia) isoflavone tablet (43.5 mg derived from red clover) or a placebo of identical appearance daily for 12 months. Each isoflavone tablet contained 26 mg biochanin A, 16 mg formononetin, 1 mg genistein, and 0.5 mg daidzein. Urine samples were collected at baseline and at 6 and 12 months for the measurement of the isoflavones biochanin A, formononetin, genistein, and daidzein. At baseline and at 12 months, blood pressure was measured and blood samples were collected for the measurement of lipid and hormone

concentrations. The effect of apoE genotype on baseline blood pressure, blood lipids, and blood clotting factors was also assessed.

Urinary excretion of total isoflavones (biochanin A + formononetin + genistein + daidzein) increased significantly ($P < 0.001$) in the isoflavone group from baseline to 6 months and from baseline to 12 months but decreased in the placebo group. No significant treatment effects on changes in triglyceride and total, high-density-lipoprotein, and low-density-lipoprotein concentrations were observed. A significant interaction between treatment group and menopausal status ($P = 0.02$) and plasminogen activator inhibitor type 1 ($P = 0.01$) for the change in triglycerides was observed. The change in plasminogen activator inhibitor type 1 or fibrinogen was not significantly different between treatment groups, and no significant interactions between apoE genotype and treatment group for the change in these variables were observed. No significant treatment effects on diastolic or systolic blood pressure and no interactions between menopausal status and treatment group were observed. Interactions between isoflavone treatment and apoE genotype tended to be significant for changes in total ($P = 0.06$) and low-density-lipoprotein ($P = 0.05$) cholesterol, and the differences between groups were significant.

In the population of women as a whole, no significant effect of isoflavone supplementation on cardiovascular disease risk factors was observed. However, among perimenopausal women, a "potentially beneficial effect" of isoflavone supplementation on the change in triglyceride and plasminogen activator inhibitor type 1 concentrations was observed. Favorable effects of isoflavone supplementation were also observed on total and low-density-lipoprotein concentrations in women with the apoE E2/E3 genotype. Because the sample sizes of perimenopausal women and women with the apoE E2/E3 genotype were relatively small, a larger study is necessary to confirm these findings. In summary, the findings suggest that "isoflavones alone are not responsible for the well-documented effects of soy protein on blood lipids."

—*Brenda Milot, ELS*

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