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Effect of Isoflavones on Cardiovascular Health: Low But Not Out Either

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Isoflavones, an important class of flavonoids that are found at extremely high levels in soy have gained considerable attention for their potential in improving risk factors for cardiovascular disease. The three major extensively studied soy isoflavones are genistein, daidzein and glycetein [*1*]. The US Food and Drug Administration (FDA) in 1999 and the American Heart Association in (AHA) in 2000 recommended that soy protein containing foods may be protective against cardiovascular disease (CVD) [*2*, *3*]. But in 2006, the AHA analysis suggests that the use of isoflavone supplements in food or pills is not recommended [*4*]. However, strong scientific evidence has been emerging recently related to the nutritional benefits of flavonoids including isoflavones [*5*]. A recent study of flavonoid intake and the risk of ischemic stroke and CVD mortality suggest that high intake of flavonoids may be associated with decreased risk of ischemic stroke and possibly reduced CVD mortality [*6*]. In another study in U.S adults the intake of dietary flavonoids including daidzein and genistein was inversely associated with serum levels of C-reactive protein (CRP) a biomarker for chronic inflammation and a sensitive risk factor for CVD [*7*]. It is reported that genistein upregulates the gene expression of *antioxidant* enzyme manganese-superoxide dismutase (Mn SOD) and antioxidant metallothionein expression [*8*, *9*]. Increased expression of catalase in human hepatoma cells by daidzein has also been recently reported [*10*]. *In vitro* and *in vivo* studies have demonstrated that soy isoflavones genistein and daidzein may be useful antigenotoxic antioxidants by scavenging free radicals, inhibiting lipid peroxidation and protecting against oxidative DNA damage [*11*]. Recent reports reveal that genistein exhibit vascular protective effects by targeting on important signaling molecules in vascular endothelial cells including upregulation of human endothelial nitric oxide synthase [*12*]. Why is the inconsistency in clinical study reports of flavonoids? Key questions that need to be addressed include the gut bacterial metabolism of daidzein and its metabolites especially equol since it has longer half-life and greater biological activity, including superior antioxidant activity [*13*]. Recently the vasorelaxant and antioxidant activity of equal have been reported in carotid and cerebral arteries [*14*]. Using microarray analysis it has been found that isoflavone treatment in subjects who have the capacity to produce equal differentially affects gene expression as compared to non-producers, supporting the significance of equal production [*15*]. Thus the link between daidzein metabolizing phenotypes and the interaction of its metabolites at the gene level need to be further probed. And finally nutrigenomic and nutrigenetic aspects of isoflavones on CVD have to be studied in detail before any final verdict on the cardioprotective effects of these bioactive nutrients.

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References

[1] Cassidy, A. and Hooper, L.: Phytoestrogens and cardiovascular disease. *J. Br. Menopause. Soc.*, **12(2)**, 49–56, 2006.
[2] Food labeling: health claims: Soy protein and coronary heart disease. Food and Drug Administration, HHS: final rule: soy protein and coronary heart disease. *Fed. Reg.*, **64**, 57700–57733, 1999.
[3] Erdman, J.W. Jr.: AHA Science Advisory: soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutritional Committee of the AHA. *Circulation*, **102**, 2555–2559, 2000.
[4] Sacks, F.M., Lichtenstein, A., Horn, L.V., Harris, W., Kris-Etherton, P., and Winston, M.: AHA Science Advisory: soy protein, isoflavones, and cardiovascular health: a statement for healthcare professionals from the Nutritional Committee of the AHA. *Circulation*, **113**, 1034–1044, 2006.
[5] Rimbach, G., Saadatmandi, C.G., Frank, J., Fuchs, D.,

Wenzel, U., Daniel, H., Hall, W.L., and Weinberg, P.D.: Dietary isoflavones in prevention of cardiovascular disease—A molecular perspective. *Food and Chem. Toxicol.*, **43**, 1308–1319, 2008.

[6] Mursu, J., Voutilainen, S., Nurmi, T., Tuomainen, T.P., Kurl, S., and Salonen, J.T.: Flavonoid intake and the risk of ischaemic stroke and CVD mortality in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br. J. Nutr.*, In press, 2008 April 1: 1–6 (Epub ahead of print).

[7] Chun, O.K., Chung, S.J., Claycombe, K.J., and Song, W.O.: Serum C- reactive protein concentrations are inversely associated with dietary flavonoid intake in U.S adults. *J. Nutr.*, **138(4)**, 753–760, 2008.

[8] Borras, C., Gambini, J., Carmen Gomez-Cabera, M., Sastre, J., Pallardo, F.V., Mann, G.E., and Vina, J.: Genistein, a soy isoflavone, upregulates expression of antioxidant genes: involvement of estrogen receptors ERK1/2, and NFκB. *The Faseb Journal*, **20**, 2136–2138, 2006.

[9] Chung, M.J., Kang, A.Y., Lee, K.M., Oh, E., Jun, H.J., Kim, S.Y., Auh, J.H., Moon, T.W., Lee, S.J., and Park, K.H.: Water-soluble genistein glycoside isoflavones up-regulate antioxidant metallothionein expression and scavenge free radicals. *J. Agric. Food Chem.*, **54(11)**, 3819–3826, 2006.

[10] Kampkotter, A., Wiegnand, C., Timpel, C., Rohrdanz, E., Chovolou, Y., Kahl, R., and Watjen, W.: Increased expression of catalase in human hepatoma cells by soy isoflavone, daidzein. *Basic Clin. Pharmacol. Toxicol.*, **102(5)**, 437–442, 2008.

[11] Kim, N.Y., Song, E.J., Kwon, D.Y., Kim, H.P., and Heo, M.Y.: Antioxidant and antigenotoxic activities of Korean fermented soybean. *Food Chem. Toxicol.*, **46(3)**, 1184–1189, 2008.

[12] Si, H. and Liu, D.: Genistein, a soy phytoestrogen, upregulates the expression of human endothelial nitric oxide synthase and lowers blood pressure in spontaneously hypertensive rats. *J. Nutr.*, **138(2)**, 297–304, 2008.

[13] Jackmann, K.A., Woodman, O.L., and Sobey, C.G.: Isoflavones, equol and cardiovascular disease: pharmacological and therapeutic insights. *Curr. Med. Chem.*, **14(26)**, 2824–2830, 2007.

[14] Jackmann, K.A., Woodman, O.L., Chrissobolis, S., and Sobey, C.G.: Vasorelaxant and antioxidant activity of the isoflavone metabolite equol in carotid and cerebral arteries. *Brain Res.*, **1141**, 99–107, 2007.

[15] Niculescu, M.D., Pop, E.A., Fischer, L.M., and Zeisel, S.H.: Dietary isoflavones differentially induce gene expression in lymphocytes from postmenopausal women who form equol as compared with those who do not. *J. Nutr. Bichem.*, **18(6)**, 380–390, 2007.