

Estera™ Phase III

Adams MR, Golden DL, Register TC et al. The atheroprotective effect of dietary soy isoflavones in apolipoprotein E-/- mice requires the presence of estrogen receptor-beta. *Arterioscler.Thromb.Vasc.Biol.* 2002;22:1859-64.

Albertazzi P, et al. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol* 1998;91:6-11.

Alekel DL, St Germain A, Pererson CT, Hanson KB, Stewart JW, Toda T. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. *American Journal of Clinical Nutrition* 2000;72:844-52.

Anderson JW, Johnstone BM, Cook-Newell ML. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276-282.

Anthony MS, Clarkson TB. Comparison of soy phytoestrogens and conjugated equine estrogens on atherosclerosis progression in postmenopausal monkeys (abstract). *Circulation* 1998;97:829.

Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2004;79(2):326-33.

Aviram M, Dornfeld L, Rosenblat M et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *Am J Clin Nutr* 2000;71:1062-76.

Baber R, Clifton Bligh P, et al. The effect of an isoflavone dietary supplement (P-081) on serum lipids, forearm bone density and endometrial thickness in postmenopausal women (abstract 27). *Menopause* 1999;6:326.

Barnes S. Phyto-oestrogens and osteoporosis: what is a safe dose? *British Journal of Nutrition* 2003;89:S101-S108.

Bloedon LT, Jeffcoat AR, Lopaczynski W et al. Safety and pharmacokinetics of purified soy isoflavones: single-dose administration to postmenopausal women. *American Journal of Clinical Nutrition* 2002;76:1126-37.

Brooks JD, Ward WE, Lewis JE et al. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *American Journal of Clinical Nutrition* 2004;79:318-25.

Chen J, Thompson LU. Lignans and tamoxifen, alone or in combination, reduce human breast cancer cell adhesion, invasion and migration in vitro. *Breast Cancer Res Treat.*

2003;80:163-70.

Clarkson TB. Soy, soy phytoestrogens and cardiovascular disease. *Journal of Nutrition* 2002;132:566S-9S.

Constantinou AI, Mehta RG, Vaughan A. Inhibition of N-methyl-N-nitrosourea-induced mammary tumors in rats by the soybean isoflavones. *Anticancer Res* 1996;16(6a):3293-8

Cotter AC, Cashman KD. Genistein appears to prevent early postmenopausal bone loss as effectively as hormone replacement therapy. *Nutr Rev* 2004;61(10):346-51.

Crisafulli A, Marini H, Bitto A, Altavilla D, Squadrito G, Romeo A, Adamo EB, Marini R, D'Anna R, Corrado F, Bartolone S, Frisina N, Squadrito F. Effects of genistein on hot flashes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. *Menopause*. 2004 Jul-Aug;11(4):400-4.

Cunnane SC, Hamadeh MJ, Liede AC, Thompson LU, Wolever TM, Jenkins DJ. Nutritional attributes of traditional flaxseed in healthy young adults [see comments]. *Am J Clin Nutr* 1995;61:62-8.

Dean PDG, Exley D, Goodwin TW. Steroid estrogens in plants: reestimation of estrone in pomegranate-D seeds. *Phytochemistry* 1971;10:2215-6.

Demark-Wahnefried W, Price DT, Polascik TJ et al. Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. *Urology* 2001;58:47-52.

Divi RL, Chang HC, Doerge DR. Anti-thyroid isoflavones from soybean: isolation, characterization, and mechanisms of action. *Biochem Pharmacol*. Nov1997;54(10):1087-96.

Evans BA, Griffiths K, Morton MS. Inhibition of 5 alpha-reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. *J Endocrinol* 1995;147:295-302.

Exner M, Hermann M, Hofbauer R et al. Genistein prevents the glucose autoxidation mediated atherogenic modification of low density lipoprotein. *Free Radic Res* 2001;34:101-12.

Fitzpatrick LA. Soy isoflavones: hope or hype? *Maturitas* 2003;44(suppl. 1):S21-S29.

Food and Drug Administration. Food labeling: health claims, soy protein and coronary artery disease. *Federal Register* 1999;64:57699-733.

Fritz WA, Coward L, Wang J, Lamartiniere CA. Dietary genistein: perinatal mammary

cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis* 1998;19:2151-8.

Gao YH, Yamaguchi M. Suppressive effect of genistein on rat bone osteoclasts: Apoptosis is induced through Ca²⁺ signaling. *Biol Pharm Bull* 1999;22:805-809.

Gao YH, Yamaguchi M. Zinc enhancement of genistein's anabolic effect on bone components in elderly female rats. *Gen.Pharmacol* 1998;31:199-202.

Guo TL, McCay JA, Zhang LX et al. Genistein modulates immune responses and increases host resistance to B16F10 tumor in adult female B6C3F1 mice. *Journal of Nutrition* 2001;131:3251-8

Haggans CJ, Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer* 1999;33:188-95.

Haggans CJ, Travelli EJ, Thomas W, Martini MC, Slavin JL. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2000;9:719-25.

Henderson VW. Isoflavones: food for thoughtful consideration. *Menopause.* 2003;10:189-90.

Hsieh CY, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. *Cancer Res* 1998;58:3833-8.

Hutchins AM, Martini MC, Olson BA, Thomas W, Slavin JL. Flaxseed influences urinary lignan excretion in a dose-dependent manner in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2000;9:1113-8.

Hutchins AM, Martini MC, Olson BA, Thomas W, Slavin JL. Flaxseed consumption influences endogenous hormone concentrations in postmenopausal women. *Nutr Cancer* 2001;39:58-65.

Jenab M, Rickard SE, Orcheson LJ, Thompson LU. Flaxseed and lignans increase cecal beta-glucuronidase activity in rats. *Nutr Cancer* 1999;33:154-8.

Jenab M, Thompson LU. The influence of flaxseed and lignans on colon carcinogenesis and beta-glucuronidase activity. *Carcinogenesis* 1996;17:1343-8.

Jiminez del Rio M. Pomegranate extract: the fruit of healthy cholesterol and longevity. *Nutraceuticals World* 2001.

Keck AS, Finley JW. Cruciferous vegetables: cancer protective mechanisms of

glucosinolate hydrolysis products and selenium. *Integr.Cancer Ther* 2004;3:5-12

Kim ND, Mehta R, Yu W et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat.* 2002;71:203-17.

Kirk EA, Sutherland P, Wang SA, Chait A, LeBoeuf RC. Dietary isoflavones reduce plasma cholesterol and atherosclerosis in C57BL/6 mice but not LDL receptor-deficient mice. *J Nutr* 1998;128:954-9.

Kitts DD, Yuan YV, Wijewickreme AN, Thompson LU. Antioxidant activity of the flaxseed lignan secoisolariciresinol diglycoside and its mammalian lignan metabolites enterodiol and enterolactone. *Mol.Cell Biochem* 1999;202:91-100.

Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climacteric* 1999;2:79-84.

Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MA. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. *Menopause.* 2003;10:196-202.

Leong H, Firestone GL, Bjeldanes LF. Cytostatic effects of 3,3'-diindolylmethane in human endometrial cancer cells result from an estrogen receptor-mediated increase in transforming growth factor- α expression. *Carcinogenesis* 2001;22:1809-17.

Li B, Yu S. Genistein prevents bone resorption diseases by inhibiting bone resorption and stimulating bone formation. *Biol Pharm Bull* 2003;26:780-6.

Li D, Yee JA, Thompson LU, Yan L. Dietary supplementation with secoisolariciresinol diglycoside (SDG) reduces experimental metastasis of melanoma cells in mice. *Cancer Lett* 1999;142:91-6.

Mathern J, Verbruggen M. Special report: Flax lignans. *Total Health* 2003;1-15

Messina M, Flickinger B. Hypothesized anticancer effects of soy: Evidence points to isoflavones as the primary anticarcinogens. *Pharmaceutical Biology* 2002;40(supplement):6-23.

Messina M, Hughes C. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. *J Medicinal Food* 2003;6(1):1-11.

Miller CP, Collini MD, Harris HA. Constrained phytoestrogens and analogues as ER- β selective ligands. *Bioorg Med Chem Lett* 2003;13(14):2399-403.

Morabito N, Crisafulli A, et al. Effects of Genistein and Hormone-Replacement Therapy

on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J Bone Min Res* 2002;17:1904-1912.

Murkies AL, Lombard C, Strauss BJG, Wilcox G, Burger HG, Morton MS. Dietary flour supplementation decreases postmenopausal hot flushes: effect of soy and wheat. *Maturitas* 1995;21:189-95.

Nagata C, Takatsuka N, Kawakami N, Shimizu H. A prospective cohort study of soy product intake and stomach cancer death. *Br.J.Cancer* 2002;87:31-6.

North American Menopause Society. *Menopause* 2000;7(4):215-229.

North American Menopause Society. The role of isoflavones in menopausal health: Consensus opinion of the

Okazaki K, Okazaki S, Nakamura H et al. A repeated 28-day oral dose toxicity study of genistein in rats, based on the 'Enhanced OECD Test Guideline 407' for screening endocrine-disrupting chemicals. *Archives of Toxicology* 2002;76:553-9.

Phipps WR, Martini MC, Lampe JW, Slavin JL, Kurzer MS. Effect of flax seed ingestion on the menstrual cycle. *J Clin Endocrinol.Metab* 1993;77:1215-9.

Plumb GW, Pascual-Teresa S, Santos-Buelga C, Rivas-Gonzalo JC, Williamson G. Antioxidant properties of gallicocatechin and prodelpinidins from pomegranate peel. *Redox.Rep.* 2002;7:41-6.

Potter SM, Baum JA, et al. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am J Clin Nutr* 1998;68(suppl):1375S-9S.

Prasad K, Mantha SV, Muir AD, Westcott ND. Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. *Atherosclerosis* 1998;136:367-75.

Prasad K. Antioxidant Activity of Secoisolariciresinol Diglucoside-derived Metabolites, Secoisolariciresinol, Enterodiol, and Enterolactone. *International Journal of Angiology* 2000;9:220-5.

Prasad K. Dietary flax seed in prevention of hypercholesterolemic atherosclerosis. *Atherosclerosis* 1997;132:69-76.

Prasad K. Hydroxyl radical-scavenging property of SDG isolated from flaxseed. *Mol Cell Biochem* 1997;168:117-123.

Prasad K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. *Circulation*

1999;99:1355-62.

Prasad K. Secoisolariciresinol diglucoside from flaxseed delays the development of type 2 diabetes in Zucker rat. *J Lab Clin Med* 2001;138:32-9.

Rickard DJ, Monroe DG, Ruesink TJ, Khosla S, Riggs BL, Spelsberg TC. Phytoestrogen genistein acts as an estrogen agonist on human osteoblastic cells through estrogen receptors alpha and beta. *J Cell Biochem* 2003;89:633-46.

Rickard SE, Yuan YV, Chen J, Thompson LU. Dose effects of flaxseed and its lignan on N-methyl-N-nitrosourea-induced mammary tumorigenesis in rats. *Nutr Cancer* 1999;35:50-7.

Rickard SE, Yuan YV, Thompson LU. Plasma insulin-like growth factor I levels in rats are reduced by dietary supplementation of flaxseed or its lignan secoisolariciresinol diglycoside. *Cancer Lett* 2000;161:47-55.

Rivas M, Garay RP, Escanero JF, Cia P, Jr., Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr* 2002;132:1900-2.

Scheiber MD, Setchell KDR, et al. Dietary soy supplementation influences LDL oxidation and bone turnover in healthy postmenopausal women. Presented at the 81st Meeting of the Endocrine Society, San Diego, CA, June 1999.

Serraino M, Thompson LU. Flaxseed supplementation and early markers of colon carcinogenesis. *Cancer Lett* 1992;63:159-65.

Setchell KD, Faughnan MS, Avades T et al. Comparing the pharmacokinetics of daidzein and genistein with the use of ¹³C-labeled tracers in premenopausal women. *Am J Clin Nutr* 2003;77:411-9.

Singh RP, Chidambara Murthy KN, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using in vitro models. *J Agric Food Chem* 2002;50:81-6.

Somekawa Y, Chiguchi M, Ishibashi T, Aso T. Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. *Obstet Gynecol* 2001;97:109-15.

Tan KP, Chen J, Ward WE, Thompson LU. Mammary gland morphogenesis is enhanced by exposure to flaxseed or its major lignan during suckling in rats. *Exp Biol Med (Maywood.)* 2004;229:147-57.

Thompson LU, Rickard SE, Orcheson LJ, Seidl MM. Flaxseed and its lignan and oil components reduce mammary tumor growth at a late stage of carcinogenesis.

Carcinogenesis 1996;17:1373-6.

Tikkanen MJ, Wahala K, Ojala S, Vihma V, Adlercreutz H. Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance. Proc Natl Acad Sci USA 1998;95:3106-10.

Toi M, Bando H, Ramachandran C et al. Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo. Angiogenesis. 2003;6:121-8.

ung MK, Lautens M, Thompson LU. Mammalian lignans inhibit the growth of estrogen-independent human colon tumor cells. Anticancer Res 1998;18:1405-1408.

Upmalis D, Lobo R, Bradley L. Evaluation of the safety and efficacy of an oral soy extract in the treatment of vasomotor symptoms in menopausal women (abstract 30). Menopause 1999;6:327.

USDA-Iowa State University Database on the Isoflavone Content of Foods, Release 1.3 – 2002 www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html

van Elswijk DA, Schobel UP, Lansky EP, Irth H, van der GJ. Rapid dereplication of estrogenic compounds in pomegranate (*Punica granatum*) using on-line biochemical detection coupled to mass spectrometry. Phytochemistry 2004;65:233-41.

Wagner JD, Schwenke DC, Greaves KA et al. Soy protein with isoflavones, but not an isoflavone-rich supplement, improves arterial low-density lipoprotein metabolism and atherogenesis. Arterioscler.Thromb.Vasc.Biol. 2003;23:2241-6.

Washburn S, Burke GL, Morgan T, Anthony MS. Effect of soy protein supplementation on serum lipoproteins, blood pressure and menopausal symptoms in perimenopausal women. Menopause 1999;6:7-13.

Wu J, Wang XX, Chiba H et al. Combined intervention of exercise and genistein prevented androgen deficiency-induced bone loss in mice. J Appl Physiol 2003;94:335-42.

Yan L, Yee JA, Li D, McGuire MH, Thompson LU. Dietary flaxseed supplementation and experimental metastasis of melanoma cells in mice. Cancer Lett 1998;124:181-6.

Yuan YV, et al. Short-term feeding of flaxseed or its lignan has minor influence on in vivo hepatic antioxidant status in young rats. Nutr Res 1999;19:1233-1243.

Zhang Y, et al. Daidzein and genistein glucuronides in vitro are weakly estrogenic and activate human natural killer cells at nutritionally relevant concentrations. J Nutr 1999 Feb;129(2):399-405.