

## The effect of Soy protein on cardiovascular disease (CVDs): A systemic review

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Cardiovascular disease (CVD) has been considered as the major cause of mortality rate all over the world. There are several epidemiological indications which prove that soy protein can potentially help decrease the risk of developing cardiovascular diseases. This comment agrees with the results of different meta-analysis studies. The US FDA approved a health claim in 1999 according to which a relationship exists between consumption of soy protein and the reduced risk of cardiovascular diseases. Soy protein contains some bioactive component such as globulin fractions (7s and 11s) isoflavones and other parts. Soy protein reduces serum cholesterol and LDL and/or Triglyceride and enhances High Density Lipoprotein(HDL). Several studies have also indicated the effect of soy protein components serum cholesterol and LDL and/or Triglyceride and enhance HDL. Some studies have shown the effect of soy protein components on modification of hormone secretion. Inflammation, Vascular Reactivity, Blood Pressure, and Thrombosis can be considered as other mechanisms that account for the reduction of cardiovascular disease effect of isoflavones or soy proteins. In this study, the primary mechanisms for any bioactive component of soy protein in decreases cardiovascular diseases and their reasons will be considered. However CVDs risks, remain a lot unknown.

**Keywords** Soy protein; Cardiovascular disease; Coronary heart disease; LDL; HDL

### References

- [1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD. Executive summary: heart disease and stroke statistics—2015 update. *Circulation*. 2015; 131(4):434-41.
- [2] Patil YK. A Review: Atherosclerosis & Its Treatment. *PharmaTutor*. 2014; 2(4):73-7.
- [3] Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation*. 2006; 113:1034-1044.
- [4] McNamara DJ. Cholesterol and atherosclerosis. *BiochimBiophysActa*. 2000; 1529:310-320
- [5] Padhi EM, Blewett HJ, Duncan AM, Guzman RP, Hawke A, Seetharaman K, Tsao R, Wolever TM, Ramdath DD. Whole Soy Flour Incorporated into a Muffin and Consumed at 2 Doses of Soy Protein Does Not Lower LDL Cholesterol in a Randomized, Double-Blind Controlled Trial of Hypercholesterolemic Adults. *The Journal of nutrition*. 2015; 145(12):2665-74.
- [6] Greaves KA, Wilson MD, Rudel LL, Williams JK, Wagner JD. Consumption of soy protein reduces cholesterol absorption compared to casein protein alone or supplemented with an isoflavone extract or conjugated equine estrogen in ovariectomized cynomolgus monkeys. *The Journal of nutrition*. 2000; 130(4):820-6.
- [7] Nijjar PS. Role of Dietary Supplements in Lowering LDL-Cholesterol. *Nutraceuticals and Health: Review of Human Evidence*. 2016; 19:73.
- [8] Carroll KK, Kurowska EM. Soy Consumption and Cholesterol Reduction: Review of Animal and Human Studies. *The Journal of Nutrition*. 1995; 125(3 Suppl):594S-7S.
- [9] Anderson JW, Bush HM. Soy protein effects on serum lipoproteins: a quality assessment and meta-analysis of randomized, controlled studies. *Journal of the American College of Nutrition*. 2011; 30(2):79-91.
- [10] Roussouw JE, Rikkind BM. Does lowering serum cholesterol lower coronary heart disease risk?. *EndocrinolMetabClin North Am*. 1990; 19:279-97
- [11] Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol. *Atherosclerosis*. 2008; 200:13-27.
- [12] Mensink RP, Zock PL, Kester AD. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003; 77:1146-55.
- [13] Clair RS, Anthony M. Soy, isoflavones and atherosclerosis. *HandbExp Pharmacol*. 2005; 170:301-23.
- [14] Torres N, Torre-Villalvazo I, Tovar AR. Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders. *J NutrBiochem*. 2006; 17:365-73.
- [15] Cederroth CR, Nef S. Soy, phytoestrogens and metabolism: a review. *Molecular and cellular endocrinology*. 2009; 304(1):30-42.

- [16] Weggemans, R. M. & Trautwein, E. A. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis. *Eur. J. Clin. Nutr.* 2003; 57: 940–946
- [17] Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004; 134(3):574-9.
- [18] Lovati MR, Manzoni C, Gianazza E. Soy protein peptides regulate cholesterol homeostasis in Hep G2 cells. *J Nutr.* 2000; 130:2543–2549
- [19] Yang A, Yu X, Zheng A, James AT. Rebalance between 7S and 11S globulins in soybean seeds of differing protein content and 11SA4. *Food chemistry.* 2016; 210:148-55.
- [20] Riblett AL, Herald TJ, Schmidt KA, Tilley KA. Characterization of  $\beta$ -conglycinin and glycinin soy protein fractions from four selected soybean genotypes. *Journal of Agricultural and food chemistry.* 2001; 49(10):4983-9.
- [21] Adams MR, Golden DL, Franke AA, Potter SM, Smith HS, Anthony MS. Dietary soy  $\beta$ -conglycinin (7S globulin) inhibits atherosclerosis in mice. *The Journal of nutrition.* 2004; 134(3):511-6.
- [22] Lovati MR, Manzoni C, Corsini A, Granata A, Frattini R, Fumagalli R, Sirtori CR. Low density lipoprotein receptor activity is modulated by soybean globulins in cell culture. *J Nutr.* 1992; 122: 1971-1978.
- [23] Cho S-J, Juillerat MA, Lee G-H. Identification of LDL-receptor transcription stimulating peptides from soybean hydrolysate in human hepatocytes. *J Agric Food Chem.* 2008; 56:4372–4376
- [24] Nagaoka S, Miwa K, Eto M, Kuzuya Y, Hori G, Yamamoto K. Soy protein peptic hydrolysate with bound phospholipids decreases micellar solubility and cholesterol absorption in rats and Caco-2 cells. *The Journal of nutrition.* 1999; 129(9):1725-30.
- [25] Zhan S, Ho SC. (2005). Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *The American journal of clinical nutrition.* 2005; 81(2):397-408.
- [26] Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause.* 1999; 6:7–13.
- [27] Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: a placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001; 86:3053–3060.
- [28] Van Ee JH. Soy constituents: modes of action in low-density lipoprotein management. *Nutrition reviews.* 2009; 67(4):222-34
- [29] 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(6):954 – 9
- [30] Huff M.W, Roberts D, Carroll K.K. Long-term effects of semipurified diets containing casein or soy protein isolate on atherosclerosis and plasma lipoproteins in rabbits. *Atherosclerosis.* 1982; 41: 327–336.
- [31] Anthony, M. S., Clarkson T. B., Bullock, B. C. & Wagner, J. D. Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery atherosclerosis of male cynomolgus monkeys. *Arterioscler. Thromb. Vasc. Biol.* 1997; 17: 2524 –2531.
- [32] Reynolds K, Chin A, Lees KA. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol.* 2006; 98:633-40.
- [33] Wei YH, Kao SH, Lee HC. Simultaneous increase of mitochondrial DNA deletion and lipid peroxidation in human aging. *Ann. N Y Acad Sci.* 1996; 786:24-43.
- [34] Bakhit RM, Klein BP, Essex-Sorlie D. Intake of 25g of soyabean protein with or without soy bean fiber alters plasma lipids in men with elevated cholesterol concentrations. *J Nutr.* 1994; 124:213-22.
- [35] Potter SM, Bakhit RM, Klein BP. Depression of plasma cholesterol in men by consumption of baked products containing soy protein. *Am J Clin Nutr.* 1993; 58:501-6
- [36] Merrill RM, Capocaccia R, Feuer EJ, Mariotto A. Cancer prevalence estimates based on tumour registry data in the surveillance, epidemiology, and end results (seer) program. *Int J Epidemiol.* 2000; 29:197-207
- [37] Kanazawa T, Osanai T, Zhang XS, Uemura T, Yin XZ, Onodera K, et al. Protective effects of soy protein on the peroxidizability of lipoproteins in cerebrovascular diseases. *J Nutr.* 1995; 125:639S-46S
- [38] Messina M, Messina V, Setchell K. *The simple soya beans your health.* New York: Avery Publishing Group. 1994
- [39] Fassini PG, Noda RW, Ferreira ES, Silva MA, Neves VA, Demonte A. Soybean glycinin improves HDL-C and suppresses the effects of rosuvastatin on hypercholesterolemic rats. *Lipids in health and disease.* 2011; 10(1):1.
- [40] Giacomo Fassini P, de Souza Ferreira E, Aparecida da Silva M, Augusto Neves V, Demonte A. Soybean glycinin (11S) increases HDL-cholesterol in hypercholesterolemic rats. *Nutrition & Food Science.* 2012; 42(2):102-10.
- [41] Wang, Y., de Mejia, G. A new frontier in soy bioactive peptides that may prevent age-related chronic diseases. *Compr. Rev. Food Sci. Food Safety.* 2005; 4: 63–78
- [42] Singh BP, Vij S, Hati S. Functional significance of bioactive peptides derived from soybean. *Peptides.* 2014; 54:171-9.
- [43] Chen, Q.; Wood, C.; Gagnon, C.; Cober, E.R.; Frégeau-Reid, J.A.; Gleddie, S.; Xiao, C.W. The  $\alpha$ 'subunit of beta-conglycinin and the A1–5 subunits of glycinin are not essential for many hypolipidemic actions of dietary soy proteins in rats. *Eur. J. Nutr.* 2014, 53, 1195–1207.
- [44] Forsythe III WA. Soy protein, thyroid regulation and cholesterol metabolism. *The Journal of nutrition.* 1995; 125(3):619S.

- [45] Ham JO, Chapman KM, Essex-Sorlie D, Bakhit RM, Prabhudesai M, Winter L, Erdman JW, Potter SM. Endocrinological response to soy protein and fiber in mildly hypercholesterolemic men. *Nutrition research*. 1993; 13(8):873-84.
- [46] Ricketts M-L, Moore DD, Banz WJ, Mezei O, Shay NF. Molecular mechanisms of action of the soy isoflavones includes activation of promiscuous nuclear receptors. A review. *J NutrBiochem*. 2005; 16:321-30
- [47] Borradaile NM, WILCOX LJ, EDWARDS JY, Murray WH. Soy phytoestrogens, genistein and daidzein, decrease apolipoprotein B secretion from HepG2 cells through multiple mechanisms. *Biochemical Journal*. 2002; 366(2):531-9.
- [48] Libby P. Inflammation in atherosclerosis. *Nature*. 2002; 420:868-874.
- [49] Boersma BJ, Patel RP, Botting N, White CR, Parks D, Barnes S, Darley-Usmar VM. Formation of novel bioactive metabolites from the reactions of pro-inflammatory oxidants with polyphenolics. *Biofactors*. 2001;15:79-81.
- [50] Verdrengh M, Jonsson IM, Holmdahl R, Tarkowski A. Genistein as an anti-inflammatory agent. *Inflamm Res*. 2003; 52:341-346.
- [51] Nagata M, Sedgwick JB, Busse WW. Synergistic activation of eosinophil superoxide anion generation by VCAM-1 and GM-CSF. Involvement of tyrosine kinase and protein kinase C. *Int Arch Allergy Immunol*. 1997; 114 (Suppl 1):78-80.
- [52] Tanabe J, Watanabe M, Kondoh S, Mue S, Ohuchi K. Possible roles of protein kinases in neutrophil chemotactic factor production by leucocytes in allergic inflammation in rats. *Br J Pharmacol*. 1994; 113:1480-1486.
- [53] Wolle J, Hill RR, Ferguson E, Devall LJ, Trivedi BK, Newton RS, Saxena U. Selective inhibition of tumor necrosis factor-induced vascular cell adhesion molecule-1 gene expression by a novel flavonoid. Lack of effect on transcription factor NF-kappa B. *ArteriosclerThrombVasc Biol*. 1996; 16:1501-1508.
- [54] Curran EM, Judy BM, Newton LG, Lubahn DB, Rottinghaus GE, Macdonald RS, Franklin C, Estes DM. Dietary soy phytoestrogens and ERalphasignalling modulate interferon gamma production in response to bacterial infection. *ClinExpImmunol*. 2004; 135:219-225.
- [55] Sadowska-Krowicka H, Mannick EE, Oliver PD, Sandoval M, Zhang XJ, Eloby-Childess S, Clark DA, Miller MJ. (1998). Genistein and gut inflammation: role of nitric oxide. *Proc SocExpBiol Med*. 1998; 217:351-357.
- [56] Chacko BK, Chandler RT, Mundhekar A, Khoo N, Pruitt HM, Kucik DF, Parks DA, Kevil CG, Barnes S, Patel RP. Revealing anti-inflammatory mechanisms of soy isoflavones by flow: modulation of leukocyte-endothelial cell interactions. *American Journal of Physiology-Heart and Circulatory Physiology*. 2005; 289(2):H908-15.
- [57] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000; 101:1899-1906.
- [58] Squadrito F, Altavilla D, Crisafulli A, Saitta A, Cucinotta D, Morabito N, D'Anna R, Corrado F, Ruggeri P, Frisina N, Squadrito G. Effect of genistein on endothelial function in postmenopausal women: a randomized, double-blind, controlled study. *Am J Med*. 2003; 114:470-476.
- [59] Cuevas AM, Iribarra VL, Castillo OA, Yanez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr*. 2003; 57:889-894.
- [60] Walker HA, Dean TS, Sanders TA, Jackson G, Ritter JM, Chowienczyk PJ. The phytoestrogen genistein produces acute nitric oxide-dependent dilation of human forearm vasculature with similar potency to 17 $\beta$ -estradiol. *Circulation*. 2001; 103:258-262.
- [61] Steinberg FM, Guthrie NL, Villablanca AC, Kumar K, Murray MJ. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. *Am J Clin Nutr*. 2003; 78:123-130.
- [62] Yildirim A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksak G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol*. 2001; 24:711-716.
- [63] Nestel PJ, Yamashita T, Sasahara T, Pomeroy S, Dart A, Komesaroff P, Owen A, Abbey M. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *ArteriosclerThrombVasc Biol*. 1997; 17:3392-3398.
- [64] Hale G, Paul-Labrador M, Dwyer JH, Merz CN. Isoflavone supplementation and endothelial function in menopausal women. *ClinEndocrinol (Oxf)*. 2002; 56:693-701.
- [65] Teede HJ, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness—A placebo-controlled study in men and postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2003; 23:1066-1071.
- [66] Simons LA, von Konigsmark M, Simons J, Celermajer DS. Phytoestrogens do not influence lipoprotein levels or endothelial function in healthy, postmenopausal women. *Am J Cardiol*. 2000; 85:1297-1301.
- [67] Kingwell BA, Gatzka CD. Arterial stiffness and prediction of cardiovascular risk. *J Hypertens*. 2002; 20:2337-2340.
- [68] Van der Schouw YT, Pijpe A, Lebrun CE, Bots ML, Peeters PH, Van Staveren WA, Lamberts SW, Grobbee DE. Higher usual dietary intake of phytoestrogens is associated with lower aortic stiffness in postmenopausal women. *ArteriosclerThrombVasc Biol*. 2002; 22:1316-1322.
- [69] Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J ClinEndocrinol Metab*. 1999; 84:895-898.
- [70] Anthony MS, Clarkson TB, Williams JK. Effects of soy isoflavones on atherosclerosis: potential mechanisms. *The American journal of clinical nutrition*. 1998; 68(6):1390S-3S.

- [71] Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW, van der Schouw YT. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *Jama*. 2004; 292(1):65-74.
- [72] Wilcox JN, Blumenthal BF. Thrombotic mechanisms in atherosclerosis: Potential impact of soy proteins. *J Nutr*. 1995; 125:S631–S638.
- [73] Williams JK, Clarkson TB. Dietary soy isoflavones inhibit in-vivo constrictor responses of coronary arteries to collagen-induced platelet activation. *Coron Artery Dis*. 1998; 9:759–764.
- [74] Kondo K, Suzuki Y, Ikeda Y, Umemura K. Genistein, an isoflavone included in soy, inhibits thrombotic vessel occlusion in the mouse femoral artery and in vitro platelet aggregation. *Eur J Pharmacol*. 2002; 455:53–57.