
Soy and Isoflavones: A Review of the Potential Role of Phytoestrogens in the Management of Hypercholesterolemia

Antonella Dewell, MS, RD, and Clarie B. Hollenbeck, PhD



Media reports have suggested that increased consumption of soy or soyfoods may be useful in reducing cholesterol levels and the risk for coronary artery disease (CAD). This article reviews the literature on soy and isoflavones and considers the clinical applicability and utility of soy diets for hypercholesterolemic populations.

Phytoestrogens are a group of non-steroidal plant chemicals with estrogen-like activity. The similar chemical structures of 17 β -estradiol and equol, a phytoestrogen metabolite, make them virtually superimposable (Figure 1). The molecules each contain the phenolic ring and a nearly identical distance between the hydroxyl groups. Both these components are considered prerequisites for estrogen binding.¹ The estrogenic activity of genistein and daidzein, the predominant isoflavones in soy, has been determined to be 10-2 to 10-3 that of 17 β -estradiol.² However, their concentration in the plasma of individuals consuming the traditional Japanese diet (50-80 mg/d soy-derived phytoestrogens) can be 100 times higher than the concentration of endogenous estrogens.³ Thus, the plasma concentrations of these phytoestrogens would put them in a range consistent with normal physiological response.

Phytoestrogens can be categorized into three main classes: isoflavones, lignans, and coumestans. Whereas lignans and coumestans do not contribute significantly to dietary phytoestrogen intake, isoflavones are widespread in leguminous plants and present in highest amounts in soybeans. Isoflavones are associated with the protein fraction of soybeans; hence, they are present only in the whole soybean and other high-protein secondary products. Consequently, soy oils and soy lecithin are devoid of isoflavones. The isoflavone content of soybeans and other soy products is illustrated in Table 1.

Whole soybeans contain the highest concentrations of isoflavones. The concentrations become progressively lower with increasing degree of processing. The aqueous processing in tofu and the dilution of soy protein with other ingredients in soy milk and second-generation soyfoods explain the significantly reduced isoflavone content present in these products. Finally, soy protein concentrates generally contain insignificant amounts of isoflavones because they are

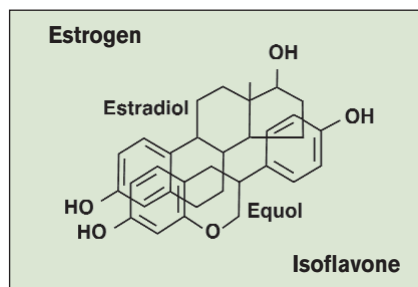


Figure 1

obtained through alcohol extraction, a technique that removes most of the isoflavones from soy.^{4,5} It is important to note that whole soybeans are not widely consumed in the Western diet. Rather, the most commonly available products for consumers in search of alternatives to animal protein sources are soy milk, tofu, and second-generation soyfoods, which contain as little as 2-23% of the isoflavone content of whole soybeans (Table 1).

Hypothesis or Fact?

Phytoestrogens, especially isoflavones, have been the highlight of media reporting and dietary recommendations from Federal and private health agencies as a result of extensive research over the past 10-12 years. The number of consumers who reportedly view soyfoods as healthy increased from 59% in 1998 to 76% in

2000. Consequently, soy food consumption has markedly increased, in part because of the extended availability and marketing of soy products by many mainstream food companies. Indeed, isoflavones are now widely available in the form of supplements and also are used as food fortificants.⁶ Soy protein and isoflavones have been heralded as a dietary approach for reducing the risk for coronary artery disease (CAD) by means of lowering serum total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations.⁷ In 1999, the Food and Drug Administration approved a claim petition stating that diets low in saturated fat and cholesterol, which include 25 g/day of soy protein, may reduce the risk of heart disease.⁸ A year later, the American Heart Association revised its Dietary Guidelines to include a recommendation that high-risk individuals with elevated total and LDL cholesterol consume soy protein containing isoflavones, in addition to making other heart-healthy diet modifications.⁹

The hypothesis that soyfoods may lower the risk of CAD stems from epidemiological observations that Asian populations, whose diets include soyfoods as a staple, have a lower incidence of CAD than populations consuming the

Table 1.
Isoflavone content in various soy products^{1,2}

Product	Isoflavones	
	(mg/g As Is)	% ³
Whole soybeans	1.0-1.6	100
Roasted soybeans	1.6	100
Texturized soy protein	1.3-1.4	100
Soy flour	1.1	85
Soy protein isolate	0.5-0.6	38-46
Tofu	0.3	23
Fermented products ⁴	0.3-0.6	23-46
Soy milk	0.2	15
Second-generation soy foods ⁵	0.03-0.3	2-23
Soy protein concentrate	0.05	4

¹Data extrapolated from references 4 and 5.

²Ranges represent variation due to variety, location, and/or year of harvest of soybeans.

³Percentage of isoflavones relative to whole soybean (mean value, 1.3 mg/g).

⁴Tempeh, miso, fermented bean curd, and bean paste.

⁵Soy hot dog, tempeh burger, tofu yogurt, soy cheese, soy noodles.

typical Western diet.¹⁰ In addition, the striking similarities in chemical structure and biological activity between isoflavones and endogenous estrogen has caused some to extol the value of isoflavones in reducing cholesterol. On the other hand, the experimental evidence in support of this notion is not as overwhelming as generally perceived, and the currently available data on the effects of soy on serum lipoproteins remain inconclusive.

A Look at Soy Research

Some researchers have examined soy protein, mostly in the form of soy protein isolate (SPI), whereas others have studied purified isoflavone extracts. Investigations using purified isoflavone supplements are quite consistent in reporting no significant effects on serum lipoproteins either in postmenopausal women or in mixed populations. These studies have used a range of 40-150 mg/d of isoflavones and examined their effect on both normocholesterolemic and hypercholesterolemic men and women.¹¹⁻¹⁶ In a key crossover study of nine mildly hypercholesterolemic postmenopausal women, 80 mg/d of isoflavones failed to alter serum lipoproteins significantly.¹² The authors observed a downward trend in LDL (6%) and an upward trend in HDL (4%), resulting in an apparent reduction of 10% in the LDL/HDL cholesterol ratio between the placebo and treatment values. However, all these differences, including total cholesterol (3%), were quantitatively very small and not statistically significant.

In our study of 36 hypercholesterolemic postmenopausal women, a much higher dosage of isoflavones (150 mg/d) over six months resulted in quantitatively similar reductions in total and non-HDL cholesterol. This also failed to reach statistical significance.¹⁴ In stark contrast to all the major studies using isoflavone extracts, one recent study reported a significant increase in HDL

cholesterol of 16-29% in postmenopausal women consuming doses of isoflavones that ranged from 28-85 mg/d.¹⁷ Interestingly, the differences in HDL cholesterol concentrations observed in these women were independent of dose. The relevance of these findings, however, is difficult to interpret given the absence of a control group. Therefore, the results of controlled experimental studies are consistent in reporting the absence of any significant effect of purified isoflavone supplements on plasma lipids and lipoproteins.

Varied Results on Soy Protein

Studies of soy protein in human populations, on the other hand, have shown variable results.¹⁸⁻²⁷ There are several reasons for such mixed findings. In general, the subjects' initial cholesterol concentrations appear to be a strong determinant of soy's effects on plasma lipids and lipoproteins, with the greatest decline occurring in individuals with hypercholesterolemia. Studies in the past 10-12 years have reported statistically significant, but quantitatively small, reductions in LDL-cholesterol and/or serum cholesterol (2.5-8.8%) in men,^{19,20} mixed populations,²¹ and premenopausal,²² perimenopausal,²³ and postmenopausal women.^{24,25} Some also showed quantitatively small increases in HDL cholesterol in postmenopausal women²⁶ and young healthy people.²⁷

Slightly higher reductions in total and LDL cholesterol (9.3-12.9%) have been reported in an often-quoted meta-analysis of 38 studies, performed from 1967 to 1994.⁷ However, when the participants were categorized according to initial cholesterol concentration, the changes in serum cholesterol concentrations clearly were dependent on initial cholesterol concentrations. For example, the cholesterol-lowering effects observed in individuals with baseline total cholesterol concentrations <260 mg/dL were in the same ranges as the studies cited above (3-7%); slightly higher reductions in serum cholesterol concentrations

(7-9%) were reported in those individuals with baseline total cholesterol between 260 and 330 mg/dL; and reductions in serum cholesterol concentrations greater than 10% were realized only in those individuals with initial total cholesterol >330 mg/dL. It is important to emphasize that a major limitation of this approach to data analysis lies in summarizing data from studies with very different research designs and study populations. The studies evaluated in this meta-analysis involved mostly men, and some premenopausal women and children. More importantly, alterations in the content of soy-protein were not the only dietary changes made in many of these studies. Changes in other dietary components such as saturated fat and cholesterol also were present in several of the studies and could explain the lower plasma cholesterol concentrations reported. Thus, even the quantitatively small changes in cholesterol concentrations reported in these studies could not be attributed solely to the presence of soy protein or soy-derived isoflavones.

Another confounding variable in studies using soy proteins involves differences in the nature of the soy protein in the control populations. Most studies investigating the effect of soy protein used SPI with various amounts of isoflavones (range: 56-170 mg/d of isoflavones). In four studies comparing soy protein with different amounts of isoflavones,^{21, 22,25,27} alcohol extraction was used to obtain the control soy protein source, with low or zero isoflavone content. This technique deprives soy not only of isoflavones but also of other components that are known to lower cholesterol concentrations (eg, saponins, phytic acid, and other alcohol-soluble phytochemicals). For this reason, one cannot exclude the possibility that these components may have played an important role in the hypocholesterolemic effects observed in these studies. Again, the available evidence does not justify the conclusion that the differences observed between intact soy

protein and alcohol-extracted soy protein are attributable to the isoflavone component associated with the intact soy protein.^{22,25,27,28} In two recent studies, involving a mixed population²⁹ and a population of hypercholesterolemic postmenopausal women,³⁰ consumption of 40-42 g/d of soy protein (80-118 mg/d of isoflavones) resulted in quantitatively similar changes in plasma lipoproteins as the studies discussed earlier. However, these two recent studies failed to reach statistically significant differences compared to the control group, which consumed milk protein.

Relation of Soy Benefit to Equol

It has been suggested that at least some of the putative beneficial effects of soy may be related to the presence of the metabolite equol, produced by intestinal microflora from daidzein, a major isoflavone present in soy.^{31,32} Equol has been shown to possess higher affinity for the estrogen receptors than the parent isoflavone daidzein and to be equivalent in binding affinity to genistein. It appears that about 50-70% of the population can produce equol, due to differences in microflora species in the large intestine. Therefore, the estrogenic effects of soy may be stronger in a sub-population of individuals who are equol producers. In addition, the LDL-cholesterol-lowering effects of soy also have been shown to be greater during the mid-follicular and periovulatory phases of the menstrual cycle in young premenopausal women, although LDL concentrations over the entire cycle are unchanged.²² Thus, there may be times when the effects of soy might be greater than others.

The changes reported in these studies,^{18-27,29,30} although statistically significant, are quantitatively similar to those observed in the studies using purified isoflavone supplements.¹¹⁻¹⁶ Therefore, it appears that the differences between the soy-based studies and the investigations of isoflavone extracts may be more apparent than real. Further, the discrep-

ancies that do exist are merely statistical in nature, rather than a reflection of actual quantitative differences in the magnitude of the data reported.³³

Statistical versus Clinical Significance

It is important to stress that statistical significance does not necessarily suggest the clinical importance or significance of any finding, a point that seems to have been lost, in any meaningful terms, in the discussion of many of the studies cited here. It is the clinical interpretation of the demonstrated differences that must assume primary importance in any discussion and any implementation of any conclusions drawn from this area of research. Even in the most well-designed studies, the magnitude of the changes obtained remains very small, ranging from 2.5-8%, with the greatest reductions observed in the most hypercholesterolemic populations. For example, the study reporting the greatest reduction (~9%) in non-HDL cholesterol (primarily LDL) also had the study population with the highest baseline cholesterol concentrations.²⁴ In this study, non-HDL cholesterol was lowered from an average of 202 mg/dL to 184 mg/dL after six months of treatment. Given that the National Cholesterol Education Program guidelines³⁴ suggest a desirable level of LDL cholesterol <130 mg/dL, it would be reasonable to conclude that the effects of this reduction would be of little clinical significance in terms of CAD.

Potential Adverse Effect of Soy

Not all studies show beneficial effects from increased soy consumption.³⁵ Most legumes, including soy, are rich in antinutrients (hemagglutinins, enzyme inhibitors, etc) and have been associated with failure to thrive and endocrine abnormalities in children.³⁶ Concentrations of soy isoflavones in the range of levels found with consumption of soy-based diets have been shown to inhibit thyroxine synthesis inducing goiter and hypothyroidism in

infants fed soy-based formulas. In some cases, these levels have led to the development of autoimmune thyroid disease. Soy isoflavones inhibit the iodination of tyrosine by *thyroid peroxidase* by competing as a substrate with tyrosine in the reaction resulting in the synthesis of mono-, di- and tri-iodoisoflavones.³⁶

Finally, high concentrations of genistein, daidzein, and other isoflavones have been reported to result in genetic abnormalities in a variety of cells including human lymphocytes, oviduct cells, and testis cells. These concentrations may possess potentially genotoxic effects.³⁶

Conclusion

Review of the evidence in the current literature on the potential role of soy protein or isolated soy isoflavone supplementation for improving plasma lipoproteins suggests few solid conclusions and raises substantial questions about the clinical importance of putative hypocholesterolemic effects. Therefore, conclusions regarding the hypocholesterolemic benefits of soy made by researchers³⁷ and health agencies^{8,9} perhaps are premature and overstated. Indeed, some have gone as far as to recommend phytoestrogens to physicians as a viable alternative to estrogen/progestin therapy for reducing lipid levels and the risk of CAD in postmenopausal women.³⁸ Interestingly, a study investigating the effect of 20 g of soy protein (an amount similar to that appearing on the FDA-approved claim on food products) on plasma lipoproteins reported only a 2.6% reduction in non-HDL cholesterol in moderately hypercholesterolemic men.²⁰

Soybeans are a very healthful food; and this article is not meant to discourage people from incorporating them into their diet. These foods are a great source of relatively complete plant protein, fiber, unsaturated fat, vitamins, and minerals; and substituting them for other sources of proteins increases the variety of nutrient intake in the diet.

However, clinical practitioners and consumers should be cautioned not to expect clinically meaningful reductions in plasma lipoprotein levels as a consequence of this dietary change. To reach a dietary intake of isoflavones within the ranges used by the studies discussed, one would have to consume about 60-120 g/day of soybeans or up to one pound of tofu (Table 1), which is impractical.

Clearly, many women are eager to find an alternative to currently available therapies for reasons that may include fear of breast cancer, intolerance to drugs, or the belief that natural substances are a better choice than pharmaceuticals. Unfortunately, soy may not be the answer for postmenopausal women at risk for CAD who are seeking to reduce their plasma cholesterol. Although the changes observed with soy protein have reached statistical significance in some clinical trials, the quantitative differences achieved are too modest to be of clinical significance in reducing CAD risk.

Therefore, based on currently available information on the effect of either soy protein or purified isoflavones on plasma lipoproteins, it would be premature to make any recommendation for their use as an alternative to established therapies managing hypercholesterolemia in either postmenopausal women or the general population. ■

Antonella Dewell and Dr. Hollenbeck are with the department of Nutrition and Food Science, San Jose State University, San Jose, California.

Their research was funded by a grant from the College of Applied Science & Arts at San Jose State University.

References

1. Tham DM, Gardner CD, Haskell WL. Clinical Review 97: Potential health benefits of dietary phytoestrogens: A review of the clinical, epidemiological, and mechanistic evidence. *J Clin Endocrinol Metab* 1998;83(7):2223-35.
2. Miksicek RJ. Interaction of naturally occurring non-steroidal estrogens with expressed recombinant human estrogen receptor. *J Steroid Biochem Mol Biol* 1994;49:153-60.
3. Setchell KDR, Cassidy A. Dietary isoflavones: biological

- cal effects and relevance to human health. *J Nutr* 1999;129:758S-67S.
4. Wang HJ, Murphy PA. Isoflavone content in commercial soybean foods. *J Agric Food Chem* 1994;42:1666-73.
5. Coward L, Barnes NC, Setchell KDR, Barnes S. Genistein, Daidzein, and their β -glycoside conjugates: Antitumor isoflavones in soybean foods from American and Asia diets. *J Agric Food Chem* 1993;41:1961-67.
6. Messina M, Gardner C, Barnes S. Gaining insight into the health effects of soy but a long way still to go: Commentary on the fourth international symposium on the role of soy in preventing and treating chronic disease. *J Nutr* 2002;132:547S-51S.
7. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333(5):276-82.
8. Food and Drug Administration. Food labeling: health claims; soy protein and coronary artery disease. *Federal Register* 1999;64:57699-733.
9. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000;102:2284-99.
10. Beaglehole R. International trends in coronary artery disease mortality, morbidity, and risk factors. *Epidemiological Review* 1990;12:1-15.
11. Nestel PJ, Yamashita T, Sasahara T, et al. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol* 1997;17(12):3392-98.
12. Nestel PJ, Pomeroy S, Kay S, et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J Clin Endocrinol Metab* 1999;84(3):895-8.
13. 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;85:1297-301.
14. Dewell A, Hollenbeck CB, Bruce B. The effects of soy-derived phytoestrogens on serum lipids and lipoproteins in moderately hypercholesterolemic postmenopausal women. *J Clin Endocrinol Metab* 2002;87(1):118-21.
15. Samman S, Lyons Wall PM, Chan GS, et al. The effect of supplementation with isoflavones on plasma lipids and oxidisability of low density lipoprotein in premenopausal women. *Atherosclerosis* 1999;147(2):277-83.
16. Hodgson JM, Puddey IB, Beilin LJ, et al. Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentrations: A randomized controlled trial in humans. *J Nutr* 1998;128:728-32.
17. Clifton-Bligh PB, Baber RJ, Fulcher GR, et al. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. *Menopause* 2001;8(4):259-65.
18. Carroll KK. Review of clinical studies on cholesterol-lowering response to soy protein. *J Am Diet Assoc* 1991;91(7):820-7.
19. Potter S, Bakhit RM, Essex-Sorlie D, et al. Depression of plasma cholesterol in men by consumption of baked products containing soy protein. *Am J Clin Nutr* 1993;58:501-6.
20. Teixeira SR, Potter SM, Weigel R, et al. Effects of feeding 4 levels of soy protein for 3 and 6 wk on blood lipids and apolipoproteins in moderately hypercholesterolemic men. *Am J Clin Nutr* 2000;71:1077-84.
21. Crouse JR, Morgan T, Terry JG, et al. A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. *Arch Intern Med* 1999;159:2070-6.

22. Merz Demlow BE, Duncan AM, Wangen KE, et al. Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women. *Am J Clin Nutr* 2000;71(6):1462-9.
23. 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(1):7-13.
24. Baum JA, Teng H, Erdman JW, et al. Long-term intake of soy protein improves blood lipid profiles and increases mononuclear cell low-density-lipoprotein receptor messenger RNA in hypercholesterolemic, postmenopausal women. *Am J Clin Nutr* 1998;68:545-51.
25. Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. *Am J Clin Nutr* 2001;73(2):225-31.
26. Scheiber MD, Liu JH, Subbiah MT, et al. Dietary inclusion of whole soy foods results in significant reductions in clinical risk factors for osteoporosis and cardiovascular disease in normal postmenopausal women. *Menopause* 2001;8(5):384-92.
27. Sanders TA, Dean TS, Grainger D, et al. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr* 2002;76:373-7.
28. Lichtenstein, AH. Got soy? *Am J Clin Nutr* 2001;73(4):667-8.
29. Teede HJ, Dalais FS, Kotsopoulos D, et al. 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(7):3053-60.
30. Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr* 2001;73(4):728-35.
31. Setchell KD, Brown NM, Lydeking Olsen E. The clinical importance of the metabolite equol—a clue to the effectiveness of soy and its isoflavones. *J Nutr* 2002;132:3577-84.
32. Lydeking-Olsen E, Meinertz H, Nilausen H, et al. Lipoprotein effects of soy milk and progesterone on prevention of bone loss in postmenopausal hypercholesterolemic women. *J Nutr* 2002;132:608S (abs).
33. Dewell A, Hollenbeck CB, Bruce B. Authors' response: Soy supplement - why is the effect so elusive? *J Clin Endocrinol Metab* 2001;87(7):3508-9.
34. National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *Circulation* 1994;89:1333-445.
35. Sirtori CR. Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symptoms and osteoporosis. *Drug Saf* 2001;24(9):665-82.
36. Fort P, Moses N, Fasano M. Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *J Am Coll Nutr*;1990(9):164-67.
37. Clarkson TB. Soy, soy phytoestrogens and cardiovascular disease. *J Nutr* 2002;132:566S-69S.
38. Ariyo AA, Villablanca AC. Estrogens and lipids. Can HRT designer estrogens, and phytoestrogens reduce cardiovascular risk markers after menopause? *Postgrad Med* 2002;111(1):23-30; quiz 3.