A multitude of substances are present in small amounts in plants that can affect mammalian biological processes relevant to cardiovascular disease and other common human diseases. However, few of the thousands of bioactive molecules have been studied well in cells or animals, and still fewer in humans. This slim evidence base notwithstanding, a staggering array of these compounds are available for our use as pricey nutritional supplements. The phytoestrogens are arguably the most intensively studied of these substances, and as a result, conclusions about them can be drawn with good scientific support. Phytoestrogens are a subcategory of compounds called flavonoids, a group composed of hundreds or more types of molecules. The 2 classes of phytoestrogens are isoflavones, notably found in soy products, and lignans, present in nuts, fruits, cereal grains, tea, and coffee. Because of their assumed health benefit, isoflavone content is advertised in many foods that contain soybeans, and isoflavones are sold as nutritional supplements.

The phytoestrogen hypothesis stemmed from several independent lines of evidence. One was the recognition that phytoestrogens had estrogenic effects in animals. Another came from epidemiological studies in Asia showing a low prevalence of cardiovascular disease and hormone-dependent cancers of the breast, endometrium, and prostate. A third was the well-established animal model of hyperlipidemia and atherosclerosis that used casein, a milk protein, and prostate. A fourth was the recognition that soy phytoestrogens slowed the progression of coronary atherosclerosis. Several mechanisms were postulated, including endothelial vasodilation, antiinflammatory effects, and antithrombotic effects. However, the effects of phytoestrogens on atherosclerosis or cardiovascular disease in humans have not been studied either in clinical trials or in prospective epidemiological studies.

The study by van der Schouw and colleagues gives us much needed information on phytoestrogens in the range of usual intake in a western population, Dutch women. In this observational study, women 49 to 70 years old completed a diet and health questionnaire and were followed up for more than 6 years. The authors found that a high phytoestrogen intake, in isoflavones and lignans, is not associated with decreased incidence of cardiovascular disease. Strengths of the study are the representativeness of the population and the relatively large number of cases of cardiovascular disease, 519. Limitations include the absence of measurements of blood and urine isoflavones and lignans as biomarkers to confirm dietary intake of phytoestrogens and incomplete information on soy isoflavones in the diet questionnaire. Thus, the relationship of phytoestrogen intake and cardiovascular disease needs to be studied in other large population-based cohorts. The authors reported a protective association of lignan intake and cardiovascular disease in smokers. This finding emerged from testing many subgroups of the population, and the hypothesis of a smoker-lignan interaction was not specified prospectively, weakening its validity. The authors speculated that the antioxidant properties of lignans would be especially therapeutic in smokers. However, this line of thinking has not proved true for several other dietary antioxidants.

This “negative” finding on dietary phytoestrogens and cardiovascular disease needs contextual interpretation. Is it consistent with the evidence from phytoestrogen trials on cardiovascular risk factors such as blood lipids or blood pressure? Is the upper part of the intake range in Holland too low to have biological effects, and would higher daily amounts of phytoestrogens be needed for cardiovascular health? In Japan, the intake of isoflavones is more than 10 times that in Holland. The same group of researchers recently reported that soy isoflavones did not affect blood lipid risk factors in a large clinical trial in Dutch postmenopausal women. The amount given to the participants was 99 mg, in the upper range of intake for Asian populations.

A beneficial action of isoflavones was considered a promising hypothesis to explain inconsistent results of trials of soy protein as modulators of blood lipid risk factors, and a large literature has developed, primarily during the past 10 years.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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In 1995, a meta-analysis concluded that soy protein lowers serum cholesterol in moderate to severe hypercholesterolemia but did not have benefits in those with total cholesterol <255 mg/dL.9 There was much variation among the results of individual studies, and no effect of dose of soy protein. These 2 facts led investigators to look for other explanations for the effects of soy protein preparations, and attention turned to the isoflavones that were present in some soy protein products that were not treated with alcohol during their isolation from soybeans. Alcohol washing was a common step in manufacturing the soy protein isolate used in many food products, including soy protein powder and “soy burgers,” although it is used less often now. In trials, isoflavones were used in doses corresponding to the upper range of Asian populations, e.g., 100 mg/d, either with soy protein or as a pill. Results were discouraging. In 1999, the Food and Drug Administration, although giving a generous interpretation of studies of soy protein and LDL cholesterol and a coveted health claim for soy protein, noted that the evidence did not favor a protective role for soy isoflavones as a component of soy protein products.10 Most subsequent studies in people with average serum cholesterol or hypercholesterolemia did not find significant LDL reduction,8,11–15 and a recent meta-analysis found no significant lowering of LDL cholesterol.16 Soy isoflavones did not affect other lipid risk factors, including HDL cholesterol, triglycerides, or lipoprotein(a). Overall, the evidence does not favor lipid effects from soy isoflavones. Isoflavones also did not affect blood pressure.12–15,17 Thus, the lack of association of cardiovascular disease and isoflavone intake in food in Dutch women is entirely consistent with the extensive clinical trial evidence that has developed on risk factors for cardiovascular disease.

The phytoestrogen hypothesis logically extended to other hormone-related conditions. Phyoestrogens, as weak agonists, could possibly ameliorate symptoms of the menopause and perhaps make up some of the deficiency in estrogen as a cause of osteoporosis. Phytoestrogens could antagonize the adverse effects of natural estrogen on breast or the uterine endometrium, or protect the prostate by reducing the action of testosterone. Conversely, phytoestrogens could act directly to stimulate hormone-related cancers. Is there any evidence for a clinically important hormonal effect of isoflavones in women? After considerable study in clinical trials, isoflavones clearly do not lessen menopausal hot flushes,18,19 and their effect on osteoporosis is mixed, with studies showing mild benefit or no effect.8,20,21 Epidemiology and scant clinical trials do not provide a clear picture of whether phytoestrogens have any effect, beneficial or harmful, on hormone-related cancers.22–25

Where does this leave us for using phytoestrogens to prevent or treat cardiovascular disease and other conditions? There is little basis now for considering phytoestrogens cardioprotective. Evidence does not show beneficial estrogenic actions for the menopause. In view of the rampant promotion of isoflavone-containing supplements, often for presumed benefit for women, the evidence to date is a cautionary tale of scientific optimism and unrestrained commercialism outstripping the development of evidence. Regulatory law on dietary supplements encourages this mismatch between hypothesis and reality. Nonetheless, phytoestrogens and other flavonoids remain an interesting group of molecules with diverse biological effects yet to be fully explored, either as pharmacological agents or as components of the diet.

References


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