
Soy beans

Soy Isoflavones

Introduction

Isoflavones are a class of phytochemicals found in soybeans, chickpeas, and other legumes. Soybeans have the highest concentration of isoflavones, as well as the highest concentration of the individual isoflavones thought to contain medicinal properties – genistein and daidzein. Isoflavones have antioxidant properties that protect the cardiovascular system from LDL oxidation. Isoflavones are also a type of phytoestrogen that have been studied for their role in the prevention of osteoporosis and symptoms of menopause, as well as breast and prostate cancer.

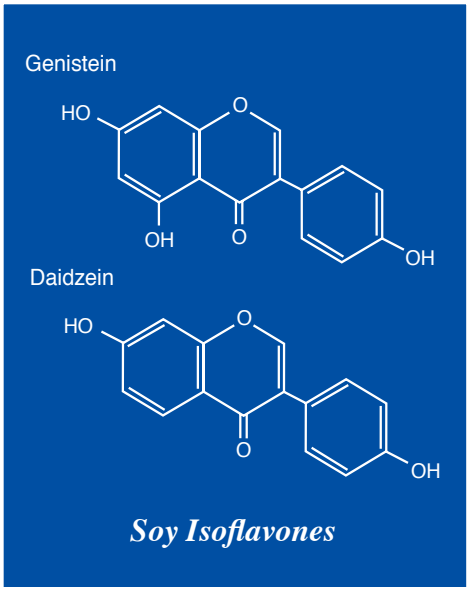
Biochemistry

The principal isoflavones in soy are genistein, daidzein, and their metabolites. Genistein has a hydroxyl group in the 5-position, giving it three hydroxyl groups, while daidzein has two. Isoflavones are members of the flavonoid family of plant compounds, which is in turn a member of the group of plant constituents known as polyphenols. Isoflavones are not as ubiquitous in nature as other flavonoids such as flavones and flavonols, being found primarily in one subfamily of Leguminosae, the Pailionoideae family.[1] Genistein is formed from biochanin A, and daidzein from formononetin.[2] Genistein and daidzein also occur in soy products in the form of their glycosides, genistin and daidzin.

Pharmacokinetics

Isoflavones undergo extensive metabolism in the intestinal tract prior to absorption. In the case of soy isoflavone glycosides, intestinal bacterial glucosidases cleave the sugar moieties, releasing the biologically active isoflavones, genistein and daidzein. In adults, genistein and daidzein are further transformed by bacteria to the metabolites equol, O-desmethylangolensis, dihydrogenistein, and p-ethylphenol. Because of soy intake by livestock, isoflavone metabolites

are also consumed in dairy products and meat.[3] In at least one study, genistein was well absorbed in the small intestine by human subjects fed a soy beverage.[4] After absorption, isoflavones are transported to the liver; the effectiveness of this hepatic first-pass clearance influences the amount that reaches peripheral tissues.[4] Isoflavones and their metabolites are eliminated primarily via the kidneys.[5]



Mechanisms of Action

There are many proposed mechanisms for the therapeutic effects of isoflavones, including inhibition of protein tyrosine kinase (PTK), binding to estrogen receptors (although soy's inhibition of cancer cell growth does not seem to be entirely estrogen dependent),[6] inhibition of production of reactive oxygen species,[6] induction of DNA strand breakage resulting in apoptosis or cell death,[7] inhibition of angiogenesis,[8] modulation of sex steroid binding protein,[9] inhibition of 5 alpha-reductase,[10] inhibition of P-form phenolsulfotransferase (PST) -mediated sulfation,[11] inhibition of thrombin formation and platelet activation,[12] and increased LDL receptor activity.[13]

Clinical Indications

Cancer

There is considerable epidemiological evidence, including a review of 21 studies on 26 different cancer sites,[14] that soy isoflavones might provide protection from several types of cancer. These same researchers examined 26 different animal studies and found 17 of them demonstrated soy's protective effect from experimental carcinogenesis. *In vitro* studies found genistein to be a very potent inhibitor of angiogenesis.[8] Case-control, epidemiological, animal, and *in vitro* studies all point to the effectiveness of soy isoflavones for the prevention of breast cancer.[15-18] Epidemiological, animal, and *in vitro* evidence suggest soy isoflavones could help prevent prostate cancer.[19-22]

Cardiovascular Disease

Soy isoflavones inhibit atherosclerotic plaque formation by intervening at several steps in thrombus formation. Arterial thrombus formation is generally initiated by an injury to the endothelial cells lining the blood vessels. One of the first events after an injury is thrombin formation. This leads to a cascade of events, including platelet activation, resulting in thrombus formation. Genistein has been found to inhibit thrombin formation and platelet activation.[23] The pathogenesis of atherosclerotic plaque formation also involves, in addition to lipid accumulation, the infiltration of monocytes and T-lymphocytes into the artery wall, contributing to the thickening of the wall and occlusion of the vessel. Monocytes and lymphocytes adhere to endothelial cell surfaces via expression of certain "adhesion molecules." Infiltration and proliferation appear to be controlled by peptide growth factors. Increased levels of isoflavones, genistein in particular, appear to alter growth factor activity and inhibit cell adhesion and proliferation, all activities necessary for lesion formation in the intima of blood vessels.[24]

Soy protein supplementation also has a positive effect on lipid profiles in humans. A double-blind trial found soy supplementation, in amounts as low as 20 grams per day, effectively improved the blood lipid profile after just six weeks.[25] In another double-blind trial, 21 severely hypercholesterolemic patients – all with a history of resistance to HMG CoA reductase inhibitor therapy – ingested a soy protein drink (providing 35 grams protein per day) or placebo daily for four weeks.[26] The treatment group experienced a 6.5-7.4-percent reduction in total cholesterol levels. Although one meta-analysis suggested the isoflavone component of soy might account for up to 70 percent of its hypocholesterolemic effect,[27] there is also evidence of cholesterol-lowering effects from isoflavone-free products as well, suggesting the principal effect of soy on blood lipids may be mediated by its protein component.[28]

Osteoporosis

Animal studies have found soy protein isolates appear to enhance bone density,[29] and epidemiological evidence points to diets high in soy as a possible protection against osteoporosis.[30] A clinical study found 45 grams per day soy grits increased bone mineral density and improved vaginal cytology maturation index when compared to those given 45 grams per day wheat.[31] In a randomized, double-blind trial, supplementation with a soy protein isolate providing 90 mg soy isoflavones per day for six months produced significant increases in bone mineral content and density in the lumbar spine (but not elsewhere) of postmenopausal women compared with controls. A soy protein supplement with lower isoflavone content (56 mg per day) failed to produce this effect, suggesting an important role of isoflavones in protection of bone mineral density.[32] It is not clear what part soy isoflavones play in this protection, thus further investigation is warranted.

Menopause

Observational data indicate Japanese women, who have a dietary intake of soy isoflavones 50-100 times greater than that of Western diets, have a nearly 10-fold lower incidence of vasomotor symptoms than in U.S. or other Western women.[33] Soy isoflavones may help alleviate the physical symptoms of menopause. A two-month study compared the effect of a soy drink containing 80 mg isoflavones with a casein drink. Those taking the soy drink experienced a significant decline in hot flashes.[34] The soy group also experienced a decrease in LH and cholesterol and an increase in prolactin and growth hormone. A randomized, double-blind, multi-center trial found 60 grams soy protein per day for 12 weeks reduced the frequency of hot flashes by 45 percent in postmenopausal women, compared with a 30-percent reduction from placebo.[35] However, soy did not alter other menopausal complaints in the study. Similar results have been reported in other double-blind trials.[36,37]

Drug-Nutrient Interactions

Administration of levothyroxine concurrently with a soy protein dietary supplement results in decreased absorption of levothyroxine and the need for higher oral doses of levothyroxine to attain therapeutic serum thyroid hormone levels.[38]

In vitro and animal studies suggest genistein negates the inhibitory effect of tamoxifen on the growth of estrogen-dependent breast tumors.[39,40] Caution is warranted for postmenopausal women consuming genistein while on tamoxifen therapy for estrogen-responsive breast cancer.

Side Effects and Toxicity

Concern has been raised regarding the safety of using soy products with infants and young children because of the phytoestrogenic constituents, including the isoflavones. However, a long-term follow-up study of over 800 women and men who had been fed either soy formula or cow's milk formula during infancy found no significant differences between the soy and cow's milk groups for more than 30 outcomes, including height, weight, age of onset of puberty, breast size, or proportion of women who had had at least one pregnancy.[41]

Another concern regarding soy isoflavone supplementation is the potential that high doses might inhibit thyroid function, resulting in dietary-induced goiter. *In vitro* analysis found the isoflavones genestein and daidzein have the potential to block iodinization of tyrosine.[42] A study from Cornell University's Department of Pediatrics found the frequency of feedings with soy-based formulas early in life was significantly higher in children with autoimmune thyroid disease (31%) when compared to siblings (12%) or unrelated controls (13%).[43] Soy isoflavones have been reported to reduce thyroid function.[44] Soybean supplementation among 37 healthy Japanese adults (30 g per day for three months) led to a slight increase in TSH.[45] However, soy products have also been shown to cause an increase in thyroid function[46] or produce no change in thyroid function.[47]

Dosage

For osteoporosis prevention, 90 mg per day of soy isoflavones is recommended. For menopausal hot flashes, 60-80 mg of soy isoflavones per day appears to be effective. The amount of soy isoflavones in Asian diets is estimated to be in the range of 20-80 mg daily. Until more studies have been conducted on soy isoflavone extracts, the optimal dosage necessary to provide protection against cardiovascular disease and cancer remains unknown.

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