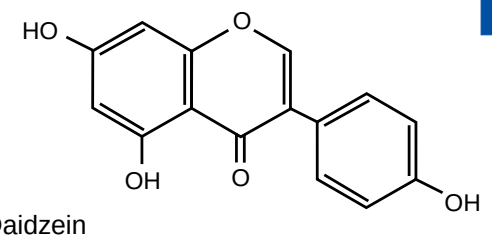
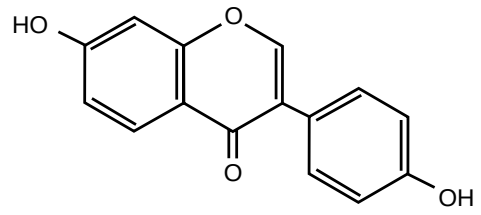
Genistein



Daidzein



Monograph

Soy Isoflavones

Description

The principle isoflavones in soy are genistein, daidzein, and their metabolites. Genistein has a hydroxy group in the 5 position, giving it three hydroxy groups, while daidzein has just two. Isoflavones are members of the large flavonoid family of plant compounds which are in turn members of the larger 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 Papilionoideae family.[1]

Absorption and Metabolism

Isoflavones undergo extensive metabolism in the intestinal tract prior to absorption. 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. In the case of the glycosides, intestinal bacterial glucosidases cleave the sugar moieties, releasing the biologically active isoflavones, genistein and daidzein. In adults, these are further transformed by bacteria to specific metabolites: equol, O-desmethylangolensis, dihydrogenistein, and p-ethylphenol. Due to soy intake by livestock, isoflavone metabolites are also consumed directly 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 where they are removed from the portal blood. However, a percentage of isoflavones in the portal blood can escape uptake by the liver and enter the peripheral circulation. The effectiveness of this hepatic first-pass clearance influences the amount which reaches peripheral tissues.[4] The isoflavones are then eliminated, primarily via the kidneys, similar to endogenous estrogens.[5]

Mechanisms of Action

There are many proposed mechanisms for the therapeutic effects of isoflavones. The mechanisms include 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,[7] induction of DNA strand breakage resulting in apoptosis or cell death,[6] 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] There is also epidemiological, animal, and *in vitro* evidence of isoflavones' effectiveness in the prevention of prostate cancer.[19-21]

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.[22] 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 the endothelial cell surfaces via the 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. Animal studies demonstrated important lipid-lowering effects of soy isoflavones. Monkeys were fed soy isolates high in isoflavones and compared in a cross-over trial with a soy isolate in which the isoflavones had been removed via alcohol extraction. LDL, VLDL, and total cholesterol:HDL ratios were significantly lowered, while HDL was significantly elevated in the group on the isoflavone-rich diet.[24] No lipid lowering effect occurred in the group on a casein diet.

Osteoporosis: While animal studies have found soy protein isolates seem to enhance bone density,[25] and epidemiological evidence points to diets high in soy as a possible protection against osteoporosis,[26] it is not clear what part soy isoflavones play in this protection. Since they appear to have important phytoestrogenic effects, it is not unreasonable to believe soy isoflavones may prove to be protective. Further investigation is warranted.

Dosage

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 dosage necessary to provide protection from diseases such as cancer, cardiovascular disease, and osteoporosis remains speculative.

Safety

Some recent concern has been raised regarding the safety of using soy products with infants and young children because of the phytoestrogenic constituents, including the isoflavones. While there has been no definitive answer to this question, millions of Asians have consumed large quantities of soy foods for hundreds of years without any apparent health risk and seemingly with health benefits. Long-term studies are needed to assess the potential beneficial or adverse effects of consuming phytoestrogens in the form of soy isoflavones early in life.

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