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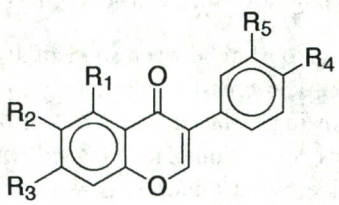
Soy Isoflavones

DESCRIPTION

Soy isoflavones are phytoestrogens (plant estrogens) found in soybeans. Phytoestrogens are plant-derived nonsteroidal compounds that possess estrogen-like biological activity. Soy isoflavones have both weak estrogenic and weak anti-estrogenic effects. They have been found to bind to estrogen receptors-alpha (ER-alpha) and beta (ER-beta). They appear to bind better to ER-beta than to ER-alpha.

Soy isoflavones comprise three main isoflavones and their glycosylated forms. The three main isoflavones are the aglycones genistein, daidzein and glycitein. They can be represented by the following structural formulas:



Soy isoflavones

	R_1	R_2	R_3	R_4
Daidzein	H	H	OH	OH
Genistein	OH	H	OH	OH
Glycitein	H	OCH3	OH	OH

The glycosylated forms of genistein are genistin, 6″-O-malonylgenistin and 6″-O-acetylgenistin; those of daidzein are daidzin, 6″-O-malonyldaidzin and 6″-O-acetyldaidzin, and those of glycitein are glycitin, 6″-O-malonylglycitin and 6″-O-acetylglycitin. The malonyl glycosides of genistein are the major forms of the soy isoflavones that are found in soybeans. Fermented soy foods, such as tempeh and miso, are rich in the soy isoflavone aglycones. The most abundant of the soy isoflavones in soybeans are the genistein glycosides (about 50%), followed by the daidzein glycosides (about 40%). The least abundant of the soy isoflavones in soybeans are the glycitein glycosides (about 5 to 10%). Soy protein derived from soybeans contains about 2 mg of genistin and daidzin per gram of protein. In soy germ, the order is different. Glycitein glycosides comprise about 40% of soy germ, daidzein glycosides about 50% and genistein glycosides about 10%.

Soy isoflavones, when marketed as nutritional supplements, are mainly present as the isoflavone glycosides genistin, daidzin and glycitin.

See also Daidzein, Equol, Genistein and Glycitein.

ACTIONS AND PHARMACOLOGY

ACTIONS

Soy isoflavones may have estrogenic, antiestrogenic and nonestrogenic activities. Soy isoflavones may also have antioxidant, anticarcinogenic, anti-atherogenic, vasoprotective and anti-osteoporotic activities. Soy isoflavones might also have activity for the treatment of menopausal hot flashes.

MECHANISM OF ACTION

Soy isoflavones have weak estrogenic activity. The order of activity in *in vivo* assays is glycitein greater than genistein greater than daidzein. They bind to estrogen receptors-alpha and beta. They appear to bind better to estrogen receptor-beta than to estrogen receptor-alpha.

The most studied of the soy isoflavones is genistein. Genistein has been found to have a number of antioxidant activities. It is a scavenger of reactive oxygen species and inhibits lipid peroxidation. It also inhibits superoxide anion generation by the enzyme xanthine oxidase. In addition, genistein, in animal experiments, has been found to increase the activities of the antioxidant enzymes superoxide dismutase, glutathionine peroxidase, catalase and glutathione reductase. Daidzein and glycitein also appear to have reactive oxygen scavenging activity. However, these isoflavones have not been studied as much as genistein has.

Regarding possible anticarcinogenic activity, again genistein has been the most studied of the soy isoflavones. Several mechanisms have been proposed for genistein's possible anticarcinogenic activity. These include upregulation of apoptosis, inhibition of angiogenesis, inhibition of DNA topoisomerase II and inhibition of protein tyrosine kinases. Genistein's weak estrogenic activity may be involved in its putative activity against prostate cancer. Other possible anti-prostate cancer mechanisms include inhibition of NF (nucle-

ar factor)-kappa B in prostate cancer cells, downregulation of TGF (transforming growth factor)-beta and inhibition of EGF (epidermal growth factor)- stimulated growth. Genistein's anti-estrogenic action may be another possible mechanism to explain its putative activity against breast cancer. Additional possible anti-breast cancer mechanisms include inhibition of aromatase activity and stimulation of sex hormone binding globulin, both of which might lower endogenous estrogen levels.

The possible anti-atherogenic activity of soy isoflavones may be accounted for, in part, by their possible antioxidant activity, particularly with regard to inhibition of lipid peroxidation and oxidation of LDL. Oxidation of low density lipoprotein-cholesterol is thought to be a major factor in the pathogenesis of atherosclerosis. Soy isoflavones may have some cholesterol-lowering activity, but the mechanism of this possible effect is unclear. Soy isoflavones have been found to improve endothelial function independent of changes in blood pressure, lipid profile or glycemic control. The mechanism of this action is unclear (see Research Summary below).

Soy isoflavones' weak estrogenic effects may help protect against osteoporosis by preventing bone resorption and promoting bone density. However, the mechanism of this possible effect is entirely speculative at this time. Soy isoflavones' weak estrogenic actions may also aid in reducing hot flash symptoms.

PHARMACOKINETICS

See Genistein, Daidzein and Glycitein.

INDICATIONS AND USAGE

Soy isoflavones may be helpful in preventing and treating some forms of heart disease and cancer. They may ameliorate some menopausal symptoms (hot flashes) and may be beneficial in preventing osteoporosis. A recent clinical trial in patients with ischemic stroke demonstrated that a soy isoflavone supplement reversed endothelial dysfunction.

RESEARCH SUMMARY

Epidemiological data suggest that higher intakes of foods containing soy isoflavones are significantly correlated with reduced incidence of heart disease and some forms of cancer. Animal, *in vitro* and human studies have provided further support for the epidemiological findings. Soy proteins were shown to lower plasma levels of cholesterol in animal models of hypercholesterolemia, and, subsequently, a meta-analysis of human studies has more recently established that soy consumption is significantly associated with reduction in plasma cholesterol levels in humans, as well. These effects are attributed, in part, to the isoflavone components of soy. Epidemiological data indicate that consumption of soy is particularly associated with reduced risk of breast, lung and prostate cancers, as well as leukemia. Here again, *in vitro* and animal research have further supported these observations.

Breast cancer incidence is reported to be four to seven times higher in women in the United States than among their counterparts in China or Japan. Dietary intake, especially intake of dietary soy, has been associated with this difference. Soy isoflavones have been shown to inhibit transcriptional factors involved in cancer metastasis, including vascular endothelial growth factor, which, in turn, is strongly associated with tumor angiogenesis, as noted in a recent editorial in the *British Journal of Cancer*. In a meta-analysis published in that journal on the epidemiology of soy exposures and breast cancer risk, researchers showed more clearly than had previously been demonstrated that a higher intake of soy isoflavones—20 mg per day or more, compared with a lower intake of about 5 mg per day—among Asian populations is associated with a consistent 29% reduction in the risk of developing breast cancer. Risk reduction was associated with higher soy intake in both pre- and postmenopausal women. And the greatest risk reduction was seen in females who had begun consuming more soy in adolescence, as opposed to those who only consumed high quantities after reaching adulthood. In the United States, the very low level of soy isoflavone intake (less than 1 mg per day) did not have any beneficial effect on breast cancer incidence. However, in the United States, another study has reported a reduction in all-cause and breast cancer-specific mortality among a cohort of breast cancer survivors who consumed higher levels of total flavonoids, particularly flavones, including soy isoflavones.

Recently, the relationship between soy isoflavones—and soy foods generally—and breast cancer has become a matter of some concern owing to *in vitro* and rodent data suggesting that isoflavones may stimulate the growth of existing estrogen-sensitive breast tumors. There is little evidence to suggest that soy isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients. Nor is there any evidence that soy isoflavone intake increases breast density in pre- or postmenopausal women or increases breast cell proliferation in postmenopausal women with or without a history of breast cancer. The majority of the epidemiology data suggest soy isoflavones to be neutral or to be protective against breast cancer, which is corroborated by recent human intervention study data.

In addition to the concern about a putative link between soy isoflavones and breast cancer, some are concerned that soy isoflavones might play a role in endometrial cancer. There is essentially no support for this notion. The endometrium is an

estrogen-responsive tissue and rodent studies have shown that the uterus is responsive to high doses of soy isoflavones. However, these rodent studies did not find that soy isoflavones play any role in endometrial cancer. Endometrial cancer effects from consumption of soy isoflavones are not supported by most of the human trials, even those with duration of up to two years. One study of longer duration—five years—did find non-cancerous hyperplasia in 3.5% of the women tested; no cases of non-cancerous hyperplasia were found in the control group. This was surprising since the normal incidence of endometrial non-cancerous hyperplasia is approximately 5%, which is the incidence that one would have expected in the control group. Although there is little to no evidence supporting a connection between soy isoflavone consumption and breast and endometrial cancer, continued surveillance and monitoring for breast and endometrial cancer in women consuming soy isoflavones is wise and warranted.

Problems associated with menopause, including osteoporosis, appear to be favorably affected in some by higher intakes of soy products and by soy isoflavones specifically. A symptom that most perimenopausal women experience is the annoying feeling of intermittent intense heat, commonly known as a "hot flash." Hot flashes result from a vasomotor response to declining estrogen levels and can be very disruptive to one's life. While hormone replacement therapy (HRT) is an effective treatment for hot flashes, many women are concerned over potential adverse events of HRT. This concern became even greater following publication in 2002 of the results of The Women's Health Initiative (WHI) Estrogen plus Progestin Study, which was stopped on July 7, 2002 because of increased risk of breast cancer and cardiovascular disease in women taking active study pills, compared with those on placebo. Many women began using soy isoflavones, which some, but not all, studies suggested might help with hot flashes. A recent review of isoflavone-hot flash studies reported that studies that consistently reported a significant decrease in hot flash symptoms (intensity and frequency) all supplied more than 15 milligrams of the isoflavone genistein (calculated as aglycone equivalents) per treatment. These benefits have been demonstrated in randomized, double-blind studies.

Soy isoflavones have also been shown to prevent bone resorption and to help increase bone density in some *in vitro* and animal studies. The synthetic isoflavone ipriflavone (see Ipriflavone), the major metabolite of which is the soy isoflavone daidzein, has demonstrated a significant ability to prevent osteoporosis in both animal models and in humans.

However, recent studies have produced mixed results with respect to the soy isoflavones and their possible effects on bone density and other variables in postmenopausal women. One recent randomized, controlled trial in which some of the healthy postmenopausal women received 25.6 grams of soy protein containing 99 mg of isoflavones daily for 12 months failed to reveal benefit in terms of improved bone mineral density, cognitive function or plasma lipids when started at the age of 60 or later. The researchers hypothesized, however, that younger postmenopausal women might benefit since, in a rat model, isoflavones were very effective in preventing bone loss when started soon after ovariectomy. Similarly, the researchers observed, estrogen has had the most favorable effects on cognitive function when administered in perimenopausal women, rather than in late postmenopausal women.

A recent randomized, double-blinded, placebo-controlled trial was performed to determine the effects of a soy isoflavone supplement on brachial flow-mediated dilatation (FMD) in patients with prior ischemic stroke. Compared with controls, FMD at 12 weeks was significantly greater in the isoflavone-treated patients. The vasoprotective effect of the isoflavones on brachial FMD was more pronounced in patients with more severe endothelial dysfunction. In addition, the isoflavone treatment resulted in a significant decrease in serum high-sensitivity-C-reactive protein levels. The researchers concluded that soy isoflavones may have an important role for secondary prevention in patients with cardiovascular disease, on top of conventional interventions.

One negative finding related to soy intake was reported recently. The authors of an epidemiological study based in Indonesia associated high intake of tofu by mainly elderly men with significantly poorer cognitive test performance, enlargement of ventricles and diminished brain weight. The study, however, was not able to control for many potentially important dietary and other variables that may have affected outcome. The British and Indonesian researchers themselves indicated that it was unclear whether the potential detrimental effects were due to the soy isoflavones or toxic additives like formaldehyde, which is used as a food preservative in Indonesia. The results of the study, while provocative, are too preliminary to support any definitive conclusions, although the toxic additive explanation appeared to be the more likely one. More research may be warranted.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Soy isoflavones are contraindicated in those who are hypersensitive to any component of a soy isoflavone-containing product. Those who are allergic to birch pollen may also be hypersensitive to soy products.

PRECAUTIONS

Pregnant women and nursing mothers should avoid the use of soy isoflavone supplements pending long-term safety

studies. Men with prostate cancer should discuss the advisability of the use of soy isoflavones with their physicians before deciding to use them.

Women with estrogen receptor-positive tumors should exercise caution in the use of soy isoflavones and should only use them if they are recommended and monitored by a physician.

Those consuming soy isoflavones should ensure that they have an adequate intake of iodide (see Adverse Reactions).

ADVERSE REACTIONS

There is a theoretical concern based on *in vitro* and animal data that soy isoflavones may increase the risk of clinical hypothyroidism in individuals with compromised thyroid function and/or whose iodide intake is marginal. Therefore, those who use soy isoflavones should ensure that their intake of iodide is adequate. Several years ago, the National Center for Toxicological Research raised this concern because their scientists found that the soy isoflavones genistein and daidzein inhibited the activity of the enzyme thyroid peroxidase (TPO) in rats, both *in vitro* and *in vivo*. TPO catalyzes the iodination of thyroglobulin, the key metabolic step in the biosynthesis of thyroid hormone. The addition of iodide to the *in vitro* media completely abolished the inhibition of TPO. While iodide-deficient animals exhibit goitrogenic responses when consuming soy isoflavones, they have no effect on iodide-sufficient animals. With regard to human studies, in the hundreds of clinical trials conducted using soy isoflavones, there have been no reported adverse thyroid effects in any of the subjects participating in the trials. A recent review of 12 studies involving consumption of soy isoflavones reported that with the exception of one study that gave mixed results, none of the other studies showed statistically significant changes in the thyroid hormones TSH, T_4 and T_3.

DOSAGE AND ADMINISTRATION

Soy isoflavone supplements containing genistin, daidzin and glycitin are available with much smaller amounts of the aglycones genistein, daidzein and glycitein. The percentages of the soy isoflavones present in a standard soy isoflavone supplement reflect the percentages of these substances as found in soybeans and are: genistin, about 50%; daidzin, about 38%; and glycitin, about 12%. A 50-mg dose of soy isoflavones—a typical daily dose—delivers 25 mg of genistin, 19 mg of daidzin and about 6 mg of glycitin. Usually, 40% of the formula is comprised of soy isoflavones. Therefore, to get a dose of 50 milligrams of soy isoflavones, 125 mg daily of soy isoflavones are required. Various observational and epidemiological studies suggest 50 mg daily of soy isoflavones approximates the dose that may have health benefits.

Soy isoflavones are also available in some functional food products.

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Soy Protein

DESCRIPTION

In October 1999, the Food and Drug Administration (FDA) approved a labeling health claim for dietary soy protein stating that it may reduce the risk of heart disease. The health claim that can be used on labels of products containing soy protein states: "Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease." In order to carry the health claim, one serving of a product must contain at least 6.25 grams of soy protein and must also be low in total and saturated fat, cholesterol and sodium.

The substantive evidence underpinning the approval of the health claim came from a meta-analysis by James W. Anderson and his University of Kentucky colleagues, published in August 1995 in the *New England Journal of Medicine*. The article reported that regular consumption of soy protein lowered total cholesterol by 9.3%, LDL-cholesterol by 12.9%, triglycerides by 10.5% and raised HDL-cholesterol by 2.5%. The average daily soy protein intake by those included in the meta-analysis was 47 grams. Interestingly, those whose soy protein intake was 25 grams daily—the amount approved in the health claim—demonstrated only a 5% decrease in their LDL-cholesterol levels. Subsequent meta-analyses and clinical studies of the effects of soy protein intake on serum lipids reported LDL-cholesterol decreases ranging from 3 to 5.3%. One study found a 3% lowering of LDL-cholesterol at a soy protein intake of 36 grams daily. A review of 22 randomized clinical trials by the American Heart Association Nutrition Committee and published in 2005 reported that those consuming 50 grams daily of soy protein showed no higher than a 3% decrease in LDL-cholesterol and concluded that they could not support the use of soy protein to lower cholesterol. The FDA is reconsidering the soy protein health claim.

Soy protein isolates have become popular items in the nutritional supplement marketplace. Most of these supplements also contain the soy isoflavones genistin, daidzin and glycitin. (See Soy Isoflavones, Genistein, Daidzein and Glycitein.)

ACTIONS AND PHARMACOLOGY

ACTIONS

Soy protein has putative lipid-lowering, antiatherogenic, antioxidant, anticarcinogenic and antiosteoporotic activities.

MECHANISM OF ACTION

Diets rich in soy protein have been found to reduce serum levels of total cholesterol, LDL-cholesterol, triglycerides and apolipoprotein B (apo B). The mechanism of the possible lipid-lowering activity of soy protein is unclear. There are a few possible explanations. Soy protein is much richer in L-arginine than is animal protein, which is richer in L-lysine. Some animal studies indicate that dietary increases in L-arginine are accompanied by decreases in cholesterol levels. Further, some studies have demonstrated that, under certain conditions, e.g., hypercholesterolemia, high intakes of L-arginine could enhance endothelial-dependent vasodilation and nitric oxide or NO production (see L-Arginine). This could contribute to the possible antiatherogenic activity of soy protein.

The soy isoflavones may also contribute to the possible lipid-lowering activity of soy protein as well as its possible antiatherogenic activity. Most soy protein products contain the isoflavones genistin, daidzin and glycitin, which have weak estrogenic effects and also may have antiestrogenic activity (see Soy Isoflavones). Oral estrogens have been shown to decrease total cholesterol and LDL-cholesterol. The soy isoflavones may have similar actions.

Interestingly, a few studies have shown that when the isoflavones are removed from the soy protein, the protein itself has little hypocholesterolemic activity. Soy isoflavones themselves do not have the same hypocholesterolemic activity as the combination of soy protein and soy isoflavones. There are probably synergistic effects of these substances that are not understood at this time.

There are also other substances associated with soy protein, including saponins, trypsin inhibitor and bioactive peptides,