Isoflavones

Isoflavones are water-soluble chemicals found in many plants. In this article, we will discuss a group of isoflavones that are phytoestrogens, meaning that they cause effects in the body somewhat similar to those of estrogen. The most investigated phytoestrogen isoflavones, genistein and daidzein, are found both in soy products and the herb red clover. Soy additionally contains glycitein, an isoflavone that is more estrogenic than genistein and daidzein, but is usually present in relatively low amounts. Red clover also contains two other isoflavones: biochanin (which can be turned into genistein) and formonenetin (which can be turned into daidzein).

Certain cells in the body have estrogen receptors, special sites that allow estrogen to attach. When estrogen attaches to a cell’s estrogen receptor, estrogenic effects occur in the cell. Isoflavones latch onto estrogen receptors too, but produce weaker estrogenic effects. This leads to an interesting two-part action. When there is not enough estrogen in the body, isoﬂavones may tend to block real estrogen from attaching to estrogen receptors, thereby reducing the net estrogenic effect. This may reduce some of the risks of excess estrogen (for example, breast and uterine cancer) while still providing some of estrogen's benefits (such as, preventing osteoporosis).

Isoflavones also appear directly to reduce estrogen levels in the body, perhaps by fooling the body into thinking that it has plenty of estrogen.

Isoflavones are widely thought to be the active ingredients in soy products. However, growing evidence suggests that there are other active ingredients as well, such as proteins, fiber, and phospholipids.

Sources

Although isoﬂavones are not essential nutrients, they may help reduce the incidence of several diseases. Thus, isoﬂavones may be useful for optimum health, even if they are not necessary for life like a classic vitamin.

Roasted soybeans have the highest isoﬂavone content: about 167 mg for a 3.5-ounce serving. Tempeh (a cake of fermented soybeans) is next, with 60 mg, followed by soy flour with 44 mg. Processed soy products such as soy protein and soy milk contain about 20 mg per serving. The same isoﬂavones found in soy are also contained in certain red clover products.
Therapeutic Dosages

When purified isoflavones from red clover or soy are used, the dose generally ranges from about 40 mg to 80 mg daily. This is considerably higher than the average isoflavone intake in Japan, which is about 28 mg daily. (Post-menopausal Japanese women may consume closer to 50 mg daily.)

There are three major isoflavones found in soy: genistein, daidzein, and glycitein. Each of these isoflavones can occur in two types or states. The first type, predominant in raw soy products, is called an “isoflavone glycoside.” In an isoflavone glycoside, the isoflavone is attached to a sugar-like substance known as a “glycone.” The second type, predominant in fermented soy products, is called an “isoflavone aglycone.” These consist of isoflavones without a glycone attached, and are also called “free isoflavones.” Since isoflavone aglycones are the most pure form of isoflavones, it has been hypothesized (but not proven) that they are more effective than other forms.

Therapeutic Uses

Soy products are known to improve cholesterol profile, but isoflavones may not be the active cholesterol-lowering ingredient in soy. Isoflavones may, however, improve other measures linked to cardiovascular risk, such as levels of blood sugar, insulin, and fibrinogen.

According to some but not all studies, soy protein or concentrated isoflavones from soy or red clover may slightly reduce menopausal symptoms, such as hot flashes and vaginal dryness.

However, isoflavones have failed to prove effective for the hot flashes that often occur in breast cancer survivors.

There is conflicting evidence regarding whether soy or isoflavones may be helpful for preventing osteoporosis, but on balance the evidence suggests a modest beneficial effect.

One study tested a purified soy isoflavone product (technically, isoflavone aglycones, as described above) for treatment of aging skin. In this double-blind trial, 26 Japanese women in their late 30s and early 40s were either given placebo or 40 mg daily of soy isoflavone aglycones for 12 weeks. Researchers monitored two types of wrinkles near the eye: “fine” wrinkles and “linear” wrinkles. The results indicated that use of the soy product significantly reduced “fine” wrinkles as compared to placebo. (Effects on “linear” wrinkles were not significant.) As a secondary measure, researchers also analyzed skin elasticity, and found an improvement in the women given the isoflavones as compared to those given placebo. Note: This was much too small a study for its results to be taken as reliable.

A small and poorly reported double-blind, placebo-controlled study provides weak evidence that red clover isoflavones might be helpful for cyclic mastalgia. A combination product containing soy isoflavones, black cohosh, and dong quai has shown some promise for menstrual migraines.

One study found that use of soy isoflavones improved the effectiveness rate of in vitro fertilization (used for female infertility).

A double-blind study performed in China found that use of a soy isoflavone supplement improved blood sugar control in healthy post-menopausal women.

In a small double-blind trial, use of soy isoflavones appeared to reduce some symptoms of premenstrual syndrome PMS. A very small study found hints that soy isoflavones might help reduce buildup of abdominal fat.
Observational studies hint that soy may help prevent breast and uterine cancer in women.\textsuperscript{9-15} If this connection is real and not a statistical accident (observational studies are notorious for falling prey to statistical accidents), the explanation may lie in the estrogen-like action of soy isoflavones. As noted above, isoflavones decrease the action of regular estrogen by blocking estrogen receptor sites, and may also reduce levels of circulating estrogen.\textsuperscript{1,2,79-82,92-96} Since estrogen promotes breast and uterine cancer, these effects could help prevent breast cancer. Soy also appears to lengthen the menstrual cycle by a few days,\textsuperscript{70,78,92} and this too would be expected to reduce breast cancer risk. However, only a large, long-term intervention trial could actually show that soy or isoflavones reduce breast and uterine cancer risk, and one has not been performed.

Observational studies also hint that soy might help prevent prostate cancer in men. Men have very low levels of circulating estrogen, so the net effect of increased soy consumption might be to increase estrogen-like activity in the body. Since real estrogen is used as a treatment to suppress prostate cancer, perhaps the mild estrogen-like activity of isoflavones has a similar effect. Isoflavones might also decrease testosterone levels and alter ratios of certain forms of estrogen, both of which would be expected to provide benefit.\textsuperscript{153,194} In one double-blind study, men with early prostate cancer were given either isoflavones or placebo, and their PSA levels were monitored.\textsuperscript{125} (PSA is a marker for prostate cancer, with higher values generally showing an increased number of cancer cells.) The results did show that use of isoflavones (60 mg daily) slightly reduces PSA levels. Whether this meant that soy actually slowed the progression of the cancer or simply lowered PSA directly is not clear from this study alone. However, in another study of apparently healthy men (not known to have prostate cancer), soy isoflavones at a dose of 83 mg per day did not alter PSA levels.\textsuperscript{126} Taken together, these two studies provide some direct evidence that soy isoflavones may be helpful for treating or preventing prostate cancer, but the case nonetheless remains highly preliminary.

According to most but not all studies, soy isoflavones do not improve mental function.\textsuperscript{96,144-146,154,170,186} One study failed to find that soy protein with isoflavones improved general quality of life (health status, depression, and life satisfaction) in post-menopausal women.\textsuperscript{125} Soy isoflavones have also failed to prove effective for reducing levels of homocysteines.\textsuperscript{171}

### What Is the Scientific Evidence for Isoflavones?

#### High Cholesterol

Numerous studies have found that soy can reduce blood cholesterol levels and improve the ratio of LDL ("bad") versus HDL ("good") cholesterol.\textsuperscript{32,33}

Although it was once thought that isoflavones are the ingredients in soy responsible for improving cholesterol profile, on balance, current evidence suggests otherwise.\textsuperscript{31,34-41,83,108,109-110,117,119,120,124,156,172,205,207} Non-isoflavone constituents of soy, such as proteins, fiber, and phospholipids, may be equally or perhaps even more important than the isoflavones in soy.\textsuperscript{96,127,195}

It is also possible that the exact types of isoflavones in a particular product made a difference. One study of red clover isoflavones found evidence that biochanin but not formononetin can reduce LDL cholesterol.\textsuperscript{128}

Another study found that soy products may at times have an unusual isoflavone profile, containing high levels of the isoflavone glycitein rather than the more usual genistein and daidzein.\textsuperscript{84} Glycitein could be inactive regarding cholesterol reduction.

Finally, some evidence hints that soy isoflavones may be only effective for reducing cholesterol when it is converted by intestinal bacteria into a substance called equol.\textsuperscript{129,189} It appears that only about one-third of people have the right intestinal bacteria to make equol.
Menopausal Symptoms

Although study results are not entirely consistent, the balance of the evidence suggests that isoflavones from soy may be helpful for symptoms of menopause, especially "hot flashes."

Improvements in hot flashes, as well as other symptoms, such as vaginal dryness, have been seen in many studies of soy, mixed soy isoflavones, isoflavone aglycones, or genistein alone. However, the effects have been slight or non-existent in other studies. At least two studies found that people who are equol producers (see previous section) may experience greater benefits.

The herb *Pueraria mirifica*, which also contains a number of isoflavones, has also shown some benefit for menopausal symptoms.

However, several other studies have failed to find benefit with whole soy or concentrated soy isoflavones. Another study failed to find benefit with a mixture of soy isoflavones and black cohosh.

Isoflavones from red clover have also shown inconsistent benefit with the largest and most recent trial finding no reduction in hot flash symptoms.

Furthermore, in double-blind, placebo-controlled trials, soy or purified isoflavones failed to reduce hot flashes among survivors of breast cancer.

What can one make of this mixed evidence? The problem here is that placebo treatment has a strong effect on menopausal symptoms. In such circumstances, statistical noise can easily drown out the real benefits of a treatment under study. Estrogen is so powerful for hot flashes and other menopausal symptoms that its benefits are almost always clear in studies; most likely, soy or concentrated isoflavones have a more modest effect, not always seen above the background.

Osteoporosis

Estrogen has a powerfully protective effect on bone. Study results on whether isoflavones have the same effect have produced inconsistent results. On balance, it is probably fair to summarize current evidence as indicating that isoflavones (either as soy, genistein, mixed isoflavones, or tofu extract) have at least a modestly beneficial effect on bone density.

The best evidence is for genistein taken alone. In a 24-month, double-blind study of 389 postmenopausal women with mild bone loss, use of genistein at a dose of 54 mg daily significantly improved bone density as compared to placebo. (All participants were additionally given calcium and vitamin D.)

However, it is not clear that isoflavones consumed in the diet, even at high concentrations, is beneficial. For example, in a placebo-controlled study involving 237 healthy women in the early stages of menopause, the consumption of isoflavone-enriched foods (providing an average of 110 mg isoflavone aglycones daily) for 1 year had no effect on bone density or metabolism.

Interestingly, one small, but long-term study suggests that progesterone cream (another treatment proposed for use in preventing or treating osteoporosis) may decrease the bone-sparing effect of soy isoflavones.

Bone is always subject to two influences: bone building and bone breakdown. Estrogen primarily works by reducing the bone breakdown part of the equation, thereby leading to a net result of increased bone growth. Growing evidence suggests that isoflavones act on both sides of this equation, directly stimulating new bone creation while at the same time slowing bone breakdown.

There is mixed evidence that isoflavones are more effective for osteoporosis in people who have the intestinal bacteria to produce equol.

Menstrual Migraines
In a 24-week, double-blind study, 49 women with menstrual migraines (migraine headaches associated with the menstrual cycle) received either placebo or a combination supplement containing soy isoflavones and extracts of dong quai and black cohosh. Beginning at the 20th week, use of the herbal supplement resulted in decreased severity and frequency of headaches as compared to placebo. However, it is not clear which of the ingredients in the combination was helpful. The authors of the study apparently considered black cohosh and dong quai as phytoestrogens, but the current consensus is that they do not belong in that category.

Safety Issues

Studies in animals have found soy isoflavones essentially nontoxic. The long history of the use of soy as food in Asia would tend to suggest they are safe as well. Even though absolute safety cannot be assumed from historical consumption of soy as food, it is reassuring to note that researchers found no evidence of ill effects when they gave healthy postmenopausal women 900 mg of soy isoflavones a day for 84 consecutive days. In Japan, the maximum safe intake level of soy isoflavones has been set at a total of 70 to 75 mg daily (food plus supplement sources).

Still, concerns have been raised about estrogenic and other potential side effects of excessive soy isoflavone intake. Overall, the estrogenic effect of soy isoflavones in women appear to be fairly minimal. Nonetheless, it is not zero. According to most but not all studies, use of soy has enough of an estrogen-like effect to slightly alter the menstrual cycle and change levels of sex hormones in young women. Thus, some of the risks of estrogen could, in theory, apply to isoflavones as well.

Estrogen also stimulates uterine cells, leading to an increased risk of uterine cancer. Most studies have found that isoflavones do not stimulate uterine cells. However, one fairly large (365 participants) and long-term (5 years) study did find uterine stimulation in 3.37% of women on isoflavones and 0% of those on placebo. This could indicate a slightly increased risk of uterine cancer with high-dose isoflavone use.

Similarly, preliminary studies and reports have raised concerns that intensive use of soy products or isoflavones by pregnant women could exert a hormonal effect that impacts unborn fetuses. Use of soy formula by infants is also of concern along these lines, as an infant subsisting on soy formula has a relatively enormous isoflavone intake; on a per-weight basis, it may exceed the average Asian adult isoflavone intake by a factor of ten.

The drug tamoxifen blocks estrogen and is used to help prevent breast cancer recurrence in women who have had breast cancer. One animal study found that soy isoflavones might remove the benefit of tamoxifen treatment.

One double-blind study of post-menopausal women found the use of red clover isoflavones at a dose of 80 mg daily for 90 days resulted in increased levels of testosterone. The potential significance of this is unclear. In men, isoflavones might decrease testosterone levels, but the effect appears to be slight at most.

Other concerns relate to soy’s potential effects involving the thyroid gland. When given to individuals with impaired thyroid function, soy products have been observed to reduce absorption of thyroid medication.
addition, some evidence hints that soy isoflavones may directly inhibit the function of the thyroid gland (though perhaps only in people who are iodine deficient). To make matters more confusing, studies of healthy humans and animals given soy isoflavones or other soy products have generally found that soy either had no effect on thyroid hormone levels or actually increased levels. The bottom line: In view of soy’s complex effects regarding the thyroid, individuals with impaired thyroid function should not take large amounts of soy products except under the supervision of a physician.

While fears have been expressed by some experts that soy isoflavones might interfere with the action of oral contraceptives, one study of 36 women found reassuring results.

Some evidence suggests that the isoflavone genistein might impair immunity. One study in mice found that injected genistein has negative effects on the thymus gland (an organ that is important for immunity) and also causes changes in the prevalence of various white blood cells consistent with impaired immunity. Although the genistein was injected rather than administered orally, the blood levels of genistein that these injections produced were not excessively high; they were comparable to (or even lower than) what occurs in children fed soy milk formula. In addition, there are several reports of impaired immune responses in infants fed soy formula. While it is too early to conclude that genistein impairs immunity, these findings are a potential cause for concern.

One observational study raised concerns that soy might impair mental function in adults. However, observational studies are far less reliable than clinical trials. Direct studies designed to test the potential effects of isoflavones on brain function, and lasting up to 12 months, have found either no effect or a slightly positive effect on brain function. While this does not rule out a harmful long-term effect on cognition, it is reassuring.

There exists one case report in which soy isoflavone supplements caused migraine headaches in a man who had never experienced migraines before; presumably this was a highly individual reaction, such as an allergy. Similarly, while soy products are sometimes recommended for reducing blood pressure, there is also a well-documented case report in which use of high dose soy isoflavones caused extreme elevation in blood pressure in a woman participating in a scientific study (of soy isoflavones).

Some researchers have raised concern that genistein may influence the ability of blood to clot properly. A placebo-controlled study involving 104 healthy women, however, found no evidence that the isoflavone genistein had any significant adverse effect on blood clotting.

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Last reviewed August 2011 by EBSCO CAM Review Board
Last Updated: 8/1/2011