The Remarkable Health Benefits of Soy Isoflavones

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ABSTRACT: *Epidemiological studies indicate that the traditional Asian diet, rich in soybeans and soy foods, is associated with a significantly lower risk to heart disease, osteoporosis, and cancers of the breast, prostate, and colon. Symptoms of menopause, such as hot flashes, irritability, and spontaneous sweats, are also less prevalent among Asian women. This is in strong contrast to those cultures whose diets are typically low in soy, legumes, and fresh fruits and vegetables and high in animal products and saturated fats. Research focuses on the inflavones found in soy-genistein and daidzein-as major contributors to this phenomenon. Isoflavones are a class of phytoestrogens that influence estrogen receptor binding, lower triglycerides and total cholesterol, function as antioxidants, exert antiproliferative effects, and inhibit platelet activating factor and thrombin formation. The multiple health benefits of soy, when taken daily over time, parallel many of the positive effects of hormone replacement therapy (HRT) while simultaneously protecting breast and endometrial tissue. Soy isoflavones can be considered an important supplement for those women seeking natural alternatives to HRT, as well as men and women of any age who want to enjoy the many health benefits associated with soy consumption.*

In recent years, the potential health benefits of soybeans and soy foods have become increasingly recognized because of the health benefits seen in the traditional Asian diet, which is very high in soy foods, low in saturated fat, and high in dietary fiber. Epidemiological studies have shown a correlation between the consumption of soy foods and low rates of certain diseases, including coronary heart disease, hormone-dependent cancers such as breast, prostate, and colon cancer, osteoporosis, and problems associated with menopause and menstrual irregularities. In the United States and other Western countries where the risk of these diseases is high, the typical diet is high in saturated fat, low in dietary fiber, and low in soy foods when compared to Asian nations.

Soybeans are legumes that are rich in phytoestrogens, plant compounds that are structurally similar to estrogen and possess weak estrogenic activity. Although phytoestrogens are found in a variety of plants, soybeans and whole grains appear to be the most abundant source among commonly consumed foods. Soy foods, in particular, are rich in essential fatty acids, arginine and other potentially bioactive compounds, as well as a class of phytoestrogens known as isoflavones, which are believed to provide many of the health protective effects seen in the traditional Asian diet. Other well known phytoestrogens include the lignans, which are abundant in whole grains, and coumestans, which are found primarily in alfalfa and bean sprouts.

The three main isoflavones present in soy are genistein, daidzein, and glycitein. In most non-fermented soy foods, such as tofu,

they occur predominantly as glycosides (genistin, daidzin, and glycitin), while fermented soy foods, such as tempeh and miso, contain greater levels of the unconjugated aglycone forms (genistein, daidzein, and glycitein) as a result of enzymatic hydrolysis during fermentation. The glycoside forms are converted by intestinal bacteria into the biologically active isoflavones, genistein and daidzein. These are further transformed by bacteria to metabolites such as equol. Significant individual variation in isoflavone metabolism exists, especially in the capacity of gut microflora to synthesize equol.

Genistein and daidzein concentration levels vary considerably among soybean crops and the different soy foods available. On average, a typical serving of a first generation soy food such as tofu or soymilk contains around 35 to 40 mg of total isoflavones. Second generation soy foods such as soy hot dogs and soy cheese contain fewer isoflavones as a result of processing. Other soy products, like soy sauce and some soy protein concentrates, have very little or no isoflavone content because of processing techniques that involve alcohol extraction. Table 1 lists the typical isoflavone profile of a variety of soy foods.

Table 1. Isoflavone Content of Soy Foods.

Soy Food	Estimated Total Isoflavones per Serving (1/2 cup)	Total Genisteins (sum of genistein & genistin)	Total Daidzeins (sum of daidzein & daidzin)
Tofu	40 mg	1.4 mg/g	0.6 mg/g
Soybeans	35 mg	0.6 mg/g (roasted)	0.5 mg/g (roasted)
Tempeh	40 mg	0.7 mg/g	0.4 mg/g
Miso	40 mg	0.8 mg/g	0.5 mg/g
Soymilk	40 mg	1.8 mg/g	1.5 m/g

HEALTH BENEFITS OF SOY ISOFLAVONES

Isoflavones appear to exert a variety of physiological effects that afford protection against symptoms associated with sex hormone decline or imbalance as with menopause, as well as age-related diseases including cancer, cardiovascular disease, and osteoporosis.

- **Hormone Balancing Effects**

Isoflavones are reported to exert a balancing effect on reproductive hormones in both pre- and postmenopausal women. It appears that they exert mild agonistic (estrogenic) an antagonistic (antiestrogenic) effects, depending on the level of endogenous estrogen present. Isoflavones possess weak strogenic activity and compete with the more potent endogenous estrogens at the receptor site, thereby reducing the total estrogen burden on the body. In this respect, the isoflavones are regarded as exerting antiestrogenic effects. Conversely, as natural estrogen production declines with the onset of menopause, isoflavones may help to offset this decline through their estrogenic effects. Theoretically, problems associated with estrogen imbalance, such as endometriosis, cervical dysplasia, breast cancer, menstrual irregularities, and symptoms commonly seen with both premenstrual syndrome (PMS) and menopause, may improve with soy isoflavone intake.

It should also be noted that two forms of the estrogen receptor, α and β, have been identified that differ in tissue distribution, binding affinity, and biological function. Therefore, different target cells may respond differently to the same estrogenic stimulus depending on the radio of expression of the two receptor subtypes in the cell. This helps to explain how phytoestrogens and the new

designer estrogen drugs such as tamoxifen and raloxifene-called selective estrogen receptor modulators (SERMs)-behave like estrogens in some tissues but block its action in others.

The hormone modulating effects of soy isoflavones have recently been demonstrated in several human studies. In one study, the consumption of 60 g of soy protein (containing 45 mg isoflavones) per day for one month was shown to affect reproductive hormone levels in premenopausal women, resulting in longer menstrual cycles (increased number of days between menstruation). Follicular phase length was increased by an average of 2.5 days, whereas no significant change in luteal phase length was observed. The investigators reported a significant suppression in midcycle surges of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) during the dietary intervention with soy protein, in addition to a9.6% decrease in plasma cholesterol levels.

In another study, young women consuming 36 ounces of soymilk daily (providing 200 mg of isoflavones) for one month also experienced longer menstrual cycles (28.3 +/- 1.9 days before soymilk feeding, increasing o 31.8 +/- 5.1 days during the month of soymilk feeding) and lower serum estradiol levels; effects which persisted for 2 to 6 menstrual cycles after discontinuation of the soymilk.

The hormone modulating and menstrual cycle lengthening effects of soy isoflavones may have significant implications with regard to breast cancer risk. Women with shorter menstrual cycle have a greater lifetime exposure to estrogen due to the increased number of cycles in their lifetime. Furthermore, because breast cells proliferate two to three times more rapidly during the luteal phase than during the follicular phase, a significant increase in menstrual cycle length, particularly follicular phase length, is beneficial in lowering the risk for breast cancer.

- **Menopausal Symptoms**

Postmenopausal Japanese women who consume soy foods experience significantly reduced symptoms of menopause and are less likely to use HRT compared to American women who do not included soy foods in their diet. Although there are conflicting studies in this area, several well-controlled studies have documented a reduction in menopausal symptoms with soy protein.

In a randomized, double-blind study, women who received 45 g of soy flour per day reportedly experienced a 40% reduction of hot flashes after a period of 6 weeks compared to women who received the same amount of wheat flour. All of the women included in the study had been amenorrheic for at least 12 months and were experiencing at least 14 hot flashes per week. Another double-blind study demonstrated that a so isoflavone supplement (50 mg/day) was effective in reducing the frequency and severity of hot flashes in 177 postmenopausal women who were experiencing 5 or more hot flashes per day.

- **Cancer**

A significant body of research, including epidemiological, in vitro, and animal studies, suggests that soy isoflavones may help to reduce cancer risk, specifically breast, prostate, and colon cancer. For example, women in China, where soy consumption is high, have a lower risk for breast cancer and 36% lower plasma estrogen levels when compared to women in Britain, where soy consumption is low. In

addition, Asian men who smoke and drink alcohol, but consume soy foods, still have lower rates of some cancers, including prostate cancer, when compared to Western men.

A recent case-control study was conducted to assess the association between phytoestrogen intake and the risk of breast cancer. A total of 144 women with newly diagnosed early beast cancer were matched with healthy controls. Urinary excretion of phytoestrogen, including isoflavones, was measure over 3 consecutive days to determine phytoestrogen intake. The results showed that increased excretion of some phytoestrogens, notably daidzein and the isoflavone metabolite, equol, was associated with a substantial reduction in breast cancer risk.

Several anticancer mechanisms of soy isoflavones, primarily genistein, have been proposed. One of the most researched mechanisms is the inhibition of enzymes whose actions promote cell differentiation through their effects on growth factor-stimulation. Several different tumor promoting enzymes, especially DNA topoisomerases, tyrosine kinases, and ribosomal S6 kinase, have been reported to be inhibited by genistein and, in some cases, by other isoflavnes.

Soy isoflavones may also help to prevent breast cancer by shifting estrogen metabolism toward more beneficial metabolites. Evidence is accumulating that specific estrogen metabolites, primarily 16α-hydroxyestrone (16α-OH) and 4-hydroxyestrone (4-OH), may increase the risk of breast cancer by increasing both cell proliferation and direct DNA damage. Conversely, 2 hydroxyestrone (2-OH) may induce apoptosis and thereby inhibit cell proliferation, an important mechanism in the prevention of cancer. Two recent studies found that increased soy isoflavone consumption decreased urinary excretion of the genotoxic estrogen metabolites 16α-OH and 4-OH, indicative of their decreased formation, and significantly increased the 2-OH: 16α-OH ratio in both pre- and postmenopausal women.

Another proposed mechanism of cancer growth inhibition by isoflavones is the inhibition of angiogenesis, the growth of blood vessels that feed tumors. By interfering with angiogenesis, isoflavones deprive tumors of the blood vessels that accommodate their growth and may keep them from growing and spreading to other parts of the body.

Soy isoflavones and other phytoestrogens can also increase the production of sex hormone binding globulin (SHBG), which effectively reduces estrogen stimulus because only unbound estrogens can enter target-tissue ells and induce biological activity. Because SHBG has been found to exert a negative control on estrogen action in human breast cancer cells, a stimulation of SHBG production would therefore lower the risk for hormone-dependent cancers. This also supports epidemiological studies that show the SHBG values are lower in breast cancer patients compared to healthy vegetarian women. As a note of caution, increased production of SHBG may lead to a decrease in free thyroxine; thus it may be prudent to monitor thyroid stimulating hormone (TSH) in women who initiate soy protein or isoflavone supplementation.

While soy isoflavones look promising in the prevention of breast and other cancers, the use of these substances in the treatment of active cancer is controversial. It appears that high concentrations of genistein are necessary to inhibit growth of cultured

cancer cells, much higher than would be achieved through dietary consumption of soy products. The uncertainties surrounding soy's varying does-dependent activity and the applicability of in vitro and animal studies to humans suggests a role of isoflavones as chemopreventive rather than chemotherapeutic agents. In addition, while in vitro studies have been conducted on the combined effect of genistein and tamoxifen in breast cancer cells, further research is needed before any recommendation can be made.

- **Cardiovascular Disease**

Soy consumption has been established in experimental models to reduce cardiovascular disease. Sirtori et al. reported that the substitution of soy protein for animal protein in the diets of hypercholesterolemic humans led to a marked decrease in the concentration of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides without significantly affecting high-density lipoprotein (HDL) cholesterol concentrations. This coincides with epidemiological evidence, which suggests that populations consuming soy in fairly high amounts have lower coronary heart disease mortality than those who consume high amounts of animal protein. While soy consumption is known to reduce cholesterol in hypercholesterolemic subjects, a recent study showed that a high isoflavone diet consumed for 3 menstrual cycles (approximately 129 mg per day) lowered LDL cholesterol up to 10% and lowered the ratio of LDL to HDL cholesterol by 13.8% in premenopausal women with normal cholesterol levels.

A variety of mechanisms for the hypocholesterolemic effect of soy protein have been postulated. They include interruption in the enterohepathic circulation of cholesterol and bile acids, direct modification of lipid metabolism by amino acids, and alterations in hormone secretions, which, in turn, affect lipid metabolism and lipemia. The isoflavones of soy, as mentioned previously, have long been established to be weak agonists of endogenous estrogen and may contribute to the cholesterol-lowering effects of soy protein. Insulin, in particular, is a key factor in the risk of cardiovascular disease and soy protein has been reported to decrease insulin, which results in a decrease in total cholesterol, LDL cholesterol, and triglycerides.

Isoflavones may also be of benefit in the prevention of atheosclerosis. The growth of atherosclerotic plaques on arterial walls is preceded by a chain of events. Initially, injuries to the endothelial cells lining blood vessels stimulate formation of vascular lesions composed of smooth muscle cells, followed by the generation of thrombin at the site of injury. This leads to platelet activation, thrombin formation, and the stimulation of smooth muscle cell proliferation. Plaque formation also involves lipid accumulation and the infiltration of monocytes and T lymphocytes into the arterial wall, which may be governed by polypeptide growth factors. Genistein has been shown to not only inhibit thrombin formation and platelet activation, but to alter growth factor activity and inhibit cell adhesion and proliferation, all activities necessary for the progression of atherosclerosis.

- **Antioxidant Properties**

A number of studies have shown that isoflavones have antioxidant properties. Both daidzein and genistein inhibit the free radicals, hydrogen peroxide and superoxide anion, while genistein has been shown to increase activity of the antioxidant enzymes,

catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. Soy isoflavones therefore can act directly as antioxidants or indirectly by enhancing antioxidant enzymes. Furthermore, a recent study showed that soy isoflavone supplementation (50-100 mg/day) decreased oxidative DNA damage in humans.

Isoflavones can also exert their antioxidant protective effects on LDL cholesterol. LDL cholesterol oxidation is one of the main causes of the progressive hardening and blocking of arteries in artherosclerosis. Therefore, these antioxidant properties represent yet another mechanism in which soy isoflavones may help to prevent atherosclerosis.

- **Osteoporosis**

Osteoporosis is a bone disorder characterized by decreased bone mass, enhanced bone fragility, and increased susceptibility to bone fractures. In women, the menopausal decline of ovarian estrogen production leads to a pronounced acceleration of bone loss for about 5 to 10 years following menopause. The most widely used and most effective treatment for slowing this bone loss and preventing osteoporosis is estrogen replacement therapy. However, this therapy has numerous side effects that have prompted researchers to study natural alternatives that are safe and effective.

There are several beneficial effects of soy isoflavones on bone tissue that may help prevent the development of osteoporosis. Both osteoblasts and osteoclasts have been suggested as target cells for action by genistein and daidzein. Osteoblasts are bone cells that help with bone formation and are involved in secreting collagen to form a matrix, which in time becomes calcified. Another type of bone cell is the osteoclast, which resorbs previously made bone and contains lysomes that release acid hydrolases capable of dissolving calcium phosphate and attacking one matrix. The bone-conserving action of soy is considered to result from the direct estrogen receptor-mediated action of genistein on osteoblasts and their precursor cells.

A recent longitudinal study of women aged 30-40 years who were followed for 3 years showed a strongly beneficial effect of dietary soy isoflavone intake in maintaining spinal bone mineral density. Additionally, Dalais et al. reported that 45 mg/day of soy isoflavones, consumed over two 12-week periods, increased bone density in 13 postmenopausal women in a double-blind, randomized, placebo-controlled, cross-over study. Prevention of osteoclastic activity may also be related to the ability of isoflavones to inhibit tyrosine kinase since osteoclasts are usually dependent on its activity.

Soy intake has also been suggested to protect against bone loss by mechanisms independent of its estrogenic effects. Benefits of soy may be due to enhancement of calcium absorption and retention. A high protein diet increases urinary calcium excretion. However, studies have shown that plant protein, such as soy, does not increase urinary calcium excretion compared to animal protein and may result in a higher absorption of calcium.

CONCLUSION

Compelling research indicates that soy and its individual constituents have numerous health benefits. The primary isoflavones, genistein and daidzein, as well as their metabolites, exert a wide array of effects that appear to offer protection against cancer, cardiovascular disease, and

osteoporosis. Soy may also be helpful in relieving menopausal symptoms and promoting hormone balance. While the majority of studies demonstrating the benefits of soy have used whole soy foods, soy isoflavone supplements may provide many of the same benefits. The recommended intake is 60 mg to no more than 120 mg per day.

An area of concern that some may have regarding the consumption of soy isoflavone supplements is the issue of genetically modified (GM) soybeans. While there is a great deal of controversy surrounding this subject, there are many sources of organic soy products available for those who are concerned. In addition, soy isoflavone supplements are available that use non-GM, or "identity preserved," soybeans. To be sure this is what you are getting, you should ask the manufacturer to provide documentation certifying that their product does not contain isoflavones derived from GM soybeans.