Pharmacological activities of Genistein, an isoflavone from soy (Glycine max): Part II—Anti-cholesterol activity, effects on osteoporosis & menopausal symptoms

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Phytoestrogens represent a family of plant compounds such as isoflavones, flavones and lignans. A wide range of commonly consumed foods contains appreciable amounts of different phytoestrogens such as isoflavones and lignans. Soy and its products are particularly good sources of isoflavones and lignans. The evidence reviewed here represents the beneficial effects of most potential and promising isoflavone, Genistein in various types of diseases such as osteoporosis, cardiovascular diseases, menopausal symptoms by accumulating evidence from molecular and cellular biology experiments, animal studies, and, to a limited extent, human clinical trials. This review suggests that phytoestrogens may potentially confer health benefits related to various diseases such as cardiovascular disorder, menopausal symptoms, and osteoporosis.

Isoflavones of soy are important and fast-growing segments in the study of the relationship between health and nutrition. Of the isoflavones contained in soy (Glycine max), two—Genistein and Daidzein—seem to hold the most promise from the therapeutic point of view. Genistein and Daidzein are present in high concentrations (up to 3 mg/g) in soybeans. Soy (Glycine max) also contains Genistin and Daidzin, which are sugar containing isoflavones molecules. During digestion, intestinal bacteria cleave or cut off the sugar molecules, creating still more Genistein and Daidzein. Research suggests that soy isoflavones act in four distinct ways: as estrogens and antiestrogens, as cancer-enzyme inhibitors, as antioxidants and as immune enhancers. Accumulating evidence from molecular and cellular biology experiments, animal studies and human clinical trials suggest that isoflavones may confer health benefits related to cardiovascular diseases, osteoporosis, menopausal symptoms and other diseases.

Genistein—Menopausal Symptoms
During woman's post menopausal period in life, the production of estrogen by the ovaries is reduced. The drop in blood-estrogen levels triggers common symptoms of menopause e.g. hot flashes; insomnia; heavy sweating (especially at night, which further contributes to insomnia); headaches; mood swings; nervousness and irritability; depression, vaginal dryness and soreness. Based on life expectancy trends, women face the prospect of spending the last one-third to one-half of their lives in a state of hormonal imbalance. However, experiences vary from culture to culture around the world. For example, Asian women are typically one-third as likely as American women to report symptoms and there appears to be an actual difference in the severity and incidence of symptoms. Hot flushes are uncommon in women from countries where the consumption of soy products is high, such as in Asian countries. In fact, there is no precise Japanese word to describe hot flushes. Japanese women reported much less night sweats and hot flushes than Canadian women did. Another study found that urinary excretion of isoflavones in Japanese women was 100 to 1000 times higher than in American and Finnish women and that the high consumption of soy products may partly explain why Japanese women report having fewer hot flushes.

Although women can reduce postmenopausal symptoms by taking exogenous estrogen, the compliance is very poor (about 10% of women older than fifty-five years). The development of SERMs (Selective Estrogen Receptor Modulators) were designed to retain the benefits of estrogen without its unwanted effects. That is ideally, SERMs exert estrogenic actions in tissues where that effect is thought to be beneficial, such as the bones and the heart, but would have
lessened menopausal symptoms, lowered blood pressure and resulted in a healthier blood lipoprotein profile. The supplements led to these benefits without the side effects associated with conventional hormone replacement therapy. A recent review on common alternative remedies for treatment of symptoms attributed to menopause. The conclusion was "In available controlled studies, the strongest data support phytoestrogens for their role in diminishing menopausal symptoms related to estrogen deficiency and for possible protective effects on bones and cardiovascular system."

Genistein—Bone Disease (Osteoporosis)

Osteoporosis is a reduction in bone tissue resulting in brittle and fragile bones prone to fracture, usually occurring in postmenopausal women and elderly men. However, women are at greater risk for osteoporosis, because they have a lower peak bone mass (smaller skeletons), and they also lose bone more rapidly after menopause. Because differences in peak bone mass, women are an important determinant of the risk of developing osteoporosis later in life, osteoporosis is often considered to be a "pediatric disease with a geriatric outcome". The changes in bone mass and shape are due to hormonal changes, deficiency of calcium, deficiency of vitamin D, and low peak bone mass.

Osteoporosis is a problem of immense magnitude. Statistics from the National Osteoporosis Foundation indicate that one in three women over fifty years of age will suffer a fracture in her lifetime. Estrogen replacement therapy (ERT) is one of the mainstays for the prevention and treatment of osteoporosis in postmenopausal women. However, ERT may have undesirable effects and risks, and compliance with ERT regimes tends to be low. Epidemiological studies have shown a lower incidence of osteoporosis among population consuming high soy diets compared to western population.

There are two types of cells in bone, one that makes bone (osteoblasts) and one that destroys bone (osteoclasts). Because of the drop in estrogen, the cell type that destroys bone starts to become predominant. Osteoclasts are usually dependent on the activity of the enzyme tyrosine kinase by inhibiting its activity; thus, tyrosine kinase inhibitors are candidates to prevent osteoporosis. Genistein is well known as tyrosine kinase inhibitor and as such can be used in preventing osteoporosis. A study presented at the "Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease" which was held in Brussels, Belgium, Sept 1996, indicates that Genistein suppresses osteoclasts function in vitro and in vivo at concentrations consistent with a tyrosine kinase mechanism, and has low toxicity. Another study presented at this symposium reviewed the effect of Genistein administration on bone loss in ovariectomized rats. The study showed that Genistein protected rats from bone loss associated with cessation of ovar-
Studies published later supported this effect. In a study conducted with postmenopausal women, they were given daily soy supplements. After six months, the women consuming soy isoflavones had a significant increase in bone mineral content and density in their lumbar spines, compared with the control group. Similar trends were noted for other skeletal areas.

Studies on various experimental animal models indicate that Genistein has a direct inhibitory effect on bone resorption (assimilation) in tissue culture. Other studies showed that Genistein and Genistin have an anabolic effect on bone metabolism in elderly rats and Genistein reduces both trabecular and compact bone loss and that this protective effect differs from that of estrogen, since it depends on stimulation of bone formation rather than on suppression of bone resorption. Given the promising results in animal models, one study investigated the effectiveness of soy diet rich in isoflavones in modulating the bone loss in estrogen-deficient, postmenopausal women. The results indicate significant increases in both bone mineral content and bone mineral density in the lumbar spine. Other studies showed that isoflavones are also estrogenic enough to promote bone formation. In fact, the European drug—Ipriflavone, used to treat osteoporosis, is a synthetic isoflavone; Daidzein is one of its metabolites.

More recently, John J.B. Anderson published a review, which covered published reports of epidemiological and experimental studies of humans, animal models, isolated tissues and cells in structure, concluded that isoflavones (particularly Genistein and Daidzein), at optimal doses, result in improved bone mass.

Genistein and Heart Disease

Although progress has been made in prevention and treatment of cardiovascular disease, it remains the number one killer of men and women in the United States, accounting for more than 40 percent of all deaths. Of all the cardiovascular diseases heart disease, primarily heart attack, has received the most attention. Atherosclerosis is a process in which material called plaque, builds up in an artery wall at the site of an injury, reducing blood flow. Complete blockage of this plaque-narrowed artery results in a heart attack. Atherosclerosis is present in most heart attacks. Susceptibility to atherosclerosis is determined by a combination of genetic and environmental factors, including diet, especially diet rich in cholesterol. Men are much more prone to atherosclerosis than women. Women are protected pre-menopausally at least by their estrogens and their death rate is 3.5-fold less. Lower incidence of heart disease has also been reported in populations consuming large amounts of soy products. Lipoproteins are responsible for the transport of the major blood lipids and are classified as LDL cholesterol—low-density lipoproteins (main carrier of cholesterol), VLDL—very-low-density lipoproteins (the “bad” cholesterols), and HDL cholesterol—high-density lipoproteins (the “good” cholesterol). The function of the LDL’s is to carry most of the cholesterol in the body from the liver to the body’s cells, while the HDL’s carry cholesterol back to the liver for disposal. This process protects the body from developing atherosclerosis. Only oxidized LDL-cholesterol is taken up by macrophages within the endothelial cells lining the arterial wall and ultimately contributing to atherosclerotic plaque formation. Although dietary soy protein is well recognized for its beneficial effects in the promotion of cardiovascular wellness, Anthony and colleagues have conducted two studies with monkeys. In these studies soy protein rich in soy isoflavones favorably affected serum lipid concentrations while soy protein from which the soy isoflavones had been extracted had a minimal impact. These primate studies suggest that soy isoflavones may account for 60-70 percent of the effects of soy protein.

Isoflavones and Reduction in Cardiovascular Disease via Several Distinct Mechanisms

Reduction of LDL cholesterol increasing HDL-cholesterol

In a recent study, sixty-six hypercholesterolemic postmenopausal women were given a diet with isolated soy protein containing high amount of isoflavones. There was a significant reduction in LDL cholesterol and a significant increase in HDL cholesterol in the group receiving a protein diet with different
amounts of isoflavones compared with women consuming pure isolated protein extract. During a 6-month intervention cross-over study, Anthony et al. fed prepubertal monkeys a moderately atherogenic diet in which the protein was soy protein isolate either with the isoflavones Genistein and Daidzein intact or containing only the trace amounts still present after the isoflavones are removed. When compared to the soy protein diet, the soy protein with isoflavones significantly decreased LDL-cholesterol and VLDL-cholesterol by 30-40% in both males and females and significantly increased HDL-cholesterol in females. All sex hormones were normal, and at necropsy, it was found that the isoflavones had no adverse effects on either male or female reproductive systems. Crouse and his colleagues studied 156 patients with moderately elevated cholesterol levels who were randomly assigned to receive soy drink containing soy protein either with or without isoflavones. Another group of patients got beverage containing casein, the principal protein of cow’s milk. Soy drinks containing isoflavones reduced both total cholesterol, and low-density lipoproteins. In patients who started with a high LDL cholesterol, the effects was even more dramatic—a 10% reduction. Soy protein from which isoflavones were removed by alcohol extraction had no such effect. Genistein may be able to protect LDL against oxidative damage. Studies examined the capability of a range of isoflavones to enhance the resistance of LDL to oxidation. It was found that Genistein to be the most potent antioxidant both in the aqueous and in the lipophilic phases.

**Improving arterial elasticity**

21 menopausal and premenopausal women were given 80-mg daily isoflavones (45 mg Genistein) over 10-week periods. Systemic arterial compliance (arterial elasticity), which declines with age in the women tested, improved significantly compared with the placebo. It was concluded that the beneficial effect of the soy isoflavones on the arterial health of premenopausal and menopausal women improved to the “same extent as is achieved with conventional hormone replacement therapy”.

**Beneficial effect on blood lipoproteins via estrogenic mechanism**

Estrogens are known to protect against heart disease in several ways including lowering the levels of LDL cholesterol and raising the level of HDL cholesterol. The functions of estrogen help to explain the lower rate of heart disease in women before menopause. Genistein binds with the estrogen receptor (ER) beta, similar to the natural estrogen. The predominance of ER beta in the cardiovascular system suggests that Genistein may be partly responsible for the lower incidence of heart disease in soy-consuming countries. A study showed that the isoflavones in soy improve cardiovascular disease risk factors without apparent deleterious effects on the reproductive system of prepubertal monkeys.

**Inhibition of Cell Proliferation**

Genistein inhibits the tyrosine kinase enzymes, which play a role in the arterial-wall changes that represent the first step in the process of atherosclerosis. The effect of Genistein is more significant in hyperlipidemic cells. Genistein can also inhibit cell adhesion, alter platelet activating factor and inhibits cell proliferation involved in atherosclerotic lesion formation. Moreover, it also inhibits the activity of smooth muscle cell replication, which helps to prevent plaque formation on artery walls. A recent study in the University of Washington, Seattle, found that Genistein selectively inhibited the growth of smooth muscle cells in arteries. Platelet-derived growth factors are believed to play an important part in the proliferation of smooth muscle cells in the atherosclerotic plaque.

**Metabolism, Bioavailability and Toxicity of Genistein**

As mentioned above, in soy foods, the aglycones Genistein and Daidzin are mainly present in the glucoside forms Genistin and Daidzin, e.g. in soybean milk powder, only 4-5% of the isoflavones are in the form of aglycones. Absorption of soybean isoflavones may begin in the proximal small intestine. Lower down in the intestine, the gut bacterial de-conjugating enzymes hydrolyze the isoflavone glycosides to produce Genistein and Daidzin. In addition, glucosidases of intestinal microflora in the lower bowel can liberate the aglycones, thereby promoting their absorption. The intestinal microflora, however, also extensively metabolize and degrade the isoflavones, thereby prohibiting their re-absorption from the lower bowel. After absorption, isoflavones are extensively transformed by phase II enzymes thus making their retention in the human body unlikely. Following transformation, isoflavones undergo urinary and biliary excretion. In a clinical study, Genistein was
shown to have relatively poor bioavailability. The considerable variation in Genistein bioavailability among seven female subjects in a similar study was attributed to the relative ability of gut microflora to degrade isoflavones. Despite the relatively low bioavailability of isoflavones, Genistein may still be absorbed in sufficient quantities to exert potentially beneficial biological effects. Since one-third of the world’s population consume substantial amounts of soy, and hence Genistein, and have low rates of cardiovascular disease, it can be concluded that in humans, Genistein is not toxic and may indeed be the cause of the lower risk of these diseases. The administration of up to 50 mg of Genistein in the form of one or more tablets is reported to have no significant toxicity and no or few side effects.

Conclusion

It may be concluded that Genistein is potentially beneficial in treating diseases such as menopause and osteoporosis as well as in the prevention of cardiovascular disease. In view of the multi-faceted benefits of this soy isoflavone, it may seem prudent to shift towards soy-rich diets. However, soy foods contain the β-glycoside, Genistin and conversion to the active aglycone form is dependent upon the activity of the gut microflora which in turn results in wide variations in the bioavailability of Genistein from soy products. Consequently, the administration of Genistein in the form of a standardized dietary supplement is a convenient means of ensuring improved absorption with the resulting potential health benefits.

References

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