

## Soy Isoflavonoids as Nutraceutical for Human Health: An Update

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### Abstract

Isoflavones are the most abundant phytoestrogen in soybeans which are structurally similar with 17  $\beta$ -estradiol. The antioxidant property of genistein and daidzein are well established in different experimental and clinical models. Isoflavones compounds have been found effective in the management of diabetes. It reduces low-density lipoprotein and triglycerides and hence minimizes the risk of coronary heart disease. Soy isoflavones was found useful for treatment of osteoporosis by inhibiting tyrosine kinase. In soy isoflavones, genistein is effective in the treatment of cancer by acting on androgen receptor and inhibiting tyrosine kinases. In this update many nutraceutical and medicinal uses and applications of soy isoflavones have been investigated such as treatment and prevention of cardiovascular diseases, cholesterol lowering, osteoporosis, diabetes, cancer, cognitive decline, and menopausal symptoms.

**Keywords:** Soybeans; Daidzein; Genistein; Isoflavones; Osteoporosis; Phytoestrogens

### Introduction

Soybeans (*Glycine max*) serve as one of the most valuable crops in the world, World output will be 281.9 million metric tons in the 2013-14 seasons; in India the production of soybean 1000 metric tons in the 2013-14 seasons [1].

Soybeans are found to have genistein and daidzein isoflavones which are nonsteroidal estrogen mimicking phytoestrogen [2]. Some of the other phytoestrogen include lignans, coumestans, and prenylflavonoids [3]. Soybeans are suggested to have many health benefits such as the healthy functioning of bowels, heart, kidney, liver, lowering of serum cholesterol levels and reduction in the risk for coronary heart disease (CHD), reduction in the risk for breast cancer, and osteoporosis in women, and alleviation of the disturbances caused by menopause [2].

### Intakes, Metabolism and Bioavailability of Soy Isoflavonoids

Soybeans have various bioactive compounds such as saponins, protease inhibitors, phytic acid, and isoflavones [4]. The most important isoflavones in soy is genistein; and others are composed by daidzein and glycitein. The metabolism of isoflavones is different from that of parent compounds [5]. While isoflavones are in soy; it is fully bound by sugars and produces genistin, daidzin, and glycitin [2]. Soy isoflavones have weak estrogens, and they can function as agonists, partial agonists, or antagonists to endogenous estrogens and xenoestrogens at estrogen receptors [6,7].

### Significance of Soy Isoflavonoids in Prevention of Cardiovascular Disease

The main cause of heart disease and atherosclerosis is Diabetes; uncontrolled diabetes causes damage to your body's blood vessels making them more prone to damage from atherosclerosis and hypertension [8]. Although many risk factors, such as cigarette smoking and hypertension, contribute to the risk for coronary heart disease (CHD), lipid abnormalities are the major factors. Low-density lipoprotein (LDL) penetrates the walls of blood vessels where it is oxidized by free radicals and accumulates as a gruel-like material that blocks the blood vessel to cause thrombosis [9]. Soy protein has many antiatherogenic effects. It decreases LDL cholesterol and tends to increase HDL levels [6]. Soy isoflavones has antioxidant activities and protect LDL from oxidation. Soy protein lowers blood cholesterol levels [10]. Soy protein is better than animal protein for health [11]. Past studies concluded that soy protein lowers total cholesterol, LDL cholesterol and triglycerides without lowering HDL cholesterol in hypercholesterolemic humans [12]. Even adding soy protein to an omnivorous diet 25 g per day may be enough to lower cholesterol levels [13]. The studies with rhesus monkeys observed that isoflavones associated with soy protein enhance the cholesterol-lowering effects [14].

### Cholesterol-Lowering and Isoflavonoids

Estrogen administration into postmenopausal women has been observed to produce cardio-Protective benefits [15]. Torres has reported that exact bimolecular mechanisms for this cardio-protection are unclear but it is likely that actions mediated both through the estrogen receptors, and independently of the estrogen receptors [16]. In populations consuming large amounts of soy products found to be have lower incidence of heart diseases [17]. Hoie reported that soy protein incorporated into a low-fat diet can reduce cholesterol and LDL-cholesterol concentrations [11]. Anthony have studied the soy isoflavones effect on cardiovascular risk factors in peripubertal rhesus monkeys and inflammatory markers in atherosclerotic [8], ovariecto-

mized monkeys and found that soy protein intake and high isoflavones intake led to significantly greater decreases in serum LDL cholesterol than low isoflavone intake, indicating that isoflavones have LDL-cholesterol-lowering effects which are independent of the soy protein [18]. Consumption of soy protein by postmenopausal women for six months showed a significant decrease in non-high-density lipoprotein (HDL) cholesterol and a significant increase in mononuclear cell LDL receptor mRNA and HDL cholesterol in both of the soy isoflavone groups compared to the control group [19]. Indeed, consumption of soy protein in high-risk middle-aged men (45 to 59 years of age) in Scotland significantly decreased non-HDL cholesterol and blood pressure, compared to the control treatment [17].

### Antioxidant Action Soybean Isoflavonoids

As per Bouker, et al. [20], genistein has been indicated to have antioxidant properties. Genistein has a potential antioxidant effect on hydrogen peroxide production by 12-O-tetradecanoylphorbol-13-acetate-activated HL-60 cells. Amigo-Benavent's studies on feeding genistein to mice significantly enhanced the activity of antioxidant enzymes in the skin and small intestine [21]. In the *in vivo* soy isoflavones showed antioxidant property by elevating the antioxidant catalase and superoxide dismutase enzyme activity in various organs of rat [22]. As per Lee, et al. [23] the molecules other than isoflavones may have a synergistic effect on *in vivo* antioxidant enzyme inductions of tofu (a soft white substance made from mashed soya beans, used chiefly in Asian and vegetarian cooking). Another Liu, et al. [24] study revealed that daidzein enhances catalase promoter activity at 100  $\mu\text{mol/L}$  in a reporter gene assay and at 200  $\mu\text{mol/L}$  in Northern blot experiments but shows only little antioxidant capacity.

Stroke patients were given a soy cream product (10.6% protein) that reduced lipid per-oxidation in molecules of low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein cholesterol, and high-density lipoproteins (HDL) [6]. Another study found that genistein inhibited the oxidation of LDL cholesterol in the presence of copper ions or superoxide/nitric acid radicals *in vitro*. In addition, this research suggested that genistein effectively protected human endothelial cells from damage by oxidized lipoproteins [23].

### Arterial function

Arterial function is vital to the prevention of ischemic changes in the organs that the arteries deliver blood to, and is particularly relevant to ischemic heart disease [9]. Flow-mediated vasodilatation worsened in the men and had no significant effect in the postmenopausal women [25]. In a placebo-controlled, randomized, crossover study with 21 pre- and postmenopausal women treated for five weeks with a supplement delivering 80 mg total soy isoflavones/day, a significant improvement was reported in systemic arterial compliance, but had no effect on flow-mediated vasodilation [15].

### Role of soy isoflavonoids for management of osteoporosis, cognitive decline, and menopausal symptoms

Osteoporosis is characterized by reduced bone mass and structural deterioration of bone tissue occurring in women and is primarily related to aging and hormone deficiency [15]. Drugs that act on resorptive pathway and build new and improved skeletons are specifically recommended to treat bone loss [15]. Practical studies on genistein showed a positive effect on osteoporotic bone by decreasing osteoclastic resorption factor, such as collagen C-telopeptide, and

increasing osteoblastic formation markers, such as bone-alkaline phosphatase. Genistein has also shown to selectively antagonize the bone catabolic effects of parathyroid hormone in osteoblasts by reducing parathyroid hormone-induced increases in soluble receptor activator of nuclear factor- $\kappa\text{B}$  ligand and reversing decreases in osteoprotegerin expression *in vitro* [26]. The mechanism of action of isoflavones seems to act independently on osteoclasts via non-estrogenic mechanisms because there are no estrogen receptors in the nuclei of osteoclasts [27]. Isoflavones act on osteoclasts by inhibition of tyrosine kinase [28]. Although the mechanisms of isoflavones on osteoporosis are still not completely known, evidence from *in vitro* studies suggests that they act in multiple ways, via genomic and non-genomic pathways and via both osteoclasts and osteoblasts [29]. Soy isoflavones stimulate the activity and proliferation of bone-building cells, namely osteoblasts to maintain bone mass against the action of osteoclast cells, which release acid and enzyme to dissolve bone.

The osteoblast cells produce a collagen core and coat it with an adhesive substance, which is present in the bone and finally calcium adheres to the collagen to form a new bone tissue. Mechanism of action of soy isoflavones in the treatment of osteoporosis, (a) Osteoclast cells carried via bloodstream to bone, (b) Cells firmly attach themselves to the bone, (c) Cells release acid and enzymes that dissolve the bone, (d) Osteoclast cells [19,15].

### Potential role of soy isoflavonoids in management of menopausal complexities, cancer prevention, hormone-dependent cancer prevention, estrogens and risk of breast cancer

The role of isoflavonoids in the prevention of cancer and in particular hormone dependent cancers such as breast and prostate cancer is currently extensively investigated [30]. Messina, et al. reported that consumption of soy foods rich in isoflavones has been weakly associated with reduced colon cancer [31]. Risk of prostate cancer in men occurs in the same generation but for breast cancer risks in women the increase is observed in the next generation [20]. Breast cancer is one of the most lethal diseases in women [32]. Increased soy intake has been associated with a minimized risk of breast cancer in two out of four epidemiological studies that examined a wide range of dietary components in relation to breast cancer risk [33,34]. Colon cancer risk is influenced by estrogen exposure. Breast and prostate cancer is much less prevalent in countries, where there is an abundance of soy phytoestrogen in the diet [20].

### Mechanisms of Anticancer Action of Isoflavonoids

The compound of soybean like isoflavones, saponins, phytates, protease inhibitors and phytosterols are identified as anticancer drugs but the isoflavones are weak estrogens. Soyabean compounds can work as anti-estrogens by combining with estrogen receptors in place of the potent physiologic estrogens, thus blocking them from exerting their effects [28,35,36]. Pubertal exposure to genistein that is administered via either injections or fed has consistently been found to lower the incidence or multiplicity of subsequent carcinogen-induced, estrogen-dependent mammary tumors. Genistein inhibits the proliferation of MDA-MB-231 human breast cancer cells in cell culture and the probable mechanism is inhibition of the cell cycle at G2-M [37]. Isoflavonoids have biphasic effects on the proliferation of breast cancer cells in culture; at concentrations greater than 5 mM genistein exhibits a concentration-dependent ability to inhibit both growth

factor-stimulated and estrogen-stimulated cell proliferation. Genistein at low concentrations can stimulate the growth of estrogen receptor-positive MCF-7 cells [38,39]. However, genistein does not stimulate the growth of estrogen receptor-negative breast cancer cells [22,40], it only inhibits cell proliferation in these cell lines.

### Care and Concern for Using Soy Isoflavonoids

In some of previous animal health studies phytoestrogen was found to be a cause for infertility therefore there is concern for using same for the humans. Isoflavones obtained from clover species was responsible for infertility syndrome in sheep [41]. The studies on peripubertal rhesus monkeys do not show any bad effect of soybean and also there is no such abnormalities found in the places of high soy consumptions.

### Conclusions

This update reviewed the available information with related to consumption of soy foods, soy isoflavones and their usefulness in breast cancer incidences. There is demand in production and consumption of soy foods in the world. There is epidemiological proof showing increasing soy consumption and a minimized risk of recurrence of breast cancer. The high consumption of soybean foods is found to lower breast cancer incidences, lowering cholesterol levels, cardiovascular diseases, management and menopausal problems

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