

Soy isoflavone: The multipurpose phytochemical (Review)

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Received April 10, 2013; Accepted May 21, 2013

DOI: 10.3892/br.2013.129

Abstract. Soy isoflavones are compounds found in soybean and soybean products. They have been reported to possess numerous physiological properties, such as antitumor, anti-menopausal (female) osteoporosis and anti-aging. They have also been reported to improve learning and memory skills in menopausal women and aid in the prevention and treatment of heart disease, diabetes and Kawasaki disease (KD). In this review, the effects of soy isoflavones on various diseases were analyzed. Based on the analysis, it was hypothesized that the function of soybean isoflavones in the prevention and treatment of various diseases results from their phytoestrogen and antioxidant properties. However, due to their phytoestrogen properties, it is recommended that the risks of soy isoflavone intake as food and/or medical treatment be further evaluated.

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1. Introduction

Asian populations have consumed foods made from soy beans for centuries, whereas in the West, certain subpopulations,

specifically Seventh-day Adventists and vegetarians, have used soyfoods for ~100 years, although the quintessential soyfood tofu was first introduced on a large scale to the general US population in the early 1970s. Health-conscious and ecologically-minded consumers were particularly attracted to soy at that time since it was perceived as a source of high quality protein, low in saturated fat, that was more efficiently produced compared to animal sources of protein. A significant increase in soyfood consumption occurred during the last decade of the 20th century, mainly due to the belief among many consumers that soyfoods may offer health benefits, independent of their nutrient content. This increased interest is best viewed in the context of the general recognition that plants contain large quantities of potentially beneficial, non-nutritive, biologically active components, commonly referred to as phytochemicals. This knowledge led to the concept of functional foods [initially referred to as designer foods by the National Cancer Institute (NCI)] and to soy being one of the first foods widely acknowledged to fall into this category (1). Soy isoflavones contain 12 different isoforms that are divided into four chemical forms: aglycone (daidzein, genistein and glycitein), glucoside (daidzin, genistin and glycitin), acetylglucoside (acetyldaidzin, acetylgenistin and acetylglycitin) and malonylglucoside (malonyldaidzin, malonylgenistin and malonylglycitin). Soy isoflavones were demonstrated to possess numerous biological functions, such as antioxidant (2), inhibitory on cancer cell proliferation (3), anti-inflammatory (4) and preventive of coronary heart disease (5) and osteoporosis (6).

Over the last 22 years, there has been a considerable amount of research on the health effects of soy consumption, which may be largely attributed to the presence of isoflavones in the soybean. Isoflavones first came to the attention of the scientific community in the 1940s, as a result of fertility problems observed in sheep grazing on a type of isoflavone-rich clover (1). In the 1950s, due to their estrogenic effects in rodents, isoflavones were investigated for use as possible growth promoters by the animal feed industry, although shortly thereafter it was demonstrated that isoflavones may also act as antiestrogens (1). Despite this early study, it was not until the 1990s, mainly due to research sponsored by the US NCI, that the role of soyfoods in disease prevention started to attract significant attention. Subsequently, isoflavones and soyfoods were investigated on their ability to alleviate hot flashes and inhibit bone loss in postmenopausal women. In 1995, soy protein attracted worldwide attention for its ability to lower cholesterol levels (1). At that same time, isoflavones started to be widely discussed as

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Key words: soy isoflavone, phytochemical, disease, phytoestrogen, antioxidant ability

potential alternatives to conventional hormone replacement therapy (1). In 2002, it was hypothesized that individuals harbouring intestinal bacteria capable of converting the soybean isoflavone daidzein into the isoflavan equol were more likely to benefit from soy intake (1). More recently, *in vitro* and animal studies have raised questions regarding the safety of exposure to isoflavones for certain subsets of the population, although human data are largely inconsistent with these concerns (1).

2. Effects of soy isoflavones on cancer

Melanoma and breast tumor cells are capable of degrading the extracellular matrix via a proteolytic cascade that includes urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs). At non-cytotoxic concentrations (0.1-50 μ M), genistein dose-dependently promoted spindle-cell morphology and significantly reduced motility in the two cell lines. Genistein inhibited uPA secreted by F3II cell monolayers, while inducing an increase in the proteolytic activity of B16 cells. By contrast, the compound did not modify the MMP-9 and -2 secretion by tumor cells. These data suggest that tumor cell migration and proteolysis are associated with the antitumor and antiangiogenic activity of the soy isoflavone genistein (7).

Recent studies have demonstrated that soy and isoflavone intake exerts a protective effect against postmenopausal breast cancer (8-10). The overexpression of HER2 promotes the malignant transformation of breast epithelial cells. Genistein enhanced the cytotoxic effect of adriamycin (ADR) at low doses (less than IC_{50}) against the human breast cancer cell. This enhancing effect was mainly attributed to the increase of necrotic-like, rather than apoptotic, cell death. In conjugation with this event, significant inactivation of HER2 and Akt in the breast cancer cell was caused by the combination of genistein and ADR. These results suggest that genistein enhances the necrotic-like cell death of breast cancer cells through the inactivation of the HER2 receptor and Akt in combination with ADR (11). Statistical data demonstrated that high isoflavone intake (combined RR/OR=0.68, 95% CI: 0.52-0.89) may be associated with reduced breast cancer risk in Asian populations, particularly in postmenopausal women. However, results of studies conducted on Western populations indicated no significant differences, which may be due to the low intake of isoflavone (12).

A previous study by Akaza *et al* (13) was the first to confirm that there is an association between prostate cancer and isoflavone intake. In a later study, Kurahashi *et al* (14) demonstrated that isoflavone intake was associated with a decreased risk of localized prostate cancer. However, a study by Perabo *et al* (15) reported no convincing clinical proof or evidence that genistein may be beneficial in prostate cancer therapy. Between 2008 and 2012, five out of six studies reported a significant association of isoflavones with a decreased risk of prostate cancer (16), two of which consistently demonstrated that daidzein converted to equol by intestinal bacteria leads to a significantly reduced risk of prostate cancer (16).

3. Osteoporosis and soy isoflavones

The first clinical trial in this area to report a benefit was published in 2001 (17). The prevalence of age-related bone loss

is higher in women compared to men and in 25-30% of aging women this loss results in major orthopedic problems (18). Natural or surgical menopause results in an initial phase of rapid bone loss followed by a period of slower skeletal deterioration (19). This rapid phase of bone loss occurs within the first 10 years following the cessation of menses or surgical removal of the ovaries (20). The ovarian hormone deficiency associated with menopause results in an increased rate of bone turnover and leads to an imbalance between resorption and formation, thereby accelerating bone loss (21). A previous meta-analysis reported that soy isoflavones significantly increased the bone mineral density by 54% and decreased the bone resorption marker urinary deoxypyridinoline by 23% compared to baseline in women. A sensitivity analysis indicated that the effect of soy isoflavones on bone mineral density and deoxypyridinoline was significant. Postmenopausal women experience a sharp decrease in estrogen concentration, leading to an increased rate of bone remodeling, which is associated with decreased bone mineral density and increased risk of fractures (20,22,23).

4. Effects of soy isoflavones on learning and memory

A previous study indicated that estrogen use increases the performance on certain tests of cognition, particularly in postmenopausal women (20). Short-term high-dose soy bean intake altered the levels of total plasma testosterone and improved spatial cognition in women (24). Isoflavone supplementation exerted a favorable effect on cognitive function, particularly verbal memory, in postmenopausal women (25). Consumption of dietary phytoestrogens resulting in high plasma isoflavone levels may significantly affect sexually dimorphic brain regions, anxiety, learning and memory (26). Dietary soy-derived phytoestrogens may affect learning and memory and alter the expression of proteins involved in neural protection and inflammation in rats (27). Soy isoflavones may also affect the cholinergic system of the brain and reduce age-related neuronal loss and cognition decline in male rats (28). There are proposed mechanisms for the neuroprotective effects of isoflavones. Genistein protects cells from H_2O_2 -induced toxicity (29). H_2O_2 is a reactive oxygen species (ROS) that may cause neuron damage (30-33). Genistein, a phytoestrogen capable of crossing the blood-brain barrier, has been reported to exert an antioxidant effect against the insults of ultraviolet (UV) radiation and chemicals (34). This antioxidant effect of soy may protect against neurodegenerative diseases. Previous findings suggested that the mechanisms by which phytoestrogens, particularly genistein, protect neuronal cells include its antioxidant activity, as well as the activation of estrogen receptors (ERs) and upregulation of brain-derived neurotrophic factors (34). This improvement in cognitive ability in phytoestrogen-treated females may be due in part to the increased presence of choline acetyltransferase mRNA in the frontal cortex, which was associated with protection and enhancement of cognitive function (35). Furthermore, phytoestrogens significantly affect the brain calcium-binding protein calbindin (CALB), which acts as a buffer by binding intracellular calcium and plays an important role in mediating cell proliferation, programmed cell death (apoptosis) and neurotoxicity (27,36). Soy isoflavones were shown to improve learning and memory function in menopausal women and it

was recently reported that they may improve learning and memory impairment induced by A β 1-42 in rats, maintain A β homeostasis in the brain, regulate the disordered expression of RAGE/LRP-1, and restrain RAGE-related NF- κ B and inflammatory cytokine activation in neurovascular structures (27,36). These results suggested that soy isoflavones may protect A β -impaired learning and memory in rats and the mechanism of action may be associated with the regulation of vascular A β transportation and vascular inflammatory reaction.

5. Effects of soy isoflavones on coronary heart disease

Soy protein-containing foods are a rich source of isoflavone phytoestrogens, such as genistein and daidzein. There is growing interest in these substances, since a high dietary intake of soy-containing foods has been associated with lower rates of chronic diseases, including coronary heart disease (37). Soy phytoestrogens bind weakly to the estrogen receptor (ER) and some bind more strongly to ER- β compared to ER- α . A previous meta-analysis indicated that isoflavone phytoestrogens decreased plasma cholesterol concentrations in subjects with initially elevated levels, but had little effect on subjects with normal serum cholesterol concentrations (37). These substances may also exert beneficial effects on arterial endothelial function, which was also confirmed by Beavers *et al* (38). In addition to these potentially antiatherogenic effects, numerous laboratories are investigating other possible mechanisms, including the antioxidant and anti-proliferative properties of these substances (39). A previous study by Tikkanen and Adlercreutz (37) demonstrated that dietary supplementation with soy-derived isoflavones reduced the *in vitro* oxidation susceptibility of low-density lipoprotein (LDL). It was hypothesized that lipophilic phytoestrogen derivatives may be incorporated into LDLs, increasing their oxidation resistance and antiproliferative efficacy *ex vivo*, which theoretically are antiatherogenic effects. Another study by Chan *et al* (40) demonstrated that a 12-week isoflavone treatment reduced the serum levels of high-sensitivity C-reactive protein and improved brachial flow-mediated dilatation in patients with clinically manifest atherosclerosis, thus reversing their endothelial dysfunction status. The authors of that study suggested that their findings may have important implications regarding the use of isoflavones as secondary prevention in patients with cardiovascular disease, in addition to conventional interventions.

6. Effects of soy isoflavones on diabetes

Type 2 diabetes is a result of chronic insulin resistance and loss of functional pancreatic β -cell mass. Over the past 10 years, numerous studies demonstrated that genistein possesses antidiabetic properties, such as direct effects on β -cell proliferation, glucose-stimulated insulin secretion and protection against apoptosis, independent of its functions as an estrogen receptor agonist, antioxidant, or tyrosine kinase inhibitor (41). Its effects are structure-specific and not common to all flavonoids (42). While there are limited data available on the effects of genistein consumption in diabetic humans, there are several animal and cell-culture studies that demonstrated a direct effect of genistein on β -cells at physiologically relevant

concentrations ($<10 \mu\text{M}$) (41). The effects appear to involve cAMP/PKA signaling and a previous study suggested an effect of gene expression on epigenetic regulation (41).

Genistein was shown to relieve diabetic peripheral painful neuropathy, revert proinflammatory cytokine and ROS overproduction and restore the nerve growth factor (NGF) content of the diabetic sciatic nerve. Genistein was also shown to restore the glutathione (GSH) content and the ratio of reduced to oxidized glutathione (GSH/GSSG), improve the antioxidant enzyme activities, decrease ROS and lipoperoxide levels in the brain and liver and restore the inducible and endothelial nitric oxide synthase (iNOS and eNOS, respectively) content and superoxide dismutase activity in the thoracic aorta. Hyperglycaemia and weight loss were not affected. Genistein was able to reverse diabetic allodynia, oxidative stress and inflammation, as well as ameliorate NGF content and vascular dysfunction, thus suggesting its possible therapeutic use for diabetes complications (43).

7. Anti-photoaging effects of soy isoflavones

A previous study demonstrated that the protective effects of soy isoflavones against UVB radiation may be related to their antioxidant activities (44). Moreover, the soy isoflavone extract inhibited UVB-induced keratinocyte death and suppressed UVB-induced intracellular H₂O₂ release, which reduced oxidative stress. Furthermore, it decreased epidermal thickness and inhibited COX-2 and proliferating cell nuclear antigen expression. The activation of p38, c-Jun N-terminal kinase and extracellular signal-regulated kinase 1/2 (ERK1/2) were triggered by UVB and counteracted by treatment with soy isoflavone extract (44-46).

8. Kawasaki disease and soy isoflavones

Kawasaki disease (KD) is a diffuse vasculitis occurring in children, with a predilection for the coronary arteries. Recent data from a genetic study emphasized the role of specific immune receptors in the pathogenesis of KD. The functions of the Fc γ receptors (Fc γ Rs) are modulated by soy isoflavones, genistein in particular. Epidemiological data from Hawaiian populations suggested an association between soy consumption and KD. These observations form the basis of the hypothesis that isoflavones are involved in KD pathogenesis by modulating the function of the FcGRs and disrupting the balance between the activation and inhibition of the inflammatory response (47).

9. Risks of soy isoflavones

Despite the considerable enthusiasm regarding the potential health benefits of soyfoods and isoflavones, there is also growing concern regarding their safety, based largely on their estrogen-like properties. Isoflavones are classified as phytoestrogens and mixed estrogen agonists/antagonists as well as endocrine disruptors (48-50). Evaluations of isoflavone safety have been conducted by governmental and quasi-governmental agencies in several European countries, Japan and Israel and the European Food Safety Authority is currently conducting another evaluation (1). These concerns are based almost exclusively on *in vitro* and animal studies (human studies, including

clinical and epidemiological data, are supportive of safety) and the most notable among these is that isoflavone-containing products pose a risk to estrogen-sensitive breast cancer patients and women at high-risk of developing this disease and that isoflavone exposure via the consumption of soy-based infant formula may negatively affect the long-term development of infants (51-52).

10. Conclusions

In this study, the properties and role of soybean isoflavones in the prevention and treatment of several diseases were presented, which comprise antitumor, antimenopausal (female) osteoporosis and antiaging properties, improvement of learning and memory skills of menopausal women, prevention and treatment of heart disease, diabetes and KD. Based on the assessment of these diseases under the effect of isoflavones, it was concluded that the function of soybean isoflavones in the prevention and treatment of various diseases largely results from their phytoestrogen and antioxidant properties. Although soybean isoflavones have been demonstrated to exert beneficial effects on the prevention and treatment of several diseases, possible adverse reactions have recently become the focus of attention. Therefore, more clinical trials are required to evaluate the effects of isoflavones on the prevention of disease development and their role in the treatment of various diseases, either alone or in combination with conventional therapeutic methods.

Acknowledgements

This study was supported by grants from the Program of Science and Technology Development of Shandong (2011YD19005; 2011YD21022) and Natural Scientific Foundation of Chinese Shandong Province (ZR2010CQ031).

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