Octa Journal of Biosciences
International peer-reviewed journal
Octa. J. Biosci. Vol. 1(2): 170-176

ISSN 2321 – 3663
December, 2013

Octa Journal of Biosciences
journal homepage: www.sciencebeingjournal.com

Research Article

Beneficial Role of Soybean Phytoestrogens

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A R T I C L E I N F O

Received: 16 Jul. 2013
Revised: 10 Aug. 2013
Accepted: 20 Nov. 2013

Keywords: Electrophoresis, Esterase isozymes, Tissue specificity, *Macrognathus aculeatus, Mastacembalus armatus*

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A B S T R A C T

Phytoestrogens are naturally occurring plant compounds which have oestrogenic and/or anti-oestrogenic activity. They are present in many human foodstuffs including beans, sprouts, cabbage, spinach, soybean, grains and hops. Among these phytochemicals is the broad class of nonsteroidal estrogens called phytoestrogens, and in the past decade there has been considerable interest in the role of isoflavones because of their relatively high concentrations in soy protein. The isoflavones in modest amounts of ingested soy protein are biotransformed by intestinal microflora, are absorbed, undergo enterohepatic recycling, and reach circulating concentrations that exceed by several orders of magnitude the amounts of endogenous estrogens. These phytoestrogens and their metabolites have many potent hormonal and nonhormonal activities that may explain some of the biological effects of diets rich in phytoestrogens. Epidemiological studies suggest that foodstuffs containing phytoestrogens may have a beneficial role in protecting against a number of chronic diseases and conditions. For cancer of the prostate, colon, rectum, stomach and lung, the evidence is most consistent for a protective effect resulting from a high intake of grains, legumes, fruits and vegetables; it is not possible to identify particular food types or components that may be responsible. Dietary intervention studies indicate that in women soya and linseed may have beneficial effects on the risk of breast cancer and may help to alleviate postmenopausal symptoms. Soya also appears to have beneficial effects on blood lipids which may help to reduce the risk of cardiovascular disease and atherosclerosis. It is concluded that dietary phytoestrogens may have a role in the prevention of several types of chronic disease including certain cancers.

INTRODUCTION

Phytoestrogens have attracted greater attention among the public and in the medical community in recent years because of many evidence from several studies (Ranich et al.,2001) suggesting that consumption of plant-based foods rich in these phytochemicals may be beneficial in human health. The surveys and nutritional intervention studies in humans and animals suggest that dietary phytoestrogens play an important role in controlling of menopausal symptoms and a variety of disorders, including cardiovascular disease, cancer, hyperlipidemia, osteoporosis, and various forms of chronic renal disease (Velasquez et al., 2001). The Food and Drug Administration authorized the use on food labels of health claims associated with soy protein and the reduced risk of cardiovascular disease (FDA 1999). Several studies in humans and animals have shown that soy protein reduces plasma total cholesterol and LDL cholesterol. Evidence is also emerging that consumption or supplementation of foods rich in phytoestrogens may have a beneficial effect on diabetes mellitus and obesity in animals and humans.

The majority of phytoestrogens found in typical human diets can be categorized into two primary classes: isoflavones and lignans. Phytoestrogens in the diet may have a role in modulating hormone-related diseases based on their structural similarity to the estrogens 17b-estradiol and diethylstilbestrol. Many of the potential health benefits of phytoestrogens may be attributable to metabolic properties that do not involve estrogen receptors, such as their influence on enzymes, protein synthesis, cell proliferation, angiogenesis, calcium transport, Na1/K1 adenosine triphosphatase, growth factor action, vascular smooth muscle cells, lipid oxidation, and cell differentiation.

BIOLOGICAL SOURCE PHYTOESTROGENS:

High concentration of phytoestrogens is found in legume plants and also found in grains, vegetables and fruits distributed across the plant kingdom. Isoflavones are most common phytoestrogens found in legumes. Isoflavones are part of the isoflavonoids, which are mainly in distributed to the Fabaceae family and more specifically to the subfamily Papilionaceae (Dewick, 1993).

Phytoestrogens in Soy

Soybean (*Glycine max*) belongs to the family Fabaceae and has highest levels of protein and oil (Duke, 1981). Medicinally it has been reported for healthy functioning of the heart, kidneys, liver and stomach. It has been well known that soybeans contain high amounts (100-300 mg/100 g) of two isoflavones glycosides, daidzein and genistein and a third major compound, glycitein, was reported later (Nairn et al. 1973). In case of some fermented soy product a catecholic conversion product of glycitein, 6,7,4-trihydroxyisoflavone was also reported. Consumption of soy protein has shown to decrease the lipid peroxidation and lowered the probability of atherosclerosis in rabbits (Van der Schouw *et al.*, 2000). Isoflavone-intact soy protein has found to decrease the LDL and increase the high-density lipids (HDL) cholesterol level, which indicate that the active components are found in the soy protein portion (Clarkson and Anthony, 1998). Several reports indicate that soy isoflavone pills improved arterial compliance but did not show effects on plasma lipids (Clarkson and Anthony, 1998). The risk of breast cancer in premenopausal women was found to reduce who consume a soy rich diet while others indicate a non-significant reduction of this risk (Hargreaves *et al.*, 1999). The duration of soy consumption is also very important parameters to control the risk of breast cancer. There are limited studies to suggest that soy consumption in adult life is protective against breast cancer, however, high levels of consumption (Peeters *et al.*, 2003) or consumption throughout life could potentially reduce the risk of breast cancer. Presently soy isoflavones have not been reported to show significant effects on eudiometrical tissue.

PROCESSING OF SOYBEAN

The processing of soybeans as described by Snyder and Kwon (1987) may be summarized as: soybeans selected for processing are graded, cleaned, dried (up to 10% moisture content) and remove the hull. Soybean hulls are processed to make fibre additives for breads, cereals, snacks and livestock feed. The dehulling product of are rolled into full-fat flakes and used in animal feed or processed into full-fat flour. The next step is to extract the crude oil and refining to produce cooking oil, margarine and shortening. Defatted soy flakes are used to produce animal feed and related to variety of soya products, including soy flour, soy concentrates and soy isolates. These soya products are used extensively in foods manufactured and help to retain moisture and improve their shelf life, and they also act as emulsifiers. Soy flour is produced by grinding the defatted flakes. The soy flour adds protein and improves the crust colour and shelf life of baked goods. Soy isolates are produced by a chemical process and resulting product with about 90% protein content. Soy isolates contain no fibre or carbohydrates. Soy isolates are applicable in many dairy-like products. Soy concentrates are mainly prepared by removing the soluble sugars from defatted flakes contain about 70% protein.The concentrates are used in protein drinks, as soup bases and in gravies. Due to fat and water absorption properties soy flour and soy protein concentrates are utilized in meat products. Soy flour, soy concentrates or soy isolates, moistened and mixed with a variety of additives (Wolf *et al, 1981*).

All soy proteins and soy foods, which are available for human consumption, contain significant amounts of the isoflavones daidzein and genistein, either as the aglycone (unconjugated form) or as different types of glycoside conjugates. Soy proteins low amounts of glycitein conjugates (Naim et al., 1973) and all of which can be separated by reversed-phase HPLC. Soy hypocotyledon or germ contains high concentrations of conjugates of glycitein (Kudou et al.1991). The malonyl and acetyl glycosides are very sensitive to heat and readily convert to the more stable b-glycoside (Barnes and Coward, 1994). The relative proportions of above conjugates can vary considerably among different soy foods, which depend on the extent of processing of the soybean, (Wang and Murphy, 1994).

ACTION OF PHYTOESTROGENS

Two molecular mechanisms of isoflavones have been proposed to explain phytoestrogenic effects on human health. Phytoestrogens interact with enzymes and receptors and pass through cell membranes (Adlercreutz, 1998b) and above interactions allow them to bind to Ers. The phytoestrogen and receptors complex induce specific estrogen-responsive gene products and stimulate ER-positive breast cancer cell growth (Kurzer and Xu, 1997), which alter ER structure and affect transcription. Some molecular mechanisms of action include estrogenic and antiestrogenic effects on ERs, while other may not directly interact with ERs (Messina and Loprinzi, 2001). There is several nongenomic effects that do not involve Ers are as: inhibition of tyrosine kinase, induction of cancer cell differentiation, influence DNA topoisomerase activities, suppression of angiogenesis and antioxidant effects of phytoestrogens (Kurzer and Xu, 1997). Some other effects potentially influence the biosynthesis and metabolism of steroids and fatty acids, sex steroid binding proteins and the transmembrane transfer of hormones to a membrane (Benassayag *et al.*, 2002). Phytoestrogens affect the enzymes activity essential for hormone conversions and lowering the biological activity of sex hormones in target organs, which reduce the cancers (Adlercreutz, 1998b). Some phytoestrogens are able to induce estrus cycle in mammals similar as estrogen-like compounds. Several factors as; administration, dosage, metabolism and the ingestion of other pharmacological substances affect the activities and the bioavailability of phytoestrogens. (Kelly *et al.*, 1995). The effectiveness of phytoestrogens are also depends upon target tissue, concentration, number and type of ER and the presence or absence of endogenous estrogens. (Glazier and Bowman, 2001).

DIETARY SOYBEAN AND ITS EFFECT ON GLUCOSE AND LIPID METABOLISM

Glucose and lipids metabolism is a complex process and regulated by peptides and steroid hormones. Many studies indicates the consumption of soy-containing food have an effect on glucose and lipid metabolism by regulating hormones. Several studies on human showed that soy polysaccharides reduce the postprandial glucose and triacylglycerol concentrations (Ahmed et al., 1976), suggesting that role of soy polysaccharides in soy glucose tolerance and hyperlipidemia. Several reports indicate that the health beneficial effect of soybean may be due to proteins in soybean. Soy proteins are rich in amino acid arginine and glycine, which play major role in insulin and glucagon secretion from the pancreas. Thus, the decrease in cholesterol seen with soy protein may be due to the decreased insulin-glucagon ratio caused by arginine and glycine. In an early study in gerbils, feeding soy protein in place of casein increased plasma concentrations of insulin, thyroxin, and thyroid-stimulating hormone. Decreased postprandial serum concentrations of insulin and glucose with a significant reduction in serum total cholesterol were found in healthy pigs with soy-protein feeding compared with casein (Beynen et al., 1990). More recently, Lavigne et al 2000 evaluated the effects of controlled feeding with various types of dietary proteins on glucose tolerance and insulin sensitivity in healthy male Wistar rats. And found change in the level of hormones. In an important study in case of ovariectomized cynomolgus monkeys it was found that soy protein significantly improved insulin sensitivity and glucose effectiveness in compared with casein Thus, it is confirmed from these studies that soy-based diets may provide potential benefits in conditions associated with impaired glucose tolerance, hyperlipidemia, and reduced insulin sensitivity.

HEALTH BENEFITS OF PHYTO-OESTROGENS

Effect of Isoflavones On Obesity and Diabetes Mellitus

Diabetes mellitus and Obesity are two important nutritional disorders and become major public health problem. Obesity is a disorder of energy balance and is associated with hyperinsulinemia, insulin resistance, and abnormalities in lipid metabolism. Diabetes mellitus is a metabolic disorder in which abnormalities in insulin secretion and insulin action, an altered endocrine system, and endogenous glucose production that leads to hyperglycemia. In many cases with type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes there is abnormalities in lipid metabolism, which further increase the risk of premature cardiovascular disease. Various dietary interventions to control obesity and diabetes should target these abnormalities to control excess body weight, hyperglycemia, and dyslipidemia have included low-energy and low-fat diets and the consumption of vegetables, fruit, and grains; foods with a high fiber content; and antioxidants. Phytoestrogens have been shown to have a beneficial effect by improving serum lipids and modifying LDL oxidation, the basal metabolic rate, and insulin stimulated glucose oxidation.

Soy and obesity

Several studies suggest that soy as a good source of dietary protein has significant antiobesity effects. Bosello et al 1998 reported that total cholesterol, LDL cholesterol, VLDL cholesterol, and triacylglycerol decreased more with soy than with casein. Thus, the reduction in excess body weight appeared to be due to a low energy intake rather than to the source of protein. Several studies reported increased insulin sensitivity in rats fed isolated soy proteins compared with rats fed casein (Baba et al., 1992). A 37-kDa protein in soy appears to modulate insulin action on fat decomposition in vitro (Makino et al., 1998). Hurley et al (1998) studied the interaction between dietary protein and carbohydrate on energy metabolism in rats. Soy-protein isolate and starch also lowered plasma glucose and insulin concentrations. These studies indicate that the nature and composition of macronutrient (protein, carbohydrate, or fat) is also significant in energy metabolism and weight reduction.

Soy and diabetes mellitus

Many studies with soybean suggest that soy has major effects on regulating diabetes mellitus (Tab.1). Several studied show the effect of soy protein in type 2 diabetic subjects with obesity, hypertension, and proteinuria. They observed no beneficial effect on renal function or proteinuria in these subjects when soy protein was one-half of the daily protein intakes. However, they did observe a reduction in hyperlipidemia and in cholesterol and triacylglycerol concentrations. In a recent study by Hermansen et al (2001) in type 2 diabetic subjects, soy protein with its associated isoflavones and fiber reduced LDL cholesterol, apolipoprotein B-100, and triacylglycerol as compared with a casein diet with cellulose but had no effect on glucose metabolism, as shown by the lack of change in hemoglobin A1c. Thus, soybean and its components have beneficial effects on lipid concentrations in healthy and type 2 diabetic subjects (Tab.2). Vedavanam et al (1999) suggested that soy isoflavones may be beneficial for diabetic subjects because of their estrogenic activity and their ability to prevent glucose-induced lipid peroxidation and inhibit intestinal glucose uptake by decreasing sodium-dependent glucose transporter, which results in a reduction in postprandial hyperglycemia

Soy intake can reduce glucagons and plasma glucose levels, increase first-phase insulin and improve intra-arterial glucose tolerance test (Jeppesen et al., 2006). It is also demonstrated that soy protein consumption reduces hyperinsulinemia by stimulating insulin secretion to a lower extent. However, the exact mechanism remains unknown. Possible suggested mechanisms include a tyrosine kinase inhibitory action, changes in insulin receptor numbers and affinity, intracellular phosphorylation and alterations in glucose transport (Sorenson et al., 1994).

Breast Cancer

In vitro studies have established that phytoestrogens are weakly estrogenic in nature and have ability to bind mammalian estrogen receptors to a low degree. Coumestrol has the greatest affinity, only ten to twenty times lower than estradiol, and genistein about 100 times less; daidzein and equol bind about 1000 times less (Maggiolini et al., 2001). At low concentrations of phytoestrogen, cell proliferation is stimulated in ER cell lines only which suggest that the phytooestrogens are acting via the ER. Both the ER-Y and ER-Z forms are found to be involved in the stimulation of cell proliferation by phytoestrogens. At low concentrations genistein and quercetin show agonists for ER-Y as well as ER-Z. Several other anti-cancer effects of is flavones are reported which are not related to their anti-estrogenic properties. Genistein is known to inhibit enzyme tyrosine kinases, which are mainly responsible for phosphorylation of proteins required for cell division. It is found that it inhibit growth in many cell lines which do not have estrogen receptors, suggests that these effects may be independent of any anti-estrogen effects. Genistein has also found to inhibit the enzyme topoisomerase (DNA repair enzyme), and to affective as an antioxidant, thus potentially preventing oxidative DNA damage.

Prostate Cancer

Prostate cancer is predominent hormone-related cancer in men.High-fat diets are presently linked to increased risk of the disease. In animal models, the studies investigating the effects of soybean showed reduced tumor genesis. Like isoflavones, lignans they also inhibit 5Y reductase.

Antiviral Properties

Genistein inhibit the SV-40 entry into cells by blocking the tyrosine phosphorylation of caveolin-1. It is also reported that genistein block SV-40-induced up regulation of c-myc and c-jun and delaying in the onset of SV-40 DNA synthesis. Signaling pathway inhibition is also affected by phytoestrogens. Tyrosine phosphorylation of eps15 is essential for entry of viras into cells but use of genistein significantly inhibit the infectious entry of JCV possibly by inhibiting viral induced phosphorylation. It has been studied that flavonoids and isoflavonoids are effective for inhibiting the activity of topoisomerase II.

Cardiovascular Diseases and Artherosclerosis

A number of studies have supported a protective role of phytoestrogens in modulating cardiovascular disease (CVD) risk markers. Consumption of soy foods has been associated with reduced serum cholesterol. Several recent findings indicate that both soy protein and isoflavones are very effective in cholesterol lowering. Isoflavone consumption led to a 30% decrease in plasma cholesterol levels and a 50% reduction in atherosclerotic lesion area in a strain of mice with low HDL (high-density lipoprotein) cholesterol. Some vasodilatory activity of Soy phytoestrogens is reported in some in special conditions. A recent study in mildly hypercholesterolemic individuals found little effect of soy protein or phytoestrogens on plasma antioxidant capacity or biomarkers of oxidative stress (Vedavanam et al., 1999). Isoflavones both daidzein and genistein detoxify the free radicals, hydrogen peroxide and superoxide. The genistein has been shown to enhance the activity of the antioxidant enzymes as; catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. Hence soy isoflavones act directly as antioxidants or indirectly by enhancing antioxidant enzymes activity.

TABLE 1. Effects of dietary soy in humans with diabetes mellitus

Test	Diet	Amount	Effects	Reference
Humans				
Type 2 diabetic	Soy protein and fiber compared with casein with cellulose	50 g protein/d, 20 g fiber/d, and 150 mg isoflavones/d	Decreased LDL cholesterol triacylglycerol, and apolipoprotein B-100; no change in HDL cholesterol and hemoglobin A1c	Hermansen *et al.*, 2001
Type 2 diabetic subjects with obesity and hypertension	Soy protein diet compared with animal-protein diet	1 g protein/kg body wt	Decreased total cholesterol and triacylglycerol	Anderson *et al*., 1998
Obese type 2 diabetic	Soy olysaccharide compared with low fiber	10 g fiber as single meal	Decreased postprandial hyperglycemia and triacylglycerol; no effect on serum insulin	Tsai *et al.*, 1987
Type 2 diabetic	Soy hull	26–52 g fiber/d	Improved glucose intolerance and decreased VLDL cholesterol triacylglycerol, and glycated hemoglobin	Mahalko 1984

TABLE 2. Food sources of isoflavones (micrograms per g)

S.No.	Food	Total isoflavones	Daidzein	Genistein	Glycetin
1	Roasted	2,661	941	1,426	294
2	Soy flour	2, 014	412	1,453	149
3	Soy granule	2,404	917	1,225	262
4	Tofu	532	238	245	49
5	Tempeh	865	405	422	38
6	Soy hot dog	236	55	129	52
7	Soy bacon	144	26	83	35
8	Tempeh burger	386	95	255	36
9	Tofu yogurt	282	103	162	17
10	Flat noodle	127	15	56	56

Hormone Balancing Effects of Isoflavones

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 estrogenic activity and compete with the more potent endogenous estrogens at the receptor site. In this respect, the isoflavones are regarded as exerting antiestrogenic effects. A natural estrogen production declines with the onset of menopause; isoflavones may help to offset this decline through their estrogenic effects. A major problem associated with estrogen imbalance as; endometriosis, cervical dysplasia, breast cancer, menstrual irregularities, found to improve with soy isoflavone intake. The hormone modulating effects of soy isoflavones have recently been demonstrated in several human studies. One important study indicate that 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. 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. The hormone modulating and menstrual cycle lengthening effects of soy isoflavones may have significant implications with regard to breast cancer risk.

CONCLUSION

Phytoestrogens can be a significant contributor of nonsteroidal estrogens of dietary origin that may have health effects that are especially relevant to women's risk of hormone-associated diseases. Structurally, the plant estrogens share many similarities with endogenous estrogens. It has been shown that the phytoestrogens can bind to estrogen receptors, which is similar to endogenous estrogens. Functionally, it is supposed that the phytoestrogens may exert both estrogenic and antiestrogenic effects depending on circulating levels of endogenous sex hormones. The major source of dietary phytoestrogens, are associated in both men and women with low rates of cardiovascular disease, cancer, and osteoporosis and in postmenopausal women with smaller numbers of hot flushes. Phytoestrogens are supposed an important dietary factors affording protection against hormone-dependent cancers and diseases in vegetarians and semi vegetarians. Isoflavones affect multiple signaling pathways through the activation of both intracellular and membrane ERβ, as well as interaction with the metabolism of steroid hormones. Therefore, the impact of isoflavones on physiological processes in the organism seems to be very complex and may be related to large number of factors. Soy proteins may improve obesity and diabetes by reducing insulin resistance and reduce adiposity by inhibiting insulin secretion from the pancreatic cells or by inhibiting lipogenesis and enhancing lipolysis in liver and adipocytes. Isoflavones and lignans may also exert beneficial effects on tissue lipids through their antioxidative actions. Some of these mechanisms have been suggested by in vivo studies but most have been shown in vitro. Increasing consumption of soy, soy products, and plant based foods, in general, is consistent with current recommendations to increase fiber and antioxidant intakes while lowering and replacing sources of saturated fat and cholesterol in the diet.

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