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12. Soybean constituents and their functional benefits

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Abstract. Soybean [Glycine max (L.)] is in use for more than 5000 years in China and South East Asia as food. Epidemiological studies show its importance in prevention of several diseases. Recently, an upsurge of consumer interest in the health benefits of soybean and soy products is not only due to its high protein (38%) and high oil (18%) content, but also due to the presence of physiologically beneficial phytochemicals. Past several years of clinical and scientific evidences have revealed the medicinal benefits of the soy components against metabolic disorders (cardio-vascular diseases, diabetes and obesity *etc.*) as well as other chronic diseases (cancer, osteoporosis, menopausal syndrome and aneamia *etc.*). Many of the health benefits of soy are derived from its secondary metabolites, such as, isoflavones, phyto-sterols, lecithins, saponins *etc.* In this review we discuss the bioactive components of soybean and their role in prevention, maintenance, and/or curing of diseases.

1. Introduction

The term ‘functional foods’ was first introduced in Japan in the mid-1980s and refers to processed foods containing ingredients that aid specific bodily functions in addition to being nutritive [1]. The soybean [*Glycine* max(L.) Merrill] a native of China, have been extensively used as important

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source of dietary protein and oil throughout the world. Though, soybean is a widely cultivated crop, most of it is used as the raw material for oil milling, and the residue (soy meal) is mainly used as feedstuff for domestic animals [2]. Dry soybean contain 36% protein, 19% oil, 35% carbohydrate (17% of which dietary fiber), 5% minerals and several other components including vitamins [2].

Several years of rigorous scientific and clinical research has established that most of the components of soybean have beneficial health effects as characterized by its preventive potential for the so-called life-style-related diseases. The impact of most of the nutritionally and physiologically functional components of soybean [3] have been summarized in Table 1.

Table 1. Functional components of soy and their impact [3].

α-Linolenic acid	Essential fatty acid, hypotriglyceridemic, improves heart health
Isoflavones	Estrogenic, hypocholesterolemic, improves digestive tract function, prevents breast, prostate, and colon cancer, bone health, improve lipid metabolism
Lecithins	Improve lipid metabolism, improve memory and learning abilities
Lectins	Anti-carcinogenic, immunostimulator
Linoleic acid	Essential fatty acid, hypocholesterolemic
Peptides	Readily absorbed, reduce body fat, anticancer
Phytosterols	Hypocholesterolemic, improves prostate cancer
Protein	Hypocholesterolemic, antiatherogenic, reduces body fat
Saponin	Regulates lipid metabolism, antioxidant

2. Constituents of soybean

2.1. Proteins

Soybean contains 35–40% protein on a dry-weight basis, of which, 90% is comprised of two storage globulins, 11*S* glycinin and 7*S* β-conglycinin [2,4]. These proteins contain all amino acids essential to human nutrition, which makes soy products almost equivalent to animal sources in protein quality but with less saturated fat and no cholesterol. Soybean also contains the biologically active protein components hemagglutinin, trypsin inhibitors, α-amylase and lipoxygenases [2]. As per the FDA's 'Protein Digestibility Corrected Amino Acid' source method, soybean is not only high quality protein, but it is now thought to play preventive and therapeutic roles for several diseases [5].

2.2. Oil

Soybean contains roughly ~19% oil, of which the triglycerides are the major component. Soy oil is characterized by relatively large amounts of the polyunsaturated fatty acids (PUFA), *i.e.*, ~55% linoleic acid and ~8% α-linolenic acid, of total fatty acids [6] (Fig. 1). Linoleic acid in soy oil is an essential fatty acid (EFA) belonging to the ω-6 family of PUFAs, which exerts important nutritional and physiological functions. Even the α-linolenic acid is also an EFA belonging to ω-3 fatty acid family, and plays an important role in the regulation of a number of metabolic pathways. However, due to the presence of lipoxygenases in soybean, linoleic acid renders the soybean oil prone to rancidification [2]. The minor components of crude soybean oil are phospholipids, collectively called lecithin, as well as phytosterols, and tocopherols.

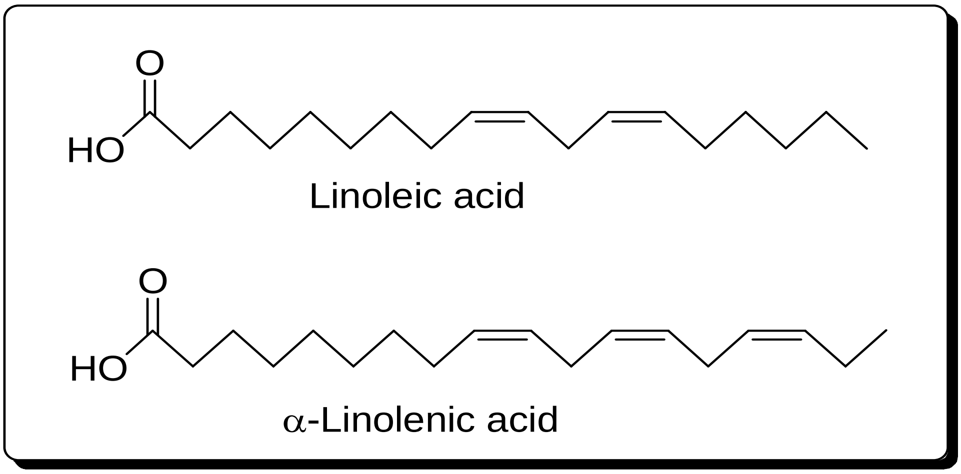


Figure 1. Two EFAs present in soy oil.

2.3. Carbohydrates

Soybean contains ~35% carbohydrates, most of which is nonstarch polysaccharides. It also contains oligosaccharides [5] such as, stachyose (4%), and raffinose (1.1%). Stachyose is a tetraose with a galactose-galactose-glucose-fructose structure, while raffinose is a triose with a structure of galactose-glucose-fructose. Polysaccharides are composed mainly of insoluble dietary fiber. Soybean curd refuse (Okara) contains soluble polysaccharides with galacturonic acid as its underlying structure. In addition to use as a dietary fiber supplement, soluble polysaccharides have been used to modify the physical properties of various foods [7].

2.4. Vitamins and minerals

Soybean is a better source of B-vitamins [2] compared to cereals, although it lacks B_{12} and vitamin C. Soybean oil also contains tocopherols [2,3], which are excellent natural antioxidants. Soybean oil contains α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol in trace amount (mg/kg). Soybean also contains ~5% minerals [3]. It is relatively rich in K, P, Ca, Mg, and Fe. Soy ferritin can supplement reasonable quantities of iron.

2.5. Isoflavones

Isoflavones is a sub-group of heterocyclic plant phenolic category called flavonoids. Besides isoflavones, the other subclasses of flavonoids include flavones, flavonols, flavanols, aurones, red and blue anthocynin pigments, and chalcones. In isoflavones the phenyl ring B is connected at position 3 of 1,4-benzopyrone ring (Fig. 2).

The soybean is most abundant source [8] of isoflavones (up to 3 mg/g dry weight) in the nature. Soybean contain three types of isoflavone aglycone *viz.*, daidzein, genistein and glycitein; each of them present in three glycosidic forms in addition to their aglycone form (Fig. 3). Daidzein, genistein and their glycosides contribute to >90% of total isoflavone; whereas glycetein and its glycoside are present as minor component (<10%), only.

Isoflavones are structurally similar [6] to mammalian estradiol as shown in Fig. 4, and can bind to both α and β isoforms of estrogen receptor (ER), thus called phytoestrogens. Though, the isoflavones are not essential nutrients that are required to support life, still they exert many beneficial health effects, therefore, are of immense help for maintaining healthy life.

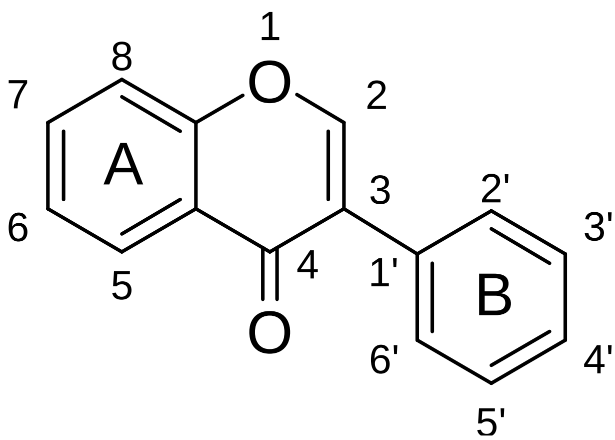


Figure 2. Basic structure of isoflavones.

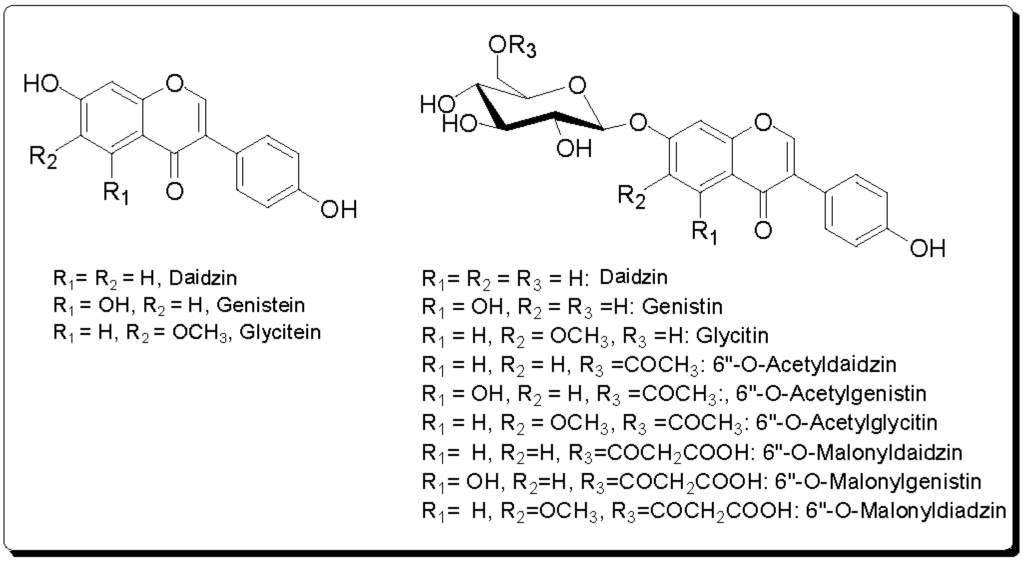


Figure 3. Chemical Structures of 12 isoflavones found in soybean.

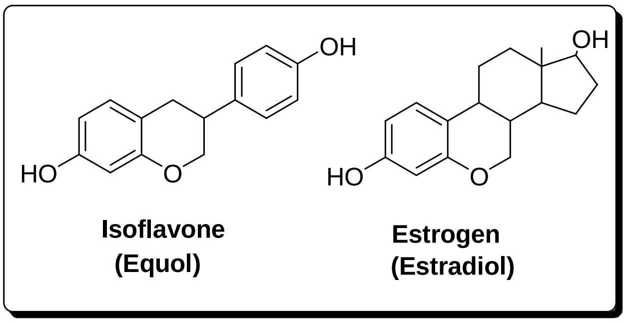


Figure 4. Comparison of equol (isoflavone metabolite) and estradiol structure.

2.6. Phytosterols

Soybean oil contains about 300 to 400 mg of plant sterols per 100 g. The major components of soy sterols are β-sitosterol (53 to 56%), campesterol (20 to 23%), and stigmasterol (17 to 21%) [9]. These phytosterols differ from cholesterol only in the structure (Fig. 5) of their side chains; sterols differ from stanols in being unsaturated versus saturated at the C5-C6 double bond in their B ring. These sterols are proven to have cholesterol-lowering activity, though the mechanism is not completely understood [10].

2.7. Phospholipids

Soybean oil contains 1-3% phospholipids [2,3], of which ~35% phosphatidyl choline, ~25% phosphatidyl ethanolamine, ~15% phosphatidyl inositol, ~5-10% phosphatidic acid. The phospholipids are removed from the

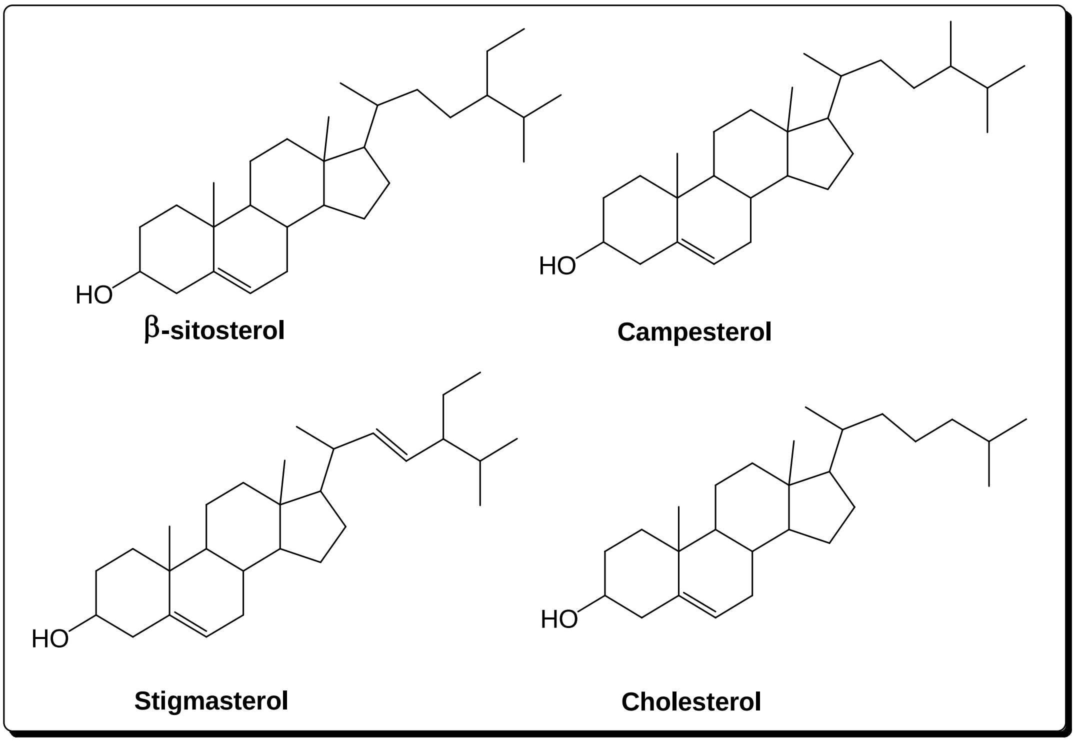
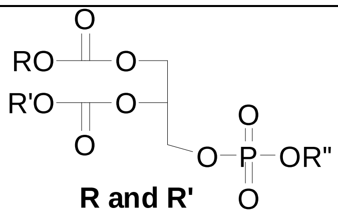


Figure 5. Soy phytosterols and their structural similarity with cholesterol.

Table 2. Soy phospholipids and their structure.

	Name	**R''**
 **R and R' same or different fatty acids**	Phosphatidyl choline	$-CH_2CH_2NH_3$
	Phosphatidyl ethanolamine	$-CH_2CH_2N(CH_3)_3$
	Phosphatidyl inositol	$(CH(OH))_6$
	Phosphatidic acid	H

oil mainly during the 'degumming' process and are used as a natural food emulsifier. They are polar lipids and contribute to the structure of cell membrane. The structure of soy phospholipids are given in the Table 2.

2.8. Saponins

Soybean also contains ~2% soy saponins (triterpene glycosides) which are currently attracting lot of scientific attention. Soybean saponins have unique chemical structures and physiological functions. Soy saponins are oleonane type triterpene glycosides. They can be classified according to type of aglycon, the moiety attached at the C-22 position on the aglycon, and the carbohydrate sequences at the C-3 position on the aglycon [11,12]. A representative structure is shown in Fig. 6. So far, total 30 soy saponins are reported, but their presence and quantity differ from genetic and agronomical variation. Soy saponins are found to have several biological activities [13] such as hepatoprotective, anti-hyperlipidemic, anti-cancer, anti-oxidative, and anti-HIV *etc.*

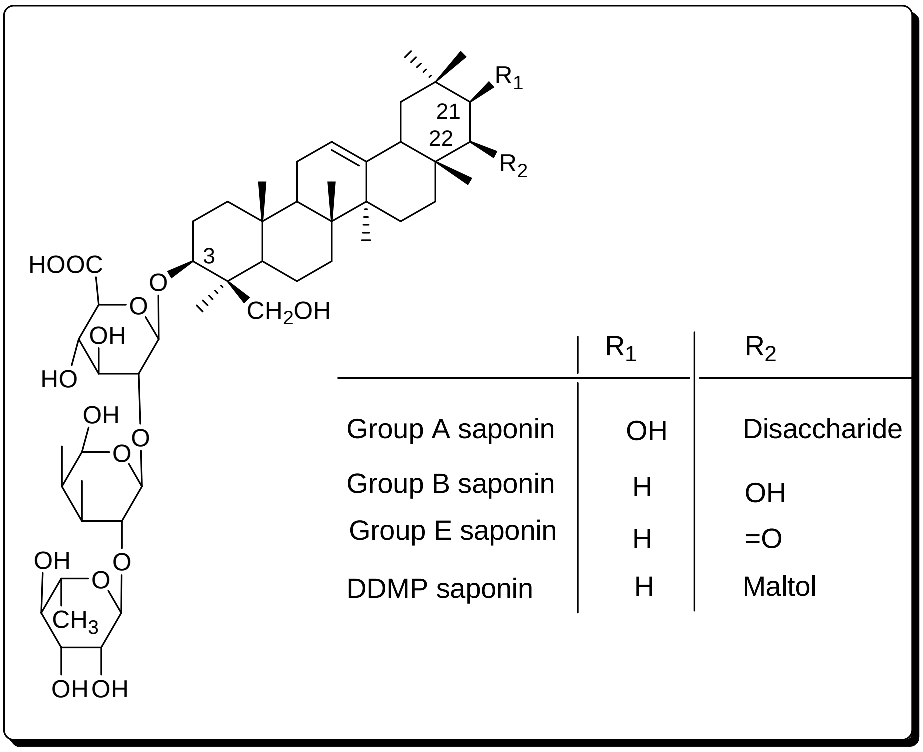


Figure 6. The chemical structure and types of soy saponins.

2.9. Ferritins

Soybean contains ferritin, a multimeric iron storage protein [14]. It is now well proven that the iron from soybean ferritin is as much absorbed and bio-available as much it is from the animal products [14]. Therefore, soybean is recommended to be incorporated in the diet of people suffering from anemia.

3. Health benefits of soybean

The health effects of soy components have been extensively studied through human clinical trials, experimental animal studies, and *in vitro* cell culture studies. Going further, we will confine our discussion to various scientifically validated/supported heath benefits of soybean consumption to ameliorate various human health issues, though there are few studies which present less promising and unfavorable role of soybean in human health.

3.1. Soybean and cardiovascular disease

Cardiovascular disease (CVD) includes all diseases that affect the heart and blood vessels, such as coronary heart disease (CHD), coronary artery disease, dyslipidemia, and hypertension [15]. Looking at present scenario CVD has become one of the major health problems around the world including developing countries.

The role of soy in the prevention of CVD, particularly LDL cholesterol–lowering effects, has been the subject of numerous controlled clinical studies [15]. In 2006, a study [16] reported findings from a 1-year trial in which 66 individuals who adhered well to the portfolio diet (31.8% of participants) experienced reduced serum LDL cholesterol levels by 29.7%. In response to increased interest and the expanding body of knowledge in soy and health [17], the U.S. Food and Drug Administration (FDA) approved in 1999 a health claim for use on food labels [18] which stated that daily diet containing 25 g/day of soy protein, which is also low in saturated fat and cholesterol, may reduce the risk of heart disease. Modest reductions in serum LDL cholesterol levels have been achieved with soy intake, especially for subjects with hypercholesterolemia [15]. Soy protein consumption in several human controlled clinical trials ranged between 14 and 113 g/day (with a median of 36 g/day). The beneficial effects which have been documented include decreased low-density lipoprotein (LDL) concentrations, triglycerides, lipoprotein, C-reactive protein, homocysteine, oxidized LDL, and blood pressure, and increased high-density lipoprotein (HDL) concentrations [17,19-24]. In these studies, the amount of isoflavones prescribed was up to 185 mg/day with a median of 80 mg/day.

The lack of understanding of the mechanism remains an obstacle for a better acceptance of soybean protein by clinical community. There are different hypothesis to explain these mechanisms. One of these hypothesis is that amino acid composition or distribution in soybean change the cholesterol metabolism, possibly, due to changes in endocrine status, because there are alterations in insulin: glucagon ratio and thyroid hormone concentrations [25], as well as an increase in plasma thyroxin concentrations which is related to reduced plasma cholesterol [26]. Another hypothesis proposes that non-protein components such as saponins, fibre, phytic acid, minerals and isoflavones associated with soybean protein affect cholesterol metabolism. Several *in vitro* and *in vivo* studies have shown favourable effects of isoflavones in a variety of atherosclerosis models [27]. These include the reduction of homocysteine levels in plasma [28], prevention of LDL oxidation [29], improvement of vascular reactivity [30], inhibition of proinflammatory cytokines, or cell adhesion proteins [31,32], inhibition of reactive nitrogen species [33], as well as reduction of platelet aggregation [34].

Legumes are relatively rich in soluble fiber, which may play an important role in the prevention of heart disease [35]. The major effects of soybean soluble fibers on serum lipoproteins appear to be related with bile acid binding and with a decrease in the reabsorption of bile acid [36]. Therefore, there is an increase in the cholesterol used to synthesize bile acids [37]. Also the fermentation of soluble fibers in the colon produces short-chain fatty acids that contribute to reduce hepatic cholesterol synthesis [38]. It has been shown that propionic acid, one of the short-chain fatty acids, decreases the hepatic cholesterol [39]. Moreover, the attenuation in the synthesis of cholesterol in the liver leads to reduction in serum insulin concentrations, which in turn, reduces the activation of an enzyme that participates in cholesterol synthesis. Perhaps, on the other hand, it might also be due to an alteration of the bile acid profile in the liver [37].

There is also a hypothesis that isoflavones may inhibit atherosclerotic development, because they have antioxidant properties against LDL oxidation, which generates a cascade of events producing atherosclerotic plaques. Additionally, isoflavones possess a hypocholesterolemic effect, due to the interaction of isoflavones with estrogenic receptors. Serum cholesterol concentrations may decrease by this mechanism, also.

Another component of soybean is phytosterols. The mechanism underlying the capability of plant sterols/stanols to reduce plasma LDL cholesterol levels relates to their structural similarity to cholesterol (Fig. 5). This enables them to compete with cholesterol for incorporation into micelles, which are translocated over the brush border membrane, from the gut into the plasma, *via* intestinal cholesterol transporters, known as NPC1L1 and SR-BI [40,41]. Moreover, free phytosterols are assumed to be taken up by enterocytes directly and to prevent cholesterol from being esterified by blocking the ACAT system and subsequent transport to the mesenteric lymph. Free sterols/stanols are hypothesized to stimulate the ABC-ATP binding cassette mediated enterocytic cholesterol transfer back to the intestinal lumen for excretion from the body. Consequently, sterols/stanols will significantly down regulate the cholesterol influx and stimulate the efflux over the brush border membrane [42].

In brief, various components of soybean might be contributing independently towards its overall cardiac health benefits. To overemphasize the importance of one and/or another component may not be able to justify the total effect of soybean on cardiovascular system.

3.2. Soybean and cancer

In the last two decades, many groups of researchers have suggested that the regular consumption of soybean is associated with the relatively lesser risk of different cancers in countries that include soybean in their diets [6,43,44]. Researchers have evaluated dietary differences between Japan and the Western nations to try to explain variations in death rates from cancer [45]. A number of soy components have been investigated for potential anticancer activity. Soybean contains several components with anticancer activity, such as, isoflavones, protease inhibitors, phytosterols, saponins, phenolic acids, and phytates. Most of the data support that predominantly isoflavones are responsible for the anticancer effects of soybean [6,43,45].

Based on the estrogenic activity of isoflavones, they can possibly be used for prevention and treatment of hormone dependent cancers [47]. Prevailing hypothesis is that isoflavones may act like antiestrogen when they are in a high estrogen concentration, and like estrogen when they are in a low estrogen environment. Genistein, one of the two primary isoflavones, may be contributing its anticancer effects due to its very good antioxidant properties. The anticancer effects of genistein are also due to the fact that it is a specific inhibitor of protein tyrosine kinase, MAP kinase, ribosomal S6 kinase, topoisomerase II, which form part of growth factor-stimulated signal transduction cascades in normal and transformed cancer cells. It has also been proved *in vitro*, that genistein increases concentrations of TGF-β, which may inhibit the growth of cancer cells. Moreover, genistein has an important role as a potent inhibitor of angiogenesis *in vitro* [43]. Japanese people with high phytoestrogens (isoflavone) plasma levels, have low incidence of breast, prostate, and colon cancer. This also indicates the safety aspect of isoflavones and soybean consumption [47].

3.2.1. Breast cancer

Several studies suggest that consumption of soy foods during childhood and adolescence in women reduces the risk of breast cancer in later part of life. The growth of both estrogen-dependent and estrogen independent breast cancer cells *in vitro* has been inhibited by genistein, but it is not clear if the concentrations reached *in vitro* could be reached *in vivo.* Studies have shown that soybean intake may help in preventing the initiation of breast cancer cells [6,43].

3.2.2. Prostate cancer

It is known that estrogens cause programmed cell death of prostate cancer cells and inhibit enzymes associated with different processes in the development of cancer [47]. Soybean foods may be a factor contributing to the diminution of prostate cancer mortality of the soy consuming populations. Genistein has been shown to reduce DNA synthesis in human prostate cells *in vitro* and inhibit testosterone effect in prostate cancer development in rats [48]. Prostate cancer is also reported to be associated with increased levels of dihydrotestosterone, and soybean isoflavones are known to inhibit 5α-reductase, which is involved in the conversion of testosterone to dihydrotestosterone [49]. However, the mechanism by which soybean may prevent prostate cancer still remains unclear and controversial [50].

3.2.3. Colon cancer

Epidemiological evidences show protective effects of soybean products on colon cancer. *In vitro* studies on soybean products have shown an antiproliferative effect even on cells of gastrointestinal tract among the various other cell types [51]. An important role in colon cancer is attributed to dietary fiber from soy, which also reduces the risk of other chronic diseases in digestive system. The fermentation of soy fiber in colon produces an increase of short-chain fatty acids that present a potential protective effect against colon cancer and bowel infections through inhibition of putrefactive and pathogenic bacteria, respectively [52]. Nonetheless, scientific evidence in support of the protective effect of soybean isoflavones on colon cancer is limited [47].

3.3. Soybean and menopause

Menopause is a natural stage of life all women experience as they age. Thermoregulatory disturbances like hot flashes (HF), night sweats, mood swings and lack of energy can make menopause one of the most physically and emotionally miserable times in a woman's life [53]. HF arises as a sudden feeling of heat in the face, neck, and chest [54]. Menopausal hormone therapy (MHT) is the most effective therapy for vasomotor symptoms [55]. However, current data have indicated adverse effects of MHT by increasing the risk of *e.g.* stroke, breast cancer and gallbladder disease [56].

Dietary soy has gained much attention since reports of reduced menopausal discomfort and reduced morbidity incidence of several hormone-dependent diseases in soy consuming Asian compared with non-soy consuming Western populations. Epidemiological studies in Japanese women suggest that consumption of soy products has a protective effect against menopausal symptoms [57-59]. In Japan, the total isoflavone intake from soy food averages from 25 to 50 mg per day. A small proportion of the Asian population (<10%) seems to consume more than 100 mg isoflavones per day [60].

Isoflavones bind to the estrogen receptors in certain cells in the body and produce weak estrogenic effects, especially when an inadequate amount of estrogen is present in the body [61]. Over 20 human studies have tested the hypothesis that soy products alleviate post menopausal symptoms [62,63]. In these studies, perimenopausal women as well as postmenopausal women who suffered menopausal symptoms consumed soy proteins for 4 weeks or longer. These studies show that the soy isoflavone do have the beneficial health effects on menopausal symptoms.

In summary, though the available human studies seem to show a few conflicting results in terms of the consistent efficacy of soy isoflavones in alleviating post menopausal symptoms, from the epidemiological studies it can be stated that isoflavone do help the regular soybean consumer to better manage their post menopausal symptoms.

3.4. Soybean and osteoporosis

The loss of estrogen during menopause puts women at greater risk to develop weaker bones and joints as they age. Menopause leads to rapid decrease in estrogen levels, which causes bone breakdown and loss of more calcium *via* urine. Over time, bones may become weak and brittle with tiny holes inside, this condition is called osteoporosis.

Phytoestrogens help prevent osteoporosis in the presence of subnormal endogenous estrogen [64]. Studies in Asia reveal that women in Shanghai, China, who ate sumptuous amount of soy foods, were one-third less likely to experience a fracture than Chinese women who consumed lower amount of soy [65]. This observation has led to the hypothesis that soybean or soybean isoflavones are a possible alternative option for the prevention of osteoporosis. Randomized controlled studies [66,67] that used isoflavone extracts or pure genistein reported that soy isoflavones have a mild but significant and independent effect on the maintenance of bone mineral density at doses ranging between 35 to 54 mg of aglycone equivalent. The mechanism of isoflavones on bone health is yet to be understood.

3.5. Soybean and diabetes

Soybean diet may be a good option in type 2 diabetes individuals due to its effect on hypertension, hypercholesterolemia, atherosclerosis and obesity, which are very common diseases in diabetic patients [68].

Furthermore, substituting animal protein for soybean or other vegetable protein may also decrease renal hyperfiltration, proteinuria, and renal acid load and therefore reduces the risk of renal disease in type-2 diabetes [69]. Soluble fiber from soybean may be useful because of its insulin-moderating effect. It is generally accepted that a high fiber diet, particularly soluble fiber, is useful to control plasma glucose concentration in diabetics. Soybean fiber intake has also been implicated for the improvement of the blood glucose levels of diabetics [43]. It also increases fecal excretion of bile acid and therefore may cause a low absorption of fat [20,69].

Though further research is needed, it can be suggested that diabetic patients with soybean diets show several potential advantages, such as, reduced insulin resistance, renal damage, and fatty liver, thereby improving their quality of life.

3.6. Soybean and obesity

Obesity poses a major public health challenge since it is a well recognized independent predictor of premature mortality [70]. The dramatic increase in the occurrence of overweight and obesity over the past several decades is attributed in part to changes in dietary and lifestyle habits, such as rapidly changing diets, increased availability of high-energy foods, and reduced physical activity of peoples in both developed and developing countries [71]. Ingestion of foods with high protein content is well known to suppress appetite and food intake in humans [72].

Several nutritional intervention studies in animals and humans indicate that consumption of soy protein reduces body weight and fat mass in addition to lowering plasma cholesterol and triglycerides. In obese humans, dietary soy protein also reduces body weight and body fat mass in addition to reducing plasma lipids [73].

Several lines of evidence suggest that soy protein may favorably affect lipid absorption, insulin resistance, fatty acid metabolism, and other hormonal, cellular, or molecular changes associated with adiposity. It is well established that soy protein consumption reduces serum total cholesterol, LDL cholesterol, and triglycerides as well as hepatic cholesterol and triglycerides. Studies in animals indicate that soy protein ingestion exerts its lipid-lowering effect by reducing intestinal cholesterol absorption and increasing fecal bile acid excretion, thereby reducing hepatic cholesterol content and enhancing removal of LDL [74,75]. Dietary soy protein has also been shown to directly affect hepatic cholesterol metabolism and LDL receptor activity [76].

4. Conclusion

Several nutritional advantages could be obtained by incorporating soybean based foods in the diet. Soybean represents an excellent source of high quality protein with a low content in saturated fat, with no cholesterol, and a great amount of dietary fiber. Therefore, the possible use of soybean in functional food design is very promising, since the consumption of soybean protein and dietary fibre seems to reduce the risk of cardiovascular diseases and to improve glycemic control. Furthermore, soybean and several of its components have shown in various *in vitro*, *in vivo*, and human clinical studies their effectiveness and potential role in the prevention and treatment of different diseases. The use of soybean in food form for several centuries assures us of its safety and nutritive value for human health. Consequently, it is imperative for all the conscious societies to incorporate this abundantly available ‘treasure of functionality’ in their daily diet and harness the complete benefit of this yellow ‘miracle’ seed.

References

1. Arai, S., Studies on functional foods in Japan: State of Art. *Biosci. Biotech. Biochem.,* **1996**, *60,* 9-15.
2. Liu, K.S., Chemistry and Nurtitional Value of Soybean Components. In Soybean: Chemistry, Technology, and Utilization, Chapman & Hall, New York, **1997**, pp. 25-113.
3. Sugano, M., Ed., Soy in Health and Disease Prevention, CRC Press, FL, USA, **2006**.
4. Saio, K., Yamagishi, T., Yamauchi, F. *Cereal Chem.*, **1986**, *63*, 493-496.
5. Grieshop, C.M., Kadzere, C.T., Clapper, G.M., Flickinger, E.A., Bauer, L.L., Frazier, R.L., Fahey, G.C. *J. Agric. Food Chem.*, **2003**, *51*, 7684-7691.
6. Messina, M.J., Soybean foods: their role in disease prevention and treatment. In Soybean: Chemistry, Technology, and Utilization. Chapman and Hall: New York, USA, **1997**, pp. 442-447.
7. Espinosa-Martos, I., Ruperez, P. *Nutr. Hosp.*, **2006**, *21,* 92-96.
8. Kudou, S., Fleury, Y., Welti, D., Magnolato, D., Uchida, T., Kitamura, K., Okubo, K. *Agric. Biol. Chem.,* **1991**, *55,* 2227-2233.
9. Ozawa, Y., Sato, H., Nakatani, A., Mori, O., Hara, Y., Nakada, Y., Akiyama, Y., Morinaga, Y. *J. Oleo Sci.,* **2001**, *50,* 217-223.
10. Law, M.P. *Biomedical J.,* **2000**, *320,* 861-864.

11. Kudou, S., Tonomura, M., Tsukamoto, C., Uchida, T., Sakabe, T., Tamura, N., Okubo, K. *Biosci. Biotechnol. Biochem.,* **1993**, *57,* 546-550.
12. Tsukamoto, C., Kikuchi, A., Harada, K., Kitamura, K., Okubo, K. *Phytochemistry,* **1993**, *34,* 1351-1356.
13. Yoshiki, Y., Kudou, S., Okubo, K. *Biosci. Biotechnol. Biochem.,* **1998**, *62,* 2291-2299.
14. Lonnerdal, B. *Am. J. Clin. Nutr.,* **2009**, *89,* 1680S-5S.
15. Van Horn, L., McCoin, M., Kris-Etherton, P.M., Burke, F., Carson, J.A., Champagne, C.M., Karmally, W., Sikand, G. *J. Am. Diet. Assoc.,* **2008**, *108,* 287-331.
16. Jenkins, D.J., Kendall, C.W., Faulkner, D.A., Nguyen, T., Kemp, T., Marchie, A., Wong, J.M., de Souza, R., Emam, A., Vidgen, E., Trautwein, E.A., Lapsley, K.G., Holmes, C., Josse, R.G, Leiter, L.A., Connelly, P.W., Singer, W. *Am. J. Clin. Nutr.,* **2006**, *83,* 582-591.
17. Anderson, J.W., Johnstone, B.M., Cook-Newell, M.E. *New Engl. J. Med.,* **1995**, *333,* 276-282.
18. Food and Drug Administration: *Soy: Health Claims for Soy Protein, Questions About Other Components*. Food and Drug Administration, Rockville, MD, **2000**.
19. Baum, J.A., Teng, H., Erdman, J.W., Weigel, R.M., Klein, B.P., Persky, V.W., Freels, S., Surya, P., Bakhit, R.M., Ramos, E., Shay, N.F., Potter, S.M. *Am. J. Clin. Nutr.,* **1998**, *68,* 545-551.
20. Reynolds, K., Chin, A., Lees, K.A., Nguyen, A., Bujnowski, D., He, J. *Am. J. Cardiol.,* **2006**, *98,* 633-640.
21. McVeigh, B., Dillingham, B., Lampe, J., Duncan, A. *Am. J. Clin. Nutr.,* **2006**, *83,* 244-251.
22. Allen, J.K., Becker, D.M., Kwiterovich, P.O. *Menopause,* **2007**, *14,* 106-114.
23. Yildirir, A., Tokgozoglu, S.L., Oduncu, T., Oto, A., Haznedaroglu, I., Akinci, D., Koksal, G., Sade, E., Kirazli, S., Kes, S. *Clin. Cardiol.,* **2001**, *24,* 711-716.
24. Zhan, S., Ho, S. *Am. J. Clin. Nutr.,* 2005, ***81,*** 397-408.
25. Potter, S.M. *J. Nutr.,* **1995**, *125,* 606-611.
26. Forsythe, W.A. *J. Nutr.* **1995**, *125,* 619-623.
27. Cassidy, A., Griffin, B. *Proc. Nutr. Soc.,* **1999**, *58,* 193-199.
28. Jenkins, D.J.A., Kendall, C.W.C., Jackson, C.J.C., Connelly, P.W., Parker, T., Faulkner, D., Vidgen, E., Cunnane, S.C., Leiter, L.A., Josse, R.G. *Am. J. Clin. Nutr.,* **2002**, *76,* 365-372.
29. Kapiotis, S., Hermann, M., Held, I., Seelos, C., Ehringer, H., Gmeiner, B.M. *Arterioscler. Thromb.Vasc. Biol.,* **1997**, *17,* 2868-2874.
30. Steinberg, F.M., Guthrie, N.L., Villablanca, A.C., Kumar, K., Murray, M.J. *Am. J. Clin. Nutr., 2003, 78,* 123-130.
31. Takano-Ishikawa, Y., Goto, M., Yamaki, K. *Phytother. Res.,* **2003**, *17,* 1224-1227.
32. Rimbach, G., Weinberg, P.D., de Pascual-Teresa, S., Alonso, M.G., Ewins, B.A., Turner, R., Minihane, A.M., Botting, N., Fairley, B., Matsugo, S., Uchida, Y., Cassidy, A. *Biochim. Biophys. Acta.,* **2004**, *1670,* 229-237.
33. Yen, G.C., Lai, H.H. *J. Agric. Food. Chem.,* **2003**, *51,* 7892-7900.

34. Gottstein, N., Ewins, B.A., Eccleston, C., Hubbard, G.P., Kavanagh, I.C., Minihane, A.M., Weinberg, P.D., Rimbach, G. *Br. J. Nutr.,* **2003**, *89,* 607-616.
35. Kushi, L. H., Meyer, K. M., Jacobs, D. R. *Am. J. Clin. Nutr.,* **1999**, *70,* 451-458.
36. Anderson, J.W., Major, A.W. *Br. J. Nutr.,* **2002**, *88*, 263-271.
37. Malkki, Y. *Cereal Foods World*, **2001**, *46,* 196-199.
38. Anderson, J.W., Hanna, T.J. *J. Nutr.* **2002**, *129,* 1457-1466.
39. Delzenne, N.M., Kok, N. *Am. J. Clin. Nutr.,* **2001**, *73,* 456-458.
40. Clifton, P. *Atherosclerosis,* **2002**, *3,* 5-9.
41. Sane, A.T., Sinnett, D., Delvin, E., Bendayan, M., Marcil, V., Menard, D., Beaulieu, J.-F., Levy, E. *Lipid Res.,* **2006**, *47,* 2112-2120.
42. Plat, J., Mensink, R.P. *FASEB J.,* **2002**, *16,* 1242-1247.
43. Messina, M.J. *Am. J. Clin. Nutr.,* **1999**, *70,* 439-450.
44. Lichtenstein, A.H. *J. Nutr.,* **1998**, *128,* 1589-1592.
45. Johnson, I.T., Anti-tumour properties. In Functional Foods. Woodhead Publishing, Cambridge, England, **2000**, pp. 141-162.
46. Craig, W.J. *J. Am. Diet. Assoc.,* **1997**, *97,* 199-204.
47. Adlercreutz, H. *Lancet Oncol.,* **2002**, *3,* 364-373.
48. Adlercreutz, H., Mazur, W., Bartels, P., Elomaa, V.-V., Watanabe, S., Wahala, K., Landstrom, M., Lundin, E., Bergh, A., Damber, J.-E., Aman, P., Widmark, A., Johansson, A., Zhang, J.-X., Hallmans, G. *J. Nutr.,* **2000**, *130,* 658-659.
49. Yi, M.A., Son, H.M., Lee, J.S., Kwon, C.S., Lim, J.K., Yeo, Y.K., Park, Y.S., Kim, J.S. *Nutr. Cancer.,* **2002**, *42,* 206-210.
50. Weber, K., Setchell, K., Stocco, D., Lephart, E. *J. Endocrinol.,* **2001**, *170,* 591- 599.
51. Davies, M.J., Bowey, E.A., Adlercreutz, H., Rowland, I.A., Rumsby, P.C. *Carcinogenesis,* **1999**, *20,* 927-931.
52. Guillon, F., Champ, M.M.J. *Br. J. Nutr.,* **2002**, *88,* 293-306.
53. Freedman, R.R. *Am. J. Med.,* **2005**, *118 (12B),* 124-130.
54. WHO, Research on the menopause in the 1990s. Report of a WHO scientific group, World Health Organization, *Tech. Rep. Ser.* **1996**, *866,* 1-107.
55. National Institutes of Health, State-of-the-Science Conference statement: Management of menopause-related symptoms. *Ann. Intern. Med.,* **2005**, **142,** 1003-1013.
56. Flesch-Janys, D., Slanger, T., Mutschelknauss, E., Kropp, S., Obi, N., Vettorazzi, E., Brendle, W., Bastert, G., Hentschel, S., Berger, J., Chang-Claude, J. *Int. J. Cancer,* **2008**, *123,* 933-941.
57. Nagata, C., Shimizu, H., Takami, R., Hayashi, M., Takeda, N., Yasud, K. *Climacteric,* **1999**, *2,* 6-12.
58. Setchell, K.D.R., Cassidy, A. *J. Nutr.,* **1999**, *129,* 758-767.
59. Albertazzi, P., Pansini, F., Bonaccori, G., Zanotti, L., Forini, E., De Aloysio, D. *Obstetrics & Gynecology,* **1998**, *91,* 6-11.
60. Messina, M., Nagata, C., Wu, A.H. *Nutr. Cancer,* **2006**, *55,* 1-12.
61. Duffy, R., Wiseman, H., File, S.E. *Pharmacol. Biochem. Behav.,* **2003**, *75,* 721-729.
62. Faure, E., Chantre, P., Mares, P. *Menopause,* **2002**, *9*, 329-334.

63. Brouns, F. *Food Res. Int.,* **2002**, *35*, 187-193.
64. Setchell, K., Lydeking-Olsen, E. *Am. J. Clin. Nutr.,* **2003**, *78 (Suppl),* 593S-609S.
65. Zhang, X., Shu, X., Li, H., Yang, G., Li, Q., Gao, Y., Zheng, W. *Arch. Intern. Med.,* **2005**, *165*, 1890-1895.
66. Morabito, N., Crisafulli, A., Vergara, C., Gaudio, A., Lasco, A., Frisina, N., D'Anna, R., Corrado, F., Pizzoleo, M.A., Cincotta, M., Altavilla, D., Ientile, R., Squadrito, F. *J. Bone Miner. Res.,* **2002**, *17,* 1904-1912.
67. Chen, Y., Ho, S., Lam, S., Ho, S., Woo, J. *J. Clin. Endocrinol. Metab.,* **2003**, *88,* 4740-4747.
68. Holt, S., Muntyan, I., Lik**v**er, L. *Alternative and Complementary Therapies,* **1996**, *2(2)*, 79-82.
69. Jenkins, D.J.A., Kendall, C.W.C., Marchie, A., Jenkins, A.L., Augustin, L.S. A., Ludwig, D.S., Barnard, N.D., Anderson, J.W. *Am. J. Clin. Nutr.,* **2003**, *78,* 610-616.
70. Flegal, K.M., Graubard, B.I., Williamson, D.F., Gail, M.H. *JAMA*, **2005**, *293*, 861-1867.
71. Popkin, B.M. *Public Health Nutr*., **1988**, *1,* 5-21.
72. Anderson, G.H., Moore, S.E. *J. Nutr*., **2004**, *134,* 974S-979S.
73. Velasquez, M.T., Bhathena, S.J. *Int. J. Med. Sci.,* **2007**, *4*, 72-82.
74. Greaves, K., A., Wilson, M.D., Rudel, L.L., Williams, J.K., Wagner, J.D. *J. Nutr.,* **2000**, *130,* 820-826.
75. Wright, S.M., Salter, A.M. *Comp. Biochem. Physiol.,* **1998**, *119B,* 247-254.
76. Kirk, E.A., Sutherland, P., Wang, S.A., Chait, A., Leboeuf, R.C. *J. Nutr.,* **1998**, *128,* 954-959.