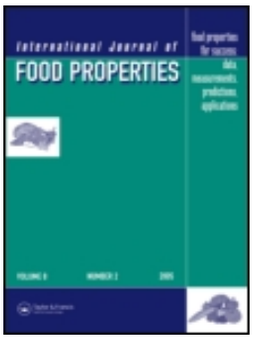

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MECHANISMS INVOLVED IN THE THERAPEUTIC EFFECTS OF SOYBEAN (*GLYCINE MAX*)

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Soybeans contain nutritional and medicinal properties. It is a rich source of quality proteins, phytosterols, fibers, and other biologically active compounds, notably daidzein and genistein. Soybeans provide health benefits due to their functional ingredients such as proteins, polysaccharides, and isoflavones. These functional ingredients play a vital role in the reduction of different types of cancer, cardiovascular diseases, postmenopausal problems, diabetes, and some neurodegenerative disorders. This review primarily envisages the different mechanisms involved in the therapeutic effects of soybean components as well as their contribution toward the reduction of different diseases.

Keywords: ***Soybeans, Proteins, Isoflavones, Mechanisms, Health benefits.***

INTRODUCTION

Soybean (*Glycine max*) is a leguminous crop, differing from other grain legumes because of the presence of high amounts of beneficial components like proteins, fibers, phytosterols, and isoflavones (ISOs).[1,2] Due to the high oil content and quality proteins, the soybean was identified as an excellent source of food across the world.[3] Globulins are the major storage proteins comprising nearly 90% of the total soybean proteins and are classified as glycinin and β-conglycinin.[4] The nutritional value of soybean proteins is equal to that of animal proteins because of the presence of all the essential amino acids vital for human health.[5]

Soybeans contain 35% carbohydrates in the seed and 40% in soybean meal, which are mainly composed of digestible sugars, starch, as well as non-digestible oligosaccharides.[6] Soybeans also contain minor amounts of saponins which are amphiphilic in nature and are derived from water soluble sugar residues closed to a lipid soluble aglycone. The saponin

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content of soybean varies from 0.5 to 2%, imparting a bitter taste but providing health benefits.[7]

Soybeans also contain different phytochemicals like sterols. The major sterols found in soybeans are sitosterol and stigmasterol. Other minor components are campesterol, stigmasterol, Δ7-avenasterol, and brassicasterol.[8] These phytosterols have a cholesterol lowering effect by interfering with the absorption of cholesterol in the blood serum.[9] Soybean oil also contains α -, γ -, and δ– tocopherols (vitamin E) which acts as an antioxidant.[10] The main functional components of soybeans are the biologically active compounds termed ISOs which are an important members belonging to the class of phytoestrogens. There are 12 different types of ISOs reported in soybeans, mainly categorized into four groups, namely, acetylglucoside, glucoside and malonylglucoside, aglycon and each of these groups contains three ISOs.[11,12] The most important ISOs in soybeans are genistein and daidzein which are similar to mammalian estradiol, with respect to structure.[13] Genistein, daidzein and their conjugates of β-glucosides are present in high concentrations (up to 3 mg/g) in soybeans while glycosides make up to 97–98% of the all the ISOs in the soybean.[14]

Soy ISOs play their role as antioxidants in both *in vivo* and *in vitro* conditions, by inhibiting the bleaching of β-carotene, which is a precursor of vitamin A, by inhibiting the rancidity of fats as well as increasing the hepatic cytosolic glutathione peroxidase activity.[15] These ISOs reveal a key role in reducing the risk of cancer.[16] There are some specific soy based food items like natto, miso, and soy sauce, which are mainly fermented and act as the main source of isoflavone aglycones.[17–19] Soybeans have received increased attention as a functional food because of their beneficial physiological effects in controlling and preventing a wide variety of chronic and degenerative diseases such as cardiovascular diseases, obesity, diabetes, and cancer. This review mainly envisages the different mechanisms involved in the reduction of diseases by the soybean bioactive components.

Health Implications of Soybeans

Many health benefits are associated with the use of soybean and these positive effects of a soy diet have been credited to the ISOs, mainly genistein.[20] The utilization of soybean is associated with a modulation of the immune system,[21] antioxidation,[22] inhibition of carcinogenesis,[23] and its ability to lower the cholesterol level.[24] There are different soybean cultivars, but black soybean is proven to be superior to other cultivars due to its higher ability to act as an antioxidant.[25] The most important medicinal properties of black soybean include its ability to act as a detoxificant, anti-inflammatory, and source of improvement of the blood plasma profile.[25] Different soybean components such as proteins, phytosterols, fiber, and polysaccharides play their role in the reduction of diseases, but the soy ISOs are chiefly associated with control of chronic diseases because of their antioxidant activities.[26] The role of the different soybean components along with the mechanism of action for the control of different diseases is discussed as follows:

Reduction of Carcinogenesis

Soybeans play an essential role in the reduction of carcinogenesis, especially hormone dependent cancer, because of the presence of phytoestrogens like daidzein and genistein.[27] Isoflavonoids are the most important and potentially anticarcinogenetic compounds naturally present in dietary soybeans and are mainly involved in the reduction

of breast cancer.[28,29] Along with these, soy saponins are also reported to have role in reduction of colorectal cancer, particularly in females.[30] The most important ISOs found in soybeans are daidzein and genistein which have a significant role in the reduction of different types of cancers.[31–33] Daidzein is considered to be a more bioavailable compound than genistein, however, the anticancer effect of soybean is mainly due to the genistein. There are different mechanisms through which genistein act against cancer such as by interrupting or disturbing the enzyme mechanism which is responsible for cancer production, by controlling the body hormones, by blocking the availability of the vital nutrients, and restricting the oxygen supply to the tumor.[34]

Different studies have shown that genistein not only plays an important role in the suppression and inhibition of different types of tumors, but is also involved in the inhibition of the vascular endothelial cells.[35] Genistein has shown its chemo preventive effect against the development of induced mammary tumor when used in dietary supplements or given by subcutaneous injections.[35] Genistein has displayed this chemo preventive effect at the level of tumor promotion and progression, as by its action tumor formation cannot be prevented, only the growth and appearance of the tumor can be delayed.[36]

Mechanism of absorption of genistein. The detailed mechanism of absorption of genistein is depicted in Fig. 1. When soybeans are ingested and passed through the gastrointestinal (GI) tract, the micro flora present there act upon the soybean and

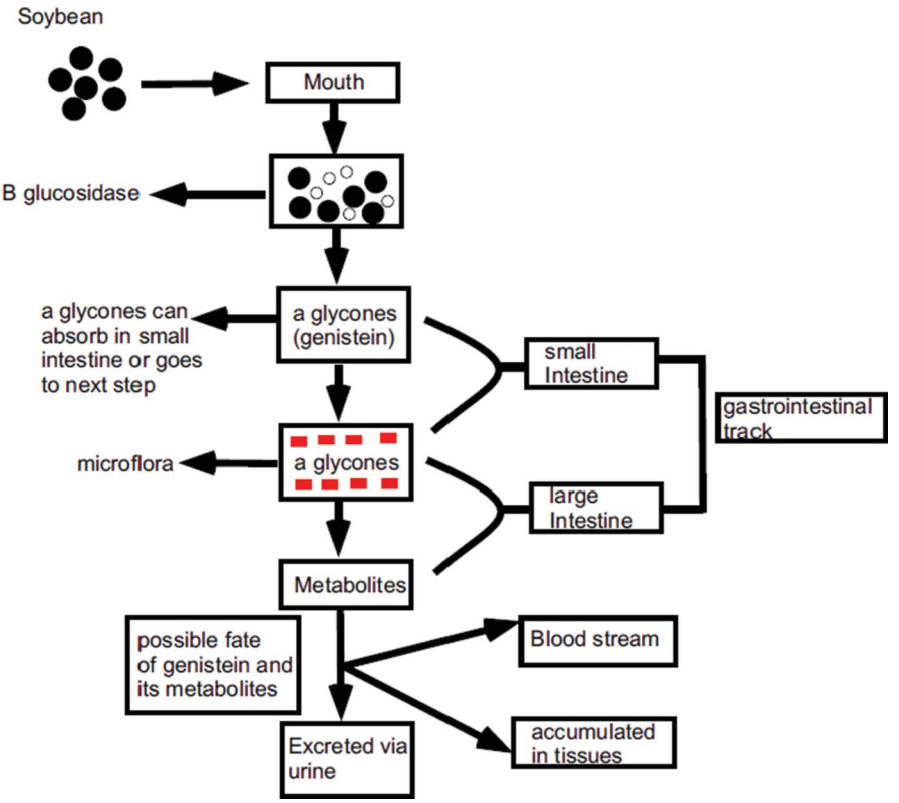

Figure 1 Absorption of genistein in intestinal tract.

release the compounds like β-glucoside and genistein. Thereafter, the genistein enters into the blood stream, accumulates in the tissue cells, or is excreted via the urine. The isoflavone glucosides are hydrolyzed by the action of β-glucosidases to produce aglycones like genistein in the small intestine, which are either absorbed as such in the small intestine or passed into the large intestine for further metabolism by the action of the intestinal microflora present in the large intestine into its component metabolites such as equol and O-desmethylangolensin.[37]

Studies on the soybean effect in rats revealed that genistein and its principal metabolite, genistein 7-*O*-β-glucuronide, are not only well absorbed from the intestines, but are efficiently extracted from the portal blood into the liver and excreted into the bile.[38] The fact that the portal blood contained predominantly genistein 7-*O*-β-glucuronide after the duodenal infusion of genistein in rats suggest that this phase II conjugation step occurred in the gut wall, rather than in the liver. However, the liver has the natural ability to produce glucuronidate genistein. The peripheral blood in these animals contained only genistein 7-*O*-β-glucuronide, for which a delay in biliary excretion was also observed. The origin of genistein 7-O-β-glucuronide in the peripheral blood is consistent with studies in humans ingesting up to 1 mg/kg body wt/day.[39]

The consequences of an efficient enterohepatic circulation of genistein and its metabolites are as follows (1) genistein may accumulate within the enterohepatic circuit, and (2) it may be excreted with a long half-life.[40] An important factor that could alter the initial intestinal absorption and the enterohepatic recycling of genistein is bacterial metabolism. Researchers found that the genistein is less bioavailable than diadzein as urinary output of geistein was lesser than diadzein.[41] Similarly, it was also observed that genistein was well absorbed from the intestines and excreted into bile with only a small proportion appearing in urine.[38]

It has been reported that 85% of the soybean ISOs could be degraded or hydrolyzed in the intestine as human intestinal bacteria have the ability to metabolize ISOs and release the ISOs aglycones.[41,42] Although several groups of bacteria have β-glucosidase activity but the lactobacilli, bacteroides, and *bifidobacteria* play an important role in the hydrolysis of several plant β-glucosides present in human diet, such as glucosides of the flavonoids and ISOs to produce aglycones.[41] Some bacteria in the human large intestine also have β-glucuronidase and arylsulfatase, which can cause the liberation of aglycones from the conjugates of the liver phase and biotransformation.[43] On the other hand, there are certain strains of Clostridium,[44] which are present in in the human lower GI tract which can cleave the C-ring of many flavonoids, such as kaempferol (3,4',5,7-tetrahydroxyflavone), quercetin (3,3',4',5,7-pentahydroxyflavone), and naringenin (4',5,7-trihydroxy flavanone), and produce monophenolic compounds by the anaerobic action.[45] It is well known that the ISOs of soybeans are quickly absorbed via the GI tract and attain their highest concentrations within a few hours of ingestion. The pharmacokinetics of genistein in mice when administered orally, or via the intramuscular and intravenous routes, revealed that genistein is rapidly removed from the blood compartment, with an apparent general availability of 12%.[46]

ISOs present in soybeans have the ability to bind the esterogen receptors[47] as they bind both forms of the estrogen receptor (ER) which are α and β; however, a great attraction has been noted for the β form. Cancer proliferation can be suppressed by ER_β.[48] An analysis of the flavonoids and isoflavonoids using the transcriptional response assay revealed that genistein has the highest estrogenic activity while daidzein has moderate activity and hesperetin has the lowest activity.[49] Soy ISOs (genistein and daidzein) can also control

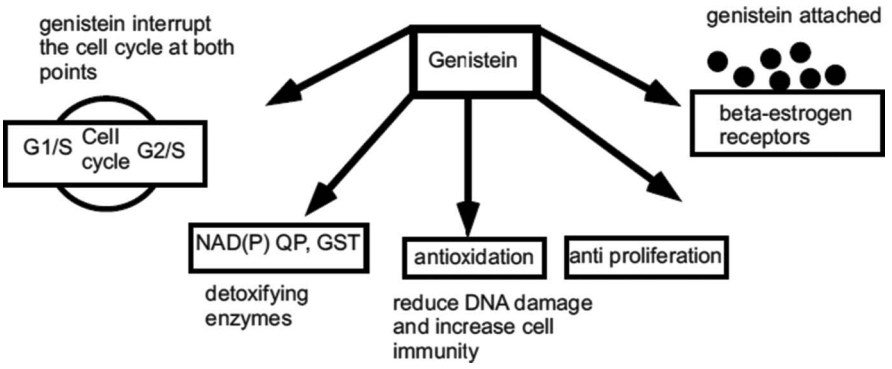

Figure 2 Mechanisms involved in the reduction of carcinogenesis.

the cancer by reducing the oxidative damage to the DNA in cell cultures.[50,51] Different mechanisms involved in the prevention of cancer by genistein are depicted in Fig. 2.

Chemical examination of the flavonoids and isoflavonoids revealed that they were able to donate a single electron and they acted like derivatives of the ring structures. They can act as antioxidants by capturing the superoxide anion,[52] lipidperoxy-radicals, single oxygen,[53] and/or by hydrogenation they can stabilize the free radicals which play their role in the processes of oxidation or complexing with those species which causes oxidation.[54] Genistein also scavenge hydrogen peroxide very effectively.[55] An *in vitro* study of rats revealed the antioxidant activity by the genistein including the inhibition of nicotinamide adenine dinucleotide posphate (NADPH) and adenosine diphosphate (ADP)-dependent lipid peroxidation as well as the inhibition of the oxidation of linoleic acid and β-carotene.[56,57]

Another property of these ISOs is their anti-proliferative effect, which is one of the anti-carcinogenic properties of the ISOs. Research pertaining to the effect of these isoflavonoids on human and animal health revealed the fact that they do not have a toxic effect on humans and animals along with their anti-proliferative activity.[58] Their main property is to inhibit the cell growth, which includes the inhibition, reversion, or retardation of enhanced cellular proliferation. These flavonoids present in plants act as a protective agent against fungal and bacterial growth, therefore, they act as phytoalexins.[59] Genistein and some other isoflavonoids had revealed their anti-proliferative effect on breast cancer and liver cancers.[60] For case of breast cancer, when these isoflavonoids were administered in high doses of 50 μM, they performed their action by acting on the cancer of the breast MCF-7 by mechanism which was independent of the ERs.[61] These ISOs can also cause the cell cycle reduction or apoptosis was induced for reduction of the cancer. There are two main points in the cell cycle of cancer cells in cultured conditions which are interrupted by the isoflavonoids one is G1/S and the second is G2/M.[31]

A study pertaining to the effect of genistein on human myelogenous leukemia and lymphocytic leukemia revealed that 5–20 μg/ml of genistein can cause the arrest of the cell cycle of both the diseases mentioned above, at both the G1/S and G2/M points.[62] Similarly, the utilization of 0.1–25 mg/mL amount of genistein along with some synthetic isoflavonoids analogues inhibited the proliferation of intestinal cells as well as induced apoptosis cancer *in vitro* conditions.[63] Similarly, Genistein when taken in amount of 60 μM, can arrest the human gastric cancer cells at the point of G2/M.[64] Genistein along

with other isoflavonoids like diadzein, and biochanin when taken in a dose of 0–50 μM can restrict the growth of bladder cancer and murine cells in humans by angiogenesis, cell arrest and apoptosis.[65] It is also stated that these concentrations of genistein mentioned above will also help in the reduction of apoptosis in human prostate cancer and have the same effect on the cell lines of Jurkat T-leukemia.[66] When genistein is administered in a dose of 30 μM it can control the non-small-cell linings of lung cancer by arresting the G2/M in the cell cycle by up regulation of p21 and by inducing apoptosis.[67] Similarly, when genistein is injected as medicinal doses during the pre-pubertal and neonatal periods it caused a suppression of the development of the mammary tumor which was chemically induced.[36,68] Soybean ISOs also have the capability of inducing detoxification enzymes of phase II in the cells resulting in the protection of cells from neo plastic and toxic effects of carcinogens.[69] The threshold level for chemical carcinogens can be modulated by the induction of these phase II detoxifying enzymes, leading towards the resistance of the body cells against the action of these carcinogens.[70,71] Talalay explained that many carcinogens require a complete metabolic process for their performance, therefore the enzymes present in phase I make them the proximate carcinogens by the oxidative process.[70] Talalay et al. found that these potential carcinogens will be detoxified by phase II enzymes and will be converted to the inactive form which can be easily excreted.[71] A good example of the phase II detoxifying enzymes is presence of NAD (P) H: quinone reductase (EC 1.6.99.2) and GST (EC 2.5.1.18), which are induced in the cells in coordination with the carcinogens, quinone reductase carried out the two electron reduction which can protect the cell from mutagenicity and carcinogenicity which are the result of one electron reduction.[31]

Soy saponins are also involved in the control of colon cancer mainly by controlling the adenocarcinoma cells. Soy saponins can control these cells by the reduction of COX2 (cyclooxygenase 2) and PKC (protein kinase C), reduction in expression of COX2 and PKC, interfering with NF_KB dependent signaling pathway by reducing the degradation of IkBα, as NF_KB is the most frequently studied signal transduction cascade, which is a participant of the inflammatory responses during carcinogensis.[72] There are some mitogens which causes the release of free NF_KB which include TNF-α, TPA, and IkB kinase causing phosphorylation, decomposition, and dissociation of $I_KBα$ from NF_KB. The presence of NF_KB in the free form will induce the expression of COX2 by binding with nuclear binding sites.[73] Soy saponin will control inflammatory activities due to its possible mechanism of indirect interaction with the cell membrane, by inhibiting the NF_KB as it will disturb the mitogens and cell membrane interaction.[3] Soy saponin also has an antioxidant activity which save the DNA from oxidative damage.[74] Soy saponin contains 2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP), which are strong antioxidants that act as free radical scavengers resulting in the suppression of the activity of COX2.[3] Soymilk and other soy supplements have shown similar results in humans.[75,76]

High intake of soybeans in adolescence lowers the risk for breast cancer in adulthood.[77] Wakai et al. revealed a fact that a product of soybeans that is called as miso soup has a positive relation with lungs cancer[78] while another soybean based fermented product known as tofu, is found to be effective against ovarian cancer as well as showed a reducing effect on lung cancer generation.[79] According to Yan soybeans can reduce prostate cancer up to 30%.[80] It was observed that soy ISOs are inhibiting growth factor-induced signal transduction in bladder cancer cells.[81] Generation of new blood vessels or angiogenesis in the primary bladder is significantly correlated with the tumor stage and the presence of vascular invasion and suggested to be a free predictive indicator for patients having persistent transitional cell carcinoma in the bladder. Angiogenic growth factors are

found to be increased in the urine of patients with bladder cancer, particularly those with a later stage of the disease.[82] Soy ISOs were reported to control bladder cancer by the inhibition of cell proliferation mainly due to G_2/M cell cycle arrest. Studies in mureins MB49 and MBT-2 cell lines showed reduced cell number with successive increase in the dose of genistein.[65] Studies also revealed that soybean based food also play a crucial role in reduction of colon cancer along with reduction of cancer of the breast cells.[56,57] Genistein has the ability to reduce the cell growth of HGC-27 which is a derivative of human gastric cancer, inhibiting the cell cycle at G2-M, and shows growth reduction of the NIH3T3 cells.[83] Especially with reference to colon cancer genistein has shown its effect by inhibiting the AOM3-induced formation of ACF in the colon of male rats.[84,85] Along with prevention of cancer soybean especially the polysaccharides of the black soybean are helpful for post treatment problems such as myelosuppression which occur after chemotherapy or radiotherapy.[86,87] When patients are treated with PSBS-SCM, there is a rise in the formation of a colony of cultured cells of bone marrows as compared with normal SCM which can be reduced by five days of regular utilization of the polysaccharides of black soybean.[88]

Lowering of Cholesterol

Soybeans have an advantageous impact on the risk factors for cardiovascular diseases which include a reduction of blood or liver triglycerides, a reduction in the of level of low density lipoproteins (LDL), an increase in the level of high density lipoproteins (HDL) and the ratio of both lipoproteins cholesterol, and controlling blood pressure.[89–91] Soy protein was reported to reduce the absorption of cholesterol in the intestines as well as concentrations of plasma cholesterol as soybean proteins have shown greater ability to reduce the cholesterol especially the LDL as compared with casein in the animal models.[92] Some non-digestible fractions of soy proteins are involved in the reduction of blood cholesterol.[93]According to Baum et al., the use of 40 g of soy proteins can cause a 5% increase in the HDL and a 7% decrease in the non-HDL cholesterol.[94] The detailed mechanism of the cholesterol lowering effect of soybean proteins is depicted in Fig. 3. Soy cream can reduce the size of the LDL particles while soymilk can protect the LDL from per oxidation. The combined utilization of soybean has shown significant effects on the lipid profile, especially a decrease in the LDLs and a rise in the HDLs.[95] In addition to soy proteins, soybean ISOs are also reported to be responsible for the control of LDL oxidation.[96] The exact mechanism of the cholesterol lowing effect of soybeans is unknown, but different possible mechanisms of the cholesterol lowering effect of soybeans can be depicted as follows:

Proposed mechanism 1 (bile acid excretion). This mechanism revealed that soybean proteins are responsible for an increase in bile acid production and excretion via the feces as investigated in rabbits and rats.[97,98] This mechanism creates such conditions by which the cholesterol is kicked out from the body. When the bile acid production is increased to maintain this state, the hepatic cholesterol system shifts and provides the cholesterol for the bile acid. During this process, the activity of the LDL receptors is also increased and the whole mechanism is finally responsible for a reduction in the cholesterol from the blood.[99] The presence of a similar mechanism in humans and species other than rats and rabbits is not very consistent.[100,101] According to Iwami et al., there is a correlation between the hydrophobicity of protein hydrolysates and its ability to bind with the bile acid.[102] They also found that the peptide with a high binding ability with the

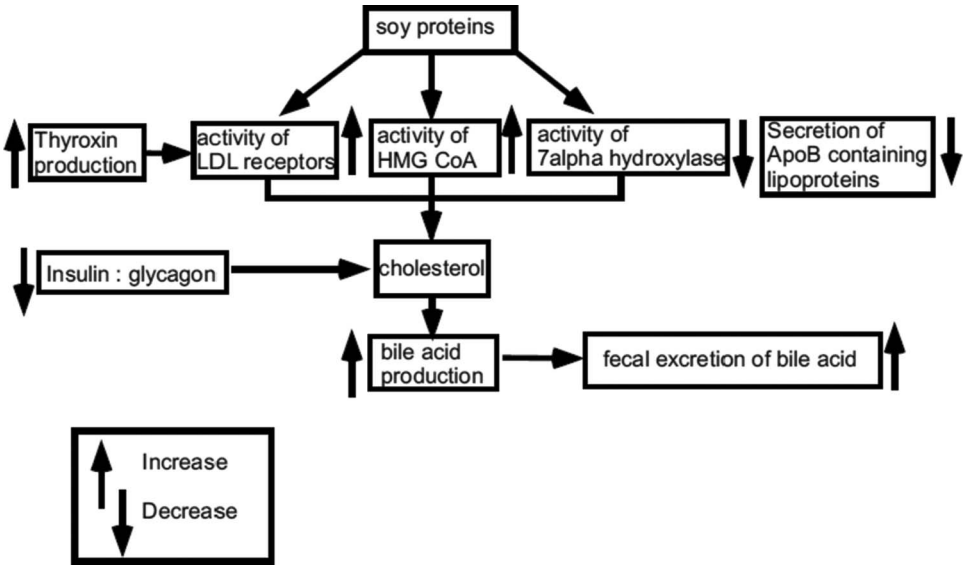

Figure 3 Proposed mechanisms of cholesterol reduction.

bile acid has a greater capacity to reduce the cholesterol by restricting the reabsorption of the bile acid in ileum. Nagaoka et al. explained that the Jejunum is also a part of this mechanism.[103] According to them, an inhibition of the micelles solubility of cholesterol causes the reduction in the cholesterol absorption and this is achieved by the direct interaction of the cholesterol mixed micelles and soybean protein peptic hydrolysates with the bound phospholipids in the jejunal epithelia, therefore, collectively this mechanism involve both the jejunal and ileal effects.

Proposed mechanism 2 (hepatic metabolism). According to this mechanism, there is a direct effect of the soy proteins on the hepatic metabolism of the cholesterol. Soy protein peptic hydrolysates have a greater ability to reduce the cholesterol than the casein tryptic hydrolysates.[103] The degree of the cholesterol lowering effect of the soy proteins depend on the extent of the fecal steroid excretion as an increase in the activity of the 3-hydroxy-3-methylglutaryl co-enzyme A (HMG CoA) reductase was observed when soy protein was fed to rats.[104] The consumption of soy protein was reported to cause the elevation in the rate of removal of the LDL and other LDL by hepatocytes in rabbits and the mononuclear cells of humans.[105,106] The hepatic metabolism of cholesterol is associated with a lowering of the 7α- hydoxylase activity and increase in the activity of the apolipoprotein B and E receptor as well as the activity of the HMG CoA reductase.[104,107] Besides soy proteins, soy ISOs were also reported to decrease the plasma cholesterol by arresting the hepatic assembly as well as by inhibiting the secretion of apoB-containing lipoproteins.[108] The assembly of apoB together with lipids, is one of the complex processes for the preparation of the secretion competent element and the soy ISOs can affect any of the key factors which in returns affects the cholesterol level. Borradaile et al. found that the soy ISOs reduce the production of apoB from the hepetic cells called as $HepG_2$ and restrict the apoB secretion by inhibiting the cholesterol production, and by esterification of the cholesterol. They also restrict the activity of the microsomal triacylglycerol transfer protein (MTP).[108]

Proposed mechanism 3 (endocrine system). The endocrine system is also directly affected by the soy proteins as their utilization causes an alteration in the of hormone concentrations.[109,110] These alterations in hormones include an increase in the thyroxine, and the free thyroxine index and sometimes an increase in the thyroid stimulating hormone is also reported in animals, however, triiodothyronine is not affected.[111] These alterations occur in the concentrations of the insulin and glucagon ratio, as the utilization of the soy proteins decreases the ratio of insulin and glucagons.[112] The high ratio of insulin and glucagon is considered as risk factor for coronary heart diseases (CHD) because they can stimulate the lipogenesis. These variations in hormone secretions mainly the thyroid hormone cause an enhanced activity of the LDL receptors, an enhanced activity of the HMG CoA reductase and an increased bile acid excretion resulting in the reduction of the total and LDL cholesterol level.[113]

Protection from Atherosclerosis

Atherosclerosis is a drastic heart disease consisting of plaques made up of three main regions; one of them is the fibrous cap while the other two regions are the shoulder and necrotic core regions. The fibrous cap overlies the necrotic core and it act as a support for the holding vessel.[114] The accumulation of LDL particles in the artery walls followed by oxidation is considered to be one of the basic factors for the onset of the early phase of atherosclerosis.[115] Histological identification has shown lipid deposits to be the cholesterol crystal clefts and a considerable feature of atherosclerotic which were found in the center of the necrotic core.[116,117]

Diets rich in soy beans may show the positive effects on the atherosclerotic development by increasing the concentration of genistein inside the plasma.[39] The estrogenic activity of soy ISOs especially of genistein, provide an opportunity of binding the ER resulting in the reduction of atherosclerosis as well as other subsequent CHDs. Genistein is also known to be one of the tyrosine kinase inhibitors and the inhibition of tyrosine kinase also helps to control the prevalence of atherosclerosis.[89] The ability of genistein to bind the esterogen receptor is due to its structural resemblance with human estrogens.[118] The presence of the esters of estrogen fatty acid in the tissues of human and their alliance with lipoproteins has shown an opportunity that derivatives of lipophilic phytoestrogen may be formed and then incorporated into the lipoproteins, resulting in an elevation of the enhanced antioxidant activity of these phytoestrogens.[119,120]

Studies revealed that the oxidation of human serum samples, mediated by copper, can be affected by the presence of genistein, daidzein, equol, and O-desmethylangolensin as the presence of 1 and 10 mmol/l genistein inhibits the creation of diene which is conjugated in the serum of humans when the serum is in the diluted state.[15] The tyrosine kinase inhibition ability of soy ISOs can affect the LDL oxidation as well as the use of a single concentration of genistein (150 mmol/L) is reported to reduce cell-mediated and copper mediated oxidation of LDL to about 77 and 67%, respectively. Genistein acts differently in different conditions and systems as genistein plays its role as a good antioxidant more effectively in pro-oxidant system which is metal-dependent when compared with another system which is termed the peroxyl radical system.[121]

The exact mechanism of genistein acting as an antioxidant is not clear. There is a strong relationship between the structure of flavonoid and antioxidant activities. The presence of the C-ring with the 3 hydroxy substitute and the B-ring with an o-diphenolic arrangement is recognized as fundamentals importance for the abilities of

radical scavenging and chelating. Both these rings are not present in genistein, however, it consists of a group which is functional in nature. That group is the ketone and the double bond on carbon 2, 3 on the C ring and ring containing 3 phenolic hydroxyl groups, which maybe the reason for its antioxidant properties.[122,123]

Genistein has the ability to inhibit the relocation and proliferation of smooth muscle cells, thus contributing a lot towards the control of atherosclerosis.[124] Studies have revealed that when unesterified genistein was incubated with the plasma of human beings, it has shown to bind with the HDL and LDL particles, because human plasma has the ability to change the genistein into derivatives which are lipophilic and are integrated into both LDL and HDL.[125] Soy ISOs can also lower the chances of atherosclerosis by affecting the thrombosis which is also one of the causes of atherosclerosis. Genistein has a major role in limiting the activity of platelets, inhibiting the thrombus formation[126,127] reducing the platelet serotonin uptake and inhibiting aggregation.[128,129]

Prevention of Diabetes

The different mechanisms involved in the prevention or reduction of diabetes by soybean components are depicted in Fig. 4. Glucosidases are enzymes for carbohydrate digestion and these enzymes are present in the brush-border cell at the surface membrane of the intestine. Glucosidase inhibitors are very important with reference to their role as remedial agents for some diseases mainly for degenerative diseases.[130] Genistein has proven itself as inhibitor for α-gucosidases. Genistein acts as a specific inhibitor for α-glucosidase which is an important enzyme for the digestion of carbohydrates and also

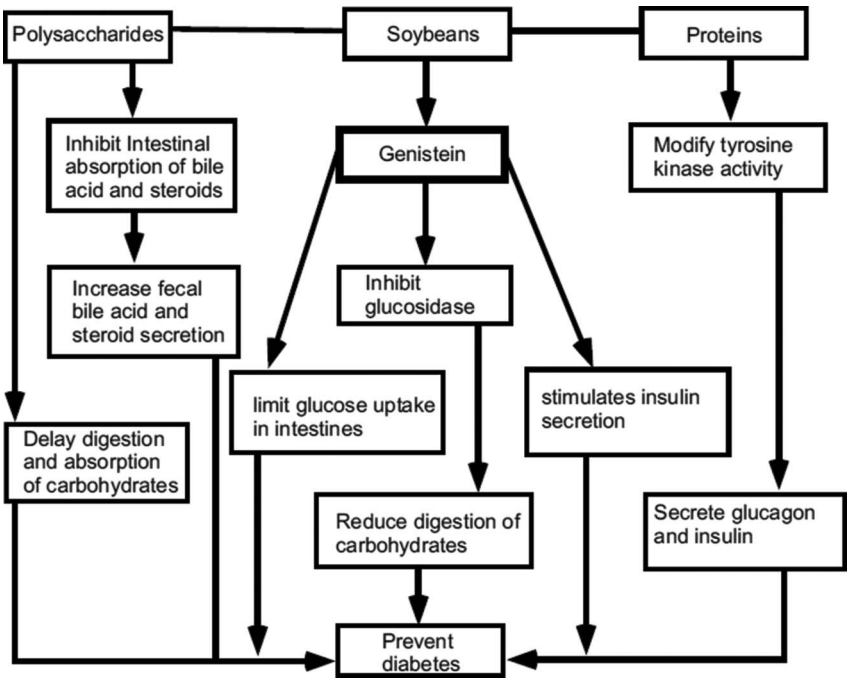

Figure 4 Mechanisms involved in the prevention of diabetes.

plays an important role in the processing of glycoproteins and glycolipids. This enzyme is also responsible for many metabolic disorders like diabetes, the attachment of viruses, and formation of cancer.[131] Studies revealed that genistein reduces the α-glucosidases activity in a dose dependent manner. It was supposed that genistein at least acts as an analog of glucose which is a partial analog or it binds the binding sites of the α-gloucosidases of glucose. The effect of genistein on α-glucosidases can be improved by the treatment of α-glucosidases with genistein for one hour before the start of enzyme reaction at 30°C, therefore, it can be stated that the inhibitory activity of genistein against α-glucosidase can be increased by this pretreatment.[132] Phytoestrogens, especially genistein, have a positive effect on the homeostasis of glucose by limiting the uptake of glucose into the intestinal brush boarder membrane vesicles.[133] In *in vitro* studies it was revealed that by enhancing the glucose stimulated insulin secretion genistein boosts the secretion of basal insulin in the cell lines and also reduces the proliferation of the cells of the pancreatic islets.[134] The effect of genistein on the secretion of insulin is mainly related to its tyrosine kinase inhibiting ability,[135] as well as its ability to activate the pathway of cyclic adenosine monophosphate/protein kinase-A.[134]

In addition to soy ISOs, soy derived proteins are high sources of glycine and arginine,[136] the amino acids having a key role in the secretion of glucagon and insulin by the pancreas.[137] Soybean proteins are also involved in the improvement of peripheral insulin sensitivity and glucose tolerance especially fasting glucose tolerance in rats.[136] The secretion and action of insulin is affected by the tyrosine kinase activity when it is modulated because it acts as a key in the action and secretion of insulin. The interaction of insulin with its receptors results in the β-subunit's tyrosine autophosphorylation resulting in the activation of tyrosine kinase receptors.[138,139]

The soluble dietary fibers, an important part of soybean causes the reduction of carbohydrate absorbance and a rise in the excretion of bile acid through the feces, which ultimately helps to control diabetes and fat absorbance.[140–142] Jang et al.[143] explained that the peptide mixture, especially black soybean peptides, acts as anti diabetic agents by different mechanisms such as the suppressions of hepatic endoplasmic reticulum stress and maintenance of insulin resistance. Due to the utilization of the soybean as food, the incidence of type 2 diabetes is lesser in the Asian countries as compared with western countries and it is also stated that fermented soy products may have a better prevention potential against type 2 diabetes.[144] The utilization of soybean based diets improved response of insulin to glucose in the offspring suffering from a limitation of proteins during pregnancy and lactation periods.[145] The products made from added proteins like use of soybean and dairy proteins in gluten free bread is useful for malnourished persons, especially in the case of celiac disease; this fact revealed that the soybean is also useful for patients with celiac disease.[146–149]

Management of Postmenopausal Problems

It is described that menopausal problems including hot flushes, disturbances of mood and sleep, as well as postmenopausal disorders can also be managed by the soybean.[150] Postmenopausal women are at risk of coronary artery diseases.[151] Phytoesterogens have many other effects which are not hormonal. These include a rise in the concentration of globulins, which are sex hormone binding, resulting in the reduction of free circulating endogenous hormones.[152] Phytoesterogens are polyphenolic nonsteroidal substances like dietary estrogen, and are found in more than 300 different plants.[153] These are

mainly divided into ISOs, isoflavanones, coumestanes and lignans.[49,154] ISOs may cause a reduction in the biological activity and decreases the estrogen level by motivating the manufacture of globulin that binds the plasma sex hormone and also causes the inhibition of aromatizes in humans.[155] These phytoesterogens also affect the weight of utriene. The effect of different types of diets such as genistein (700 μg/g diet), phytoestrogen-free diet, and an ISO-high diet (232 μg daidzein and 240 μg genistein/g) on utriene. weight and gene expression was observed, and genistein was found to strongly increase the wet weight of utriene.[156] A soybean-based diet has also shown improvement in the cholesterol and apolipoprotein level of the postmenopausal women. The utilization of 101 mg of aglycone ISF along with 25 g of soy protein as a supplement on a daily basis resulted in 11 and 8% reduction of LDL cholesterol and apolipoprotein B, respectively. Moreover, it also caused a reduction of 6.8% in diastolic and 9.9% in systolic blood pressure.[157] Soybean especially controls menopausal problems in type 2 diabetics,[158] as soybean fibers are involved in control of the glucose mechanism in diabetics.[159] The functional ingredients and phytoestrogens of soybean are also involved in bone formation and reduction of the bone loss especially in postmenopausal women.[160] Soybean increases the bone formation marker which is a bone-specific alkaline phosphatase[161] and attenuated bone loss from the spine of premenopausal women.[162,163]

Control of Obesity

The phytoestrogens of soybeans are also reported to have a role in the control of obesity.[164] Genistein present in the soybean has the ability to reduce the size of the fat pads which cause obesity, however, not only genistein, but daidazin also have anti-obesity actions in obese mice.[165,166] Gao et al.[167] also found that the soybean is involved in control of obesity due to which it can be used in energy restricted diets to control obesity.

Management of Proinflammatory and Neurodegenerative Disorders

Proinflammatory pathways may be attenuated by genistein by the inhibition of the extra expression of inflammatory reactions and proinflammatory mediators in the microvascular endothelial cells of the human brain. The proinflammatory cerebromicrovascular environment is considered very critical in the early events which are pathologic in nature.[131] In addition, rising evidences has recommended that when nonsteroidal anti-inflammatory drugs are used as treatment, they have shown lower risk for initiation of many neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD).[168,169] These studies have proven that the inflammatory responses in the brain are related to the dysfunction of the vascular endothelium and have a key role in the pathogenesis of neurodegenerative diseases. Soy ISOs are responsible for the protection of the central nervous system (CNS).[170–172] Work done on animal models revealed that the primary isoflavone in soybean, which is genistein, has to act as the neuroprotector in the case of mouse model with stroke and familial amyotrophic lateral sclerosis.[171,173] Tertiary butylhydroperoxide or thapsigargin can cause apoptotic cell death and early treatment by genistein can protect the cortical neurons from such cell death.[170,174] Microglia, which are stimulated by the lipopolysaccharide, produce proinflammatory mediators, and genistein may provide protection of the dopaminergic neurons by inhibiting the manufacture of these proinflammatory mediators.[172] Dietary ISOs like daidzein and genistein have shown protective effects on the inflammatory responses in the vascular endothelium as these

have shown a significant decrease in TNF-α induced MCP-1 secretion in (HUVEC) human umbilical vein endothelial cells.[175] Genistein has shown its protective effect against injury of the microvascular endothelium in the human brain by decreasing the regulation of the extra expression of the proinflammatory mediators like MCP-1, IL-1β (cytokines), TNF-α, IL-8 (chemokines), and ICAM-1 (adhesion molecule) as well as by decreasing the transmigration of blood leukocytes.

Control of HIV Infections

Studies have shown that genistein restricts the infection of HIV-1 in main human macrophages by exerting an oppressive effect on the production of TNF-α by the primary macrophages after signaling induced by the glycoprotein 120 challenge and/or TNF-α.[176,177] It is expected that genistein would have the ability to control the spread of the wild type infection of HIV-1 in the cell culture. Genistein can reduce the TNF-α production which acts as an effective interference with signaling by the glycoprotein 120. Ingestion of a soybean meal, three times in a week, by HIV patients has shown better results, as 93% were feeling better, up to 86% had shown a lower level of sickness, and up to 61.3% had a higher amount of total white blood protein and other blood proteins.[178] The HIV protease inhibitor (PI) ritonavir (RTV) is an important factor which may cause vascular injury through oxidative stress, but soy ISOs have the potential to prevent this vascular injury. These ISOs are also capable of controlling the cardiovascular complications which are associated with HIV.[179]

Prebiotic Effect

Another benefit of the soybean is related to presence of oligosaccharides in soybeans because these oligosaccharides will act as a prebiotic for the intestinal microorganisms[180] and causes a rise in the number of probiotics in the intestine, and when fermented soymilk is used, it will improve the whole ecosystem of the GI bacteria.[181] This rise in the probiotics will reduce the chances of a malfunctioning GI tract, which is mainly due to the invasion made by bacteria, and these probiotics will improve the barrier function of the GI tract.[182] There are a lot of positive health effects which are associated with the soybean and its meal due to which soybean utilization is increasing worldwide.

CONCLUSION

Soybeans are a crop rich in different functional ingredients, including some excellent proteins, fibers, phytosterols, and saponins along with phytoesterogens like genistein and daidzein. The health benefits of the soybean are related to the chemopreventive effect of soybeans against various chronic diseases like cardiovascular, cancers, and diabetes. There are various other diseases which can also be managed by the use of the soybean. Therefore, the soybean could be an integral part of functional foods, as well as it could be used in the food industry for improvement of product quality.

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