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Chemical properties, health benefits and threats of soy isoflavones

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ABSTRACT

Isoflavones, from soy and other plant sources are of interest because of their estrogenic, antifungal, and antibacterial activities. Soybeans contain three major isoflavones: genistein, daidzein, and glycitein. Soy isoflavones share structural features with the animal estrogen, 17-ß estradiol. This structural similarity allows these compounds to bind to estrogen receptors and sex hormone binding proteins. Considering the estrogenic activity of soy isoflavones, it is important to understand how these compounds affect the reproductive hormones and also knowingthehealthaspects of these compounds.

Key Words: soy isoflavones, biological action, chemistry, therapeutic benefits.

INTRODUCTION

Certain naturally nonnutrientcompounds have the potential to prevent or delay the onset of chronic diseases in humansand animals. These natural compounds, called*phytochemicals*, are present in fruits, vegetables, grains, legumes, herbs, and seeds [30].

Among the phytochemicals is a broad class of nonsteroidal estrogens called *phytoestrogens.* Phytoestrogens, also known as plant estrogens or dietary estrogens, areclassified into three major categories: isoflavones, resorcyclic acid lactones, and coumestranes [12]. Isoflavones are the major phenolic compoundsfound in soybeans [96].

This phenolic compounds are structurally or functionally similar to estradiol-17ß or that produce an estrogenic effect [27]. Plantderived estrogens bind competitively to both estrogen a (ERa) and estrogen ß (ERß) receptors and activate them [35].These estrogen mimics have been shown in animal models and in limited clinical investigations to be protective in the prevention of cardiovascular disease, osteoporosis and hormone-dependent cancers [3,45]. It is well recognized that people who consume traditional diets rich in fermented soy foods and beans (mainly the leguminosae) experience less breast, uterine and prostate cancers and increase in semen quality[53].

As a result of these numerous benefits of soy based isoflavones, there is much interest regarding the increased use of soy based products as a component of healthy diets.

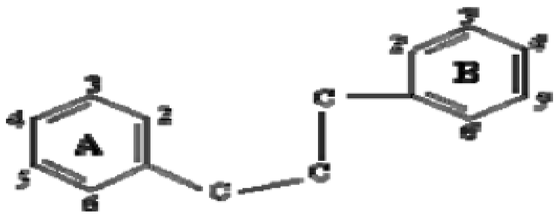
It is possible that isoflavones in animal feed could be transferred and/or accumulated into the resulted animal products, such as meat and eggs. In this way, people could benefit from these phytochemicals through foods of animal sources, and the consumption of isoflavones could be increased without altering deeply rooted food habits[7,34].In this article, we review the clinical and experimental evidence for the possible benefits and risks of ingestion of isoflavones.

Structure of isoflavones

Isoflavones are flavonoids which structure is characterized by the presence of two phenol rings linked together by a three carbon bridge[40].The basic structure of flavonoids is based on the 15 carbon skeleton, i.e. C6 – C3 – C6.

The two C6 represents the number of carbon atoms of the two phenyl groups and the C3 represents the number of carbon atoms that bridge the two phenyl rings by a linear three carbon chain. Figure 1 explains the above description in most convenient way[40].

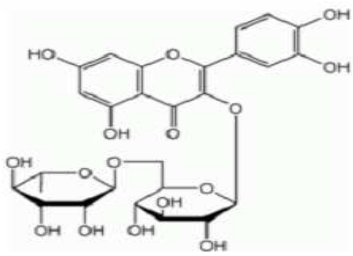
Figure 1.Basic structure of flavonoid



Other well known phytoestrogens are lignans such as secoisolariciresinol, coumestans. All these have been extensively investigated due to their potential as protectors of human health[88].

Figure 2.Example of Glycoside

Glycoside = Aglycone + Glycone (sugar)



Chemistry of isoflavones:

Flavonoids, are widely distributed in terrestrial plants, but isoflavonoids are restricted primarily to leguminous plants. They have been widely used as taxonomic markers within the leguminoseae. Isoflavones are the most abundant isoflavonoids. Isoflavones and coumestants have been identified as the most common estrogenic compounds in these plants [61].Overall, it seems that nearly every plant is able to synthesize phytoestrogens, but their concentrations in most plants are negligible [89]. Soybeans are the largest source of isoflavones with concentrations ranging from 118 mg/100g to 306 mg/100g[84].

Figure 3.Structural comparison between genistein, estradiol and daidzein:

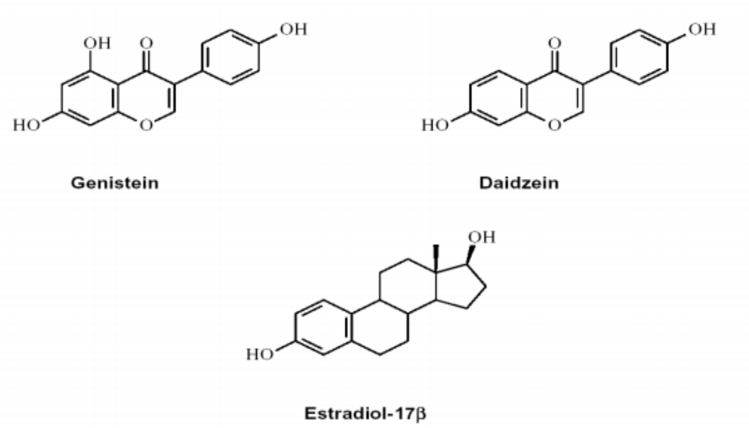


Figure 4.Soybean isoflavones and derivatives:

Compound	**R_3**	**R_4**	**R_5**
Daidzin	H	H	H
Genistin	OH	H	H
Glycitin	H	OCH_3	H
6"-O-Acetyldaidzin	H	H	$COCH_3$
6"-O-Acetylgenistin	OH	H	$COCH_3$
6"-O-Acetylglycitin	H	OCH_3	$COCH_3$
6"-O-Malonyldaidzin	H	H	$COCH_2COOH$
6"-O-Malonylgenistin	OH	H	$COCH_2COOH$
6"-O-Malonylglycitin	H	OCH_3	$COCH_2COOH$

Isoflavones are found mainly in their glycoside form this means that part of the molecule is linked with different number of sugars. If the linkage of the sugar to the flavonoid aglycone is through an OH group then these are called as O glycosylflavonoids and if the linkage is through C-C bond then these are called as C-glycosylflavonoidsand this has an effect on their absorption and retention within the human body[71].Isoflavones of nutritional interest are substituted derivatives of isoflavone, being related to the parent by the replacement of two or three hydrogen atoms with hydroxyl groups as shown in Fig 3. In genistein X_1 and X_2 are substituted with hydroxyl group (OH) whereas in daidzein X_1 and X_2 is substituted with hydroxyl group (OH) and hydrogen (H) respectively[52].The parent isoflavone is of no nutritional interest.

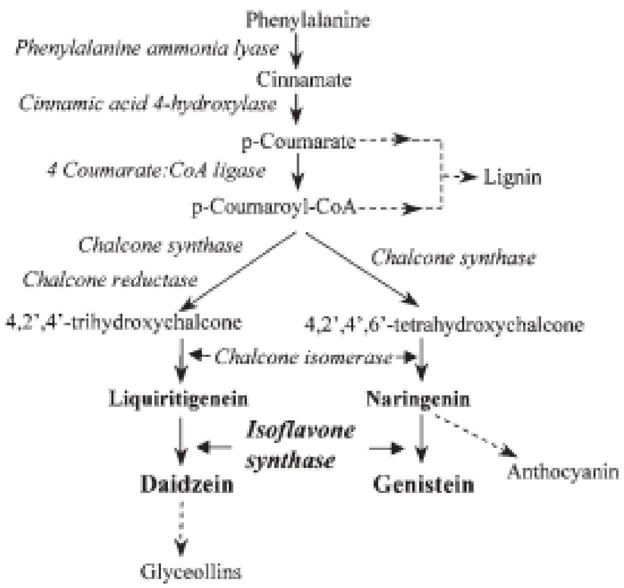
In soybeans there are 12 different isoflavone isomers: three aglycones (free isoflavones), three β-glucoside derivatives, three acetyl-glucoside derivatives and three malonyl-glucoside derivatives [71].

It is considered that the phenol ring is a key structural element to be able to attach to the estrogen receptors and the flavonoid isomeric configuration increases their similarity to human estrogens[37].

Isoflavone in soybean and red clover:
Total isoflavones contents in Japanese varieties grown in two different years (1991 and 1992) were estimated to be from 2041 to 2343 µg/g and from 1261-1417µg/g, respectively [71]. The isoflavone content in soybean seeds varies depending on the variety and environmental conditions when grown. Losses of isoflavones due to processing of seeds for traditional soy foods or protein products can reach 50% or more. The different anatomical parts of soybeans have different isoflavone contents. Eldridge and Kwolek [23] stated that cotyledons contain 80 to 90% of total soybean isoflavones and hypocotyls contain the difference.

The soil micro-organisms such as *Rhizobium* species establish nutritionallybeneficial symbiotic relationship by fixing the atmospheric nitrogen in root nodules on host plant cells of the family *Legnminosae*[57].Soybean plant uses isoflavones to stimulate soil-microbe rhizobium to form nitrogen-fixing root nodules[52]. In addition, these compounds are used as defenses against predators, parasites and diseases, for interspecies competition, and to facilitate the reproductive processes (coloring agents, attractive smells, etc) and hence they are called as the *First Line of Defense*[1].

Figure 5.A simplified diagram of the phenylpropanoid pathway



Red clover is one of the richest sources of isoflavonesand second identified source of isoflavones with relevant concentrations. There is a total of 31 different isoflavones found in red clover. Out of the aglycones mentioned above, genistein, and daidzein are the most abundant [80].Red clover has been recently studied because of its consumption by sheep. RossiterandBeck[64] stated thatsheep that were grazing on pastures containing red clover had multiple fertilityproblems.

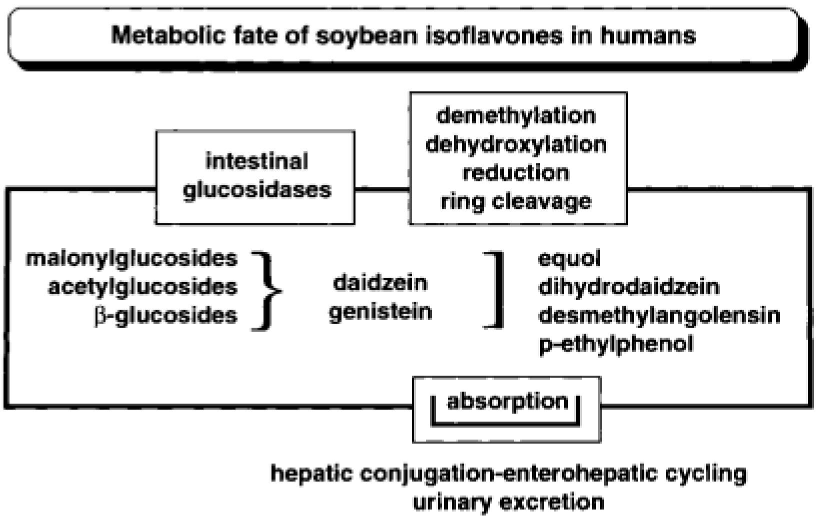
Immature animals were showing signs of estrus, ewes were unable to get pregnant and those that were pregnant often miscarried. The clover in thesepastures had high amounts of the isoflavones, formononetin and biochaninA [80].

Biosynthesis of isoflavone:
Isoflavones are produced via a branch of the general phenylpropanoid pathway that produces flavonoid compounds in higher plants. The phenylpropanoid pathway begins from the amino acid phenylalanine, and an intermediate of the pathway, naringenin, is sequentially converted into the isoflavone genistein by two legume-specific enzymes, isoflavone synthase, and a dehydratase. Similarly, another intermediate naringenin chalcone is converted to the isoflavone daidzein by sequential action of three legume-specific enzymes: chalcone reductase, type II chalcone isomerase, and isoflavone synthase [52].

Absorbtion and metabolism of isoflavone:
For isoflavones to be able to protect against different chronic diseases, the main requirements to consider are their effective absorption, metabolism, distribution and excretion, in other words, their bioavailability [31].

Isoflavones are consumed with food, absorbed in the gastrointestinal (GI) tract, and finally, excreted in the urine. They will be subjected to different chemical and physical environments throughout the GI tract.

The isoflavones found in soybeans are mainly glycosides; very small concentrations are found as aglycones [32].After ingestion, soybean isoflavones are hydrolyzed by intestinal glucosidases, which release the aglycones, daidzein, genistein and glycitein (Fig. 3). These may be absorbed or further metabolized to many specific metabolites including, equol and *p*-ethylphenol[71].



Isoflavone digestion will depend on the individual, it has been shown that not all women can turn isoflavone glycosides into their respective aglycones, due to differences in their micro flora. This is crucial in the absorption process since glycosides cannot be absorbed by enterocytes [73,89].After absorption, isoflavones pass through the liver where they can be glucuronidated or sulfated or left as aglycones. This can also significantly affect their bioactivity since glucuronides are believed to be pharmacologically inactive [90].Isoflavones may be further metabolized by the large intestine's microflora into other metabolites such as equol and O-desmethylangolensin (O-DMA) [11].

It has been noted that after absorption most isoflavones are found in urine and plasma as glucuronides, aglycones and sulfates.The percentages of glucuronides isoflavones were60% and 70% of total isoflavones in urine and plasmaof women that consistently consume soy milk [95].Aglycones only accounted for 5% in urine and 20% in plasma of the total isoflavones. To a lesser extent there are other aspects that can also influence isoflavone bioavailability, gender, food matrix and processing conditions among them[36,55]

Biological action of isoflavone:

There is now a considerable evidence showing potential beneficial effects of dietary phytoestrogens for many hormone-dependent conditions[73].The reported health benefits include relief of menopausal symptoms, reduction of osteoporosis, improvement in blood cholesterol levels, and lowering risk of certain hormonerelated cancersand coronary heart disease[44,49,74].Isoflavones behave similarly to hormone treatment estrogens but their estrogenic strength is weaker [48,89]. However, despite the relative low strength of isoflavones in comparison to estrogenic hormones, they may still exert physiological effects because isoflavone levels found in serum of soy consuming individuals can be as much as 1000 fold higher than endogenous estrogens [40].

The main estrogen which isoflavones mimic is Estradiol-17β. This estrogen is produced in the ovaries and acts through the estrogen receptors ERα and ERβ [35]. Until 1995, it was assumed that there was only one ER and that it was responsible for mediating all of the physiological and pharmacological effects of natural and synthetic estrogens and antiestrogens. However, in 1995, a second ER, ERβ, was cloned from a rat prostate cDNA library[51].

ERαis held responsible fortissue proliferationand therefore considered to be crucial in cancerous development [59].

Isoflavones binds to ERα with a ten times lower affinity than estradiol17β, but its dissociation is close to that of estradiol-17β[70].As previously noted, genistein has a very similar structure to estradiol in many aspects. These similarities aid in isoflavone binding to the active site of the receptors. The main similarity is the intermolecular distances between the hydroxyl groups; these groups determine the hydrogen bond interaction with the amino acids of the receptors [82].

It has been suggested that an optimal pattern of hydroxylation seems to be necessaryfor a flavonoid to have estrogenic activity[46]. The flavonoids with hydroxylsubstituents at 4 and 7 positions are estrogenic, and an additional hydroxyl group at the 5position – like that possessed by genistein increases estrogenic activity [46]. On the other hand, if a flavonoid has more than four hydroxyl substituents, (such as flavonol quercetin) or has a 4-methoxylated substituents (such as hesperitin), the estrogenic activity is abolished[46].

Similarity of phytoestrogens to estrogens at the molecularlevel provides them the ability to mildlymimic and in some cases act as an antagonist toestrogen [91]. Isoflavones can also alter the pattern of synthesis or metabolism for the endogenous hormones [91]. Thesoy isoflavones act by (1) Inhibiting the enzyme 17--hyroxysteroid oxidoreductase, type 1, which converts the relatively impotent estrone to the much more potent estradiol; (2) occupying the estrogen receptor, thus acting as antagonists to the naturally produced estradiol, inhibiting its effects [2,84].Oestrogenic action appearstohave *a* useful prophylacticeffect against many oestrogendependent disorders in adults, including mammary and prostatictumors[21].However, the same effect is deleterious in infants.

According Yildiz [91] the key structural elements crucial for the estradiol-like effects of soy isoflavones are:

• The phenolic ring that is indispensable for binding to estrogen receptors
• The ring of isoflavones mimicking a ring of estrogens at the receptors binding site
• Low molecular weight similar to estrogens (MW=272)
• Distance between two hydroxyl groups at the isoflavones nucleus similar to that occurring in Estradiol
• Optimal hydroxylation pattern.

Disadvantage of isoflavones:
It must be remembered that phytoestrogens may exert biological activity by other mechanisms. For example, the isoflavone genistein is a potent selective inhibitor of tyrosine kinase in human and rat myometrial cells[15].

Isoflavones act as estrogen receptor, depending on the hormonal status of the animal or man. Isoflavonoids act as ER agonists or antagonists at concentrations 100-1000 times higher than that of estradiol-17β[2].It is therefore possible that the consumption of a diet rich in plant-derived estrogens could affect endogenic hormone production.Cassidy *et al*,[17] observed that themidcyclepeaks of luteinizinghormone and follicle-stimulating hormone were suppressed and in premenopausal women the length of the follicular phase of the menstrual cycle is increased during an isoflavone-rich diet.

The serum estradiol-17β concentration is unaffected [17] or decreased, the progesterone level is decreased [43], and the serum testosterone concentration is unaffected or reduced by dietary soflavone supplementation[76].

The prime concern in relation to estrogenic compounds such as the soy isoflavones is the potential for chronic endocrine system and reproductive toxicity and alterations to the immune system.

Weber *et al*,[85]indicated that consumption of dietary phytoestrogens resulting in very high plasma isoflavone levels over a relatively short period can significantly alter body and prostate weight and plasma androgen hormone levels without affecting gonadotropin levels.Opalka *et al*,[53] suggested that dietary exposure to phytoestrogens had a slight effect on in vitro testicular secretion in ganders. In vitro treatment with phytoestrogen inhibited testosterone production by Leydig cells.

Glover and Asinder[28] stated that lipid peroxidation of epididymal sperm was significantly increased in animals fed a high phytoestrogen diet for 3 days. Disruption of the steroid regulation of the epididymis by phytoestrogens may alter its function, resulting in decreased quality of sperm, and thereby reducing fecundity.

Delclos *et al*, [22]administered Genistein in a soy and alfalfa-free diet and was observed abnormal cellular maturation in the vagina at 625 and 1250 ppm, and abnormal ovarian antral follicles were observed at 1250 ppm. In males, aberrant or delayed spermatogenesis in the seminiferous tubules relative to controls was observed at 1250 ppm.

Reproductive disturbances have been reported to occur in sheep and rabbits fed the soybean plant as a large part of the diet. The administration of exogenous estrogen to the immature chicks has been shown to result in impressive increase in oviduct size and weight. These are proportional to the amount of isoflavone given[52]. In other research, genistein fed to pregnant rats results in offspring with reduced BW and reduced feed consumption of the dams and pups [22]. Moreover, there are effects on reproductive development of male pups with decreased ventral prostate weights and aberrant or delayed spermatogenesis[22]. But Faqi *et al.*,[25] did not find any negative effect of isoflavones on reproductive index of male rats. It is possible that soy isoflavones exert estrogenic (agonist) or antiestrogenic (antagonist) effects. Evidence from rodent models strongly supports soy isoflavones as having antiestrogenic activity. Soy isoflavones antagonize estrogen-induced behaviors and estrogen receptor α- and β-dependent gene expression in the brain [56] and inhibit the effects of endogenous estradiol on uterus weight and the percentage of B lym-phopoietic cells in bone marrow [24].Wilhelms*et al,*[87] showed that soy isoflavones had no effect on average daily gain, feed consumption and feed:gain ratio in Japanese quail. They suggested that high concentrations of isoflavones in the diet may exert modest endocrine disruptor-like effects on the reproductive system of the male, but not the female, quail.

The role of isoflavones in health and diseases:

Unlike the adverse effect of phytoestrogens, some researchers investigate the beneficial effect of isoflavones.

Bone metabolism:

Soy isoflavones have been shown to attenuate bone loss in perimenopausal women [6] and in ovariectomized rats [9]. It has been hypothesized that isoflavones are the reason by which bones have increased calcium retention; therefore, increasing bone mineral density [63]. Although both genistein and daidzein are effective in preventing bone loss, daidzein is the more potent of these two compounds [58].Zn, Mn and Cu are essential trace elements needed for optimal formation of bone matrix and bone mineralization. These elements act as cofactors for some specific enzyme. For example, Zn acts as o component of ALP, which is involved in formation of bone mineral matrix, and deficiency of Zn causes skeletal defects[65]. Sahin *et al*,[67] reported that dietary genistein supplementation reduced excretion of bone minerals and improved bone heat-stressed quails and moreover increased availability of Ca and P. Choi *et al*,[20] in their research showed that genistein increase proliferation and differentiation of osteoblast-like cells and collagen synthesis and decrease intracellular Ca concentration in osteoclasts in animals. Bliar *et al,*[14] reported that genistein inhibits avian osteoclastic activity and can reduce bone loss in ovariectomized rats.

Cancer:

Plantderived estrogens have anti-carcinogenic effects on both hormone dependent and hormone independent cancers *in vitro*, in animal models and also epidemiologically. Santell *et al*,[69] reported that higher concentrations of genistein inhibit the growth and the DNA synthesis of breast cancer cells in cultures *in vitro*.

They have been shown to possess antioxidant activity [66,86] which might be related to their anticancer, antiinflammatory, and cardioprotective effects. It has been demonstrated that isoflavones decrease the production of free radicals in plasma, liver, brain, testes, and kidney of male rabbits [92].The antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx)[81].The CAT convert H2O2to HO, and the SOD catalyze the dismutation of the superoxide radical anion. Diets containing isoflavone (150 and 250 mg/kg) obviously elevated antioxidant enzymatic levels in various organs of rats fed diets containing partially oxidized oil [41].Cai and Wei [16] suggested that dietary genistein, 1 of the 2 majorcomponentofISF,enhancestheactivitiesofantioxidant enzymes in various organs in SENCAR mice. In vitro, genistein elicits potential positive and negative immune-modulating effects. Low concentrations of genistein in vitro have been reported to elicit greater natural killer cell activity [94] andantiviralreplicationand attachment [93].High concentrations of genistein in vitro have been reported to reduce macrophage and natural killer cell and phagocytosis rates through the inhibition of tyrosine kinase activity [75] and to lower T and B lymphocyte production through the suppression of topoisomerase II [19].

Cardiovascular health:
Isoflavones have been continuously studied regarding their capability to reduce LDL cholesterol which is attributed as the main reason for cardiovascular diseases [60].Additionally, isoflavones have not only been able to lower LDL cholesterol, but also increased HDL cholesterol, inhibited lipid peroxidation and lowered blood pressure [48].

It remains unclear what components of soy contribute to its protective affects. Several studies suggest that a component of soy proteins lowers LDL cholesterol levels by increasing the expression of LDL receptors [34,42]. Other studies suggest that thecholesterol-lowering effects of soy can be attributed to soyisoflavones, the most abundant of which are genistein, daidzein and glycitein. Soy isoflavones have been shown to decrease total, VLDL and LDL cholesterol levels while increasing HDL in monkeys. Genistein also is a potent antioxidant, scavenging both hydrogen peroxide and superoxide anion [86].In addition, genistein has been shown to inhibit platelet activation [54] and growthfactor activity [34].Inhibition of these processesmay be attributable in part to the fact that genistein is aprotein tyrosine kinase inhibitor [5]. Tyrosine kinase activity is required for intracellular growth factorsignaling, and growth factors such as platelet-derived growthfactor are believed to play a role in cell migration and proliferation in atherosclerosis [34].Thus, soy isoflavones, including genistein, may confer protection from increased susceptibility to atherosclerosis through a variety of mechanisms.

The cholesterol-loweringand antiatherosclerotic mechanisms of soy may include reduced absorption of dietarycholesterol [29],increased LDL receptor quantity and activity [13,34], the reduced arterial permeability of LDL, and the reducedarterial concentration and delivery of LDL [83]. Oxidized LDL is more prone than unoxidized LDL to remain in vessel wall and to induceatherosclerosis. In man, the intake of genistein and daidzein decreases LDL oxidation[79].Adipose tissue is highly responsive to estrogen. Human and mouse adipose tissue expresses both estrogen receptor (ERα-) and ERβ[8].Loss of circulating estrogen after ovariectomy leads to increased body and adipose weights, and this is prevented or reversed by estrogen replacement [47].Estrogen can affect adipose tissue indirectly through modulating appetite or energy expenditure. Estrogen also directly decreases the activity of lipoprotein lipase (LPL), a lipogenic enzyme that regulates adipocyte lipid uptake. Ovariectomy increases LPL activity and lipid deposi-tion in adipocytes, and 17 β-estradiol reverses this [50].In addition to estrogenic effects, genistein has effects on protein tyrosine kinases, apoptosis, cell proliferation, and angiogenesis [26] and could potentially affect adipose tissue through these mechanisms. So, it has been suggested that eggs containing the isoflavone might be an effective method for preventing geriatric diseases such as hypercholesterolemia.

The role of soy isoflavone in animal feed:
Jiang *et al*,[33] investigate the effects of synthetic soybean isoflavone on growth performance, meat quality and antioxidation in male broilers. In this research, fed diets supplemented with 0, 10, 20, 40, or 80 mg of ISF/kg, respectively. Results showed that adding 10 or 20 mg of ISF/kg, increased final BW, weight gain and feed intake. In this study, MDA production of the breast muscle decreased by adding isoflavone in diet (above 10 mg/kg) in male broilers. This finding suggested that isoflavone improved antioxidative status of male broilers by elevating the activity of antioxidant enzymes. The addition of 20 and 40 mg of ISF/kg diet significantly increased the pH value of breast muscles. This result may be attributed to a decreased LD production in muscles postmortem [38,62].Cassidy [18] stated that the isoflavone may act as estrogen agonist or antagonist depending on dose, duration of use, individual metabolism, and intrinsic estrogenic state. On the other hand, the protective effects of isoflavonoids were dependent on the chemical structures of these compounds [10].

Lin *et al*,[39] determined whether dietary isoflavone genistein could be transferred and/or accumulated into the eggs of Japanese quail and stated that genistein could be transferred and accumulated into the egg yolks of Japanese quail by dietary supplementation of genistein. The higher dietary dose resulted in a higher genistein concentration in egg yolks during the peak period.

In another research, Saitoh *et al*,[68] administered isoflavone in laying hens diet and measured the contents of isoflavone transferred to egg yolk. They concluded that the concentration of isoflavone in the blood began to increase in the laying hens 24 hrs after the start of feeding with a high concentration isoflavone-diet. This concentration peaked on the 12th day of the examination, and the high concentration status was maintained throughout the rest of the study. Feeding a high concentration of isoflavone to laying hens affected the cholesterol concentration in the yolk during the early stages of the feeding period, but this returned to the basal level for the remainder of the study period.

Sahin *et al*,[67] evaluated the effect of dietary supplementation with genistein on the nutrient use and mineral concentrations in tibia and serum of quails reared at high environmental temperature. The result showed that apparent digestibility of dry matter (DM), crude protein (CP) and ash was significantly improved by genistein supplementation. Moreover, adding genistein to diets decrease tha amounts of minerals in the excreta. They suggested, since genistein has a protective effect against heat stress, it may help the pancreas to function properly including secretion of digestive enzymes, thus improving retention of minerals. Their findings indicate that genistein has a direct stimulatory effect on bone mineralization, increasing bone Ca and P concentration. These results may have implications in the use of soy isoflavones for the prevention and treatment of osteoporosis in humans.

Akdemir and Sahin [4] showed that genistein supplementation increased egg production and egg quality and decreased yolk MDA level in quail without affecting vitamin A, and vitamin E levels. It also enhanced yolk genistein levels, which may improve oxidative stability of eggs. Enrichment of egg yolk with genistein thus provides a functional food that could potentially benefit human health.

CONCLUSION

With this epidemiologic and cell line evidence, intervention studies are now an appropriate consideration to assess the clinical effects of isoflavones because of the potentially important health benefits associated with the consumption of foods containing these compounds. This review suggests that isoflavones are among the dietary factors affording protection against cancer, heart disease and osteoporosis. Clearly, much research is required to clearly define the pharmacological effect of dietary isoflavones.

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