

Review Article

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Isoflavones: Biosynthesis, Health Promoting Effects and Bioavailability

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ABSTRACT

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Isoflavones are one of the various phytochemicals present in soybean considered responsible for its health benefits. Isoflavone come under the class of polyphenolic compounds and are of different chemical forms. In soybean genistein, daidzein and their glycosidic forms are the major isoflavones present. In addition to these small amounts of glycitein and its derivatives are also present. A branch of phenyl propanoid pathway is responsible for isoflavone biosynthesis from simpler precursors. Isoflavone synthase is the key enzyme of this pathway. After action of this enzyme other modifications like glycosylation and malonylation can occur. Due to its structural similarity to estrogens, isoflavones show agnostic and sometimes antagonistic activity, which is considered responsible for anti-cancerous properties of soybean. However, bioavailability is a key factor for bioactivity. The use of microbial fermentation/isolation of efficient hydrolyzing enzymes can make the isoflavones more bioavailable in human digestive system.

Introduction

Soybean is the most important legume crop grown around the globe. It is believed to have first domesticated in China around eleventh century B.C. or perhaps a bit earlier. It is used mainly for edible oil extraction, animal feed and food purpose. Soybean seed contains about 18% oil, 38% protein and 15% each of soluble and insoluble carbohydrates (<http://www.nrcsoya.nic.in/soyfood.htm>). Its oil contains a large proportion (61%) of poly-unsaturated fatty acids (PUFAs) about 15% saturated and 24% monounsaturated fatty acid. Among the PUFAs 55% is linoleic acid while the linolenic acid content is about 10%. Soybean oil has omega 3/omega 6 fatty acids ratio around 1:7.5 which is significantly higher than other vegetable oils. Due to high amount of PUFAs soybean oil is effective in

lowering the blood cholesterol level and low density lipoprotein thus is good for heart patients. It also contains high quantity of vitamin E (tocopherols) which is helpful in coronary heart diseases and cancer and possibly acts through synergistic mechanism along with other phytochemicals (Rui, 2004). High biological value and PDCAAS (protein digestibility corrected amino acid score) make soy protein nutritionally comparable to animal proteins like casein, egg and beef (Sarwar, 1989).

Phytochemicals are the naturally occurring plant chemicals that have biological effects. Soybean has a high quantity of phytochemicals such as isoflavones, tocopherols, saponins, phytosterols and

lecithin. Owing to the presence of these phytonutrients several health benefits such as reduction in heart diseases instances, hormone dependent cancers like breast cancer and osteoporosis have been associated with consumption of soybean. However, most of these beneficial effects have been correlated with significantly high levels of isoflavones (Dastmalchi and Dhaubhadel, 2015).

Isoflavones are a class of secondary metabolites whose production is limited to Papilionaceae family. In isoflavones the position of one aromatic ring is shifted. While most flavonoids have B ring attached to position 2 of C ring, isoflavones have B ring attached to position 3 of C ring (Fig. 1). Major Isoflavones present in soybean are genistein, daidzein and glycitein. They conjugate with sugars to form \square \square glucosides (genistin, daidzin), which in turn can be acylated to form 6''-O-malonyl glucosides and 6''-O-acetyl glucosides etc. In plants, isoflavones occur predominantly in these conjugated forms and aglycones are present only in small amounts. In soybean, isoflavone content and composition vary depending upon variety, processing etc. (Tanahindarto *et al.*, 2013).

Biosynthesis

Isoflavones are synthesized via a branch of phenylpropanoid pathway starting from Phenylalanine Ammonia Lyase (PAL) and ending with isoflavone synthase. Isoflavone synthase (IFS) is a cytochrome P450 mono-oxygenase bound to endoplasmic reticulum is the ultimate enzyme involved in the pathway. In soybean, two isoforms of this enzyme are present (Jung *et al.*, 2000). An increased activity of IFS may cause increased generation of isoflavones because it is the key regulatory enzyme involved in isoflavone production (Pregelj *et al.*, 2010). The isoflavone synthase was shown to be carrying

out isoflavone biosynthesis from flavanone via hydroxylation coupled to aryl migration (Steele *et al.*, 1999). Naringenin and liquiritigenin (both flavanones) act as substrate for isoflavone synthase and result in formation of genistein and daidzein respectively. Glucosyl and malonyl-transferases often act on these aglycones to form conjugates with glucosyl and malonyl residues. In soybean glycosidic forms are abundant while the aglycones are found only in small amount. Two genes encoding isoflavone synthase were identified from soybean exploiting the nature of enzyme as a protein of cytochrome P450 family by screening yeast ESTs of soybean and expressed it in *Arabidopsis* resulting in production of isoflavones in *A. thaliana* which otherwise doesn't synthesise isoflavones (Jung *et al.*, 2000). This further established the role of IFS as a key enzyme in isoflavone synthesis. Dhaubhadel *et al.*, (2008) identified the glucosyltransferase (UGT73F2) and malonyltransferase (GmMT7) in soybean which are responsible for formation of glucosyl- and malonyl- conjugates respectively. Both of these enzymes were found to be localized in cytoplasm. Suzuki *et al.*, (2007) cloned and characterized a cDNA encoding malonyl-CoA: isoflavone 7-O-glucoside-6''-O-malonyltransferase an enzyme catalyzing malonyl transfer to isoflavone 7-O- \square -D-glucosides to produce corresponding isoflavone 7-O-(6''-O-malonyl- \square -D-glucoside).

Factors influencing isoflavone accumulation in soybean seeds

Soybean seeds have total isoflavone content in a range from 0.05% to 0.5% of the dry matter. Although individual isoflavones vary within this range in soybean seeds but it is well established that genistein, daidzein and their conjugates are present in high and nearly equal amount. Glycitein and its conjugates on

the other hand are present in lesser amount (Lee *et al.*, 2004). Several factors influence the isoflavone content and composition in soybean like genotype, location and year of seeding. Due to the potential health promoting effects of isoflavones several studies have been done for determining the isoflavone profile so that genotypes having better health promoting effects can be selected. Xu and Chang (2008) studied the isoflavone content in 30 American soybean genotypes. They found that the total isoflavone content varied from 1.18 mg/g to 2.86 mg/g. Among different isoflavones genistein and its conjugates were most abundant (69%). Wang and Murphy (1994) studied the impact of seeding year upon isoflavone profile and observed a significant effect of seeding year upon isoflavone content but such a relationship was absent for seeding location. However, Hoeck *et al.*, (2000) reported that location of seeding can have an impact on the isoflavone accumulation in soybean. In an conclusive study Lee *et al.*, (2003) reported variation of isoflavone content in 15 soybean genotypes with a range of 2.20 to 6.45 mg/g in the year 1998, 3.19 to 9.5 mg/g in the year 1999 and in the year 2000 isoflavone content varied from 2.93 to 4.83 mg/g. They also observed that year of seeding tends to influence isoflavone content more as compared to genotype and location differences. Effects of location and seeding year can in part be explained by temperature differences due to planting date or those occurring during seed development.

Dhaubhadel *et al.*, (2003) studied the isoflavonoid biosynthesis and accumulation in developing seeds and found that developing soybean embryos have an ability to synthesize isoflavonoids *de novo* but transport from maternal tissue may in part also contribute to isoflavonoid accumulation in seed. Also the isoflavone synthase 2 (IFS2) was found to be induced upon pathogen infection, UV light

and its expression levels correlated well with the isoflavone accumulation while the IFS1 (another isoform) was expressed in an almost ubiquitous manner. Kudou *et al.*, (1991) reported that in the mature seeds isoflavone accumulate to the greatest extent in hypocotyls and were lowest in seed coat. Isoflavone synthase transcripts were detected primarily in the roots and seeds. The expression pattern of IFS1 in soybean was found to be consistent with the physiological roles of isoflavonoids as defence compounds against pathogens and signal molecules to symbiotic bacteria in soybean (Subramanian *et al.*, 2004). Isoflavone level in soybean was found to be altered by phytochrome mediated light treatments (Kirakosyan *et al.*, 2006). Isoflavone content was found to decrease upon drought during seed development (Gutierrez-Gonzalez *et al.*, 2010) similar results were obtained for high temperature stress (Chennupati *et al.*, 2012). Dastmalchi *et al.*, (2016) studied the subcellular localization and interactions of major enzymes involved in isoflavone biosynthesis.

Isoflavone synthase, the key enzyme involved in isoflavone biosynthesis and cinnamate 4-hydroxylase (both P450 enzymes) were found to be anchored to endoplasmic reticulum (ER). These enzymes were also found to be interacting with the soluble enzymes involved in phenylpropanoid pathway and isoflavone biosynthesis viz. chalcone synthase, chalcone reductase and chalcone isomerase. Through such interactions these soluble enzymes are tethered to the endoplasmic reticulum.

Interactions between soluble enzymes also have a role to play in maintaining this protein complex. All these findings point towards the existence of protein complex (isoflavonoid metabolon) mediating metabolic flux. Another interesting finding of the same study is the interaction of GmCHR14 only with the GmIFS2 but not with GmIFS1 (both

catalyzing same reaction). GmCHR14 is responsible for the production of isoliquiritigenin (metabolite specific only to legumes). Isoliquiritigenin is acted upon by IFS to convert it into daidzein which can further produce phytoalexins. This interaction thus might be playing an important role under stress conditions.

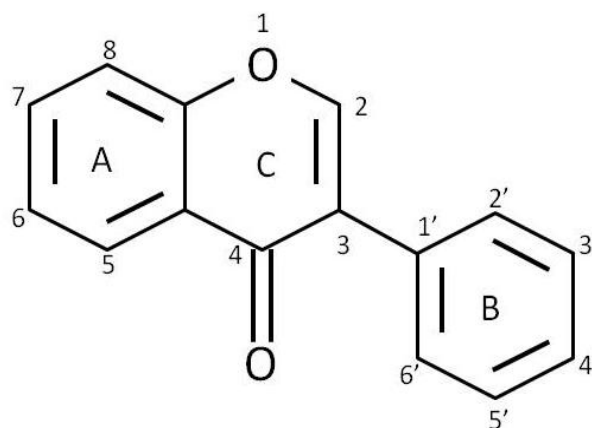
In most of the non-leguminous plants precursor of isoflavone biosynthesis pathway i.e. flavanones are present but absence of IFS makes these plants unable to accumulate isoflavones. Many efforts have been made for accumulating isoflavones in non-leguminous plants but with limited success possibly because substrate is not present in sufficient amount to create sufficient amount of flux (Shih *et al.*, 2008; Tian and Dixon, 2006; Jung *et al.*, 2000; Yu *et al.*, 2000). Pandey *et al.*, (2014) made an effort for co-expression of AtMYB12, an Arabidopsis transcription factor which up-regulates genes of phenyl propanoid pathway viz. CHS, CHI, etc. and GmIFS1 genes in tobacco. Expression of these genes resulted in accumulation of substantial amount of genistein glycoconjugates. Treatment with these transgenic plants showed improved

osteoprotective effect in Oestrogen-deficient mice.

Biological roles of isoflavones in plants

Isoflavones are found almost exclusively in legumes and have several different biological activities (Veitch, 2007). In legumes, isoflavones mediate plant-microbe interaction, induce Nod gene of nitrogen fixing bacteria. Subramanian *et al.*, (2006) provided direct genetic evidence that isoflavones are essential for nodulation of soybean roots, due to their ability to stimulate nod genes present in *Bradyrhizobium japonicum*. They also observed that although isoflavones have an ability to modulate polar transport of auxin but isoflavones are not necessary for nodulation of soybean roots. Isoflavones also serve as precursors of more complex phytoalexins involved in plant defence. Simpler isoflavones like daidzein and genistein themselves also have antimicrobial activity. So it comes as no surprise that isoflavone biosynthesis is induced by biotic elicitors i.e. Jasmonic acid and salicylic acid (Farag *et al.*, 2008; Shinde *et al.*, 2009).

Fig.1 Isoflavone backbone



Health promoting effects of isoflavones

Lower incidences of oxidation linked diseases in soybean eating populations in comparison to Western countries was shown to be caused due to presence of antioxidant compounds like isoflavones (Sarkar and Li., 2003) in soybean. Cassidy *et al.*, (1994) observed that isoflavones decrease incidence of hormone-dependent breast and prostate cancers and osteoporosis due to structural similarity of isoflavone to estrogens because of which they can interfere with binding of estrogens to receptors and thus increase follicular phase length and/or delay menstruation. In a review of studies conducted to know efficacy of soy in improving symptoms of breast cancer; Fritz *et al.*, (2013) found that higher soy consumption, may have protective function against the breast cancer development, mortality as well as recurrence. Protective effects of genistein in prostate cancer are attributed to epigenetic changes occurring via histone acetylation, demethylation and chromatin remodelling and thus causing activation of tumor suppressor genes (Majid *et al.*, 2008; Kikuno *et al.*, 2008). Isoflavones have ability to bind to both α and β type of estrogenic receptors especially to the α receptors. Depending on the level of endogenous estrogen present and tissue type the effect of isoflavones can be estrogenic or anti-estrogenic (Kuiper *et al.*, 1998; Kuiper *et al.*, 1997). In case of reproductive tissues i.e. breast, prostate, uterus the risk of hormone dependent cancer decreases due to anti-estrogenic effects of isoflavones. In non-reproductive tissues isoflavones have preventative effects towards hypercholesterolemia and osteoporosis due to estrogenic effects. Isoflavones show weak estrogenic activity i.e. 10^{-2} to 10^{-4} times as that of 17β -estradiol. Among genistein and daidzein the estrogenic activity of genistein is ten times more as compared to daidzein. Isoflavones also show biological activity in

ways other than their interaction with estrogenic receptors e.g. Genistein inhibit 3α and 17β hydroxysteroid activity and suppresses the synthesis of enzymes involved in estrogen metabolism (Whitehead *et al.*, 2002). Genistein also inhibits the tyrosine kinase activity of epidermal growth factor (EGF) receptor (Akiyama *et al.*, 1987). Obesity is considered as a major risk factor involved in the development of breast cancer. Lifelong exposure to isoflavones causes a decrease in chances to develop obesity in female rats which in turn reduces the risk for development of breast cancer (Kurrat *et al.*, 2016). Dong *et al.*, (2013) treated prostate cancer cells with different concentrations of genistein, daidzein (25-200 mM) and combination of these at a concentration 25 or 50 mM. A low dose combination (25/50 μ M daidzein and 50 μ M genistein) showed synergistic effect on inducing apoptosis while only the 50 μ M daidzein + 50 μ M genistein combination had an impact on cell cycle. Also the daidzein was poorly taken up by prostate cancer cells than genistein.

Isoflavones as antioxidants

Pratt and Birac (1979) reported that antioxidant activities of soybeans can largely be attributed to isoflavones. Among various isoflavones genistein was found to be most potent antioxidant, both in the aqueous and in the lipophilic phases (Ruiz *et al.*, 1997). However, isoflavones undergo extensive metabolism in the gut and liver, which might affect their biological properties, 8-hydroxydaidzein was found to be most potent scavenger of hydroxyl and superoxide anion radicals. Isoflavone metabolites also exhibited higher antioxidant activity than parent compounds in standard antioxidant (FRAP and TEAC) assays (Rimbach *et al.*, 2003). Patel *et al.*, (2001) reported that isoflavones inhibit lipid peroxidation stimulated in both metal dependent and independent manner.

However, isoflavones remained in native state and were not consumed which is inconsistent with classical antioxidants involved in chain terminating peroxy radical scavenging reactions. Antioxidant activity makes a major contribution towards the ability of isoflavones to reduce the risk of colon cancer (Mac Donald *et al.*, 2005) and cardiovascular diseases (Diplock, 1994; Rice –Evans *et al.*, 1997). Wiseman *et al.*, (2000) investigated the possible effects of soy-isoflavone rich diet on the lipid peroxidation and LDL oxidation by comparing it with a diet containing soybean from which isoflavones were extracted. They observed that consumption of soybean containing isoflavones increased the LDL's resistance towards oxidation and reduced the amount of lipid peroxidation. Djuric *et al.*, (2001) studied the effect of soy isoflavone supplementation on oxidative damage in blood and observed a decrease in level of oxidative damage to DNA in human and suggested that this may be one of the mechanisms responsible for cancer preventative properties of isoflavones.

Bioavailability of Isoflavones

Bioavailability of isoflavones in humans is affected by various factors. Some of these factors are ratio of glycosidic/aglycone form, dose, source, gender, food matrix etc (Nielsen and Williamson 2007). The aglycones show better absorption than glycosidic forms in the digestive tract (Sepehr *et al.*, 2009). Because the hydrolysis of glycosidic forms is essential for isoflavone absorption, the isoflavone aglycones are biologically active forms. Da silva *et al.*, (2011) studied the effect of fermentation on isoflavone forms in whole soybean flour. Fermented whole soybean flour showed conversion of glycosidic forms into aglycones. Walsh *et al.*, (2003) proposed that the isoflavones bioavailability from foods containing fat and protein is more than that of supplements due to enhanced bile secretion.

This occurs because micellarization appears to be required for bioaccessibility of isoflavone aglycones. Isoflavones upon *in-vitro* gastrointestinal digestion show high bioaccessibility which is sufficient enough to be absorbed and to impart health benefits (Rodríguez-Roque *et al.*, 2013). Genistein and glycitein get degraded into metabolites with no apparent estrogenic activity but the daidzein may get metabolized into equol having higher estrogenic potential (Setchell *et al.*, 2002; Simons *et al.*, 2005).

Future prospects

Seeing the trend of malnutrition problem in India and the potential role soybean can play in addressing this problem, the opportunities are immense. The presence of phytochemicals like isoflavones can help in popularising soy-based products by marketing it as a 'functional food' due its well-known health promoting effects. The biosynthetic pathway of isoflavones is well established, although lesser is known about the formation of phytoalexins from isoflavones. This can be the area of interest for plant biologists especially those working in the area of plant pathology. Bioavailability is important to achieve maximum possible health benefits from isoflavones. Using microbes either for fermentation or isolating catalytically efficient enzymes for conversion into bioactive form may be another promising area for future.

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