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Abstract

Soy, which contains a form of phytoestrogen known as isoflavones, impacts the biological activity of humans at all stages. There are many aspects to consider when determining whether soy is beneficial. Since the hormone estrogen plays a significant role in maintaining the biochemical and homeostatic conditions of an individual, it follows that the disruption of estrogenic levels can be detrimental. There are many hormone- dependent diseases that can be linked to one's diet, and the possibility of utilizing phytoestrogens, such as soy, to prevent or control hormonal irregularities is compelling. This paper explores the effects that phytoestrogens, specifically soy, can have at various stages of hormonal progression.

Introduction

Recently, soy has been garnering attention for its estrogen-like qualities. One group of chemicals found in soy are phytoestrogens, a non-steroidal class of estrogens. Of the numerous phytoestrogens, the study of the role of isoflavones has been isolated because of their high concentration in soy. Crucial to understanding soy's "estrogen-like" qualities is understanding isoflavones' chemical makeup. In soy specifically, isoflavones present as glycosides, which are bound to sugar molecules. When the isoflavone glycosides are digested and released, the isoflavone presents as aglycones. This includes compounds such as genistein, daidzein, and glycitein.

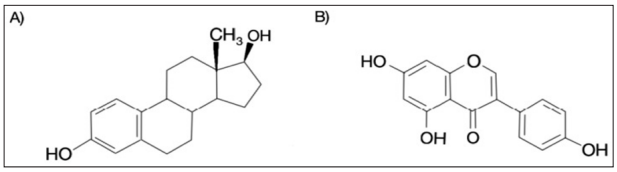

Figure 1. Chemical structures of 17β-estradiol (A) and genistein (B) (Thangavel, 2019)

Structurally, these isoflavones are similar to a form of estrogen, 17β-estradiol, as shown (fig, 1). The phenolic ring on the isoflavones is a crucial part of its structure which chemically allows the phytoestrogen to attach to estrogen receptors, thus promoting "estrogen-like" activity. Once the isoflavone is bound to an estrogen-receptor complex, the phytoestrogen can act as an estrogen agonist or antagonist. Based on various factors, such as the concentration levels of the phytoestrogen and endogenous estrogen, the specificity of the receptor, and the particular tissue that the phytoestrogen is targeting, the soy will either act as an estrogen inhibitor or stimulant. This holds promise as a physiologically beneficial method of regulating hormonal abnormalities. Dietary estrogen has shown potential in alleviating postmenopausal symptoms, reducing the risk of breast cancer, and bone resorption. However, soy is dosage- dependent, and a high intake of soy in infancy may lead to some physical signs of sexual maturation at a young age. Soy has also been a contributing factor for both very early and late menarche. There is a concern for early maturation, as it can cause hormone- related cancers such as breast cancer. Therefore, the consumption of soy that leads to the binding of isoflavones to sex-hormone binding globulins (SHBG) necessitates much research to determine all possible outcomes (Setchell, 1998).

Methods

The following research is based on the analysis of numerous articles from various databases, that include but are not limited to The Touro College Library online, PubMed, and ProQuest. The National Center for Biotechnology (NCBI), and BioMed Central (BMC) were additional sources of data as well.

Discussion

Infants

Soy- based infant formula (SBIF) has been used for over 100 years. SBIFs were developed as an alternative to cow's milk-based formula for infants that were lactose intolerant or required vegan replacement. Recent data has shown that SBIF is used by approximately 20%-25% of Americans. SBIF has a high concentration of isoflavones; the concentration levels vary from 32 to 47 mg isoflavones/L of formula. According to research, "infants fed SBIF are exposed to a 6–11 fold higher level of isoflavones on a body weight basis than adults. Additionally, circulating isoflavone levels of these infants were 13,000–22,000 times greater than circulating levels of 17-β-estradiol." (Dinsdale et al., 2010) The effect of an infant consuming and absorbing this high of a dosage of an estrogenic-like substance can have long-term consequences. This is because SBIF is primarily used from birth to one years old, which is a stage of development that is "particularly sensitive to dietary and environmental compounds." However, it is exceedingly difficult to track soy formula's precise long-term effects on reproductive health. In order to so, all participants must be monitored before reaching puberty and all through the child-bearing years; this would allow the possible differences in reproductive health and organ development to be determined. Since that would require long-term compliance, a retrospective approach has been taken to analyze the effects on those who consumed SBIF. However, as a retrospective study, there are the limitations of recall bias and environmental differences, such as smoking, physical activity and history of diseases, which make it difficult to determine

the accuracy of the results. No reports were given of long-term adverse effects for the male infants fed SBIF. At six months of age, female infants were reported to have increased vaginal cell maturation. There did not seem to be any vaginal discharge or breast development that was out of the ordinary. However, when children at two- years -old were still fed SBIF, there was an increase in the pervasiveness of breast tissue development in these children. Furthermore, the study reported that formula feeding in general, whether soy- or cow's milk-based, can cause greater ovarian volume, an increase in the numbers of ovarian cysts per ovary, and lower testicular volume.

On the other hand, SBIF and soy in general seem to prevent breast cancer. High levels of isoflavone enhance differentiation of the mammary glands, which leads to greater protection against chemically-induced mammary cancer. This was proven through a study in which genistein treatment was given, resulting in "fewer terminal end buds and advanced development and ductal elongation." As the least mature terminal ductal structures, it follows that terminal end buds are the most susceptible to possible carcinogens. Therefore, reducing the number of terminal end buds can lead to lower incidences of breast cancer. This is due to the fact that, "Part of the terminal end bud differentiates according to each estrous cycle, giving rise to alveolar buds that consist of lobule structures that are more mature and less susceptible to chemical carcinogens." This treatment of genistein increased the number of lobules, which shows that there is a potential protective effect against mammary cancer. The exact mechanism in which genistein affects mammary gland development is unclear; however, according to these findings, genistein clearly displayed estrogenic-like behavior (Dinsdale et al., 2010).

Table 1

Exposure	No. (%)	≤10 years	11 years	14 years	≥15 years
		rRR (95% CI)	rRR (95% CI)	rRR (95% CI)	rRR (95% CI)
Soy formula					
Ever	1,066 (4)	1.21 (0.94-1.54)	0.95 (0.78-1.15)	1.17 (0.98-1.40)	1.28 (1.06-1.56)
None	27,027 (96)	1.00	1.00	1.00	1.00
Breast fed					
Ever	12,961 (41)	1.01 (0.92-1.11)	1.00(0.93-1.08)	1.03(0.96-1.10)	0.96 (0.89-1.04)
None	18,478 (59	1.00	1.00	1.00	1.00

Relative Risk Ratios for Early and Late Menarche in Association with Early-Life Exposures in Women Aged 35 to 59 years at Baseline in the Sister Study, 2003-2009 (n = 33,501) (D'Aloisio et al., 2013)

Further studies show that high soy exposure during the prenatal and infant stages can cause early onset puberty, specifically menarche. Early menarche (≤10-11 years old) is just one of the factors that are considered when determining whether a female reached puberty; however, it is the most commonly used benchmark. There are many issues associated with early development, such as adult obesity, type 2 diabetes, metabolic syndrome, and other markers of cardiovascular disease. A study was done to determine the various factors involved in early menarche, soy being among them. The Sister Study enrolled 50,884 American and Puerto Rican women between the ages of 35-74. The study was interested in finding whether certain early-life exposures are related to the health conditions mentioned above. The authors conducted interviews that included a comprehensive family medical history. Anyone that did not have a mother to relate the early life events was excluded. The study combined those that said they "definitely" or "probably" had feeding exposures into one category, and those that responded that they "definitely did not" and "probably did not," into another category. Race/ethnicity, maternal age menarche, birth weight, birth decade, and childhood family income were also factored into the results. Results showed that, "The frequency of early menarche (≤11 years) was 20%, with 7% reporting menarche at 10 years of age or younger. The frequency of late menarche (≥14 years) was 24%, with 10% reporting menarche at 15 years of age or older."

The table above shows that SBIF can cause both early (≤10 years old) and very late menarche (≥15 years old). Although age at menarche is not the only sign of pubertal development, it is a key component; therefore, these studies are an important resource to tracking pubertal development. These findings are consistent with animal data that proves that the dose of genistein impacts whether early or late puberty will occur. "Mice administered a higher dose of genistein had a delayed vaginal opening (marker of puberty), while mice given a lower dose had an accelerated vaginal opening. Neonatal administration of genistein to mice has also produced other alterations in reproductive characteristics, including changes in estrous cycles, early reproductive senescence, and decreased fertility." In other words, the effects of neonatal administration of

genistein were greater than when genistein was administered to older mice. This makes sense considering that soy formula delivers a high dosage of its estrogenic components to infants "per unit body weight." Additionally, genistein is highly digestible and has been found in high concentrations in infants' urine and plasma. Thus, maintaining that the genistein can influence the estrogenic-like effect on these infants (D'Aloisio et al., 2013).

Furthermore, while there is no evidence that SBIF directly effects reproduction, SBIF does exert its influence on the menstrual cycle. Women who were given soy formula as infants reported prolonged menstruation and more discomfort. With all this data, the question of whether or not soy formula is safe remains. Many countries have regulations on the use of SBIF. For instance, in Europe, SBIF is a prescribed product. However, despite these regulations, there is a large percentage of infants each year that are fed SBIF (Dinsdale et al., 2010).

Male Reproduction

Considering isoflavones' estrogenic qualities, it follows that there can be estrogenic effects on males that consume high concentrations of soy. There are not many cases reported of soy stimulating feminizing effects on men, such as gynecomastia. However, a study was done on an instance of hypogonadism and erectile dysfunction that was linked to high intake of soy. A 19-year-old male that was recently diagnosed with type 1 diabetes began experiencing complete loss of libido and erectile dysfunction. Until the previous year, he had been in perfect health. He stated he had a heterosexual preference, was sexually active, had satisfactory libido, denied any history of orchitis or undescended testicles, had normal testicular size, and body hair pattern. Additionally, he denied any androgen abuse, hormonal medication, drug abuse, or psychiatric disorders. He had never had a sexually transmitted disease, no visual or muscular mass and strength changes, and no headaches. The one notable difference in his lifestyle was that he had taken on a vegan diet, which included high levels of soy (360 mg/day), due to his recent diagnosis of diabetes. A lab assessment revealed that he had low free and total testosterone levels, with increased levels of dehydroepiandrosterone (DHEA). His symptoms began after he started his vegan diet, which included products such as soy milk, soy cookies, tofu, soy sauce, soy nuts, and soybeans. Beforehand, he had been consuming the average American 2,000- kcal diet. After stopping his vegan and soy diet, his symptoms improved over the course of 12 months. These improvements were consistent with the gradual normalization of his testosterone and DHEA levels. The table below shows the progression of the patient's levels of total and free testosterone, as well as the levels of DHEA normalizing over a period. The insufficient blood levels of free testosterone, which causes hypogonadism and erectile dysfunction, normalized after the cessation of the soy diet, indicating that the high levels isoflavones may have been the cause.

The correlation between testosterone and soy may be explained by research on animals. "Animal studies have shown that isoflavones can bind to the estrogen receptor expressed by testosterone-producing Leydig cells, thereby affecting Leydig cell differentiation and testosterone production, which ultimately leads to reproductive toxicity." Therefore, consuming high levels of isoflavones can stimulate similar bioactivity in males. Another possibility is that the estrogen- like isoflavones can cause a negative feedback mechanism that interferes with the DHEA conversion to testosterone. As the DHEA converting enzymes 3-b-hydroxysteroid dehydrogenase and 17-b-hydroxysteroid dehydrogenase are inhibited through the isoflavones genistein and daidzein present in soybean, the negative feedback is facilitated. The inhibition is what can lead to a decrease in testosterone. Another possible way in which the isoflavones decreased the free testosterone levels can be through the increase of the sex hormone-binding globulin (SHBG), which is produced by the estrogenic activities of isoflavones. The increase of SHBG leads to more binding of the SHBG with the total circulating testosterone, which means there will be less free testosterone; this also further explains why the total circulating testosterone levels were within normal range (table 2). However, because there were missing SHBG measurements during the vegan diet, this hypothesis cannot be confirmed. There were nine more studies done in which the highest level of isoflavone concentration given was 139 mg/d, as opposed to the 360 mg/d given in this study. As this was the only study done that there was clearly a testosterone decrease with

Table 2

Serum Concentration	Normal ranges	Day 0: cessation of vegan diet	Day 15	Day 158	Day 724
Total testosterone (ng/dL)	260–1000	339	344	361	463
Free testosterone (pg/mL)	50–210	35.5	41.4	57	86.8
Free testosterone (%)	1–2.7	0.95	1.2	1.6	1.9
Unconjugated DHEA (ng/dL)	180–1250	1976			714
Estradiol (pg/mL)	7.6–42.6			19	30
Progesterone (ng/mL)	0.2–1.4			1.7	1.5

(Partial) Hormone profile at cessation of vegan diet and during 2-y follow-up (Siepmann et al., 2011)

the consumption of soy, researchers speculate that there is an "isoflavone intake threshold" for symptoms to occur. There is also the possibility that since the composition of soy products has evolved over the years, there might have been differences in the soy products of the previous studies. While further studies are necessary, this case report successfully indicates that a high consumption of isoflavones is related to hypogonadism and decreased free testosterone (Siepmann et al., 2011).

Menopause

Phyto-estrogens that are administered in an environment that has a high concentration of endogenous estradiol have an antagonist effect on the estrogen receptors. In that case, the isoflavones act as an inhibitor. However, when there is a decrease of endogenous estrogen, such as hypogonadism and menopause, an administration of isoflavones will stimulate estrogenic bioactivity (Casini et al., 2006). Menopause symbolizes the end of a women's reproductive life and is characterized by the cessation of menstrual periods for 12 consecutive months, which normally occurs between 45-55 years of age. Aside from the cessation of menstrual periods, there are additional symptoms, such as hormonal disturbances, hot flashes, night sweats, sleeping disorders, vaginal dryness, joint pain, mood swings, reduced bone density, and cardiovascular disease (Sunita et al., 2011). This mainly occurs because the menopause transition results in estrogen deficiency. Estrogen regulates appetite, cholesterol levels, carbohydrate and lipid metabolism, and protects bone. Therefore, when a woman is estrogen- deficient, the possibility of obesity, osteoporosis, and cardiovascular disease is more prevalent. To combat the hormonal imbalance, there are various forms of hormone replacement therapies (HRT). However, there are a host of issues with the with the HRT available, because the treatments available can cause diseases such as thromboembolism, uterine hyperplasia, uterine cancer, increased risk of breast, ovarian, and endometrial cancers, coronary heart disease, and stroke. Therefore, in more recent years women have been turning toward more natural methods of HRT, such as soy, to alleviate menopausal symptoms. Genistein promotes an inhibitory effect on many of the common menopausal symptoms. "It should be noted that genistein acts on various molecular pathways to emulate the effects of estrogens, without being known to elicit any life-threatening adverse effects." There have been studies done to determine how effective this form of therapy may be; however, this is still a relatively recent discovery and there are many aspects that need further exploration (Thangavel et al., 2019).

The Asian diet is heavenly concentrated with soy, relative to the European and American diet. Statistically, only 20%-25% of Asian postmenopausal women experience hot flashes, whereas 70%-80% of European and Latin American postmenopausal women complain of hot flashes. Since these hot flashes are one of the main postmenopausal symptoms that women seek HRT for, researchers were compelled to discover what caused Asian women to have a lower incidence rate (Thangavel et al., 2019). There are a few studies that have reported the effectiveness of genistein in treating hot flashes. A study was done on Japanese women specifically, comparing soy intake to incidences of hot flashes. This study was conducted over six years, in which it was shown that the consumption of soy reduced the hot flashes considerably. Even at the lowest concentration of isoflavones (75.2- 115.9 g/day), the hot flashes were lower, but the response rate was definitely more successful in the women that consumed higher levels of soy (Nagata et al., 2001). Another study was done on menopausal women and found that the "administration of 30 mg of genistein for 12 weeks reduced hot flashes by 51% (9.4–4.7/day), whereas the placebo group experienced only a 27% reduction (9.9–7.1/day)." (Braxas et al., 2019) Furthermore, a randomized trial was conducted in which hot flashes were alleviated by the consumption of 54 mg/day over the course of a year. The mechanism in which genistein can inhibit the hot flashes is unclear. However, researchers speculate that the genistein diffuses through the cell's lipid bilayer "due to genistein being an effective ER (estrogen receptor) modulator." This will set off the mRNA synthesis and production of tissue-specific proteins (Crisafulli et al., 2004). While there is no definite conclusion as to why genistein inhibits hot flashes, it seems to be a successful method based on the results of the numerous studies above.

Another effect that occurs because of estrogen depletion is the change in metabolism, such as the slowing down of the body's ability to metabolize carbohydrates and lipids. Consequently, women in the menopause stage are susceptible to weight gain. Genistein was found to stimulate a metabolic rate of carbohydrates and lipids to help prevent weight gain. This occurs because genistein regulates adipose tissue by restricting lipogenesis and enhancing lipolysis in adipocytes (Szkudelska et al., 2007). Furthermore, phytoestrogen treatment "reduced obesity markers, such as total cholesterol and low-density lipoprotein (LDL) cholesterol." These are common markers that are associated with obesity and cardiovascular health (Jayagopal et al., 2002). Additionally, another study reported that after 6 to 12 months of 54 mg/day of genistein treatment there was a significant reduction in triglycerides, total cholesterol, and

LDL-cholesterol (Squadrito et al., 2013). Conclusively, soy treatment can potentially improve cardiovascular health and prevent obesity.

There seems to be a positive correlation between a soy rich diet and the inhibition of cancers, specifically breast cancer. SBIF can inhibit breast cancer as well. Most of the studies compared the association of soy-rich diet with reduced breast cancer in Asian women, compared to those in the Western world. In one case, an Asian woman who migrated to a Western country showed an increased risk for cancer. The risk of breast cancer increases with age, and this form of cancer has become one of the most common forms of cancer affecting women. As the common forms of HRT are known to increase the risk of developing breast cancer, natural methods are a compelling substitute. Genistein, the form of isoflavone that is the most abundant in soy, has shown anticancer properties in preclinical trials, thereby opening the option of attempting clinical trials. Since this bioactive compound, soy, induces apoptosis in various cancer cell lines, such as HepG2 and Hep3B, in- vitro studies have proven the efficacy of genistein as a promising chemotherapeutic agent against cancer. Table 3 summarizes some of the common menopausal symptoms and how genistein can alleviate the symptoms (Thangavel et al., 2019).

Table 3

Symptoms/Disease	Genistein Effects
Vasomotor	Reduction of hot flashes, night sweats, and sleep disturbances frequency; as well as depression symptoms and memory loss
Cardiovascular	Reduction of myocardial necrosis, macrophage and serum levels of TNF-α, severity of atherosclerosis, and myocardial infarctions incidence
Obesity	Reduction of serum concentration of total cholesterol, LDL, triglycerides, and HDL
Diabetes	Reduction of fasting glucose concentration, insulin resistance, and improves glycemic metabolism
Cancer	Reduces the incidence of breast, hepatocellular, lung, gastric, and ovarian cancer
Stress responses	Improves 5-HT metabolism, stabilizes MAO activity, and improves turnover ratio of 5-HIAA/5-HT

Abbreviations: 5-HIAA: 5-Hydroxyindoleacetic acid; 5-HT: serotonin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MAO: monoamine oxidase; TNF-α tumor necrosis factor alpha.

Effects of genistein on menopause symptoms and some related diseases.

In addition to the diseases mentioned above, osteoporosis is another disease that postmenopausal women are prone to. Since estrogen has bone- protecting properties, it follows that a lack of estrogen puts menopausal women at risk of developing osteoporosis. Soy has been reported to reduce the risk of osteoporosis in peri- and post-menopausal women. A study was done examining the effects of a heavy soy diet on the overall bone density and strength of postmenopausal women. Eighty-seven women were eligible and were assigned to consume soy or control foods daily for one year. "Bone mineral density (BMD) and bone mineral content (BMC) of the whole body, lumbar (L1-L4), and total hip were measured using dual energy x-ray absorptiometry at baseline and after one year (Arjmandi et al., 2005)." Additionally, urine and blood markers of bone metabolism were assessed. Of the eighty-seven women, sixty-two completed the one-year long study. Results showed that whole body and lumbar BMD and BMC decreased in both the soy and control groups. However, the total hip BMD and BMC did not change in either group. "Both treatments positively affected markers of bone formation as indicated by increased serum bone specific alkaline phosphatase (BSAP) activity, insulin-like growth factor-I (IGF-I), and osteocalcin (BSAP: 27.8 and 25.8%, IGF-I: 12.8 and 26.3%, osteocalcin: 95.2 and 103.4% for control and soy groups, respectively)." (Arjmandi et al., 2005) Neither group had any effect on urinary deoxypyridinoline excretion, which is a marker of bone resorption. However, according to epidemiological data, populations with soy rich diets, such as the Asians, do have a lower incidence of osteoporotic fractures. On the other hand, there are numerous factors that contribute to skeletal health; therefore, the credit of the lower rates of fractures in these populations cannot be fully attributed to soy consumption. There are a number of animal studies that did show how isoflavones positively influenced BMD. However, when it comes to human studies there are a limited number of studies that examined the effects of soy on bone. A study was set up in which the identity of the individual treatments was only revealed after the analysis was complete, to keep the results as accurate as possible. Compliance of the participants was measured based on whether participants recorded the amount of soy they consumed and if they returned the uneaten food to the study site to be tallied. This study did not show that soy protein alone can substantially prevent bone loss. However, another study did indicate that a consumption of 40 mg/day to 80 mg/day for a year resulted in positive increases in BMC of the hip of the women who are at least four years post menopause. Additionally, these women were of low body weight or had low levels of dietary calcium. In the study

done in which there was no substantial effect of soy on reversing bone loss, most of the participants were four years post-menopause; however, many did not have low body weight or calcium intake. Therefore, it is possible that the differences in these factors are what created the discrepancy of the observed results of the bone (Chen et al., 2004). As far as which form of isoflavones is the most beneficial when it comes to affecting the bone, according to studies genistein is the single isoflavone with the greatest effect. A study demonstrated that genistein at a dose of 54 mg/d combined with HRT increased BMD in early postmenopausal women. Genistein was proven to increase the BMD of the femoral neck by 3.6% and the lumbar spine by 3.0%. HRT increased femoral neck and lumbar spine BMD by 2.4 and 3.8%. The researchers speculated that the genistein "reduces bone resorption markers" and "enhances new bone formation parameters." As a result, there is a bone mass net gain (Morabito et al., 2002). According to the circulating sex hormone levels that were assessed after examining the changes in the participants after a year, the soy did not produce any estrogenic effects. However, the soy did decrease SHBG concentrations, which increases the availability of circulating estrogens. Therefore, the soy did affect estrogen levels, even though it may not have directly exhibited estrogenic qualities. However, to confirm this, it would be necessary to measure the endogenous estradiol that is circulating. While there are certainly a number of studies that show correlation between bone protection and soy, there are still too many factors that require closer examination (Arjmandi et al., 2005).

Conclusion

Many soy- related articles are published annually; however, there are still numerous questions that require further exploration. Questions include whether SBIF is indeed harmful or not, how effective of an HRT is soy when it comes to menopausal symptoms, whether the effect of isoflavones on bone is transitory, and whether soy isoflavones and lower doses of antiresorptive agents can prevent postmenopausal bone mineral loss. In the United States, advisory groups gave their recommendation regarding the safety of soy infant formula. "The North America Committee on American Academy of Pediatrics recommends soy formula only for infants with galactosemia or hereditary lactase deficiency and mentions that soy formula might be useful for families wishing to avoid formula containing animal products." (Adgent et al., 2018) While high consumption may not be advisable for infants, Asian postmenopausal women with soy rich diets benefit from the isoflavones as shown by the studies mentioned above. The efficacy of soy and its isoflavones as an alternative to HRT and as a natural estrogenic source for treatment has yet to be determined.

Although the biological effects of soy hold potential, there are limitations, such as low bioavailability and low biological estrogenic activity. This has limited the clinical applications of genistein to some extent. However, the components of soy are promising in terms of being a natural source of preventative care.

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