Journal of Food Health and Bioenvironmental Science (May - August 2023), 16(2): 64-75

Journal of Food Health and Bioenvironmental Science

Journal homepage : http://jfhb.dusit.ac.th/

Health Benefit Potentials Offered by Soy Isoflavones as a Consequence of the Various Phytochemical Properties

Sriwiang Rittisak[a]* Ratchanee Charoen[a] Wanticha Savedboworn[b] Pakkawat Detchewa[b] Wiboon Riansa-ngawong[b] & Varaporn Vittayaporn[c]

[a] *Department of Innovation and Product Development Technology, Faculty of Agro-Industry, King Mongkut's University of Technology North Bangkok, Prachinburi, 25230 Thailand*

[b] *Department of Agro-Industry Technology and Management, Faculty of Agro-Industry, King Mongkut's University of Technology North Bangkok, Prachinburi, 25230 Thailand*

[c] *School of Culinary Arts, Suan Dusit University, Bangkok, 10300 Thailand*

Article info

Article history:
Received: 31 July 2023
Revised: 18 August 2023
Accepted: 25 August 2023

Keywords:
Health benefits, Soy isoflavones, Phytochemical, Phytoestrogen

Abstract

Bioactive soy isoflavones found in soybeans and other soy products offer antioxidant and anti-inflammatory properties and have been shown to present similar structural characteristics to 17-*β*-estradiol. Moreover, they have the ability to form bonds with estrogen receptors known as phytoestrogen. They are able to serve as the estrogen agonists of the relevant antagonists, depending on the estrogenic level of endocrine, although it is understood that isoflavones are involved in many complex processes based on their activity modes and compound structures. Isoflavones are now a matter of considerable interest to researchers due to their potential health benefits, especially in addressing the onset of cardiovascular disease, hormone-dependent cancers, type 2 diabetes, problems related to menopause, osteoporosis and cognitive decline due to the aging process. This study provides an overview based on prior research of the various benefits that might be offered by soy isoflavones.

Introduction

Asia has consumed soybeans (*Glycine max* L.) and other soy products in large quantities for hundreds of years in the form of soy milk, tofu, natto, miso, tempeh and many other traditional dishes. In contrast, the West has typically consumed soy extract, soy flour and other soy proteins as ingredients in a wide range of food products (O'Keefe et al., 2015; Kim et al., 2005; Messina, et al., 2006; Riswanto et al., 2021; Qu et al., 2021). Soybeans serve as an excellent source of fatty acids, carbohydrates, proteins, oil and amino acids. Furthermore, they also provide isoflavones which are phytochemical components that play key roles in the biological defense mechanism (Messina, 1999; Chen & Chen, 2021). There are 12 different kinds of isoflavones found in soybeans, which can be categorized into the following four types: i) *β*-glucosides (glycitin, daidzin

* Corresponding Author
e-mail: Sriwiang.t@agro.kmutnb.ac.th

and genistin); ii) 6″-*O*-malonyl-*β*-glucosides (6″-*O*-malonylgenistin, 6″-*O*-malonyldaidzi and 6″-*O*-malonylglycitin); iii) 6″-*O*-acetyl-*β*-glucosides (6″-*O*-acetylglycitin, 6″-*O*-acetyldaidzin and 6″-*O*-acetylgenistin) and iv) aglycone (genistein, glycitein and daidzein) (Jung et al., 2020; Lim et al., 2021; Qu et al., 2021). The main soybean component among these various isoflavones are the 6″-O-malonyl-*β*-glucosides, while *β*-glucosides and 6″-O-acetyl-*β*-glucosides play a lesser role and aglycone is not often seen (Hoeck et al., 2000, Qu et al., 2021). Genistein, daidzein and glycitein along with their associated glucosides are the most important isoflavone aglycones, accounting for respectively 50%, 40% and 10% of the overall isoflavone concentration found within soybeans (Hassan, 2013; Riswanto et al., 2021). The capacity of the human body to absorb these isoflavones is dependent on their chemical structure (Chang & Choue, 2013; Kuligowski et al., 2022). Isoflavones exhibit similarities in their structure to that of 17-*β*-estradiol, which is a form of estrogen and accordingly, this leads to mild estrogenic activity in addition to other similar biological properties and for this reason, they are known as phytoestrogen (Chen et al., 2019). They can also be considered as a flavonoid sub-class found in plants, and offering strong antioxidant qualities (Ramachandran 2020). In recent years, the food sector has found a use for soybeans and other soy products as functional foods while numerous studies have sought to apply soybeans in the treatment of various conditions related to cognition, menopause, obesity, diabetes, cancer, osteoporosis and cardiovascular disease (Messina, 2016; Riswanto et al., 2021; Ramachandran et al., 2020). Fig. 1 shows some of the health benefits associated with isoflavones from soybeans. This current study places emphasis on soy isoflavones and offers a summary of their biological potential along with their nutritional significance and specific properties pertaining to their antioxidant qualities, anti-cancer properties and effectiveness against type 2 diabetes mellitus, osteoporosis, heart diseases, cognitive abnormalities and symptoms of menopause which have previously been detailed. It is anticipated that this work will be of interest to an audience whose interests lie within the fields of agricultural or food science and the applications of nutritional food products.

Antioxidant Properties of Soy Isoflavones

The soybean plant is a source of soy isoflavones which offer notable antioxidant properties and can deliver important health benefits. Isoflavones are compounds whose basic structure comprises a pair of benzyl rings connected by a three-carbon bridge, which is sometimes but not always closed to form a pyran ring. Compounds of this type are collectively known as flavonoids which provide a large and diverse set of plant phenolics (Liu, 1997; Erickson, 1995).

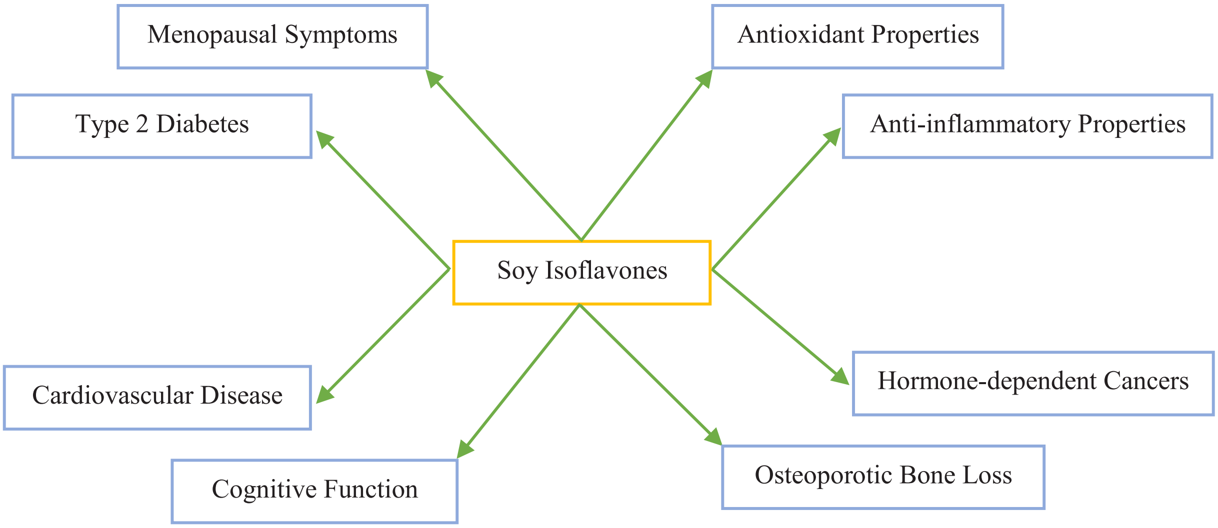

Fig. 1 The health benefits potentially offered by soy isoflavones.

The antioxidant activities of isoflavones include the scavenging of free radicals along with the capacity to reduce low-density lipoprotein (LDL). DNA is susceptible to oxidative stress and can support and enhance antioxidant enzyme expression and activity (Erba et al., 2012). Phenolic compounds can act directly as antioxidants through the scavenging of free radicals as well as act indirectly through the modulation of intracellular pro-oxidant or anti-oxidant enzymes (Schewe et al., 2008). For example, genistein inhibits radicals, thus acting as an antioxidant and can also act against cancer via the chelation of metals and the foraging of radicals. By donating hydrogen atoms from the hydroxyl group connected to the benzene ring, direct antioxidant activity takes place, thus ensuring the oxidative damage is reduced (Sawa et al., 1999; Sierens et al., 2002).

Rats that underwent treatment with daidzein exhibited greater catalase and superoxide dismutase (SOD) activity, whereas if they were treated with genistein, the SOD activity would also rise but not to the same extent (Banz et al., 2004). When mice were given soy isolate supplements that contained 400 mg/g isoflavone aglycones (226 mg/g genistein and 174 mg/g daidzein), their hepatic malondialdehyde (MDA) and conjugated dienes were found to be significantly reduced. The soy isolate served to increase catalase and SOD activity in the liver, but this was not the case for the activity of glutathione peroxidase (GSH-px) (Ibrahim et al., 2008).

The introduction of isoflavone supplements can increase antioxidant activity, which is evident through the decline in TBARs, the rise in plasma triglyceride and the reduced accumulation of body fat. However, the results of antioxidant activity which can be attributed to isoflavones could actually be in part a consequence of enhanced antioxidant enzyme activity (Yoon & Park, 2014).

Anti-inflammatory Properties of Soy Isoflavones

The inflammatory response is typically triggered by irritants, pathogens, or cell damage and serves the purpose of halting infection, repairing tissue, or removing necrotic cells (Barton, 2008). It is essential that the process is fast, specific to the target and controlled effectively to ensure that the innate immune response is not over-activated, since this could lead to severe tissue damage or the potential for chronic infections or inflammatory disorders (Garcia-Lafuente et al., 2009). The field of immunology has seen many recent advances and there has been considerable interest in the relationship between innate immunity and various diseases. It is understood that an immune response can result due to different triggering factors, but the response may occur at different levels of severity (Bernatoniene et al., 2021; Basson et al., 2021; Hariri et al., 2021). In a healthy individual or when facing a weak infection, the inflammatory response can be readily controlled and a return to normal health can be expected. However, when the response is not controlled, inflammation can be damaging and the outcome can be problematic (Hariri et al., 2021). To control inflammation, diet is a vital factor. For example, the consumption of acidic foods such as meats, which contain cholesterol and saturated fatty acids, leads to the generation of ROS (reactive oxygen species) as a part of the digestion process and as a consequence, inflammatory reactions can occur in different parts of the body (Jubaidi et al., 2021). In contrast, alkaline foods such as fruits, vegetables and legumes contain antioxidants and phytonutrients capable of eliminating ROS, thus contributing to weaker inflammatory responses (Tan et al., 2018; Xu et al., 2017).

It has been demonstrated that isoflavones can lower nitric oxide (NO) synthase 2 expression through the inhibition of nuclear factor kappa B (NF-κB) production which would normally be increased as a consequence of radiation and proinflammatory cytokines (interleukin-6, IL-6; interleukin-1 beta, IL-1β; tumor necrosis factor-alpha, TNF-α; and interferon gamma, IFN-γ) (Yu et al., 2016). Simultaneously, the activity of the anti-inflammatory enzyme arginase-1 is promoted, while radiation-induced neutrophils are prevented from gaining access to the lungs (Abernathy et al., 2015; Abernathy et al., 2017). Studies in human subjects have shown that when a soy nut diet (340 mg isoflavones/ 100 g soy nut) is followed for a period of two months, inflammation markers show signs of decline, in the case of interleukin-18 (IL-18) and C-reactive protein, while plasma nitric oxide levels are increased in post-menopausal females who have metabolic syndrome (Azadbakht et al., 2007). For post-menopausal females suffering hypertension, there is an improvement in endothelial function as well as the underlying inflammatory process in response to dietary soy nuts (25 g soy protein and 101 mg aglycone isoflavones) (Nasca et al., 2008). Furthermore, soy foods rich in isoflavones cause a decline in the C-reactive protein serum levels for patients with end-stage renal failure, while interferon γ (IFN-γ) concentrations are decreased in healthy individuals (Fanti et al., 2006; Ferguson et al, 2014).

Effects of Soy Isoflavone on Hormone-dependent Cancers

It is understood that stronger endogenous estrogens have adverse consequences in terms of breast and endometrial cancer, but it may be the case that soy isoflavones and similar phytoestrogens may mitigate this through weak estrogenic activity. In Asian nations where soy products are a major dietary component, fewer cases of breast and endometrial cancers are observed, while animal models have also provided evidence of soy isoflavones acting against cancer (Peeters et al., 2003; Sarkar & Li, 2003; Magee & Rowland, 2004).

The incidence of breast and mammary gland cancer has shown reduced levels when animals receive a diet rich in soybeans (Barnes et al., 1990). Similarly, reduced rates were seen in postmenopausal women who consumed isoflavones (Ingram et al., 1997), while there were also observable declines in the density of the mammary glands (Atkinson et al., 2004) and the proliferation of mammary gland cells (Palomares et al., 2004). This may be due to the effects upon the sex hormone binding globulin concentration exerted by the isoflavones, leading to lowered sex hormone bioavailability in tissues that depend upon those hormones (Kurzer, 2002). Furthermore, in the tissues around the periphery enzymes which promote cell proliferation, such as tyrosine kinase, can be inhibited by isoflavones (Gerosa et al., 1993; Blair et al., 1996), while estradiol availability is also reduced as a consequence of the inhibition of aromatase P450 (Kao et al., 1998).

In healthy females, studies have revealed that women using isoflavones exhibit lower rates of cancer associated with estrogen. One Japanese study showed that a diet containing soybeans would lead to a reduced incidence of breast cancer in younger women, but after menopause, there was no benefit recorded (Hirose et al., 2005). Research conducted over a three-month period showed that while minor ultrasonographic breast alterations could be observed following the consumption of soy isoflavones, the changes were shown to be sub-clinical and required no further attention upon completion of the study (Alipour et al., 2012).

Chen et al. (2014) conducted a meta-analysis examining the findings of 35 previous investigations concerning the correlations between the intake of soy isoflavone and the risk of developing breast cancer. The analysis showed that soy isoflavone reduced that risk for Asian women both pre- and post-menopause. In Western countries, however, no evidence of such a link could be found to support a similar conclusion in either pre- or post-menopausal females. Published data were sought from PubMed, Embase and the Cochrane Library with the focus on prospective cohort studies assessing the influence of isoflavone in the diet upon subsequent breast cancer onset. The data analysis included 16 research studies, comprising 648,913 sample participants and 11,169 cases of breast cancer. It was demonstrated by Zhao et al. (2019) that there was no change in breast cancer risk when women consumed soy-based foods in moderation, while a higher intake was linked to a lower level of breast cancer risk. The meta-analysis indicated that females whose dietary consumption of soy-based foods was high could enjoy a statistically significantly lower risk of developing breast cancer.

Prostate cancer cell growth can be inhibited by genistein and biochanin A at a high dosage (Peterson & Barnes, 1993), while isoflavones brought about a reduction in the prostate weight and volume in rats (Lund et al., 2001; Fritz et al., 2002). Meanwhile, men have been shown to exhibit reduced rates of prostate cancer when greater plasma concentrations of genistein are present (Travis et al., 2009).

Effects of Soy Isoflavone on Osteoporotic Bone Loss

Osteoporosis is a condition that results in bone loss. Its effects are amplified with age and it is found in both males and females, although older women are more significantly affected due to the decline in estrogen levels after the menopause. In around 30% of elderly females, bone loss causes severe orthopedic difficulties (Zheng et al., 2016; Bone et al., 2000). In 2001, the first reports were published concerning the potential benefits of isoflavones in this context (File et al., 2001). Whether menopause is surgical or natural, it is followed by a rapid bone loss in the early stages, whereupon further skeletal decline tends to subsequently occur more gradually (Gallagher, 1990). Several studies have shown that soy isoflavones have a direct influence on certain conditions affecting the bones, with one metaanalysis finding a notable increase in bone mineral density of up to 54% as a result of the influence of soy isoflavones, while urinary deoxypyridinoline, which is a bone resorption marker, declined by as much as 23% in women in comparison to the baseline. The influence of soy isoflavones on the density of bone minerals and deoxypyridinoline was demonstrated to be significant via sensitivity analysis (Wei et al., 2012; Nielsen et al., 2004; Seeman, 2004). When post-menopausal females received genistein over a period of six months, the outcome was a notable rise in bone density along with the appropriate decline in the concentration of biochemical bone resorption markers (Turhan et al., 2008). At twelve months of treatment, the bone density reached levels similar to those expected following estrogen hormonal replacement therapy (Potter et al., 1998; Morabito et al., 2002). Furthermore, the adverse consequences of estrogen therapy were not observed with treatment using isoflavones (Cornwell et al. 2004). It was noted by Polkowski & Mazurek (2000) that there may be two mechanisms that mediate the influence of isoflavones on bone metabolism. These are the effects on osteoclasts when apoptosis occurs and tyrosine-kinase activity inhibition which takes place via the modulation of membrane estrogen receptors (ERs) as consecutive changes arise in alkaline phosphatase activity. Based on this idea, it was argued by Blair et al. (1996) that when a genistein concentrate was used to wash cell osteoclast cultures, the tyrosine-kinase activity declined, followed by lower levels of bone remodeling.

Effects of Soy Isoflavone on Cognitive Function

It is believed that soy isoflavones might have a positive effect on cognitive function since they are phytoestrogens, offering activity similar to that of estrogen (Cui et al., 2019). In preclinical research, soy isoflavones have proven valuable in the removal of amyloid beta and reduction of tau phosphorylation, thereby addressing a number of diseases with pathologies similar to that of Alzheimer's (Bonet-Costa et al., 2016). In addition, the mitochondrial apoptotic pathway can be inhibited due to the anti-inflammatory and antioxidative effects of soy isoflavones, thus preventing Alzheimer's disease (Ye et al., 2017; Wang et al., 2016). Studies in animals confirm the ability of isoflavones to enhance cognitive function, while research in humans has also reported cognitive benefits derived from the use of soy isoflavones (Ozawa et al., 2013; Okubo et al., 2017; Nakamoto et al., 2018). Over the past twenty years, randomized controlled trials have been used to examine cognition function in the context of soy isoflavones, although the findings have lacked consistency (Henderson et al., 2012; File et al., 2005; Duffy et al., 2003; Fournier et al., 2007). Systematic reviews have also failed to report consistent patterns in the effects on cognition (Thaung-Zaw et al., 2017; Sumien et al., 2013). A meta-analysis was carried out by Cheng et al. (2015) concerning the influence of soy isoflavones upon females after menopause, finding positive effects on cognition. However, when males or younger females were investigated, the results which were indicative of positive outcomes for cognition were omitted from the overall analysis (Gleason et al., 2009; Thorp et al., 2009; File et al., 2001). Not all trials which involved postmenopausal females were included and the analysis also included research involving red clover, which has soy isoflavone content of only around 2% (Woo et al., 2003; Maki et al., 2009).

Effects of Soy Isoflavones on Cardiovascular Disease

In Western nations, cardiovascular disease is a leading cause of death, whereas Asian countries have a far lower incidence of heart disease (Beaglehole, 1990). While hereditary factors play a role, it is believed that nutrition may explain the huge difference between the regions. The Asian diet makes significant use of soy products, ensuring high levels of soy isoflavone consumption in Asia. It may therefore be the case that isoflavones can protect the cardiovascular system through various mechanisms (Adlercreutz, 1990; Anderson et al., 1999; Yamori, 2006). These processes are not yet understood in detail, however. Earlier research has revealed that isoflavones are able to support the amelioration of systemic arterial compliance in females undergoing menopause and those in the postmenopausal phase, albeit without affecting plasma lipids (Nestel et al., 1997). Meanwhile, research carried out in 2007 involving the use of 60 mg isoflavone daily for three months showed no significant difference in lipoprotein levels (Cheng et al., 2007). It is therefore likely that the preventive influence of isoflavones on cardiovascular disease may arise through alternative mechanisms (Brzezinski & Danenberg, 2008). For instance, daidzein and genistein release nitric oxide which causes the arteries to relax (Brzezinski & Danenberg, 2008). Even so, Wong et al. (2012) revealed no significant difference when blood pressure measurements were taken following

6 weeks of daily soy isoflavone use (80 mg). Animal studies, however, showed that in vessels with a preceding change of atherosclerosis, both soybeans and HRT bring about adverse consequences, with neither treatment capable of lowering the rates of myocardial ischemia or reperfusion injuries in either ovariectomized or diet-induced atherosclerotic monkeys. In the case of local ischemia, it has been shown that combining HRT with soybeans can increase myocardial changes (Suparto et al., 2008). It is important to note, however, that animal studies must be considered with care before concluding that human females should avoid soybean consumption following incidences of cardiovascular events. Further study would be necessary in order to make more reliable inferences (Brzezinski & Danenberg, 2008).

Effects of Soy Isoflavones on Type-2 Diabetes

T2D, or type-2 diabetes, poses a significant challenge for healthcare providers around the world. It leads to chronic insulin resistance along with the loss of functional pancreatic β-cell mass (Garg et al., 2016). A number of researchers have found that among the qualities of genistein is its antidiabetic activity, which arises from its interactions with β-cell proliferation, glucose-stimulated insulin secretion, apoptosis prevention and capacity for serving as an estrogen receptor (ER) agonist, antioxidant and inhibitor of tyrosine kinase (Gilbert & Liu, 2013). Although few studies have gathered data concerning the influence of genistein in human subjects with diabetes, animal studies and examinations of cell culture have shown that there is a direct effect upon β-cells exerted by genistein in concentrations that might arise in the body (<10 μM) (Gilbert & Liu, 2013; Wang et al., 2013). Furthermore, it has been observed that type-2 diabetes is less likely to develop in the presence of fermented soy products when compared to the effects of the unfermented version (Kwon et al., 2010). Meanwhile, Wagner et al. (2008) reported that the introduction of isoflavones can increase the insulin response to glucose challenge, as well as lower the expression of peroxisome proliferator-activated receptors (PPARs), which regulate the expression of genes. In addition, the plasma adiponectin concentration is also reduced in male monkeys, depending on the dosage. There was also an increase in adenosine monophosphate protein kinase (AMPK) activation due to soy isoflavones and this acts to regulate lipid and glucose metabolism, thus reducing the likelihood of type-2 diabetes (Stallings et al., 2014).

Effects of Soy Isoflavones on Symptoms of Menopause

For females undergoing the menopause, the symptoms which cause the greatest discomfort include sweating, hot flushes and palpitations, or vasomotor symptoms (VMS). Women suffering from such symptoms will often seek treatment (Chen & Chen, 2021). The work of St Germain et al. (2001) showed that females who consumed soybeans containing isoflavones for 24 weeks experienced decreased levels of hot flush, although this was also true of women who received soybeans without isoflavones and those who received whey proteins, so the placebo effect was apparent. The effect of the soy isoflavones is to enact the competitive inhibition of the enzyme 17-hydroxysteroid oxidoreductase (type 1), which plays the role of converting inactive estrone to significantly more active estradiol (Biniwale et al., 2022). Endothelial nitric oxide synthase (eNOS) transcription is activated when soy isoflavones bind to estrogen receptors, ultimately causing eNOS synthesis and the production of nitric oxide (NO). Heightened NO production permits the cutaneous dissipation of heat via vasodilatation. Accordingly, isoflavones are able to mitigate the problematic vasomotor symptoms (Hairi et al., 2019).

A systematic review was carried out by Jacobs et al. (2009) covering 17 randomized, placebo-controlled trials examining hot flushes and the influence of soy isoflavones. It was found that hot flushes could be reduced although consistency was not reported. There was no meta-analysis involved due to the similarity of the studies and their poor overall quality. Meanwhile, Bolanos et al. (2010) performed a meta-analysis making use of placebo-controlled randomized controlled trials which showed that vasomotor symptoms could be reduced using soy isoflavones when compared to the placebo. The systematic review by Taku et al. (2012) reached similar conclusions from the examination of 19 trials assessing the effects of synthesized soybean isoflavones as supplements that were able to reduce the incidence and strength of hot flushes. Finally, it was reported by Tranche et al. (2016) that 50 mg of soy milk isoflavones could bring about a significant decline in vasomotor symptoms for females undergoing menopause when receiving treatment for 12 weeks.

Soy Isoflavone Dosage and Health Risks

Isoflavones have long been considered a safe dietary ingredient throughout Asia, with research indicating that three-quarters of all Asians have an average daily consumption level of 65 mg of isoflavones. It can be concluded from this evidence that there are no adverse consequences to isoflavone consumption in the short term and that isoflavones are safe for human consumption (Lee & Kim, 2007; Kim, 2021).

One important consideration, however, is the potential long-term influence of isoflavones, as this may be of concern for health reasons as the outcomes are not immediately apparent. The work of Chen & Rogan (2004) argued that there are adverse consequences associated with isoflavones, having shown that the use of soy-based infant formula can hinder the long-term development of children. Exposure to genistein over the longer term can facilitate the growth of cells causing breast cancer and tumors associated with soy protein isolate show a tendency to be non-regressive, instead of growing aggressively (Andrade et al., 2015).

The dosage is another factor that can affect the health risks associated with isoflavone consumption, as one recent meta-analysis revealed that for women in Korea, the risk of cancer recurrence in epidermal growth factor receptor-2 (HER-2)-positive breast cancer is heightened due to an elevated intake of soy isoflavones (Woo et al., 2012). Tests in mice showed that genistein supplements at a high dosage of 150 mg/BW throughout a gestation period of 21 days will result in damage to the reproductive organs of the immediate offspring from the weanling stage (Lofamia et al., 2014).

It can be argued that the quantities of isoflavones typically consumed in the Asian diet are appropriate, based on the US FDA daily recommended intake of 50 mg (Chen et al., 2019; Chen & Chen, 2021). In terms of health risks, the consequences of isoflavone consumption remain a matter for ongoing debate and research and it should be taken into consideration that this study has mentioned only positive outcomes. There have not, however, been any reports of side effects of a severe nature as a consequence of isoflavone consumption to date.

Conclusion

This research examined the role of soy isoflavones in addressing a number of health conditions and diseases. The isoflavones obtained from soybeans offer anti-tumor, antioxidant, anti-inflammatory and anti-menopausal properties and can delay the process of osteoporosis. Furthermore, they can improve the memory and learning abilities of females undergoing menopause and support the management of cancer, cardiovascular disease and diabetes. Having assessed these health conditions in the context of isoflavones, it can be concluded that the phytoestrogen and antioxidant properties are the principal factors driving the relevant mechanisms. However, while soy isoflavones are understood to deliver notable health benefits when used to prevent or treat certain diseases, concerns have been raised about the potential for adverse reactions. It will therefore be necessary to conduct further studies to assess in detail the role of isoflavones in disease management, whether used independently or as part of a regimen involving combination with other treatments.

Acknowledgment

This work was supported by King Mongkut's University of Technology North Bangkok.

References

Abernathy, L.M., Fountain, M.D., Joiner, M.C., & Hillman, G.G. (2017). Innate immune pathways associated with lung radioprotection by soy isoflavones. *Frontiers in Oncology. 7,* 7.

Abernathy, L.M., Fountain, M.D., Rothstein, S.E., David, J.M., Yunker, C.K., Rakowski, J., … Hillman, G.G. (2015). Soy isoflavones promote radioprotection of normal lung tissue by inhibition of radiation-induced activation of macrophages and neutrophils. *Journal of Thoracic Oncology, 10*(12), 1703–1712.

Adlercreutz, H. (1990). Western diet and Western diseases: Some hormonal and biochemical mechanisms and associations. *Scandinavian Journal of Clinical Laboratory Investigations, 50*(Sub201), 3-23.

Alipour, S., Afshar, S., Moini, A., Dastjerdi, M., Saberi, A., Bayani, L., … Hosseini, L. (2012). Clinical and ultrasonographic changes of the breast after use of soy isoflavones. *Asian Pacific Journal of Cancer Prevention, 13*(12), 6093-6095.

Anderson, J., Anthony, M., Messina, M., & Garner, S. (1999). Effects of phyto-oestrogens on tissues. *Nutrition Research Reviews, 12*(1), 75-116.

Andrade, J.E., Ju, Y.H., Baker, C., Doerge, D.R., & Helferich, W.G. (2015). Long-term exposure to dietary sources of genistein induces estrogen-independence in the human breast cancer (MCF-7) xenograft model. *Molecular Nutrition and Food Research, 59*(3), 413-423.

Atkinson, C., Warren, R.M., Sala, E., Dowsett, M., Dunning, A.M., Healey, C.S., … Bingham, S.A. (2004). Red clover-derived isoflavones and mammographic breast density: A double-blind, randomized, placebo-controlled trial. *Breast Cancer Research, 6*(3), 170-179.

Azadbakht, L., Kimiagar, M., Mehrabi, Y., Esmaillzadeh, A., Hu, F.B., & Willett, W.C. (2007). Soy consumption, markers of inflammation, and endothelial function a cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care, 30*(4), 967-973.

Banz, W., Hauck, S., Gename, B., Winters, T., & Bartke, A. (2004). Soy isoflavones modify liver free radical scavenger systems and liver parameters in Sprague-Dawley rats. *Journal of Medicinal Food, 7*(4), 477-481.

Barnes, S., Grubbs, C., Setchell, K.D.R., & Carlson, J. (1990). Soybeans inhibit mammary tumors in models of breast cancer. In M.W. Pariza (Ed.), *Mutagens and carcinogens in the diet* (pp. 239–253). New York, NY: Wiley-Liss.

Barton, G.M. (2008). A calculated response: Control of inflammation by the innate immune system. *The Journal of Clinical Investigation, 118*(2), 413-420.

Basson, A.R., Ahmed, S., Almutairi, R., Seo, B., & Cominelli, F. (2021). Regulation of intestinal inflammation by soybean and soy-derived compounds. *Foods, 10*(4), 774.

Beaglehole, R. (1990). International trends in coronary heart disease mortality, morbidity, and risk factors. *Epidemiologic Reviews, 12*(1), 1-15.

Bernatoniene, J., Kazlauskaite, J.A., & Kopustinskiene, D.M. (2021). Pleiotropic effects of isoflavones in inflammation and chronic degenerative diseases. *International Journal of Molecular Sciences, 22*(11), 5656.

Biniwale, P., Biniwale, V., Phadke, A., & Qamra, A. (2022). Soy isoflavones in postmenopausal women: A review of current evidence. *American Journal of Clinical and Experimental Obstetrics and Gynecology, 8*(1), 1-13.

Blair, H.C., Jordan, S.E., Peterson, T.G., & Barnes, S. (1996). Variable effects of tyrosine kinase inhibitors on avian osteoclastic activity and reduction of bone loss in ovariectomized rats. *Journal of Cellular Biochemistry, 61*(4), 629-637.

Bolanos, R., Del Castillo, A., & Francia, J. (2010). Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: Systematic review and meta-analysis. *Menopause, 17*(3), 660-666.

Bone, H.G., Greenspan, S.L., McKeever, C., Bell, N., Davidson, M., Downs, R.W., … Lombardi, A. (2000). Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/estrogen study group. *The Journal of Clinical Endocrinology and Metabolism, 85*(2), 720726.

Bonet-Costa, V., Herranz-Perez, V., Blanco-Gandia, M., Mas-Bargues, C., Ingles, M., Garcia-Tarraga, P., … Vina, J. (2016). Clearing amyloid-beta through PPAR gamma/ApoE activation by genistein is a treatment of experimental Alzheimer's disease. *Journal of Alzheimer's Disease, 51*(3), 701-711.

Brzezinski, A., & Danenberg, H.D. (2008). Sex hormones, soy, and myocardial injury. *Menopause, 15*(2), 217-220.

Chang, Y., & Choue, R. (2013). Plasma pharmacokinetics and urinary excretion of isoflavones after ingestion of soy products with different aglycone/glucoside ratios in South Korean women. *Nutrition Research and Practice, 7*(5), 393-399.

Chen, A., & Rogan, W.J. (2004). Isoflavones in soy infant formula: A review of evidence for endocrine and other activity in infants. *Annual Review of Nutrition, 24,* 33-54.

Chen, L-R., Ko, N-Y., & Chen, K-H. (2019). Medical Treatment for osteoporosis: From molecular to clinical opinions. *International Journal of Molecular Sciences, 20*(9), 2213.

Chen L-R., & Chen K-H. (2021). Utilization of isoflavones in soybeans for women with menopausal syndrome: An overview. *International Journal of Molecular Sciences, 22*(6), 3212.

Chen, M., Rao, Y., Zheng, Y., Wei, S., Li, Y., Guo, T., & Yin, P. (2014). Association between soy isoflavone intake and breast cancer risk for pre-and post-menopausal women: A meta analysis of epidemiological studies. *PLOS ONE, 9*(2), e89288.

Cheng, G., Wilczek, B., Warner, M., Gustafsson, J-A., & Landgren, B.M. (2007). Isoflavone treatment for acute menopausal symptoms. *Menopause, 14*(3), 468-473.

Cheng, P.F., Chen, J.J., Zhou, X.Y., Ren, Y-R., Huang, W., Zhou, J-J. & Xie, P. (2015). Do soy isoflavones improve cognitive function in postmenopausal women? A meta-analysis. *Menopause, 22*(2), 198-206.

Cornwell, T., Cohick, W., & Raskin, I. (2004). Dietary phytoestrogens and health. *Phytochemistry, 65*(8), 995-1016.

Cui, C., Birru, R.L., Snitz, B.E., Ihara, M., Kakuta, C., Lopresti, B.J., … Sekikawa, A. (2019). Effects of soy isoflavones on cognitive function: A systematic review and meta-analysis of randomized controlled trials. *Nutrition Reviews, 78*(2), 134-144.

Duffy, R., Wiseman, H., & File, S.E. (2003). Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacology Biochemistry and Behavior, 75*(3), 721-729.

Erba, D., Casiraghi, M.C., Martinez-Conesa, C., Goi, G., & Massaccesi, L. (2012). Isoflavone supplementation reduces DNA oxidative damage and increases O-β-N-acetyl-D-glucosaminidase activity in healthy women. *Nutrition Research, 32*(4), 233-240.

Erickson, D.R. (1995). *Practical Handbook of soybean processing and utilization.* Missouri, USA: AOCS.

Fanti, P., Asmis, R., Stephenson, T.J., Sawaya, B.P., & Franke, A.A. (2006). Positive effect of dietary soy in ESRD patients with systemic inflammation--Correlation between blood levels of the soy isoflavones and the acute-phase reactants. *Nephrology Dialysis Transplantation, 21*(8), 2239–2246.

Ferguson, J.F., Ryan, M.F., Gibney, E.R., Brennan, L., Roche, H.M. & Reilly, M.P. (2014). Dietary isoflavone intake is associated with evoked responses to inflammatory cardiometabolic stimuli and improved glucose homeostasis in healthy volunteers. *Nutrition, Metabolism and Cardiovascular Diseases, 24*(9), 996-1003.

File, S.E., Hartley, D.E., Elsabagh, S., Duffy, R., & Wiseman, H. (2005). Cognitive improvement after 6 weeks of soy supplements in postmenopausal women is limited to frontal lobe function. *Menopause, 12*(2), 193-201.

File, S.E., Jarrett, N., Fluck, E., Duffy, R., Casey, K. & Wiseman. H. (2001). Eating soya improves human memory. *Psychopharmacology (Berlin), 157*(4), 430436.

Fritz, W.A., Eltoum, I.E., Cortroneo, M.S., & Lamartiniere, C.A. (2002). Genistein alters growth but is not toxic to the rat prostate. *The Journal of Nutrition, 132*(10), 3007-3011.

Fournier, L.R., Ryan-Borchers, T.A., Robison, L.M., Wiediger, M., Park, J-S., Chew, B.P., … Beerman, K.A. (2007). The effects of soy milk and isoflavone supplements on cognitive performance in healthy, postmenopausal women. *The Journal of Nutrition, Health and Aging, 11*(2), 155-164.

Gallagher, J.C. (1990). The pathogenesis of osteoporosis. *Bone and Mineral, 9*(3), 215227.

Garg, S., Lule, V.K., Malik, R.K., & Tomar, S.K. (2016). Soy bioactive components in functional perspective: A review. *International Journal of Food Properties, 19*(11), 2550-2574.

Garcia-Lafuente, A., Guillamon, E., Villares, A., Rostagno, M.A., & Martinez, J.A. (2009). Flavonoids as anti-inflammatory agents: Implications in cancer and cardiovascular disease. *Inflammation Research, 58*(9), 537–552.

Gerosa, F., Tommasi, M., Benati, C., Gandini, G., Libonati, M., Tridente, G., … Trinchieri, G. (1993). Differential effects of tyrosine kinase inhibition in CD69 antigen expression and lytic activity induced by rIL2, rIL-12 and rIFN-alpha in human NK cells. *Cellular Immunology, 150*(2), 382-390.

Gilbert, E. R., & Liu, D. (2013). Anti-diabetic functions of soy isoflavone genistein: mechanisms underlying its effects on pancreatic β-cell function. *Food and function, 4*(2), 200-212.

Gleason, C.E., Carlsson, C.M., Barnet, J.H., Meade, S.A., Setchell, K.D.R., Atwood, C.S., … Asthana, S. (2009). A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women. *Age and Ageing, 38*(1), 86-93.

Hairi, H.A., Shuid, A.N., Ibrahim, N., Jamal, J.A., Mohamed, N. & Mohamed, I.N. (2019). The effects and action mechanisms of phytoestrogens on vasomotor symptoms during menopausal transition: Thermoregulatory mechanism. *Current Drug Targets, 20*(2), 192-200.

Hariri, M., Ghasemi, A., Baradaran, H.R., Mollanoroozy, E., & Gholami, A. (2021). Beneficial effect of soy isoflavones and soy isoflavones plus soy protein on serum concentration of C-reactive protein among postmenopausal women: An updated systematic review and meta-analysis of randomized controlled trials. *Complementary Therapies in Medicine, 59,* 102715.

Hassan, S.M. (2013). Soybean, nutrition and health. In El-Shemy, H.A.El-Shemy (Ed.), *Soybean-Bio-active Compounds* (pp. 453-473). London, UK: IntechOpen Limited.

Henderson, V.W., St John, J.A., Hodis, H.N., Kono, N., McCleary, C.A., Franke, A.A., … Mack, W.J. (2012). Long-term soy isoflavone supplementation and cognition in women: A randomized, controlled trial. *Neurology, 78*(23), 1841-1848.

Hirose, K., Imaeda, N., Tokudome, Y., Goto, C., Wakai, K., Matsuo, K., …Tajima, K. (2005). Soybean products and reduction of breast cancer risk: A case-control study in Japan. *British Journal of Cancer, 93*(1), 15-22.

Hoeck, J.A., Fehr, W.R., Murphy, P.A., & Welke, J.A. (2000). Influence of genotype and environment on isoflavone contents of soybean. *Crop Science, 40*(1), 48-51.

Ibrahim, W.H., Habib, H.M., Chow, C.K., & Bruckner, G.G. (2008). Isoflavone-rich soy isolate reduces lipid peroxidation in mouse liver. *International Journal for Vitamin and Nutrition Research, 78*(4-5), 217-222.

Ingram, D., Sanders, K., Kolybaba, M., & Lopez, D. (1997). Case-control study of phyto-oestrogens and breast cancer. *The Lancet, 350*(9083), 990-994.

Jacobs, A., Sommerfield, C., Grossklaus, R., & Lampen. A. (2009). Efficacy of isoflavones in relieving vasomotor menopausal symptoms-a systematic review. *Molecular Nutrition Food Research, 53*(9), 1084-1097.

Jubaidi, F.F., Zainalabidin, S., Taib, I.S., Hamid, Z.A., & Budin, S.B. (2021). The potential role of flavonoids in ameliorating diabetic cardiomyopathy via alleviation of cardiac oxidative stress, inflammation and apoptosis. *International Journal of Molecular Sciences, 22*(10), 5094.

Jung, Y.S., Rha, C.S., Baik, M.Y., Baek, N.I., & Kim, D.O.A. (2020). Brief history and spectroscopic analysis of soy isoflavones. *Food Science and Biotechnology, 29*(12), 1605-1617.

Kao, Y.C., Zhou, C., Sherman, M., Laughton, C.A., & Chen, S. (1998). Molecular basis of the inhibition of human aromatase (estrogen synthetase) by flavone and isoflavone phytoestrogens: A site-directed mutagenesis study. *Environmental Health Perspectives, 106*(2), 85-92.

Kim, H.K., Kang, S.T., Cho, J.H., Choung, M.G., & Suh, D.Y. (2005). Quantitative trait loci associated with oligosaccharide and sucrose contents in soybean (*Glycine max* L.). *Journal of Plant Biology, 48*(1), 106-112.

Kim, I-S. (2021). Current perspectives on the beneficial effects of soybean isoflavones and their metabolites for humans. *Antioxidants, 10*(7), 1064.

Kuligowski, M., Sobkowiak, D., Polanowska, K., & Jasinska-Kuligowska, I. (2022). Effect of different processing methods on isoflavone content in soybeans and soy products. *Journal of Food Composition and Analysis, 110,* 104535.

Kurzer, M.S. (2002). Hormonal effects of soy in premenopausal women and men. *The Journal of Nutrition, 132*(3), 570S-573S.

Kwon, D.Y., Daily, J.W., Kim, H.J., & Park, S. (2010). Antidiabetic effects of fermented soybean products on type 2 diabetes. *Nutrition Research, 30*(1), 1-13.

Lee, M.J., & Kim, J.H. (2007). Estimated dietary isoflavone intake among Korean adults. *Nutrition Research and Practice, 1*(3), 206-211.

Lim, Y.J., Lyu, J.I., Kwon, S.J., & Eom, S.H. (2021). Effects of UV-A radiation on organ-specific accumulation and gene expression of isoflavones and flavonols in soybean sprout. *Food Chemistry, 339,* 128080.

Liu, K. (1997). *Soybeans: Chemistry, technology, and utilization.* New York, USA: Chapman & Hall.

Lofamia, E.A.A., Ramos, G.B., Mamon, M.A.C., Salido, F.M., Su, G.S., & de Vera, M.P. (2014). Isoflavone maternal-supplementation during periconception period: Influence on the reproductive organs of the first generation (F1) murine weanling-stage offspring. *Asian Pacific Journal of Reproduction, 3*(4), 268–274.

Lund, T.D., West, T.W., Tian, L.Y., Bu, L.H., Simmons, D.L., Setchell, K.D., … Lephart, E.D. (2001). Visual spatial memory is enhanced in female rats (but inhibited in males) by dietary soy phytoestrogens. *BMC Neuroscience, 2,* 20.

Magee, P.J., & Rowland, I.R. (2004). Phyto-oestrogens, their mechanism of action: current evidence for a role in breast and prostate cancer. *British Journal of Cancer, 91*(4), 513-531.

Maki, P.M., Rubin, L.H., Fornelli, D., Drogos, L., Banuvar, S., Shulman, L.P., & Geller, S.E. (2009). Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. *Menopause, 16*(6), 1167-1177.

Messina, M. (2016). Soy and health update: Evaluation of the clinical and epidemiologic literature. *Nutrients, 8*(12), 754.

Messina, M.J. (1999). Legumes and soybeans: Overview of their nutritional profiles and health effects. *The American Journal of Clinical Nutrition, 70*(3), 439s-450s.

Messina, M., Nagata, C., & Wu, A.H. (2006). Estimated Asian adult soy protein and isoflavone intakes. *Nutrition and Cancer, 55*(1), 1-12.

Morabito, N. , Crisafulli, A., Vergara, C., Gaudio, A., Lasco, A., Frisina, N., … Squadrito, F. (2002). Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: A randomized double-blind placebo-controlled study. *Journal of Bone and Mineral Research, 17*(10), 1904-1912.

Nakamoto, M., Otsuka, R., Nishita, Y., Tange, C., Tomida, M., Kato, Y., … Shimokata, H. (2018). Soy food and isoflavone intake reduces the risk of cognitive impairment in elderly Japanese women. *European Journal of Clinical Nutrition, 72*(10), 1458-1462.

Nasca, M.M., Zhou, J.-R., & Welty, F.K. (2008). Effect of soy nuts on adhesion molecules and markers of inflammation in hypertensive and normotensive postmenopausal women. *The American Journal of Cardiology, 102*(1), 84-86.

Nestel, P.J., Yamashita, T., Sasahara, T., Pomeroy, S., Dart, A., Komesaroff, P., … Abbey, M. (1997). Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arteriosclerosis, Thrombosis, and Vascular Biology, 17*(12), 3392-3398.

Nielsen, T.F., Ravn, P., Bagger, Y.Z., Warming, L., & Christiansen, C. (2004). Pulsed estrogen therapy in prevention of postmenopausal osteoporosis. A 2year randomized, double blind, placebocontrolled study. *Osteoporosis International, 15*(2), 168174.

O'Keefe, S., Bianchi, L., & Sharman, J. (2015). Soybean nutrition. *SM Journal of Nutrition and Metabolism, 1*(2), 1006.

Okubo, H., Inagaki, H., Gondo, Y., Kamide, K., Ikebe, K., Masui, Y., … Meada, Y. (2017). Association between dietary patterns and cognitive function among 70-year-old Japanese elderly: A cross-sectional analysis of the SONIC study. *Nutrition Journal, 16*(1), 56.

Ozawa, M., Ninomiya, T., Ohara, T., Doi, Y., Uchida, K., Shirota, T., … Kiyohara, Y. (2013). Dietary patterns and risk of dementia in an elderly Japanese population: The Hisayama study. *The American Journal of Clinical Nutrition, 97*(5), 1076-1082.

Palomares, M.R., Hopper, L., Goldstein, L., Lehman, C.D., Storer, B.E., & Gralow, J.R. (2004). Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. *Breast Cancer Research and Treatment, 88*(Suppl. 1), 4002.

Peeters, P.H., Keinan-Boker, L., van der Schouw, Y.T., & Grobbee, D.E. (2003). Phytoestrogens and breast cancer risk: review of the epidemiological evidence. *Breast Cancer Research and Treatment, 77*(2), 171-183.

Peterson, E., & Barnes, S. (1993). Genistein and biochanin a inhibit the growth of human prostate cancer cells but not epidermal growth factor receptor tyrosine kinase autophosphorylation. *Prostate, 22*(4), 335-345.

Polkowski, K., & Mazurek, A.P. (2000). Biological properties of genistein. A review of in vitro and in vivo data. *Acta Poloniae Pharmaceutica, 57*(2), 135-155.

Potter, S.M., Baum, J.A., Teng, H., Stillman, R.J., Shay, N.F., & Erdman Jr, J.W. (1998). Soy protein and isoflavones: Their effects on blood lipids and bone density in postmenopausal women. *American Journal of Clinical Nutrition, 68*(Suppl. 6), 1375S-1379S.

Qu, S., Kwon, S.J., Duan, S., Lim, Y.J., & Eom, S.H. (2021). Isoflavone changes in immature and mature soybeans by thermal processing. *Molecules, 26*(24), 7471.

Ramachandran, V., Bhongiri, B., Bairi, R., & Kumar, R.S. (2020). Potential health benefit of isoflavone. *International Journal of Research in Pharmaceutical Sciences, 11*(Suppl. 4), 2463-2467.

Riswanto, F.D.O., Rohman, A., Pramono, S., & Martono, S. (2021). Soybean (*Glycine max* L.) isoflavones: Chemical composition and its chemometrics-assisted extraction and authentication. *Journal of Applied Pharmaceutical Science, 11*(1), 12-20.

Sarkar, F.H., & Li, Y. (2003). Soy isoflavones and cancer prevention. *Cancer Investigation, 21*(5), 744-757.

Sawa, T., Nakao, M., Akaike, T., Ono, K., & Maeda, H. (1999). Alkylperoxyl radical-scavenging activity of various flavonoids and other phenolic compounds: Implications for the anti-tumor-promoter effect of vegetables. *Journal of Agricultural and Food Chemistry, 47*(2), 397-402.

Schewe, T., Steffen, Y., & Sies, H. (2008). How do dietary flavanols improve vascular function? A position paper. *Archives of Biochemistry and Biophysics, 476*(2), 102-106.

Seeman. E. (2004). Estrogen, androgen, and the pathogenesis of bone fragility in women and men. *Current Osteoporosis Reports, 2*(3), 9096.

Sierens, J., Hartley, J.A., Campbell, M.J., Leathem, A.J., & Woodside, J.V. (2002). In vitro isoflavone supplementation reduces hydrogen peroxide-induced DNA damage in sperm. *Teratogenesis, Carcinogenesis, and Mutagenesis, 22*(3), 227-234.

Stallings, M.T., Cardon, B.R., Hardman, J.M., Bliss, T.A., Brunson, S.E., Hart, C.M., … Hancock, C.R. (2014). A high isoflavone diet decreases 5′adenosine monophosphate-activated protein kinase activation and does not correct selenium-induced elevations in fasting blood glucose in Mice. *Nutrition Research, 34*(4), 308-317.

St Germain, A., Peterson, C.T., Robinson, J.G., & Alekel, D.L. (2001). Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. *Menopause, 8*(1), 17-26.

Sumien, N., Chaudhari, K., Sidhu, A., & Forster, M.J. (2013). Does phytoestrogen supplementation affect cognition differentially in males and females? *Brain Research, 1514,* 123-127.

Suparto, I.H., Williams, J.K., Fox, J.L., Yusuf, J.T.L., & Sajuthi, D. (2008). Effects of hormone therapy and dietary soy on myocardial ischemia/reperfusion injury in ovariectomized atherosclerotic monkeys. *Menopause, 15*(2), 256-263.

Taku, K., Melby, M.K., Kronenberg, F., Kurzer, M.S., & Messina, M. (2012). Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: Systematic review and meta-analysis of randomized controlled trials. *Menopause, 19*(5), 776-790.

Tan, B.L., Norhaizan, M.E., & Liew, W.P. (2018). Nutrients and oxidative stress: Friend or foe? *Oxidative Medicine and Cellular Longevity, 2018,* 9719584.

Thaung-Zaw, J.J., Howe, P.R.C., & Wong, R., (2017). Does phytoestrogen supplementation improve cognition in humans? A systematic review. *Annals of the New York Academy of Sciences, 1403*(1), 150-163.

Thorp, A.A., Sinn, N., Buckley, J.D., Coates, A.M., & Howe, P.R.C. (2009). Soya isoflavone supplementation enhances spatial working memory in men. *British Journal of Nutrition, 102*(9), 1348-1354.

Tranche, S., Brotons, C., Pascual de la Pisa, B., Macias, R., Hevia, E., & Marzo-Castillejo, M. (2016). Impact of a soy drink on climacteric symptoms: An open-label, crossover, randomized clinical trial. *Gynecol Endocrinol, 32*(6), 477-482.

Travis, R.C., Spencer, E.A., Allen, N.E., Appleby, P.N., Roddam, A.W., Overvad, K., … Key, T.J. (2009). Plasma phyto-oestrogens and prostate cancer in the European prospective investigation into cancer and nutrition. *British Journal of Cancer, 100*(11), 1817-1823.

Turhan, N.O., Bolkan, F., Duvan, C.I., & Ardicoglu, Y. (2008). The effect of isoflavones on bone mass remodelling markers in postmenopausal women. *Turkish Journal of Medical Sciences, 38*(2), 145-152.

Wagner, J.D., Zhang, L., Shadoan, M.K., Kavanagh, K., Chen, H., Tresnasari, K., … Adams, M.R. (2008). Effects of soy protein and isoflavones on insulin resistance and adiponectin in male monkeys. *Metabolism,* 2008, 57(Suppl. 1), S24-S31.

Wang, Y., Cai, B., Shao, J., Wang, T-T., Cai, R-Z., Ma, C-J., … Du, J. (2016). Genistein suppresses the mitochondrial apoptotic pathway in hippocampal neurons in rats with Alzheimer’s disease. *Neural Regeneration Research, 11*(7), 1153-1158.

Wang, Q., Ge, X., Tian, X., Zhang, Y., Zhang, J., & Zhang, P. (2013). Soy isoflavone: The multipurpose phytochemical (Review). *Biomedical Reports, 1*(5), 697-701.

Wei, P., Liu, M., Chen, Y., & Chen, D.C. (2012). Systematic review of soy isoflavone supplements on osteoporosis in women. *Asian Pacific Journal of Tropical Medicine, 5*(3), 243248.

Wong, W.W., Taylor, A.A., Smith, E.O., Barnes, S., & Hachey, D.L. (2012). Effect of soy isoflavone supplementation on nitric oxide metabolism and blood pressure in menopausal women. *The American Journal of Clinical Nutrition, 95*(6), 1487-1494.

Woo, H.D., Park, K.-S., Ro, J., & Kim, J. (2012). Differential influence of dietary soy intake on the risk of breast cancer recurrence related to HER2 status. *Nutritional and Cancer, 64*(2), 198-205.

Woo, J., Lau, E., Ho, S.C., Cheng, F., Chan, C., Chan, A.S.Y., … Sham, A. (2003). Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause. *Menopause, 10*(4), 352-361.

Xu, D.P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J., Zhang, J.J., & Li, H.B. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences, 18*(1), 96.

Yamori, Y. (2006). Food factors for atherosclerosis prevention: Asian perspective derived from analyses of worldwide dietary biomarkers. *Experimental and Clinical Cardiology, 11*(2), 94-98.

Ye, S., Wang, T-T., Cai, B., Wang, Y., Li, J., Zhan, J-H., & Shen, G-M. (2017). Genistein protects hippocampal neurons against injury by regulating calcium/calmodulin dependent protein kinase IV protein levels in Alzheimer's disease model rats. *Neural Regeneration Research, 12*(9), 1479-1484.

Yoon, G-A., & Park, S. (2014). Antioxidant action of soy isoflavones on oxidative stress and antioxidant enzyme activities in exercised rats. *Nutrition Research and Practice, 8*(6), 618-624.

Yu, J., Bi, X., Yu, B., & Chen, D. (2016). Isoflavones: Anti-inflammatory benefit and possible caveats. *Nutrients, 8*(6), 361.

Zhao, T.T., Jin, F., Li, J.G., Xu, Y.Y., Dong, H.T., Liu, Q., … Miao, Z.F. (2019). Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: A meta-analysis of prospective cohort studies. *Clinical Nutrition, 38*(1), 136-145.

Zheng, X., Lee, S-K., & Chun, O.K. (2016). Soy isoflavones and osteoporotic bone loss: A review with an emphasis on modulation of bone remodeling. *Journal of Medicinal Food, 19*(1), 10-14.