



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

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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

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 and 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). Figure 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).

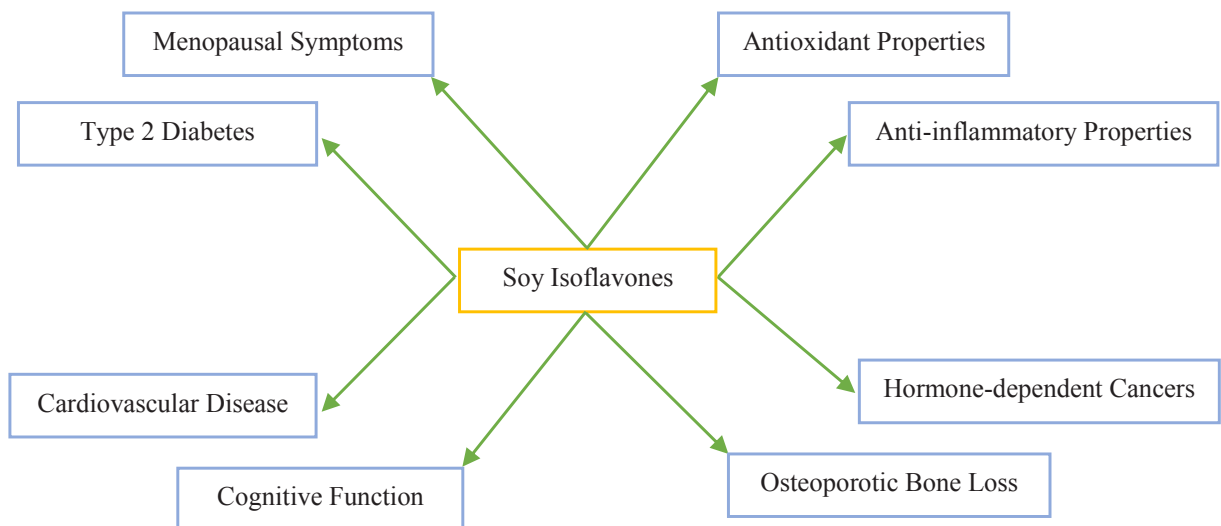


Fig. 1 The health benefits potentially offered by soy isoflavones.

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- κ B) production which would normally be increased as a consequence of radiation and proinflammatory cytokines (interleukin-6, IL-6; interleukin-1 beta, IL-1 β ; 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 ($<10 \mu\text{M}$) (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.

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